UNIVERSITAT DE BARCELONA

Reproductive factors, hormone use, and endocrine disruptors in the etiology of lymphoid neoplasms

Factors reproductius, ús d'hormones i disruptors endocrins en l'etiologia de les neoplàsies limfoides

Laura Costas Caudet

Reproductive factors, hormone use, and endocrine disruptors in the **etiology** of

LYMPHOID NEOPLASMS

LAURA COSTAS CAUDET

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Report of the Doctoral Thesis presented by

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Dr **Silvia de Sanjosé**

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Cover Page: Javier Sanz Márquez

A la família,
en el sentit ampli.

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En primer lloc als meus pares, per la seva entrega incondicional, per ser tant bones persones, i estar allà sempre que cal amb un somriure o amb el que faci falta. A la Gemma per ser més que una germana: una companya de vida. A la petitona per ensenyar-me coses que no són als llibres. A l'Edu, que m'ha donat temes per estudiar (productes químics, torns de nit). A la Marisin per ser una segona germana. Al Viedrin per la súper portada, pels seus consells de disseny gràfic, i sobretot, per acompanyar-me en aquest camí. I a la resta de la família, per ser tan peculiar i divertida.

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LIST OF ABBREVIATIONS

2,4D = 2,4-Dichlorophenoxyacetic acid

FAB = French-American-British classification

BMI = Body Mass Index

CLL/SLL = Chronic Lymphocytic Leukemia / Small Lymphocytic Leukemia

DLBCL = Diffuse Large B-Cell Lymphoma

EDCs = Endocrine Disrupting Chemicals

EGEs = Ethylene glycol ethers

ER= Estrogen Receptor

FHCRC = Fred Hutchinson Cancer Research Cancer

FL = Follicular Lymphoma

HIV = Human Immunodeficiency Virus

HL = Hodgkin Lymphoma

HT = Postmenopausal Hormone Therapy

IARC = International Agency of Research on Cancer

ICD-O= International Classification of Diseases for Oncology

iMAGE = Molecular and Genetic Epidemiology Study

IMMC = International Multiple Myeloma Consortium

InterLymph = International Lymphoma Epidemiology Consortium

JEM = Job-Exposure Matrix

LAMMCC = Los Angeles County Multiple Myeloma Case-Control Study

MM= Multiple Myeloma

NCI = National Cancer Institute

NHL= Non-Hodgkin Lymphoma

PAH = Polycyclic Aromatic Hydrocarbons

PCB = Polychlorinated Biphenyl

PCE = Perchloroethylene

REAL = Revised European-American Lymphoma classification

RPCI = Roswell Park Cancer Institute

TCE = Trichloroethylene

TEXB = Total Effective Xenoestrogen Burden

WHI = Women Health Initiative

WHO = World Health Organization

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**Equal contribution*

ABSTRACT

Lymphoid neoplasms are a heterogeneous group of cancers characterized by the neoplastic or clonal proliferation of lymphoid cells in different stages of differentiation. The incidence rate of these neoplasms has seen a rise in some western countries since the 1970s and it seems to have reached a plateau during the last decade. Incidence rates are higher in men than in women for most lymphoma subtypes; however, the causes explaining these differences by sex are unknown. We hypothetised that hormonal factors could have a role in lymphoma etiology.

The general aim of this thesis was to assess the risk of lymphoid neoplasms in relation to reproductive factors and occupational exposure to endocrine disruptors. We used different studies and populations to evaluate our hypothesis: the EpiLymph study, the InterLymph consortium, the International Multiple Myeloma Consortium, and a systematic review. As well, we developed a new tool to estimate occupational exposures to a specific type of endocrine disruptors.

We observed contradictory findings across studies and lymphoma subtypes concerning the association between lymphoma and parity, as well as hormonal contraceptives. We observed inverse associations between postmenopausal hormone therapy and lymphoma, although we noticed in our systematic review that cohort studies usually found null associations. We observed associations with lymphoma and prolonged (≥30 years) occupational exposure to endocrine disrupting chemicals, in particular for multiple myeloma and chronic lymphocytic leukemia. Associations were observed between lymphoma and prolonged occupational exposures to organic solvents, pesticides, brominated flame retardants, alkylphenolic compounds, and metals. To further explore the associations with alkylphenolic compounds, we developed a job-exposure matrix on these compounds considering relevant changes in use over time.

In conclusion, our results indicate that reproductive factors and exogenous hormone use are unlikely to play a role in lymphomagenesis. The associations between occupational exposure to endocrine disrupting chemicals and lymphoma need to be further explored in studies using a more detailed exposure assessment.

GENERAL INTRODUCTION

Lymphoid neoplasms

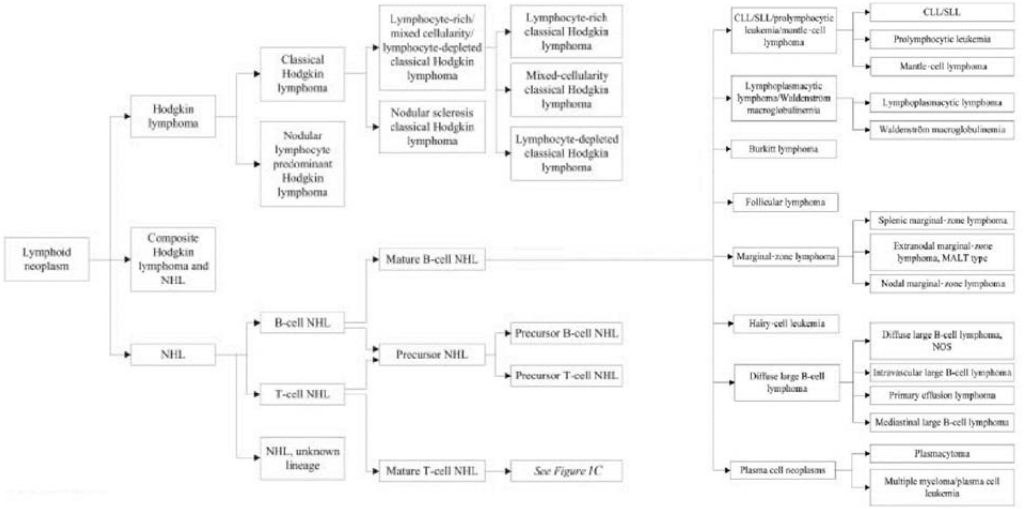
Lymphoid neoplasms are a group of cancers characterized by the neoplastic or clonal proliferation of lymphoid cells in different stages of differentiation. In general, we refer to *lymphoma* if the proliferation is located in a lymph gland, such as lymph nodes, while *leukemia* if the proliferating cells circulate in blood.

a. Classifications

Lymphoid neoplasms had numerous classifications and coding systems over time, based on clinic, molecular, genetic, immunophenotypic, and morphologic characteristics. During a long time of period, lymphomas were characterized based on morphologic features (Rappaport classification), morphology and prognosis (Working Formulation), or cell differentiation (Lukes and Collins or Kiel) [8]. The Revised European-American Lymphoma classification (REAL) incorporated clinic, genetic, immunophenotypic, and morphologic features in 1994, and replaced old classifications. In 1995, these definitions were introduced to the International Classification of Diseases for Oncology, 2nd Edition (ICD-O-2). ICD 7 and 8 were the previous coding systems, before the appearance of REAL and ICD-O-2. On the other hand, leukemias were classified until 2000 by the French-American-British classification (FAB).

In 2001, the World Health Organization (WHO) created the current 'gold standard' classification, based on REAL and FAB, and it was updated in 2008 [9]. The International Lymphoma Epidemiology Consortium (InterLymph) made a proposed hierarchical classification to group lymphoma subtypes uniformly in epidemiologic studies [8,10] (**Figure 1**).

Figure 1: Proposed WHO-based nested classification of malignant lymphoid neoplasms from the Pathology Working Group of the InterLymph.



(adapted from Morton et al [8]).

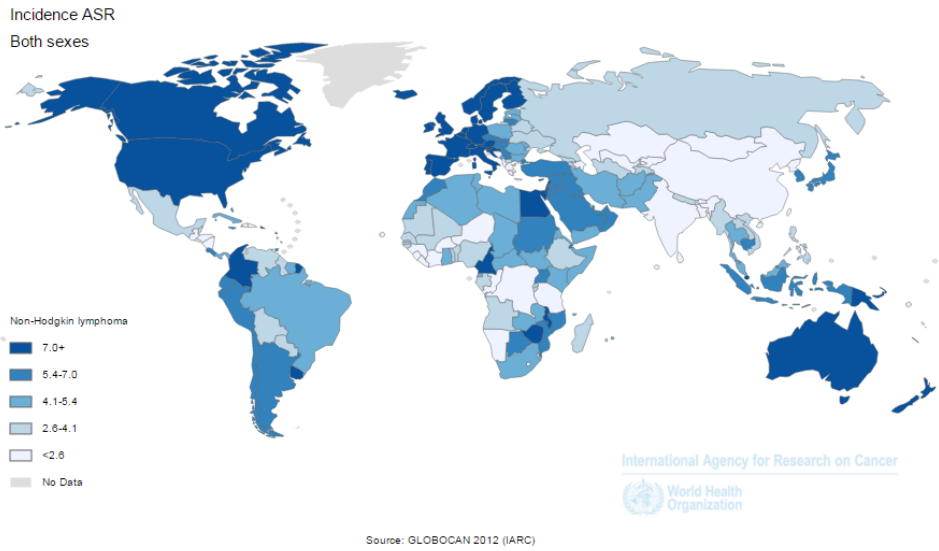
Lymphomas are classified by WHO based on cell lineage (B, T of NK) and cellular differentiation (mature or immature), among others. In general, lymphomas are stratified as Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). Among NHL, there are T-cell NHL and B-cell NHL, and among B-cell NHL, the most common subtypes are chronic lymphocytic leukemia / Small Lymphocytic Leukemia (CLL/SLL), follicular lymphoma, diffuse large B-cell lymphoma (DLBCL), and multiple myeloma (MM). Traditionally, studies published before the WHO classification considered NHL regardless of B or T-cell lineage, and excluding MM.

b. Epidemiology

Incidence rates of lymphoid neoplasms are usually higher in industrialized countries compared to developing areas (**Figure 2**). Age-adjusted incidence ratios are higher in North America, followed by Australia/New Zealand and Europe [11]. Age-adjusted incidence rate of lymphoid neoplasms in Europe is 24 per 100.000

[12], while in less developed areas is estimated to be less than 10 per 100.000 [11].

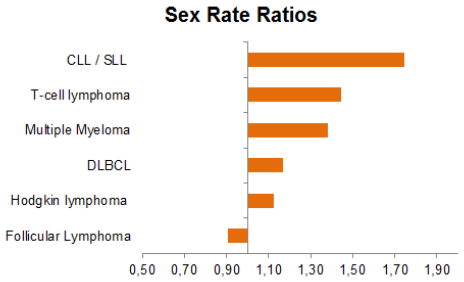
Figure 2: Age-standardized incidence rates of non-Hodgkin lymphoma worldwide.



From Globocan 2012 [11].

Incidence rates are higher in men than in women for most lymphoma subtypes (**Figure 3**) [13]. CLL/SLL, T-cell lymphoma, and MM are among the subtypes showing greater male : female rate ratios, while this sex rate ratio is usually below 1 for follicular lymphoma (**Figure 3**) [13].

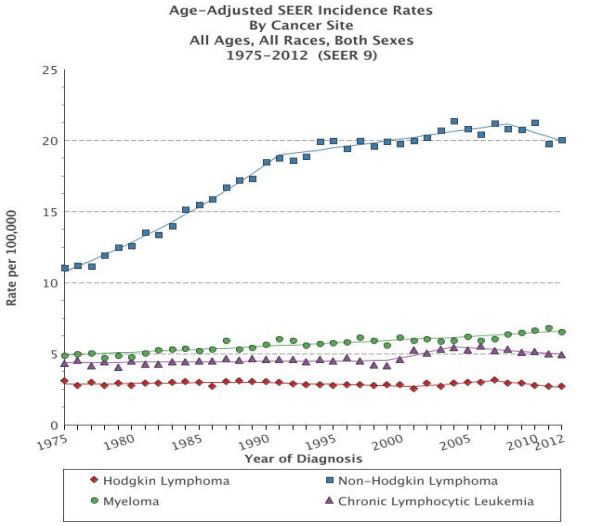
Figure 3: Incidence sex rate ratios by the largest lymphoid neoplasm subtypes based on population data from UK [13].



CLL/ SLL = Chronic lymphocytic leukemia / Small Lymphocytic Leukemia.
DLBCL = Diffuse large B-cell lymphoma.

While Hodgkin lymphoma incidence rates have remained stable over the years, non-Hodgkin lymphoma incidence has seen a rise in some western countries since the 1970s and it seems to have reached a plateau during the last decade (**Figure 4**). While human immunodeficiency virus (HIV) and changes in lymphoma classifications and registration could contribute to this increase, these factors do not completely explain this rise in incidence.

Figure 4: Lymphoma incidence time trends in the United States.



Cancer sites include invasive cases only unless otherwise noted.
Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130). Regression lines are calculated using the Joinpoint Regression Program Version 4.2.0, April 2015, National Cancer Institute.
Incidence source: SEER 9 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Atlanta).

c. Risk factors

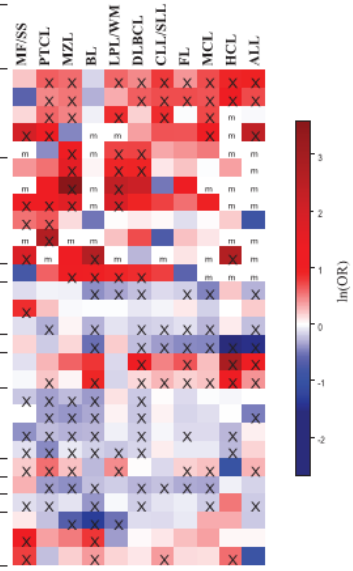
Recognized risk factors of NHL are: primary immunodeficiency disorders, HIV-infection, organ transplantation, infectious agents such as Hepatitis C virus and Human T-Cell Lymphotropic Virus - HTLV- 1, autoimmune diseases such as Sjögren's syndrome and systemic lupus erythematosus, and family history of blood malignancies [14,15]. The role of other risk factors, including lifestyle and environmental factors, remains controversial. Epstein Barr Virus infection is the main risk for HL. Studies tend to show that while some risk factors are common to most lymphoma subtypes, others are subtype-specific [16].

Recently, due to the collaborative effort from lymphoma investigators over the world, our knowledge of lymphomas etiology has substantially improved, and some risk factors have been identified. The InterLymph NHL Subtypes Project is an initiative of pooling individual-level data from 20 case-control studies (17471 NHL cases, 23096 controls) from North America, Europe, and Australia [17]. In this project, some of the identified associations were subtype-specific; while others were shared among multiple NHL subtypes (**Figure 5**).

Risks showed to be different among NHL subtypes for medical history factors (autoimmune diseases, hepatitis C virus seropositivity, eczema, and blood transfusion), alcohol consumption, tobacco smoking, and certain occupations, and in general, the greatest difference in risk factors arose between T-cell and B-cell lymphomas. In contrast, homogeneous risks among subtypes were observed for recreational sun exposure, hay fever, allergy, and socioeconomic status [16].

Figure 5: Associations for risk factors affecting one or more NHL subtypes in the InterLymph NHL Subtypes Project.

Exposure Category[A]	Specific Exposure	Prevalence (%) Cases	Prevalence (%) Cntls	P_{ASSET}	P_H	Overall NHL OR (95% CI)
Family history of hematologic malignancy[B]	Any	9.1	5.2	1.6×10^{-22}	3.5×10^{-2}	1.72 (1.54 - 1.93)
	NHL	4.0	2.0	1.7×10^{-13}	5.2×10^{-1}	1.79 (1.51 - 2.13)
	Leukemia	4.2	2.8	1.3×10^{-11}	3.9×10^{-5}	1.51 (1.29 - 1.77)
	Multiple myeloma	0.7	0.4	7.5×10^{-4}	2.2×10^{-2}	1.77 (1.15 - 2.72)
	Hodgkin lymphoma	1.1	0.6	2.0×10^{-3}	4.7×10^{-1}	1.65 (1.18 - 2.29)
Autoimmune disease[C]	Any B-cell activating disease	0.9	0.8	3.8×10^{-22}	9.8×10^{-10}	1.96 (1.60 - 2.40)
	Sjögren's syndrome	0.6	0.1	6.3×10^{-18}	7.3×10^{-9}	7.52 (3.68 - 15.4)
	Systemic lupus erythematosus	0.5	0.2	1.9×10^{-8}	1.8×10^{-1}	2.83 (1.82 - 4.41)
	Any T-cell activating disease	3.4	3.3	5.3×10^{-3}	1.2×10^{-2}	1.07 (0.95 - 1.21)
	Celiac disease	0.4	0.2	5.2×10^{-11}	5.1×10^{-8}	1.77 (1.05 - 2.99)
	Systemic sclerosis/scleroderma	0.1	0.1	5.1×10^{-3}	6.5×10^{-2}	1.03 (0.41 - 2.58)
HCV seropositivity[D]		2.3	2.2	2.3×10^{-8}	2.1×10^{-3}	1.81 (1.39 - 2.37)
Atopic disease[E]	Hay fever	18.2	20.1	9.1×10^{-9}	1.2×10^{-1}	0.82 (0.77 - 0.88)
	Eczema	9.8	9.8	5.0×10^{-5}	2.6×10^{-5}	1.01 (0.93 - 1.10)
	Allergy	22.0	24.4	5.9×10^{-5}	2.4×10^{-1}	0.86 (0.81 - 0.92)
Blood transfusion[F]	Transfusion occurring <1990	14.2	15.5	5.0×10^{-5}	1.3×10^{-2}	0.76 (0.67 - 0.87)
Anthropometric factors[G]	Body mass index as a young adult	21.1	17.9	4.2×10^{-9}	2.8×10^{-1}	1.95 (1.51 - 2.53)
	Height	53.2	52.0	1.7×10^{-3}	2.4×10^{-2}	1.20 (1.08 - 1.32)
Alcohol consumption (≥1 drink per month)	Any alcohol	69.3	72.1	8.9×10^{-8}	6.2×10^{-2}	0.87 (0.81 - 0.93)
	Wine	56.8	57.5	4.9×10^{-9}	1.4×10^{-2}	0.85 (0.79 - 0.91)
	Liquor	37.0	39.9	4.1×10^{-6}	6.6×10^{-1}	0.84 (0.78 - 0.91)
	Beer	44.9	47.2	9.3×10^{-4}	1.4×10^{-1}	0.90 (0.84 - 0.97)
Cigarette smoking[G]	Duration of smoking	57.0	56.7	2.2×10^{-5}	3.2×10^{-9}	1.06 (0.99 - 1.14)
Recreational sun exposure[G]		49.9	53.0	2.7×10^{-6}	7.9×10^{-1}	0.74 (0.66 - 0.83)
Socioeconomic status[G]		43.8	41.1	3.4×10^{-5}	6.1×10^{-2}	0.88 (0.83 - 0.93)
Occupational history[H]	Teacher	8.6	10.0	5.6×10^{-4}	6.2×10^{-3}	0.86 (0.77 - 0.95)
	Painter	2.0	1.8	4.8×10^{-3}	8.6×10^{-2}	1.22 (0.99 - 1.51)
	General farm worker	4.3	3.4	8.2×10^{-3}	3.4×10^{-1}	1.28 (1.10 - 1.50)



From Morton et al [16].

Endogenous and exogenous hormonal factors

a. Endogenous factors

Sex hormones, such as estrogens and progestogens, periodically fluctuate during the menstrual cycle, which lasts around 28 days. During the follicular phase, estrogens gradually increase until day 14 when they abruptly decrease and ovulation occurs. Then, progestogens start increasing in the luteal phase and if pregnancy does not occur, the corpus luteum regress and both estrogens and progestogens decrease and menstruation starts [18].

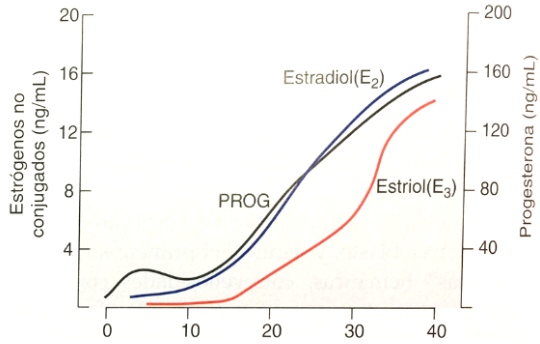
Due to these periodic fluctuations in hormonal levels during the fertile period of a woman, age at menarche and at menopause are frequently used in epidemiologic studies to estimate total time of menstrual cycling, as a proxy of an endogenous hormonal exposure.

If pregnancy occurs, estrogen levels dramatically increase until delivery (**Figure 6**). Similarly, production of progesterone increases

during pregnancy and it is 10 times higher at the end of pregnancy than in the luteal phase [18]. Prolactin has a role during breastfeeding, it also increases during pregnancy reflecting the hyperplasia of lactotropic cells from the hypophysis. Prolactin promotes breast growth in order to produce human milk after delivery.

Therefore, parity (the number of times a female has given birth), gravidity (total number of pregnancies regardless of duration and outcome), and breastfeeding are also frequently used as proxies of endogenous hormonal exposures.

Figure 6: Hormone levels during pregnancy.



From Dworkin, and Cardinali [18]*. X-axis = weeks after last menstruation. PROG = Progesterone.*

At the start date of this thesis, certain studies, but not all, had observed decreased risks of lymphoma with parity or gravidity, while the evidence on a potential protective effect of breastfeeding was very scarce. See article 5 for a summary of the literature in regard to endogenous hormonal exposures and NHL risk [5].

b. Exogenous factors

Levels of hormones can also be altered by an exogenous intake, for example of hormonal contraceptives or postmenopausal hormone therapy.

Hormonal contraception is the most commonly used estrogen therapy in the world, with more than 10% of all reproductive-age women (>100 million women worldwide) being current users of hormonal contraception. Hormonal contraception use dropped in the 1970s because of risk of thromboembolic events, particularly in smokers. Therefore, a new generation of combined contraceptives (with lower doses of estrogen and more potent progestogens) was developed, and trends in use have gradually increased since then. Rates of ever use among reproductive-age women now exceed 80% in some developed countries.

Postmenopausal hormone therapy (HT) is another common hormonal compound used for relief of menopause symptoms. Its use fluctuated in the last decades mainly because of the publication of Women Health Initiative (WHI) trial results. After extensive prescription in the 1990s, HT reached more than 20 million users globally in 2000. However, the WHI trial was stopped in 2002 because of the increased risks of coronary heart disease and breast cancer observed in the intervention group allocated to use HT, contrary to conclusions from previous observational studies. The WHI findings and results from concomitant observational studies resulted in a decrease in HT prescription of more than 50%. Previous observational studies failed to identify patterns of HT use, and their conclusions were affected by selection bias and confounding.

Both hormonal contraceptives and postmenopausal hormone therapy have been classified as Group 1 carcinogens by the International Agency of Research on Cancer (IARC) in 2005 [19]. While combined estrogen-progestagen oral contraceptives have been associated with increased risks of breast, cervix, and liver cancer, they have also been inversely associated with endometrium and ovarian cancer. Estrogen-only menopausal therapy has been associated with endometrium and ovarian cancer, and combined estrogen-progestogen menopausal therapy with endometrium and breast cancer.

Group 1 agent	Cancer on which sufficient evidence in humans is based	Sites where cancer risk is reduced	Established mechanistic events	Other likely mechanistic events
Diethylstilbestrol	Breast (exposure during pregnancy), vagina and cervix (exposure in utero) Limited evidence: testis (exposure in utero), endometrium	--	Oestrogen receptor-mediated events (vagina, cervix), genotoxicity	Epigenetic programming
Oestrogen-only menopausal therapy	Endometrium, ovary Limited evidence: breast	--	Oestrogen receptor-mediated events	Genotoxicity
Combined oestrogen–progestagen menopausal therapy	Endometrium (risk decreases with number of days/month of progestogen use), breast	--	Receptor-mediated events	Oestrogen genotoxicity
Combined oestrogen–progestagen oral contraceptives	Breast, cervix, liver	Endometrium, ovary	Receptor-mediated events	Oestrogen genotoxicity, hormone-stimulated expression of human papillomavirus genes
Tamoxifen	Endometrium	Breast	Oestrogen receptor-mediated events, genotoxicity	--

Table 1: **Hormonal treatments assessed by the IARC Monograph Working Group**

Hormonal treatments assessed by the IARC Monograph Working Group. Monograph on human carcinogens 100A [20].

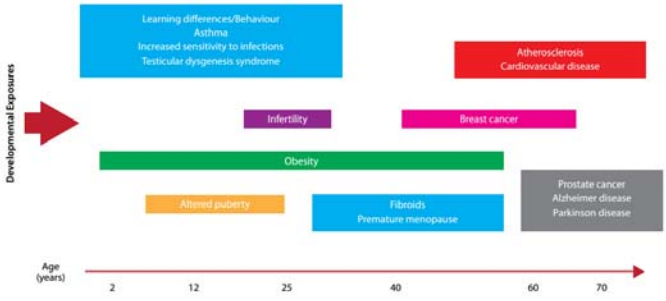
However, the role of these compounds in lymphoma etiology is not completely understood. Some case-control studies, but not cohort studies, observed decreased risks with HT consumption, while results on hormonal contraceptives were inconsistent. See article 5 for a summary of the literature in regard to exogenous hormonal exposures and NHL risk.

Endocrine disruptors

Endocrine disrupting chemicals (EDCs) are substances that interfere with hormone biosynthesis, metabolism, or action [21].

The Endocrine Society and the European Society for Paediatric Endocrinology and the Pediatric Endocrine Society put forward two consensus statements calling for action regarding endocrine disruptors and their effects [21,22]. In 2012 the WHO published a document summarizing the knowledge on EDCs in health [23]. The understanding of these compounds and their potential effects is still limited, although some of these compounds have been linked to cancer. The authors of the WHO report concluded that animal model data and human evidence support the idea that exposure to EDCs could play a role in the increased incidences of endocrine-related cancers, such as breast and prostate cancers (**Figure 7**), however, important gaps in the knowledge of EDCs and their effects still exist [23].

Figure 7: 'Examples of potential diseases and dysfunctions originating from early exposures to EDCs'.



From Bergman et al [23].

We focus in this introduction on those EDCs reported in the article 6 of this thesis (**Table 1**). Exposure to these chemicals occurs mostly through diet, and occupational exposure is also relevant in some occasions. From these chemicals, certain Polychlorinated biphenyls (PCBs), pesticides and solvents have been previously associated with lymphoma risk [14]. The role of other EDCs, such as alkylphenolic compounds and certain metals, in lymphoma etiology is not completely understood.

Table 1: Summary of endocrine mechanisms of action and IARC classifications of the EDCs included in this thesis

Compound	Main subcompounds	Mechanisms of action	IARC Classification
Polychlorinated biphenyls	None (several congenerers)	Estrogen agonists or antagonists, alteration of steroid synthesis and gene expression	Group 1
Pesticides	Organochlorines Carbamates Organophosphates Tributyltin Pyrethroids	Estrogenic and anti-androgenic effects	>75 pesticides have been evaluated since 1971, lindane (an organochlorine) classified as Group 1
Organic solvents	Ethylene glycol ethers (EGEs)	EGEs: reproductive toxicity in animal studies. Styrene: binds to estrogen receptors in vitro. Toluene, xylene, TCE: possibly interfere with hormone levels in humans. PCE: dry cleaning associated with menstrual disorders, infertility and delayed conception in women.	Group 3 (ethylene oxide derives on EGEs and it is a group 1 carcinogen)
	Styrene		Group 2B
	Toluene		Group 3
	Xylene		Group 3
	Trichloroethylene (TCE)		Group 1
	Perchloroethylene (PCE)		Group 2A
Alkylphenolic compounds	Nonylphenol Octylphenol Ethoxylates	Estrogenic effects in vitro mediated by estrogen receptors, and non-genomic responses	Not evaluated
Metals	Arsenic	See Table 2	Group 1
	Cadmium		Group 1
	Copper		Copper-8-hydroxyquinoline = Group 3
	Lead		Group 2B
	Mercury		Methylmercury compounds = Group 2B, metallic mercury = Group 3
Brominated flame retardants	Tetrabromobisphenol A, Polybrominated disphenyl ethers	Estrogen sulfotransferase inhibition	Group 2A
Polycyclic aromatic hydrocarbons	None	Anti-estrogenic effects in vitro	Group 1

a. Polychlorinated biphenyls (PCBs)

PCBs are aromatic compounds involving more than 200 congeners. They contain chlorine atoms attached to a biphenyl nucleus. PCBs were widely used as dielectric fluid in capacitors and transformers, and in building materials. In most countries, PCBs were banned in the 1980s due to concerns over their toxicity and persistence [24].

Depending on their structure, PCB metabolites can act as estrogen agonists or antagonists. Also, PCBs can directly modulate nuclear steroid hormone-dependent gene expression [24]. PCBs also interfere with steroid synthesis through aryl hydrocarbon receptor binding [25].

The IARC classified PCBs as group 1 carcinogens in 2013 based on their association with melanoma risk [24]. They also noted increased risks for NHL, although associations were not consistent and were considered as providing limited evidence [24].

b. Pesticides

Pesticides are used to protect plants from damaging agents such as weeds, fungi, or insects. They are often referred to according to the type of pest they control; for example, insecticides (such as organochlorines), herbicides (such as 2,4-Dichlorophenoxyacetic acid -2,4D-) and fungicides (such as thiram).

Some of them have the ability to interact with the endocrine system. For instance DDT, which is an organochlorine pesticide, has shown to competitively bind to androgen receptors, as well as to be an estrogen receptor (ER) agonist [26]. Carbaryl, which is a carbamate insecticide, has a weak estrogen effect [26].

Pesticides have been suggested as risk factors for NHL, as their use became widespread during the 2nd half of the 20th century. Risk of NHL has shown to be higher among farmers supporting this hypothesis. However, epidemiologic literature on lymphoma risk and occupational exposure to pesticides is inconsistent. Some studies but not others found increased risks of NHL with occupational exposure to pesticides, and heterogeneous results also

exist in regard to the specific pesticides as well as the lymphoma subtypes involved [14].

c. Organic solvents

Organic solvents are chemicals with a carbon-based structure, widely used in paints, adhesives, thinners, and resins, and also for metal degreasing and other industrial cleaning purposes. Certain organic solvents have shown to bind to estrogen receptors in vitro, and to interfere with reproductive hormone levels in humans [25].

Some solvents have been associated with lymphoma, although with inconsistent results [14,27]. The involved chemicals include benzene, toluene, styrene, trichloroethylene and tetrachloroethylene. However, their role in NHL is not completely clear. The IARC classified benzene as carcinogenic to humans (group 1) based on an increased risk of acute myeloid leukemia, while evidence for NHL; CLL and MM was limited [28].

Toluene was not classifiable as to their carcinogenicity for humans (group 3), styrene was classified as possibly carcinogenic to humans (group 2B), and tetrachloroethylene was classified by IARC as probably human carcinogens (group 2A) based on associations with bladder cancer. Trichloroethylene has been classified by IARC in 2012 as carcinogen group 1. The IARC concluded that trichloroethylene causes cancer of the kidney, and also a positive association was observed between exposure to trichloroethylene and NHL [29].

d. Alkylphenolic compounds

Alkylphenolic compounds are mainly used as non-ionic surfactants, but also in a wide range of applications. Alkylphenolic compounds are typically considered weak estrogens as they bind to the nuclear ERα with a lower affinity than 17β-estradiol in breast cancer cells [30–32]. There are several isomers of alkylphenolic compounds, and the receptor affinity increases with increasing chain length of the alkyl groups [33,34]. Even if they are usually considered to be weak estrogens in regard to nuclear responses, alkylphenolic compounds

have recently shown to induce potent non-genomic responses (those mediated by membrane ERs instead of nuclear ERs), such as prolactin release, in pituitary tumor cells [33]. These chemicals also interact with the immune system up-regulating proinflammatory cytokine expression more effectively than estrogen [35]. They increase IL-6 and TNF-α cytokines, while suppress IL-10, and have been suggested to promote autoimmune susceptibility and asthma responses among mice [35–37].

Their use in industry progressively increased over the years and decreased during the 2000s due to a European Union regulation, somehow paralleling the incidence of lymphoma over time. However, there is no previous epidemiologic study linking exposure to alkylphenolic compounds with lymphoma risk.

e. Metals

Certain metals have shown to interact with the endocrine system [38]. Cadmium is the most documented metal regarding its ability to induce estrogenic responses, although mercury, arsenic, copper and lead have also been studied, and manganese and zinc also gained some attention [38,39] (**Table 2**).

Apart from diet and occupation, tobacco is also a relevant source of cadmium. The main sources of occupational exposure to cadmium are the extraction, foundry, metallurgical, and electroplating industries. Mercury is a component in some electrical instruments and medical products. Occupational exposure to arsenic occurs in workers in the paint, ceramics, pesticide and wood preservative industries, and lead is used in batteries, cables, pigments, and was used in petrol products [38]. Occupational exposure to copper occurs in the mining industry, grinding and welding, as well as in water treatment, and electroplating industries. Water intake may be also a relevant source of exposure to copper [40].

Table 2: Endocrine mechanisms of action of metals as EDCs.

Metals	Mechanisms of action	References
Cadmium	Bond with estrogen receptors	Garcia-Morales et al., 1994;
	Inhibition of transcription of the LDL-R	Jolibois et al., 1999b;
	Inhibition of $P450_{scc}$	Kawai et al., 2002
Mercury	Induction of 3 beta-hydroxysteroid dehydrogenase	Mondal et al., 1997
	Inhibition of the type I iodothyronine deiodinase	Barregård et al., 1994
Arsenic	Stimulation or inhibition of nuclear transcription activity mediated by several hormone receptors	Kaltreider et al., 2001
	Bond with estrogen receptors	Jana et al., 2006
Lead	Reduction of the expression of the steroidogenic acute regulatory protein (StAR)	Srivastava et al., 2004
	Inhibition of LH secretion	Srivastava et al., 2004; Ronis et al., 1996
	Increased lipid peroxidation in seminal plasma	Kapserczyk et al., 2008
	Increased ROS production	Hsu et al., 1998
Manganese	Activation of the soluble guanylyl cyclase (sGC) and of cGMP-PKG system	Prestifilippo et al., 2007; Lee et al., 2007
Zinc	Membrane-stabilizing activity	Aitken and Clarkson, 1987
	Antioxidant activity	
	Inhibition of DNAase	

From Iavicoli et al [38].

The IARC concluded that there was sufficient evidence that cadmium and inorganic arsenic compounds were carcinogenic to humans as both were related with lung cancer [41]. Copper-8-hydroxyquinoline and metallic mercury were classified as group 3 carcinogens, while inorganic lead and methylmercury compounds were classified as 2B carcinogens [42].

Observed associations with lymphoma and occupational exposure to metals have been diverse: some studies found no significant associations [43–45], while others reported significantly elevated risks [46–49]. As well, the involved metals and the susceptible lymphoma subtypes were unclear.

c. Brominated flame retardants

Brominated flame retardants are used to reduce the flammability of products containing them. They possibly interfere with the estrogen metabolism through estrogen sulfotransferase inhibition [25]. The IARC recently classified exposure to polybrominated biphenyls as group 2A carcinogens, and noted a mechanistic similarity with PCBs (group 1) [24].

In regard to lymphoma risk, a small study among 19 NHL cases and 27 controls revealed a non-significantly elevated risk with high

concentrations of the flame retardant 2,2',4,4'-tetrabrominated diphenyl ether in adipose tissue (OR=3.8; 95%CI=0.7-26) [50]. Another study using serum polybrominated biphenyl levels among a Michigan cohort accidentally exposed to polybrominated biphenyls in 1973 showed a positive dose-response relation with serum levels and lymphoma [51], although it was based on small numbers.

d. Polycyclic aromatic hydrocarbons

Polycyclic aromatic hydrocarbons (PAH) are produced during incomplete combustion or pyrolysis of organic material, for example in incinerators. They are also found in cooked foods, and in tobacco smoke.

Highest levels of occupational exposure to PAHs are observed in aluminum production; mid-range concentrations are observed in roofing and paving, and the lowest are observed in coal liquefaction, coal-tar distillation, wood impregnation, chimney sweeping and power plants [52].

The IARC considered that there was sufficient evidence in experimental animals for the carcinogenicity of benzo[a]pyrene, a type of PAH, and classified it as group 1 carcinogen, based on its effects on lung cancer. The role of PAH in lymphomagenesis is unclear as they had been scarcely assessed before the initiation of this thesis. A case-control study in US had evaluated whether meat, meat-cooking methods, or PAHs from meat, were associated with NHL risk, using 458 NHL cases and 383 controls, with no significant associations [53].

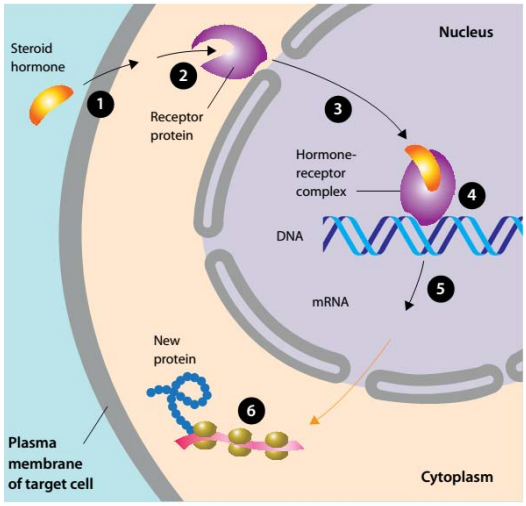
Potential mechanisms of action

Several pathways may be involved in the interaction of reproductive hormones with NHL, although the exact mechanisms are not well understood. Reproductive hormones interact with the immune system in numerous ways, and play an important role in the modulation of autoimmune diseases [54,55]. The immune response is sexually dimorphic, women produce a more vigorous cellular and humoral response than men, and suffer more often from autoimmune diseases [56]. Alterations in the immune system,

including autoimmune disorders, are established risk factors for some NHL subtypes [57], although associations differ by gender [58]. Steroid hormones also influence the delicate Th1/Th2 cytokine balance. A deregulation of this cytokine profile play a role in both autoimmune diseases [59,60] and in lymphomagenesis [61–63].

However, the steroid hormone metabolism is extremely complex, and its assessment is often confused by the different effects of hormones that depend on the type of receptor, on the target cell, on the dose, and on the divergent actions of their metabolites [54]. Furthermore, EDCs may act via very different mechanisms, for example, nuclear hormone receptors, nonnuclear steroid hormone receptors, nonsteroid receptors, enzymatic pathways involved in steroid biosynthesis and/or metabolism, and many other mechanisms [21] (**Figure 8**).

Figure 8. Examples of EDCs actions.



From Bergman et al [23]. "Many hormones act via binding to specific receptors (2) to stimulate the synthesis of new proteins (6), which then control tissue function. Some hormones also act via receptors on the membrane; in that case, the actions are more immediate in nature."

Some of the interactions between the immune and the endocrine system are driven by hormone receptors. Human lymphocytes are likely to express estrogen receptors (ER)α and ERβ [64]. The activation of these receptors leads to opposite effects and their relative proportion determines the final outcome of estrogens (or

xenoestrogens). Interestingly, Yakimchuk et al showed that ERβ2 in peripheral blood mononuclear cells is up-regulated in CLL/SLL compared to controls, contrary to ERα [65]. Other subtypes may also express ER, although results are controversial due to the different analytical procedures. Shim et al showed that MM, Hodgkin and Burkitt lymphomas cell lines, and also normal leucocytes, expressed abundant ERβ but not ERα [66]. Recent experimental evidence among mice showed that treating DLBCL with ERβ agonists significantly reduced tumor growth [67]. Also, another study among mice suggested that this effect was caused by estrogens and not androgens [68]. On the other hand, the presence and possible roles of progesterone receptors in human lymphomas or leukemias is unknown to date.

HYPOTHESES

HYPOTHESIS 1. Reproductive factors and exogenous hormone use are protective factors of lymphoid neoplasms.

1.1. Parity and gravidity are protective against lymphoid neoplasms.

1.2. Use of hormonal contraception is protective against lymphoid neoplasms.

1.3. Use of postmenopausal hormone therapy is protective against lymphoid neoplasms.

1.4. Those subtypes with greater male:female incidence ratio are the most susceptible to the effect of reproductive factors.

HYPOTHESIS 2. Occupational exposure to endocrine disruptors is a risk factor of lymphoid neoplasms.

1.5. Occupational exposure to endocrine disruptors, including polycyclic aromatic hydrocarbons, polychlorinated, organic compounds, organic solvents, pesticides, brominated flame retardants, alkylphenolic compounds, metals and others, is a risk factor of some lymphoid neoplasms subtypes.

1.6. Those subtypes with greater male:female incidence ratio are the most susceptible to the effect of endocrine disruptors.

OBJECTIVES AND RATIONALE

OBJECTIVE 1. To evaluate the role of reproductive factors and exogenous hormone use in lymphoid neoplasms etiology.

Rationale. Lymphoid neoplasms are more common in men than in women, and several NHL subtypes express hormonal receptors. Certain studies observed reduced risks of lymphoid neoplasms with reproductive factors, such as parity, and exogenous hormone use, such as postmenopausal hormone therapy. However, other studies found null associations. Both protective (ovarian and endometrial cancer) and positive associations (breast cancer) have been stablished for hormonal contraception and cancer. Hormonal contraceptives and postmenopausal hormone therapy are consumed frequently in the general population, therefore clarifying their role in women's health is essential from a public health perspective in order to understand their net effect and consequences of its use.

1.1. **Costas L**, Casabonne D, Benavente Y, Becker N, Boffetta P, Brennan P, Cocco P, Foretova L, Maynadié M, Staines A, Kane E, Nieters A, de Sanjosé S. ***Reproductive and hormonal characteristics as risk factors for lymphoma in the Epilymph Europe case-control study***. *Cancer Causes and Control*. 2012;23:195-206.

1.2. Kane E, Roman E, Becker N, Bernstein L, Boffetta P, Bracci P, Cerhan J, Chiu B, Cocco P, **Costas L**, et al. ***Menstrual and reproductive factors, and hormonal contraception use: associations with non-Hodgkin lymphoma in a pooled analysis of InterLymph case-control studies***. *Annals of Oncology*. 2012;23:2362-74.

1.3. Kane E, Amstrong B, Bernstein L, Bracci P, Cerhan J, **Costas L**, et al. ***Menopausal hormone therapy and non-Hodgkin lymphoma: a pooled analysis of InterLymph case-control studies***. *Annals of Oncology*. 2013;24:433-41.

1.4. **Costas L,** Lambert BH, Birmann BM, Moysich KB, De Roos AJ, Hofmann JN, Baris D, Wang SS, Camp NJ, Tricot G, Atanackovic D, Brennan P, Cocco P, Nieters A, Becker N, Maynadié M, Foretová L, Boffetta P, Staines A, Brown EE, de Sanjosé S. ***A pooled analysis of reproductive factors and risk of multiple myeloma from the International Multiple Myeloma Consortium.*** *Cancer Epidemiology Biomarkers and Prevention***. 2016 25:217-221.**

1.5. **Costas L**, de Sanjosé S, Infante-Rivard C. ***Reproductive factors and non-Hodgkin lymphoma: A systematic review.*** *Critical Reviews Oncology/Hematology*. 2014;92:181-193.

OBJECTIVE 2. To evaluate occupational exposure to endocrine disruptors in lymphoid neoplasms risk.

Rationale. Exposure to chemicals with potential estrogenic, anti-estrogenic, or anti-androgenic effect could partially explain differences in lymphoma incidence over time. Occupational assessments are useful approaches to evaluate the role of these compounds in cancer etiology. Certain polychlorinated biphenyls (PCBs), pesticides, and organic solvents, which are endocrine disruptors, have been associated with an increased risk of lymphoma. However, the role of other endocrine disrupting chemicals, such as alkylphenolic compounds, polycyclic aromatic hydrocarbons and flame retardants, in lymphoma etiology is still unknown. Exploring the role of endocrine disruption on lymphoid neoplasms etiology may provide insight on the nature of these neoplasms, and offer a door to cancer prevention.

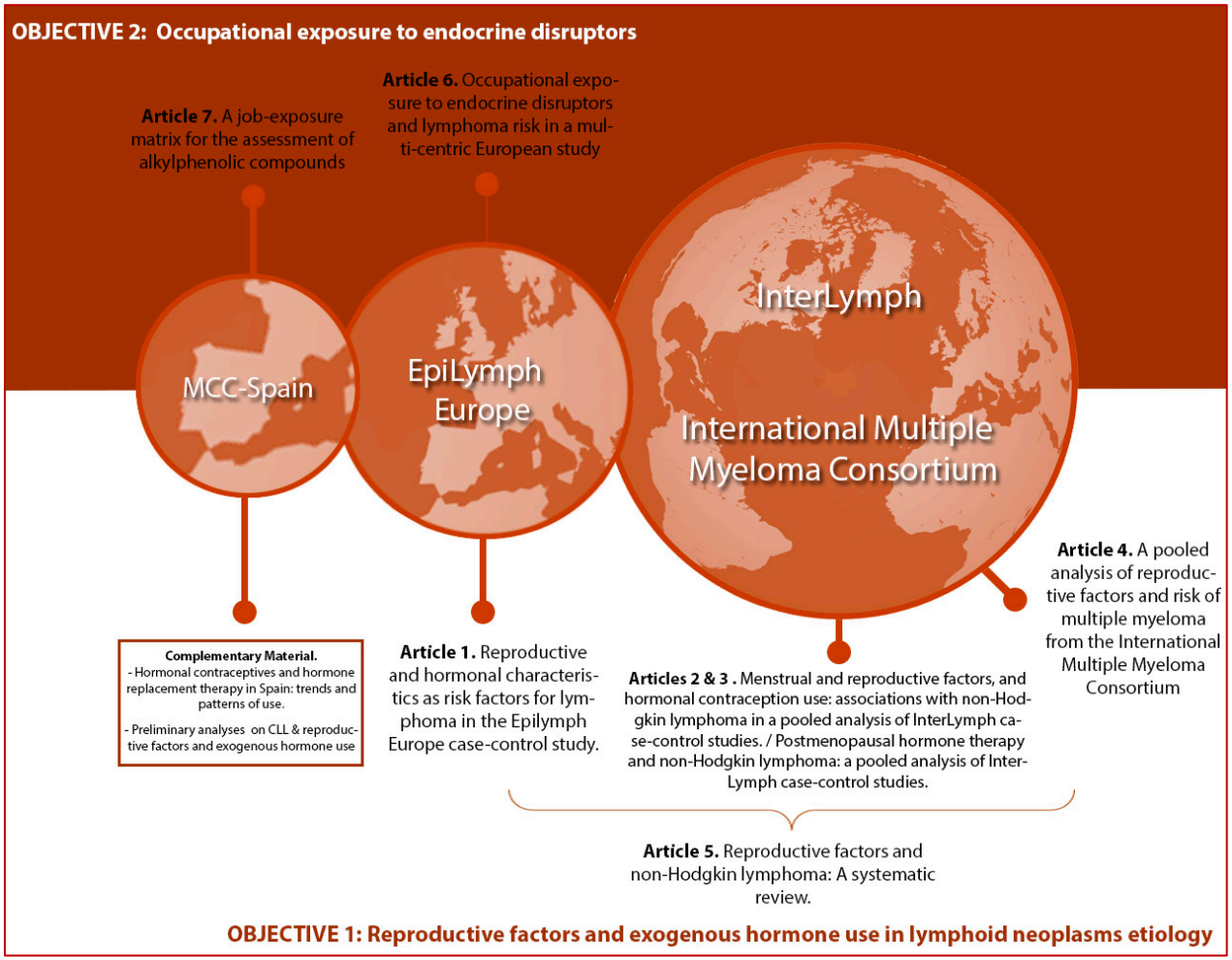
1.6. **Costas L**, Infante-Rivard C, Boffetta P, Zock JP, Van Tongeren M, Cussón A, Robles C, Casabonne D, Benavente Y, Becker N, Brennan P, Foretova L, Maynadie M, Staines A, Nieters A, Cocco PL, de Sanjosé S. ***Occupational exposure to endocrine disruptors and lymphoma risk in a multi-centric European study***. *British Journal of Cancer*. 2015;112:1251-6.

1.7. Martín-Bustamante MT, Oliete-Canela A, Diéguez M, Benavente Y, Casabonne D, Alguacil J, Kogevinas M, de Sanjosé S, **Costas L**. ***A job-exposure matrix for the assessment of alkylphenolic compounds.*** *Occupational and Environmental Medicine*. Epub: Aug 18. pii: oemed-2016-103614.

SUMMARY OF STUDIES

	Publication 1	Publication 2	Publication 3	Publication 4	Publication 5	Publication 6	Publication 7
Design	Multicentric case-control study	Pooled analyses of case-control studies			Systematic review	Multicentric case-control study	JEM development
Outcome	Lymphoma	NHL	NHL	MM	NHL	Lymphoma	Exposure scores
Study	EpiLymph	InterLymph consortium		IMMC		EpiLymph	Based on MCC-Spain study
Number of cases	994 (52 T-cell, 147 HL, 248 DLBCL, 152 CLL/SLL, 136 FL, 120 MM, 139 others)	4263 (1354 DLBCL, 1055 FL, 432 CLL/SLL, 388 marginal, 221 T-cell, 581 unclassified, 232 others)	2094 (675 DLBCL, 531 FL, 83 T-cell, 325 unclassified, 480 others)	1072 MM	28 citations from 7 cohort studies, 12 case–control studies, and a pooled analysis	2178 (518 DLBCL, 412 CLL/SLL, 334 HL, 251 FL, 276 MM, 124 T-cell, 263 others)	NA
Number of controls	1141	5971	2731	3541		2457	NA
Total number of participants	2135	10234	4825	4613		4635	NA
Exposures	Reproductive factors and hormonal contraceptives		HT use	Reproductive factors and exogenous hormone use		Endocrine disruptors	Alkylphenolic compounds
Statistical Models	Unconditional logistic regression	Logistic regression and random effects meta-analyses			NA	Logistic regression / MC-SIMEX / Generalized Additive Models	Descriptive
Statistical software	Stata 10.1	Stata 11.1		Stata 13.0	Figure 1 was done using -metan- in Stata 11.1	Stata 11.1; MC-SIMEX analyses were performed with R 3.0.2	Stata 13.0

NHL=Non-Hodgkin Lymphoma; HL=Hodgkin Lymphoma, DLBCL= Diffuse Large B-cell Lymphoma, CLL/SLL = Chronic Lymphocytic Leukemia / Small Lymphocytic Leukemia, FL= Follicular Lymphoma; MM=Multiple Myeloma; HT=Hormone Therapy; JEM=Job-Exposure Matrix; IMMC=International Multiple Myeloma Consortium; NA=Not Applicable.


OBJECTIVE 2: Occupational exposure to endocrine disruptors
Article 7. A job-exposure matrix for the assessment of alkylphenolic compounds
Article 6. Occupational exposure to endocrine disruptors and lymphoma risk in a multi-centric European study
MCC-Spain
EpiLymph Europe
InterLymph
International Multiple Myeloma Consortium
Article 4. A pooled analysis of reproductive factors and risk of multiple myeloma from the International Multiple Myeloma Consortium
Complementary Material.
- Hormonal contraceptives and hormone replacement therapy in Spain: trends and patterns of use.
- Preliminary analyses on CLL & reproductive factors and exogenous hormone use
Article 1. Reproductive and hormonal characteristics as risk factors for lymphoma in the Epilymph Europe case-control study.
Articles 2 & 3 . Menstrual and reproductive factors, and hormonal contraception use: associations with non-Hodgkin lymphoma in a pooled analysis of InterLymph case-control studies. / Postmenopausal hormone therapy and non-Hodgkin lymphoma: a pooled analysis of InterLymph case-control studies.
Article 5. Reproductive factors and non-Hodgkin lymphoma: A systematic review.
OBJECTIVE 1: Reproductive factors and exogenous hormone use in lymphoid neoplasms etiology

SUMMARY OF RESULTS

1. Reproductive factors and exogenous hormone use in lymphoid neoplasms etiology.

EpiLymph:

1.1 Parity was protective against CLL/SLL, DLBCL, and T-cell lymphoma.

1.2 Short term use (<5 years) of hormonal contraception was positively associated with DLBCL and follicular lymphoma.

InterLymph:

1.1 Associations with parity and lymphoma were null, except for follicular lymphoma.

1.2 Follicular lymphoma, but not DLBCL, was associated with hormonal contraception use.

1.3 Risks of NHL, in particular of DLBCL and follicular lymphoma, were decreased with use of postmenopausal hormone therapy.

IMMC:

1.4 MM was not associated with reproductive factors, or with hormonal contraception use.

1.5 We observed inverse associations for postmenopausal hormone therapy, although associations were heterogeneous by center.

Systematic review:

1.6 A higher proportion of studies reported protective associations with NHL when they evaluated gravidity compared to parity, usually showing an inverted J-shaped pattern, while results on postmenopausal hormone therapy were unclear.

2. Occupational exposure to certain endocrine disruptors and lymphoid neoplasms.

2.1 We observed associations with lymphoma and prolonged (≥30 years) occupational exposure to endocrine disrupting chemicals (EDCs), in particular for MM and CLL/SLL.

2.2 Regarding individual exposures, associations were observed between lymphoma and prolonged occupational exposures to organic solvents, pesticides, brominated flame retardants, alkylphenolic compounds, and metals.

2.3 Associations between lymphoma and EDCs were observed among men, but not women.

2.4 Industrial use of alkylphenolic compounds varied greatly over time; while they are still used in the plastic and rubber industry, in domestic cleaning agents their use began to decline before 1995.

ARTICLE 1

Costas L, Casabonne D, Benavente Y, Becker N, Boffetta P, Brennan P, Cocco P, Foretova L, Maynadié M, Staines A, Kane E, Nieters A, de Sanjosé S. ***Reproductive and hormonal characteristics as risk factors for lymphoma in the EpiLymph Europe case-control study***. Cancer Causes and Control. 2012;23:195-206.

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ORIGINAL PAPER

Reproductive factors and lymphoid neoplasms in Europe: findings from the EpiLymph case–control study

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Abstract
Background The study of lymphomagenesis has rarely focused on hormonal factors. Higher incidence rates are observed for many lymphoma subtypes in men compared with women suggesting an underlying association. Our goal was to investigate the association between reproductive factors and lymphomas.
Methods The Epilymph study is a multicenter case–control study carried out in six European countries from 1998 to 2004. Female cases of mature T-cell neoplasms ($n = 52$), Hodgkin lymphoma ($n = 147$), and mature B-cell neoplasms ($n = 795$), including its common subtypes, and their respective controls ($n = 1{,}141$) frequency matched by age, gender, and center were considered.
Results An odds reduction of 29% (95% CI −46 to −6%) was observed for mature T-cell neoplasms for each child increase among parous women and of 13% (95% CI −19 to −7%) for mature B-cell neoplasms; while no association was observed for Hodgkin lymphoma. By B-cell neoplasm subtypes, these associations were found for chronic lymphocytic leukemia/small lymphocytic lymphoma (−21%,

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95% CI −31 to −9%) and diffuse large B-cell lymphoma (DLBCL; −14%; 95% CI −23 to −3%). Overall, no associations were observed with age at first and last pregnancy, and ever use of hormonal contraceptives and lymphoma. Higher odds ratios for a short-term use of hormonal contraceptives (<5 years), but not for a long-term use, were observed for mature B-cell neoplasms, DLBCL, and follicular lymphoma compared with never use.
Conclusion These data support the hypothesis that increased parity confers a protective effect against lymphoma. Less clearly, our results also indicate that hormonal contraceptives could play a role.

Keywords Lymphoma · Non-Hodgkin · Hodgkin · Reproductive factors · Hormonal Factors · Pregnancy · Parity · Contraception

Abbreviations

OR	Odds ratio
CI	Confidence interval
NHL	Non-Hodgkin lymphoma
CLL/SLL	Chronic lymphocytic leukemia/small lymphocytic lymphoma
DLBCL	Diffuse large B-cell lymphoma

Introduction

Incidence rates in Hodgkin and non-Hodgkin lymphoma (NHL) are generally higher in men than in women [1]. Besides their endocrine functions, sex hormones are capable of affecting the immune system and could thus be involved in lymphomagenesis. The importance of the interaction between endocrine and immune system becomes evident in situations such as pregnancy or lactation where estrogens, progestagens, and prolactin levels increase notably. A physiological adaptation of the maternal immune system, driven by estrogens and progesterone, occurs during pregnancy in order to prevent the rejection of fetal antigens from paternal origin [2]. Hormone levels can also fluctuate due to the use of exogenous hormones such as contraceptives or treatments for menopausal symptoms.

Overall, although several studies investigated possible associations between reproductive and hormonal factors and the risk of lymphoid neoplasms, data are inconclusive. While some studies have reported a favorable effect of parity for some lymphoproliferative diseases [3–7], others have not seen a significant effect [8–15]. Associations on use of hormonal contraceptives have also been inconsistent, with some studies describing a protective effect [12, 16], while others showed no association [4, 5, 10, 17–21].

Changes produced to the immunological system driven by sex steroids could be a key factor in the modulation of lymphomagenesis. Here, we evaluate reproductive and hormonal exposures as risk factors for lymphoid neoplasms by subtypes in the European case–control study EpiLymph.

Methodology

Study design and population

The Epilymph study is a multicenter case–control study carried out in six European countries (Spain, France, Germany, Italy, Ireland, and Czech Republic) from 1998 to 2004. All consecutive patients with a new diagnosis of lymphoid neoplasm during the study period were defined as cases.

In Germany and Italy, controls were synchronically identified with cases and were sampled from the general population on the basis of census lists. In other study countries, controls were recruited from the same hospital as cases and frequency matched to them by age, gender, and study center. In hospital-based studies, potential controls were excluded if the main reason for the hospitalization was cancer, organ transplantation, and/or systemic infection, including HIV. Informed consent was obtained from all subjects prior to the enrollment, and the institutional review boards of participating centers approved the study. Additional details of the study design have been provided elsewhere [22].

Overall, the study included 2,465 controls and 2,362 incident lymphoma cases with a participation rate of 69% (ranging from 44 to 96% across study centers) and 88% (range 82–93%), respectively. Denominators used in the calculation of participation rates were the numbers of cases or controls approached to participate in the study. For cases, it was all consecutive incident cases including deceased subjects diagnosed in each center during the study period; for controls, it was the number of persons randomly selected from among newly hospitalized patients or the general population [23]. Among cases, the median time between date of diagnosis and date of interview was 1.3 months [interquartile range = 0.5–2.8 months].

Outcome classification

Cases were categorized according to the most recent World Health Organization (WHO, 2008) Classification of Neoplastic Diseases of the Hematopoietic and Lymphoid Tissues and the International Lymphoma Epidemiology Consortium (InterLymph) guidelines [24, 25]. In accordance with the WHO 2008 classification, NHL cases were described as “mature B-cell neoplasms” and “mature

T-cell neoplasms," and so 21 precursor B-cell and three precursor T-cell NHL cases were excluded. Furthermore, six cases of nodular lymphocyte predominant Hodgkin lymphoma were excluded from the analyses, since this type is considered as an entity that differs significantly from classical Hodgkin lymphoma [22]. Women with a history of organ transplantation or known seropositive status for HIV were not included in the analyses. In summary, women with a diagnosis of mature B-cell neoplasm ($n = 795$), mature T-cell neoplasm ($n = 52$), Hodgkin lymphoma ($n = 147$), and their respective controls ($n = 1{,}141$) were selected. We also performed an additional analysis in male lymphoma cases and their controls ($n = 1{,}259$ and $n = 1{,}318$, respectively) in regard to the number of children (Online Resource 1).

Exposure assessment

A common core protocol and interview were used in all countries. Participants were interviewed face-to-face by trained interviewers for information on socio-demographic factors; reproductive, familial, and medical history; travel and other lifestyle factors; use of hair dyes; sun exposure; occupational history and drugs. Use of tobacco was defined as smoking at least one cigarette or pipe per day over a period of 6 months or more. Similarly, alcohol use was defined as the consumption of at least one drink per day (beer, wine, champagne, or spirits) over a period of 6 months or more. Education was categorized into low, medium, or high based on the number of years of school and the highest level of education achieved, taking into account the different educational systems in the participants countries, as previously agreed by the Epilymph members. All data on reproductive history and exogenous hormone use were self-reported. Reproductive history questions included ever being pregnant (regardless of the length or outcome of the pregnancy), parity (number of children), calendar year of the births of the first and last child. Questions on exogenous hormone use asked women whether or not they had ever used hormonal contraceptives, and their age at first and last use. Total number of years of use was calculated excluding those periods of time that women declared to have temporarily stopped using them.

Statistical analyses

Odds ratios (OR), 95% confidence intervals (CI), and *P* values were estimated using univariate and multivariate unconditional logistic regression to determine associations between the main exposure variables and potential confounding variables and between reproductive and hormonal factors and lymphoproliferative disorders.

All multivariate models were adjusted for age (continuous), education (in three categories), and country. Analyses examining age at first and last child as well as those examining hormonal contraceptive use were further adjusted for number of children. Potential confounding effects of prior diagnosis of diabetes, hypertension, body mass index, ever being smoker, regularly intake of alcohol beverages, ever use of hair dyes, and being house owners were examined but none of them altered the estimates on pregnancy, number of children, hormonal contraceptive use, or years of use for any subtype by more than 10%. Analyses of pregnancy, number of children, age at first and last child were also adjusted for hormonal contraceptive use and years of use, and similarly, risk estimates were not altered substantially. For all variables, data were missing for less than 5% of subjects. Subjects with missing data were dropped from the analyses, with the exception of parity where a category was included for those with missing values.

Parity was categorized in five categories (0, 1, 2, 3, and 4 or more children), and age at first and last child was categorized in 5-year intervals for comparability with previous studies. Age of the mother at the first and last child birth was calculated from the calendar year they reported. We used one child as the reference category, instead of nulliparous women, since this group is heterogeneous and could include women with infertility problems, or that might have been pregnant, and therefore could have had hormonal changes that might be associated with the diseases. In addition, women who had experienced abortions or pregnancy losses (i.e., those who had been pregnant but reported no children) were excluded from the parity analyses (25 cases and 38 controls). Contraceptive duration was categorized in 5-year intervals for comparability with previous studies. Regarding the composition of contraceptives, calendar year of use is in most countries a valid proxy, since preparations used in the 1960s contained high estrogen levels, and subsequent generations of contraceptives had decreased levels of estrogens and progestins, being between 1970 and 1980 medium-dose preparations and by 1980 they had low doses of estrogens and progestins [26]. Consequently, year of first use was categorized as 1960s, 1970s, and from 1980s. The number of mature T-cell neoplasms cases who reported using hormonal contraceptives was too small to perform meaningful analyses in relation to duration and years of consumption.

Several sensitivity analyses were performed. The impact of excluding women born before 1926 (and therefore aged 35 or older when the first hormonal contraceptives were commercialized) was assessed. A 1:1 matched (on age and country) case–control analysis was performed to assess the impact of a possible unequal age

distribution between subtypes and overall controls using conditional logistic regression adjusted for education, and number of children when examining age at first and last child and contraceptive use. With the same objective, we conducted an age-restricted analysis that consisted in selecting controls of the same age range as the evaluated cases, when performing analyses by subtype. To ensure that the risk estimates were not dependent on any specific country, we performed a sensitivity analysis where every country was excluded from the models one by one. Furthermore, a two-stage sensitivity analysis was performed. The first stage was to conduct logistic regression to estimate study-specific ORs and CIs. Country-specific risk estimates were then pooled using both fixed- and random-effects models.

To test for linear trend, ordinal variables were treated as continuous variables and left endpoints of the categories were used as category values (e.g., 4 in the ≥4 children category). All linear trend tests regarding reproductive factors were performed among parous women, and those regarding contraceptive use were performed among contraceptive users. The level of significance was set at 0.05 and all tests were two-sided. All analyses were conducted with Stata software, version 10.1.

Results

Characteristics of the cases and controls included in these analyses are presented in Table 1. Compared to controls, Hodgkin lymphoma cases were younger ($p < 0.001$), had higher education level ($p = 0.01$), were more likely to be smokers ($p = 0.01$), to have used hair dyes ($p = 0.004$), to report diabetes or hypertension less frequently ($p = 0.005$ and $p < 0.001$, respectively), to have a lower parity ($p < 0.001$), and more likely to have ever used hormonal contraceptives ($p < 0.001$), but for a shorter period of time ($p < 0.001$). However, after adjustment for age and country, only duration of contraceptive use was statistically significant at the 5% level. Conversely, mature B-cell neoplasm cases were older ($p < 0.001$), and with a higher parity than controls ($p = 0.01$). Mature T-cell neoplasm cases had similar characteristics to controls.

Among controls, higher parity was associated with an increased age at recruitment (p-trend in parous < 0.0001), a lower education level (p-trend in parous $= 0.08$), a lower tobacco consumption (p-trend in parous $= 0.003$), and a self-reported hypertension history (p-trend in parous $= 0.07$) (Table 2). Although smoking habit was strongly associated with both parity and contraceptive use in the unadjusted analysis, only age, country, and education altered estimates by more than 10%, and therefore, multivariate models were not adjusted for tobacco.

Ever being pregnant showed a protective effect for diffuse large B-cell lymphoma (DLBCL) (OR = 0.7, 95% CI 0.5–1.0), while it increased the OR for multiple myeloma (OR = 2.4, 95% CI 1.1–5.3). No associations were observed for other subtypes (Fig. 1 and Table 3). Among parous women, we observed a protective effect with increasing parity for mature T-cell neoplasms and for overall mature B-cell neoplasms, showing an odds reduction of 29% for one child increase among parous women (95% CI −46 to −6%, p-trend = 0.02) and 13% (95% CI −19 to −7%, p-trend = 0.0001), respectively. This association was most apparent for chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) (odds reduction of 21% for one child increase, 95% CI −31 to −9%, p-trend = 0.001), but also for DLBCL (−14%, 95% CI −23 to −3%, p-trend = 0.02) and for other mature B-cell neoplasms (−16%, 95% CI −27 to −3%, p-trend = 0.02). Women with two or three children had lower risk of Hodgkin lymphoma compared with women with one child (OR = 0.5, 95% CI 0.3–0.9 and OR = 0.4, 95% CI 0.2–0.9, respectively), but no statistically significant trend was observed with increasing parity among parous women for this subtype (p-trend = 0.54). No association was found with age at first and last birth overall and by subtypes. The sub-analysis in men showed no association regarding number of children and risk of lymphoid neoplasms (Online Resource 1).

Countries with a more frequent use of hormonal contraceptives were Germany and Ireland (37.2%; $n = 116$ and 34.5%; $n = 29$ of controls, respectively) and with less frequent use were Italy and Czech Republic (5.1%; $n = 8$ and 9.5%; $n = 13$ of controls, respectively). Compared to long-term users of contraceptives, women who were short-term users (<5 years) were more likely to be of a more advanced age when they started using contraceptives, of a younger age when they stopped, and to have used them before 1980 (Table 2).

Overall, the use of hormonal contraceptives was not related to any of the lymphoid neoplasm subtypes. However, women using contraceptives for the shorter term had a twofold increased risk of mature B-cell neoplasms compared with never users (OR = 2.0, 95% CI 1.3–2.9) (Fig. 1). In particular, odds ratios were elevated for DLBCL and follicular lymphoma (OR = 2.5, 95% CI 1.5–4.2 and OR = 2.3, 95% CI 1.2–4.4, respectively; Table 3).

The age at first use of contraceptives was not associated with lymphoma risk overall. Longer time since last use was associated with a higher risk of Hodgkin, DLBCL, follicular, and other mature B-cell neoplasms (p-trend = 0.04, 0.02, 0.01 and 0.01, respectively). Furthermore, first use before 1980 was associated with an increased risk of mature B-cell neoplasms overall, DLBCL, and follicular lymphoma

Table 1 Descriptive characteristics of cases and controls

	Controls ($n = 1141$)	Mature B-cell neoplasms ($n = 795$)	Hodgkin lymphoma ($n = 147$)	Mature T-cell neoplasms[a] ($n = 52$)
Age (years), mean (SD)	56.5 (16.4)	60.6 (13.3)	36.1 (15.0)	58.8 (14.7)
Age (years), range	18–96	18–89	17–78	22–80
Year of birth, range	1904–1984	1910–1981	1922–1985	1918–1978
High education level, % (n)	12.7 (145)	10.1 (80)	20.4 (30)	3.9 (2)
Ever smoker, % (n)	35.4 (404)	33.0 (261)	46.3 (68)	40.0 (20)
Prior diagnosis of diabetes, % (n)	13.3 (152)	12.1 (96)	4.8 (7)	9.6 (5)
Prior diagnosis of hypertension, % (n)	35.6 (406)	34.1 (270)	14.3 (21)	28.9 (15)
Ever use of hair dyes, % (n)	72.5 (826)	75.0 (593)	83.7 (123)	74.5 (38)
Ever pregnant, % (n)	81.8 (933)	86.1 (682)	57.8 (85)	80.8 (42)
Number of children (in parous), mean (SD)	2.7 (1.8)	2.5 (1.5)	1.9 (1.7)	2.2 (1.4)
Use of contraceptives ever, % (n)	23.9 (271)	22.1 (174)	48.6 (70)	18.0 (9)
Duration of contraceptive use (in users), mean (SD)	9.4 (7.3)	8.1 (7.4)	5.7 (4.2)	8.9 (3.9)
Country, % (n)				
Spain	26.5 (302)	24.8 (197)	17.7 (26)	36.5 (19)
France	12.2 (139)	13.5 (107)	14.3 (21)	9.6 (5)
Germany	28.1 (320)	31.2 (248)	32.0 (47)	26.9 (14)
Italy	13.9 (158)	11.7 (93)	6.8 (10)	11.5 (6)
Ireland	7.4 (84)	6.7 (53)	12.9 (19)	5.8 (3)
Czech republic	12.1 (138)	12.2 (97)	16.3 (24)	9.6 (5)

Column percentages. Percentages do not include missing values

n number, *SD* Standard deviation

[a] Mature T-cell neoplasms = Mycosis fungoides/Sézary syndrome ($n = 14$), Cutaneous ($n = 2$), Angioimmunoblastic T-cell lymphoma ($n = 3$), Anaplastic large-cell lymphoma T-cell or null-cell type ($n = 14$), NK/T-cell lymphoma, nasal type/aggressive NK-cell leukemia ($n = 4$), T-cell large granular lymphocytic leukemia ($n = 1$), Peripheral T-cell lymphoma, *NOS* not otherwise specified ($n = 14$)

(OR = 1.7, 95% CI 1.2–2.4, OR = 1.9, 95% CI 1.1–3.1 and OR = 2.3, 95% CI 1.3–4.2, respectively), and before 1970 for CLL/SLL (OR = 2.5, 95% CI 1.1–5.6).

When we conducted sensitivity analyses to examine the impact of the age difference between controls and Hodgkin lymphoma, the associations with parity were not statistically significant anymore. The increased odds ratios associated with a short-term use of hormonal contraceptives compared with never users were largely driven by the German and to a lesser extent, the Italian data (data not shown). There was statistically significant heterogeneity between studies of population- and hospital-based design for a short-term use of contraceptives, but not for the reduced risk with increasing years of use that was observed in all centers (p-heterogeneity 0.004 and 0.69, respectively; data not shown). Similar results were observed with the two-stage analyses (data not shown). The rest of sensitivity analyses did not materially change the results. Further, stratifications by socioeconomic measures did not modify the observed associations (data not shown). For comparison with previous studies, we repeated the analyses using the former NHL classification (combining T and B subtypes and excluding multiple myeloma) and observed similar findings to the analyses of mature B-cell neoplasms as a whole (Online Resource 2).

Discussion

This study focused on reproductive factors and use of exogenous hormones as possible risk factors for lymphoma and of its common subtypes. Results showed a consistent protective effect in parous women for mature T-cell and B-cell neoplasms, particularly for CLL/SLL and DLBCL subtypes, with increasing number of children, and an increased risk of mature B-cell neoplasms among short-term users of hormonal contraceptives.

Our results on parity are consistent with two previous population-based case–control studies that observed a decreasing risk of NHL with increasing number of pregnancies among parous women [4, 5], but this observation is not clearly observed in other studies [8–11, 13, 27]. Nevertheless, the target has usually been NHL, combining B and T subtypes, and different analytical methods have been

Table 2 Descriptive characteristics of controls by number of children and duration of contraceptive use

	Number of children					*p-trend (parous)* [c]	Duration of contraceptive use					*p-trend (users)* [c]
	0 ($n = 245$)	1 ($n = 176$)	2 ($n = 313$)	3 ($n = 184$)	≥4 ($n = 220$)		No use ($n = 863$)	<5 years ($n = 78$)	5–9 years ($n = 67$)	10–14 years ($n = 54$)	≥15 years ($n = 61$)	
Age at recruitment, mean (SD)	44.3 (19.5)	55.7 (15.4)	57.3 (13.5)	61.4 (11.6)	66.0 (11.2)	*<0.0001*	60.7 (14.8)	41.1 (16.2)	37.3 (13.8)	47.4 (12.8)	48.3 (9.4)	*0.001*
High education level, % (n)[a]	31.8 (78)	12.5 (22)	7.4 (23)	7.6 (14)	3.2 (7)	*0.08*	9.7 (84)	23.1 (18)	26.9 (18)	22.2 (12)	18.0 (11)	*0.60*
Ever Smoker, % (n)[a]	48.2 (118)	44.3 (78)	36.1 (113)	27.2 (50)	19.6 (43)	*0.003*	28.4 (245)	51.3 (40)	53.7 (36)	64.8 (35)	63.9 (39)	*0.01*
Prior diagnosis of diabetes, % (n)[a]	6.5 (16)	11.4 (20)	12.8 (40)	16.9 (31)	20.5 (45)	*0.52*	16.2 (140)	5.1 (4)	3.0 (2)	3.7 (2)	3.3 (2)	*0.72*
Prior diagnosis of hypertension, % (n)[a]	20.8 (51)	30.1 (53)	34.5 (108)	46.7 (86)	48.6 (107)	*0.07*	41.0 (354)	19.2 (15)	7.5 (5)	18.5 (10)	26.2 (16)	*0.75*
Ever use of hair dyes, % (n)[a]	73.0 (178)	68.2 (120)	77.0 (241)	77.2 (142)	65.3 (143)	*0.83*	68.9 (593)	82.1 (64)	91.0 (61)	83.3 (45)	83.6 (51)	*0.98*
Pregnant ever, % (n)[a]	15.5 (38)	100.0 (176)	100.0 (313)	100.0 (184)	100.0 (220)	NA	84.2 (727)	67.5 (52)	59.7 (40)	83.3 (45)	90.2 (55)	*0.38*
Number of children, *mean (SD)*	NA	NA	NA	NA	NA	NA	2.4 (2.0)	1.6 (1.7)	1.2 (1.7)	1.9 (1.3)	1.7 (1.3)	*0.86*
Country, % (n)[b]												
Spain	21.2 (64)	11.9 (36)	24.8 (75)	14.9 (45)	26.8 (81)		81.5 (242)	8.8 (26)	4.0 (12)	3.0 (9)	2.7 (8)	
France	23.0 (32)	12.2 (17)	18.7 (26)	22.3 (31)	23.7 (33)		71.1 (96)	8.2 (11)	7.4 (10)	3.0 (4)	10.4 (14)	
Germany	21.3 (68)	26.3 (84)	30.9 (99)	14.7 (47)	6.9 (22)		62.8 (196)	5.8 (18)	9.6 (30)	11.2 (35)	10.6 (33)	
Italy	20.9 (33)	10.1 (16)	24.7 (39)	17.7 (28)	26.6 (42)		94.9 (150)	0.6 (1)	1.3 (2)	1.3 (2)	1.9 (3)	
Ireland	31.0 (26)	2.4 (2)	16.7 (14)	8.3 (7)	40.5 (34)		65.5 (55)	17.9 (15)	10.7 (9)	2.4 (2)	3.6 (3)	
Czech republic	15.9 (22)	15.2 (21)	43.5 (60)	18.8 (26)	5.8 (8)		90.5 (124)	5.1 (7)	2.9 (4)	1.5 (2)	0.0 (0)	
Use of contraceptives, % (n)[a]	35.8 (87)	30.9 (54)	22.2 (69)	15.9 (29)	14.2 (31)	*0.82*	NA	NA	NA	NA	NA	NA
Calendar year of first contraceptive use, % (n)[a]												
<1970	0.4 (1)	2.3 (4)	3.9 (12)	1.6 (3)	5.1 (11)		NA	18.0 (14)	9.0 (6)	16.7 (9)	1.6 (1)	
1970–1979	7.0 (17)	8.1 (14)	7.4 (23)	6.0 (11)	6.5 (14)		NA	37.2 (29)	23.9 (16)	27.8 (15)	31.2 (19)	
≥1980	28.1 (68)	19.7 (34)	10.7 (33)	8.2 (15)	1.8 (4)		NA	44.9 (35)	67.2 (45)	55.6 (30)	67.2 (41)	
Mean (SD)	1982 (3.8)	1980 (6.0)	1977 (7.1)	1978 (6.2)	1972 (7.2)	*0.49*	NA	1977 (6.9)	1980 (6.5)	1978 (7.3)	1981 (4.8)	*<0.0001*
Age starting contraceptives, mean (SD)	19.2 (3.5)	21.3 (5.6)	24.4 (7.1)	22.9 (5.8)	29.4 (7.3)	*0.49*	NA	24.6 (6.9)	21.2 (6.4)	23.2 (6.9)	20.6 (4.6)	*<0.0001*
Age finishing contraceptives, mean (SD)	27.2 (6.7)	33.0 (8.1)	35.1 (8.5)	35.9 (10.0)	38.5 (7.0)	*0.74*	NA	27.0 (6.8)	28.7 (6.5)	34.7 (7.0)	41.6 (6.5)	*<0.0001*
Time since last use of contraceptives, mean (SD)	5.2 (8.7)	9.5 (8.6)	13.7 (9.8)	13.7 (10.2)	17.3 (10.9)	*0.74*	NA	14.1 (12.0)	8.5 (10.3)	12.7 (8.7)	6.7 (7.0)	*<0.0001*

n number, *SD* standard deviation, *NA* not applicable

[a] Column percentages. Percentages do not include missing values

[b] Row percentages. Percentages do not include missing values

[c] *p*-trend represents *p* values for of linear trend test. Models are adjusted by age (continuous) and center, except the models evaluating age at recruitment and center, which are adjusted only for center and only for age, respectively

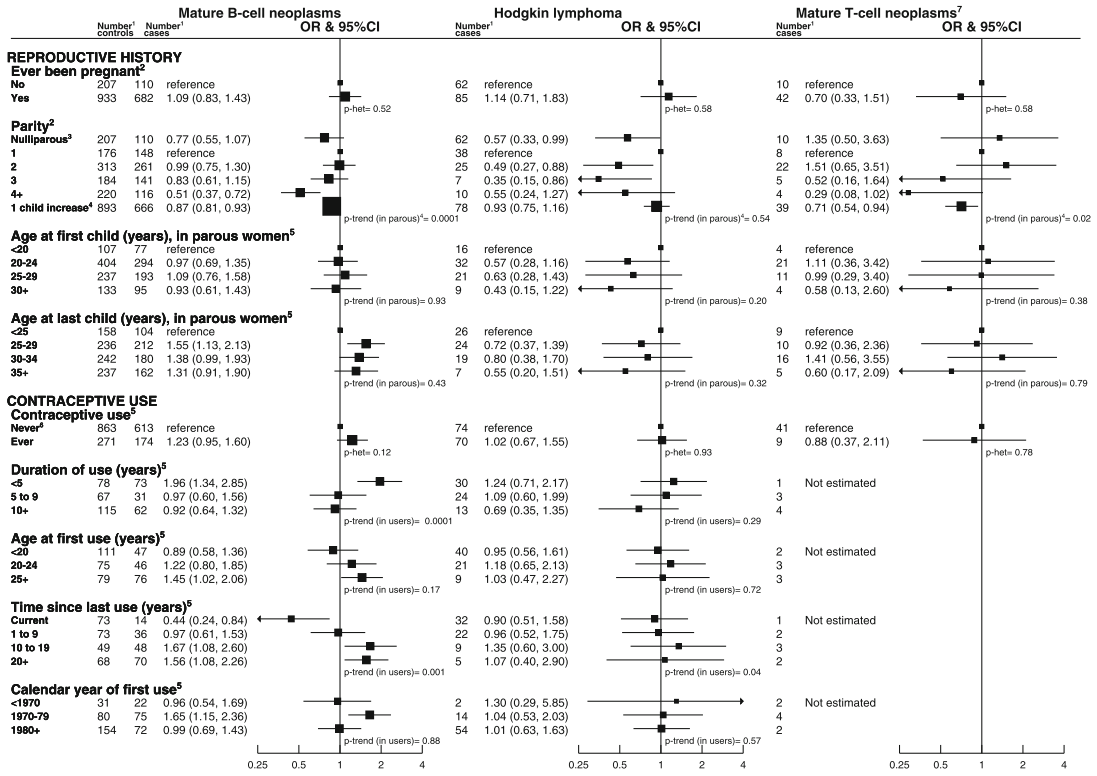
used. To the best of our knowledge, the present study is the first to report specifically a lower risk with increasing number of children for mature T-cell neoplasms. Only Zhang et al. [5] examined reproductive factors on T-cell neoplasms separately and did not find any significant association. However, the interpretation of these results was hampered by the fact that the study included only few cases of T-cell lymphoma, and the reduced risk with increased pregnancies was only apparent when they were combined with B-cell NHL. Two other studies considered B-cell NHL independently; Prescott et al. [3] found a significant protective effect for parous women compared with those who were nulliparous in the California Teachers Study cohort, but they did not observe any trend among parous women, while Nelson et al. [12] evaluated high and intermediate grade B-cell NHL cases and again, did not show variation in risk. Although there are inconsistencies in literature, our observations along with previous evidence support the idea that parity could reduce lymphoma risk.

As for lymphoma subtypes, a protective non-significant effect for CLL/SLL with increasing number of children was observed in a previous prospective study [9], in accordance with our results, but was not corroborated in either in the California Teachers cohort or in the National Institutes of Health-AARP Study cohort [3, 10]. Similarly, a decreasing trend for diffuse large-cell lymphoma with increasing number of pregnancies and livebirths was also found in a large population-based case–control study by Lee et al. [4] but not in the two previous cohort studies [3, 10], nor in two population-based case–control studies [5, 11]. Hodgkin lymphoma has frequently been linked to reproductive factors, with some studies, but not all, describing a slight-to-moderate decrease of risk with higher parity [6, 7, 13–15, 21, 28]. In our study, some protection from Hodgkin lymphoma was observed among women with two or three children. However the age-related sensitivity analyses did not show any significant association for this subtype, suggesting that these results may be due to the age discrepancy between controls and Hodgkin lymphoma. Little is known regarding multiple myeloma and reproductive factors. Two studies analyzed this subtype independently [10, 13] and did not find any association, consistent with our data. There is evidence supporting both etiologic commonality and heterogeneity for lymphoma subtypes [29]. We observed protective effects for parity in subtypes that occur more frequently in men than in women, such as T-cell neoplasms, CLL/SLL, and DLBCL, but not follicular lymphoma. Globally, our results suggest that parity could be a common protective factor for those subtypes with a higher male:female incidence rate ratio [1].

We did not observe any association regarding the age of the mother at the first and last child and the risk of mature B-cell or T-cell neoplasms, in accordance with other studies [5, 8–12], suggesting that these factors do not play a major role in the etiology of lymphomas.

The association between use of hormonal contraceptives and risk of lymphoma has also been inconsistent in previous studies. Again, most studies combined T-cell and B-cell NHL in their analyses, reporting in general no association with the use or duration of contraceptives [4, 10, 17–21]. On the contrary, Nelson et al. [12] found, in a population-based case–control study, a decreased risk for high or intermediate grade B-cell NHL among women who had ever used oral contraceptives and the OR was lower in those that had used contraceptives for 5 years or more. In accordance with this study [12], we found a decreasing risk of mature B-cell neoplasms with a longer duration of contraceptive use in women who ever used them. However, a significant higher risk of mature B-cell neoplasms—including DLBCL and follicular lymphoma subtypes—for a short-term use of hormonal contraceptives compared with non-users, not reported previously, was also found. We extended the list of potential confounders and made efforts to identify whether characteristics of short-term users were different to those of long-term users, but we could only find that the women with short duration of use were different regarding age and time of use. They were more likely to start hormonal contraceptives later in life, to stop younger, and to consume them before the 1980s than longer users, when estrogens concentration in preparations used to be higher. So, a biological process could explain this higher risk, since different concentrations may result in different effects on the immune cells with lower levels enhancing specific immune activities, and higher levels inhibiting them [30–32]. However, this association was mostly confined to Germany, and to a lesser extent to Italy, the two studies of population-based design. Although extensive sensitivity analyses showed the same results, this association should be taken cautiously and needs to be replicated in other studies.

Although the mechanisms explaining why sex hormones can be associated with the risk of lymphoid neoplasms are not yet established, it is well known that both estrogens and progestagens act in numerous immunological pathways, apart from their endocrine functions. Women produce more vigorous cellular and humoral immune responses and suffer autoimmune diseases more frequently than men [33]. Although both in vivo and in vitro models have provided inconclusive findings on the influence of sex hormones on the T-lymphocyte function, the percentage of T lymphocytes within the total lymphocyte population has been shown in vivo to be higher in women compared with men [33]. Sex hormones could mediate the reversed cytokine profile observed during pregnancy: Th1 cytokine pattern is inhibited while Th2 is enhanced [34]. The cytokine environment is crucial for the differentiation of lymphocytes to



OR: Odds ratio, CI: confidence interval, het: heterogeneity.

[1] Numbers do not always add to the total because of missing values

[2] Adjusted for age (continuous), center (country) and education (low, medium and high categories)

[3] Women who had experienced abortions and/or pregnancy losses are excluded from this category

[4] Using number of children as a continuous variable among parous women

[5] Adjusted for age (continuous), number of children (0, 1/2, and 3 or more categories), center (country) and education (low, medium and high categories)

[6] Referent category for all analyses on contraceptive use

[7] Mature T-cell neoplasms= Mycosis fungoides/Sezary syndrome (n=14), Cutaneous (n=2), Angioimmunoblastic T-cell lymphoma (n=3) Anaplastic large cell lymphoma T-cell or null-cell type (n=14), NK/T-cell lymphoma, nasal type aggressive NK-cell leukemia (n=4) T-cell large granular lymphocytic leukemia (n=1), Peripheral T-cell lymphoma, NOS (not otherwise specified)(n=14)

Fig. 1 Odds ratios of mature B- and T-cell neoplasms and Hodgkin lymphoma by reproductive factors and use of contraceptives

Th1 or Th2, with some cytokines playing a key role in this differentiation. Genetic variations in the Th1 and Th2 pathways have been found to increase the risk of NHL, suggesting that a shift of the Th1/Th2 response could have an important role in the pathogenesis of NHL [35]. Also the role of monocyte cytokine production might be important, since IL-6 plasma levels appear to be decreased in vivo by estrogens, and it has been suggested to be a growth factor in lymphoma [5, 33]. Sex hormones are capable of influencing the cytokine environment, and they might have a significant role in the immune dysregulation associated with lymphoid neoplasms.

A concern regarding this study is the self-reported nature of the information on medication use and past conditions. Misreporting of contraceptive use cannot be ruled out. However, the reliability of responses to questions on reproductive history and contraceptive use has been shown to be comparable to medical records [36, 37]. Another limitation of this study is the lack of information on some variables that could assist in understanding the role of hormones in the development of lymphomas. Data on the composition of hormonal contraceptives, doses or route of administration, for example, were not collected. Conflicting results have been reported for the association between

Table 3 Odds ratios and 95% confidence intervals for the association between reproductive factors and hormonal contraceptive use and mature B-cell neoplasm subtypes

	Controls ($n = 1141$)[a]	CLL/SLL			DLBCL		
		Cases ($n = 152$)[a]	OR	95% CI	Cases ($n = 248$)[a]	OR	95% CI
Reproductive history							
Pregnancies[b]							
Never	207	14	Ref	–	56	Ref	–
Ever	933	137	1.44	[0.79,2.61]	191	0.66*	[0.46,0.96]
p-heterogeneity=				0.24			0.03
Parity[b]							
Nulliparous[c]	207	14	0.43*	[0.22,0.87]	56	1.30	[0.81,2.10]
1	176	32	Ref	–	40	Ref	–
2	313	53	0.84	[0.51,1.37]	68	0.91	[0.59,1.42]
3	184	24	0.49*	[0.27,0.89]	42	0.91	[0.56,1.49]
≥4	220	27	0.36*	[0.20,0.66]	34	0.58*	[0.34,1.00]
One child increase[d]	*893*	*136*	*0.79**	*[0.69,0.91]*	*184*	*0.86**	*[0.77,0.97]*
p-trend (in parous)[d]=				0.001			0.02
Age at first child (years)[e]							
<20	107	15	Ref	–	18	Ref	–
20–24	404	55	0.96	[0.51,1.81]	86	1.19	[0.67,2.09]
25–29	237	41	1.22	[0.62,2.41]	52	1.29	[0.69,2.38]
≥30	133	23	1.11	[0.51,2.39]	26	1.07	[0.53,2.18]
p-trend (in parous)=				0.52			0.85
Age at last child (years)[e]							
<25	158	26	Ref	–	26	Ref	–
25–29	236	42	1.27	[0.73,2.22]	53	1.50	[0.89,2.53]
30–34	242	38	1.11	[0.62,2.00]	58	1.67	[0.97,2.86]
≥35	237	28	0.74	[0.38,1.44]	44	1.31	[0.72,2.38]
p-trend (in parous)=				0.29			0.45
Hormonal contraceptive use							
Use of contraceptives[e]							
Never used[f]	863	123	Ref	–	188	Ref	–
Ever used	271	27	1.55	[0.91,2.64]	58	1.28	[0.87,1.91]
p-heterogeneity=				0.11			0.21
Duration of use (years)[e]							
<5	78	9	1.85	[0.83,4.11]	31	2.50*	[1.50,4.17]
5–9	67	7	2.10	[0.84,5.21]	10	0.93	[0.44,1.95]
≥10	115	8	0.97	[0.43,2.19]	15	0.74	[0.41,1.36]
p-trend (in users)=				0.08			0.0003
Age at first use (years)[e]							
<20	111	4	0.72	[0.23,2.23]	17	0.91	[0.48,1.71]
20–24	75	4	0.85	[0.28,2.55]	17	1.30	[0.71,2.39]
≥25	79	17	2.11*	[1.15,3.88]	23	1.56	[0.93,2.62]
p-trend (in users)=				0.19			0.18
Time since last use (years)[e]							
Current	73	2	0.57	[0.13,2.62]	9	0.68	[0.31,1.53]
1–9	73	4	1.11	[0.36,3.43]	13	1.12	[0.56,2.21]
10–19	49	7	1.77	[0.73,4.32]	16	1.90*	[1.01,3.55]
≥20	68	12	1.83	[0.91,3.68]	19	1.46	[0.83,2.57]
p-trend (in users)=				0.51			0.02
Calendar year of first use[e]							
<1970	31	9	2.51*	[1.12,5.62]	5	0.80	[0.30,2.12]
1970–1979	80	10	1.46	[0.69,3.11]	24	1.85*	[1.09,3.12]
≥1980	154	6	0.76	[0.29,1.95]	28	1.09	[0.64,1.87]
p-trend (in users)=				0.12			0.97

Table 3 continued

	Follicular lymphoma			Multiple myeloma			Other mature B-cell neoplasms[f]		
	Cases (n = 136)[a]	OR	95% CI	Cases (n = 120)[a]	OR	95% CI	Cases (n = 139)[a]	OR	95% CI
Reproductive history									
Pregnancies[b]									
Never	15	Ref	–	7	Ref	–	18	Ref	–
Ever	121	1.76	[0.97,3.19]	113	2.36*	[1.05,5.28]	120	1.11	[0.64,1.92]
p-heterogeneity=			0.06			0.04			0.72
Parity[b]									
Nulliparous[c]	15	0.64	[0.31,1.30]	7	0.33*	[0.14,0.80]	18	0.64	[0.18,2.26]
1	23	Ref	–	25	Ref	–	28	Ref	–
2	53	1.50	[0.88,2.56]	38	0.83	[0.48,1.45]	49	0.72	[0.37,1.38]
3	26	1.21	[0.65,2.23]	26	0.84	[0.46,1.54]	23	0.98	[0.59,1.64]
≥4	17	0.76	[0.37,1.53]	21	0.49*	[0.25,0.95]	17	0.39*	[0.19,0.76]
One child increase[d]	*119*	*0.93*	*[0.80,1.07]*	*110*	*0.90*	*[0.79,1.03]*	*117*	*0.84**	*[0.73,0.97]*
p-trend (in parous)[d] =			0.31			0.14			0.02
Age at first child (years)[e]									
<20	20	Ref	–	12	Ref	–	12	Ref	–
20–24	50	0.67	[0.37,1.20]	52	1.22	[0.62,2.41]	51	1.00	[0.50,1.97]
25–29	29	0.66	[0.34,1.28]	34	1.47	[0.71,3.07]	37	1.17	[0.57,2.43]
≥30	19	0.65	[0.30,1.39]	11	0.99	[0.39,2.47]	16	0.91	[0.39,2.14]
p-trend (in parous)=			0.36			0.79			0.96
Age at last child (years)[e]									
<25	17	Ref	–	18	Ref	–	17	Ref	–
25–29	38	1.78	[0.95,3.33]	36	1.53	[0.82,2.85]	43	1.86*	[1.01,3.44]
30–34	34	1.70	[0.88,3.27]	21	1.01	[0.50,2.04]	29	1.39	[0.71,2.71]
≥35	28	1.81	[0.88,3.72]	34	1.70	[0.83,3.52]	28	1.41	[0.68,2.92]
p-trend (in parous)=			0.18			0.36			0.73
Hormonal contraceptive use									
Use of contraceptives[e]									
Never used[f]	90	Ref	–	101	Ref	–	111	Ref	–
Ever used	44	1.49	[0.93,2.38]	19	0.87	[0.48,1.58]	26	0.94	[0.55,1.60]
p-heterogeneity=			0.10			0.65			
Duration of use (years)[e]									
<5	16	2.29*	[1.19,4.41]	8	1.27	[0.56,2.91]	9	1.21	[0.55,2.63]
5–9	7	1.04	[0.43,2.53]	0	–	–	7	1.25	[0.51,3.05]
≥10	20	1.27	[0.70,2.28]	9	0.87	[0.40,1.89]	10	0.79	[0.37,1.64]
p-trend (in users)=			0.05			0.28			0.10
Age at first use (years)[e]									
<20	11	0.79	[0.37,1.72]	7	1.04	[0.41,2.62]	8	0.86	[0.36,2.06]
20–24	15	1.85	[0.95,3.61]	4	0.79	[0.26,2.37]	6	0.84	[0.33,2.12]
≥25	17	1.66	[0.91.3.01]	7	0.79	[0.34,1.81]	12	1.14	[0.58,2.23]
p-trend (in users)=			0.45			0.98			0.93
Time since last use (years)[e]									
Current	2	0.25	[0.06,1.11]	1	0.26	[0.03,2.02]	0	–	–
1–9	7	0.70	[0.29,1.70]	7	1.46	[0.57,3.70]	5	0.65	[0.24,1.79]
10–19	15	2.29*	[1.17,4.48]	3	0.61	[0.18,2.08]	7	1.23	[0.52,2.95]
≥20	19	2.08*	[1.15,3.77]	6	0.86	[0.35,2.11]	14	1.45	[0.76,2.78]
p-trend (in users)=			0.01			0.49			0.01
Calendar year of first use[e]									
<1970	4	0.93	[0.31,2.75]	1	0.25	[0.03,1.89]	3	0.59	[0.17,2.01]
1970–1979	20	2.33*	[1.29,4.19]	8	1.12	[0.50,2.53]	13	1.49	[0.76,2.93]

Table 3 continued

	Follicular lymphoma			Multiple myeloma			Other mature B-cell neoplasms[f]		
	Cases ($n = 136$)[a]	OR	95% CI	Cases ($n = 120$)[a]	OR	95% CI	Cases ($n = 139$)[a]	OR	95% CI
≥1980	19	1.03	[0.54,1.98]	9	0.98	[0.42,2.25]	10	0.77	[0.35,1.71]
p-trend (in users)=			0.77			0.43			0.48

OR odds ratio, *CLL/SLL*, chronic lymphocytic leukemia/small lymphocytic lymphoma, *DLBCL* diffuse large B-cell lymphoma, * $p < 0.05$

[a] Numbers do not always add to the total because of missing values

[b] Adjusted for age (continuous), center (country), and education (low, medium, and high categories)

[c] Women who had experienced abortions or pregnancy losses are excluded from this category

[d] As a continuous variable in parous women (for reproductive history analyses) or in contraceptive users (for contraceptive use analyses)

[e] Adjusted for age (continuous), center (country), education (low, medium, and high categories), and number of children (0, 1 + 2, and ≥3 categories)

[f] Referent for all analyses on contraceptive use

[g] Other mature B-cell neoplasms = Lymphoplasmacytic lymphoma ($n = 16$), Mucosa-associated lymphoid tissue lymphoma ($n = 48$), Splenic marginal zone lymphoma ($n = 21$), Mantle cell lymphoma ($n = 19$), Hairy cell leukemia ($n = 1$) and B-cell lymphoma—unclassifiable ($n = 34$)

lymphoma and menarche data [3–5, 8, 10], use of menopausal hormone therapy [4, 11, 12, 17, 21, 38, 39], and breastfeeding [3, 8, 21]. Unfortunately, this information was not available in our study.

The main strengths of our study are its large size, its international multicenter design, and the use of a rigorous classification and evaluation of lymphoma subtypes. Exhaustive sensitivity analyses suggest that our results in general were not due to a different age distribution between subtype-specific cases and controls. Furthermore, as recommended by Kravdal et al. and Frisch et al. [27, 40], we supplemented our analysis with a sub-analysis performed in men. The lack of association in male participants reinforces that hormonal effects are a more suitable explanation for this risk pattern rather than lifestyle or sociodemographic characteristics that are similar between men and women. Another possible explanation for our findings is selection bias, and in their paper, Grulich et al. [23] discussed that selection bias related to socioeconomic measures may be responsible for the association between birth order and NHL, since this relationship was only observed in the low socioeconomic stratum. However, our results do not seem to be explained by socioeconomic measures.

In conclusion, our data suggest a protective association between increasing number of children and risk of mature T-cell and B-cell neoplasms overall, and some lymphoma subtypes. Our data may also indicate that hormonal contraceptives could play a role in lymphomagenesis. Further assessment of the risk of lymphoid neoplasms from endogenous and exogenous hormones in large prospective studies with detailed exposure information and doses is required to better understand the role of hormonal factors in the etiology of these malignancies and confirm differences between subtypes.

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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

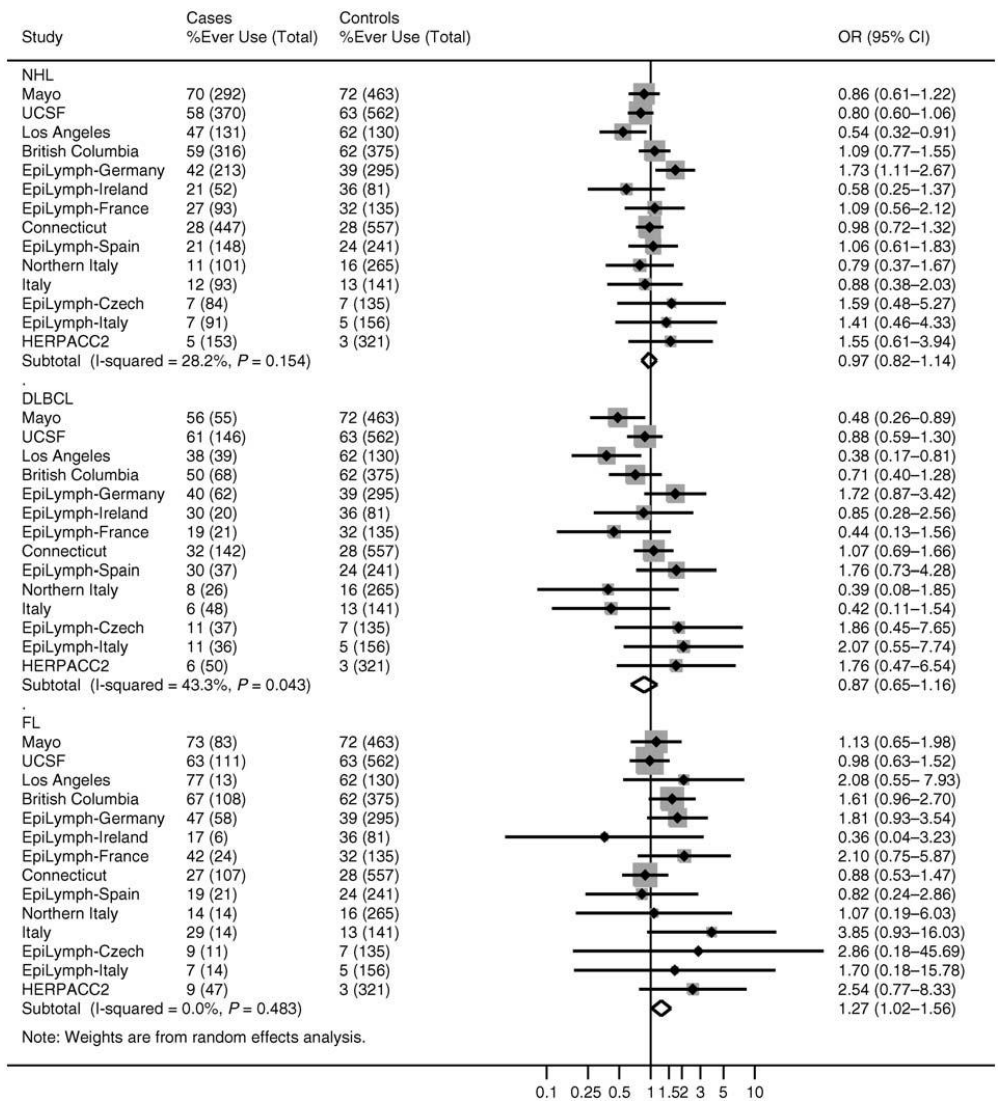

Figure 1. Study-specific associations between non-Hodgkin lymphoma, diffuse large B-cell lymphoma, follicular lymphoma and hormonal contraception use among women born 1925 or later. Studies are ordered by the percentage of control women who had ever used hormonal contraceptives. NHL, non-Hodgkin lymphoma;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

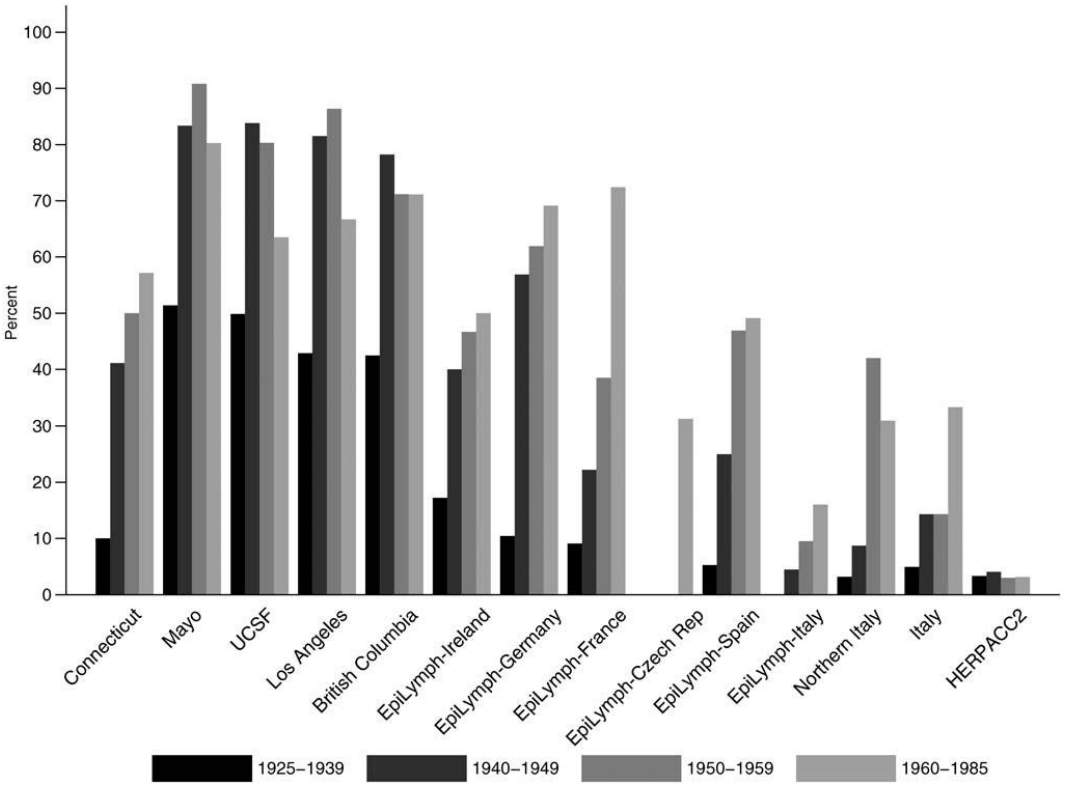

Figure 2. Percent of control women who had ever used hormonal contraception by study and birth cohort. Shading of the bars reflects the birth cohort distribution, where >40% of women were born before 1940, >25% in the 1940s and ∼15% in each of the other two time periods.

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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ARTICLE 3

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Postmenopausal hormone therapy and non-Hodgkin lymphoma: a pooled analysis of InterLymph case–control studies

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Background: Non-Hodgkin lymphoma (NHL) subtypes, diffuse large B-cell (DLBCL) and follicular lymphoma (FL) have different sex ratios and are diagnosed at ages over 60 years; DLBCL is more common in men and diagnosed at older ages than FL, which occurs more among women. This analysis of postmenopausal women examines the relationship between postmenopausal hormone therapy and NHL.

Design: Self-reported use of postmenopausal hormone therapy from 2094 postmenopausal women with NHL and 2731 without were pooled across nine case–control studies (1983–2005) from North America, Europe and Japan. Study-specific odds ratios (OR) and 95% confidence intervals (CI) estimated using logistic regression were pooled using random-effects meta-analyses.

Results: Postmenopausal women who used hormone therapy were at decreased risk of NHL (pooled OR = 0.79, 95% CI 0.69–0.90). Risks were reduced when the age of starting was 50 years or older. There was no clear trend with number of years of use. Current users were at decreased risk while those stopping over 2 years before diagnosis were not. Having a hysterectomy or not did not affect the risk. Favourable effects were present for DLBCL (pooled OR = 0.66, 95% CI 0.54–0.80) and FL (pooled OR = 0.82, 95% CI 0.66–1.01).

Conclusion: Postmenopausal hormone therapy, particularly used close to menopause, is associated with a decreased risk of NHL.

Key words: case–control studies, diffuse large B-cell lymphoma, follicular lymphoma, menopausal hormone therapy, non-Hodgkin lymphoma

introduction

Among non-Hodgkin lymphomas (NHL), different sex ratios are seen for the two most common subtypes, with diffuse large B-cell lymphoma (DLBCL) occurring among more men and follicular lymphoma (FL) among more women [1]. NHLs are also typically diagnosed at older ages and the median age at diagnosis is 70 years for DLBCL and 64 years for FL. Little is known of the causes of NHL, but factors which alter immune function such as sex hormones are thought to be involved [2, 3].

Hormone therapy for menopause has been widely studied with respect to women's health [4]. For postmenopausal women, there has been some suggestion that the current use of hormone therapy may be associated with a reduced risk of NHL [5, 6], although on the whole, no association either way has been reported and findings to date are inconclusive [5–17]. Because of the known associations with breast and endometrial cancers and cardiovascular disease, postmenopausal hormone therapy should not be used to prevent disease, nevertheless studying its relationship with NHL could inform NHL aetiology. To investigate whether there is an association

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between menopausal hormone therapy and NHL, we conducted a pooled analysis of case–control studies which are involved in the International Lymphoma Epidemiology Consortium (InterLymph).

materials and methods

Information on postmenopausal hormonal therapy was collected in nine case–control studies involved in the InterLymph Consortium. Study design details have been published [8, 10, 13, 15, 18–22] (supplementary Table S1, available at *Annals of Oncology* online) and for five studies, postmenopausal hormonal therapy data have been described [8, 10, 13, 15, 18]. Cases were identified using rapid ascertainment techniques and lymphoma diagnoses confirmed using pathologic review of reports or samples by pathologists. Controls were randomly selected from population registers or hospital or clinic patients, and were matched to cases on age and ethnicity. Each study was approved by the appropriate ethical committees and participants gave their informed consent. The studies were conducted in parts of USA, Canada, England, Italy and Japan. Six studies collected data in the late 1990s to early 2000s and three during the 1980s to early 1990s.

Lymphoma diagnoses were classified according to the International Classification of Diseases for Oncology third edition (ICD-O-3) (Mayo, British Columbia, UK and HERPACC2 studies), or the Working Formulation (Connecticut, UCSF, Los Angeles and Northern Italy studies). Methods to translate other coding schemes to ICD-O-3 have been described, and NHL subtypes were consistent with other InterLymph pooled analyses [23]. B-cell subtypes were 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). T-cell lymphomas were grouped 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). NHL was defined by the above ICD-O-3 codes as well as 9591/3, 9675/3 and 9727/3. Cases with HIV-associated lymphoma or multiple myeloma were excluded from the pooled dataset because most studies did not recruit these cases.

Women were asked about their use of postmenopausal hormonal therapies through in-person or telephone interviews, or self-completed questionnaires. Women were asked whether they had used postmenopausal hormone therapy, the age at which they started and stopped using it, and the number of years therapy was taken. Analyses were restricted to postmenopausal women, defined as women who had reported that their periods had stopped, or if this information was missing, cases who were aged 55 or older at diagnosis or interview date for controls. For most studies, it is not known whether menopause was surgically induced, as information on bilateral oopherectomy was only collected in two studies (Mayo, Los Angeles). Data on hormone therapy was censored at 1 year before diagnosis or interview date. Since hormone therapy formulation was only collected in the UCSF study [10], hysterectomy was used as a surrogate. Women who had undergone a hysterectomy from the late 1980s onwards were more likely to have been prescribed oestrogen-only preparations, while women with an intact uterus were more likely to have been prescribed combined oestrogen–progestogen therapy [4]. Potential confounders included body mass index (BMI) and socioeconomic status. BMI was calculated from self-reported height and weight, where weight was before (Mayo, British Columbia, North Italy, Italy, UK) or at (HERPACC2) diagnosis/interview, or was the usual adult weight (Connecticut, UCSF). Socioeconomic status was derived from educational attainment (Mayo, UCSF, Los Angeles, North Italy and Italy), income level (British Columbia) or census data (UK). Four studies had no data on hysterectomy (Connecticut, British Columbia, North Italy and Italy), one had no BMI data (Los Angeles) and two no socioeconomic status information (Connecticut and HERPACC2).

An anonymized dataset was supplied for each study and was checked for inconsistencies before harmonizing variables across studies. Analysis was conducted using a two-step process using Stata/IC 11.1 for Windows (StataCorp LP, Texas, 2010). First, study-specific odds ratios (OR) and confidence intervals (CI) were estimated by logistic regression adjusted for age as a continuous variable and ethnicity grouped as Caucasian or other as potential confounders. Where cell frequencies were five or less, risk estimates were computed by exact methods, with a half added to all cell frequencies if there were no cases or controls. The second step was to pool the study-specific ORs in a meta-analysis. Fixed-effects meta-analysis was used where study-specific risk estimates were homogeneous, while a random-effects model was used when heterogeneity was present. Heterogeneity was tested using Cochrane's Q test, 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 estimated by pooling the study-specific ORs for trend and were based on categorical data. To examine whether findings were consistent, sensitivity analyses were conducted stratified by factors such as study design and participation rates, and excluding ORs that were computed using exact methods.

results

Among the nine InterLymph studies, 2094 case and 2731 control women were considered postmenopausal (Table 1). The most common diagnoses were lymphomas of B-cell origin (81%), notably DLBCL (32%) and FL (25%) (Table 1). T-cell lymphoma and other B-cell subtypes such as chronic lymphocytic leukaemia/small lymphocytic lymphoma and marginal zone lymphoma accounted for <10% of cases, and NHL subtype was not known for 16%. Most women were Caucasian (90%), had gone through the menopause around the age of 47 and the median age at diagnosis was 64 years. Cases were more likely to be Caucasian, of slightly younger age, of lower socioeconomic status and to be overweight or more obese than controls; similar proportions of cases and controls had had a hysterectomy. Across studies, 37% of cases and 41% of controls reported using hormone therapy for their menopausal symptoms.

Postmenopausal women who had used hormone therapy were at decreased risk of NHL overall (pooled risk estimate = 0.79, 95% CI 0.69–0.90) compared with never users (Table 2). Inverse associations were strongest when use started at older ages (ages 50 and 54 years: pooled risk estimate = 0.74, 95% CI 0.61–0.91; aged ≥55 years: pooled risk estimate = 0.78, 95% CI 0.62–0.98). Regardless of the years hormonal therapy was used for, risks were below one, but there was no clear trend in risk. Current users were at decreased risk (pooled risk estimate = 0.70, 95% CI 0.54–0.91) while women who stopped in the 5 years before diagnosis or longer ago were not. Heterogeneity in study-specific risks among current users was moderate (I^2 = 40%) and influence analyses found that the pooled risk remained below one when each study was excluded in turn (pooled risk estimate ranged from 0.62, 95% CI 0.51–0.75, I^2 = 0%, $P_{\text{heterogeneity}}$ = 0.64 to 0.77, 95% CI 0.57–1.03, I^2 = 31%, $P_{\text{heterogeneity}}$ = 0.21). Postmenopausal hormone therapy reduced the risks of DLBCL and FL (pooled OR = 0.66, 95% CI 0.54–0.80; pooled OR = 0.82, 95% CI 0.66–1.01, respectively), but not

Table 1. Characteristics of postmenopausal women included in the pooled analysis

	Cases	Controls
	N (%)	*N* (%)
NHL subtype	2094 (100)	–
Diffuse large B-cell lymphoma	675 (32)	–
Follicular lymphoma	531 (25)	–
Other B-cell lymphoma	480 (23)	–
T-cell lymphoma	83 (4)	–
Unclassified	325 (16)	–
Age (years)	2094 (100)	2731 (100)
≤55	358 (17)	405 (15)
56–65	791 (38)	1036 (38)
>65	945 (45)	1290 (47)
Socioeconomic status	1463 (100)	1956 (100)
High	328 (22)	501 (26)
Medium	475 (32)	691 (35)
Low	655 (45)	758 (39)
Not known	5 (0.3)	6 (0.3)
Body mass index	1984 (100)	2627 (100)
Underweight (<18.5 kg m^{-2})	36 (2)	86 (3)
Normal (18.5–24.99 kg m^{-2})	1014 (51)	1420 (54)
Overweight (25–29.99 kg m^{-2})	597 (30)	751 (29)
Obese (≥30 kg m^{-2})	312 (16)	340 (13)
Not known	25 (1)	30 (1)
Hysterectomy	1098 (100)	1512 (100)
No	712 (65)	1016 (67)
Yes	373 (34)	477 (32)
Not known	13 (1)	19 (1)

Socioeconomic status data were collected in seven studies (Mayo, UCSF, Los Angeles, British Columbia, UK, North Italy and Italy), body mass index data in eight studies (Connecticut, Mayo, UCSF, British Columbia, UK, North Italy, Italy and HERPACC2) and hysterectomy data in five studies (Mayo, UCSF, Los Angeles, UK and HERPACC2). NHL, non-Hodgkin lymphoma.

of chronic lymphocytic leukaemia, marginal zone lymphoma, mantle cell lymphoma or T-cell lymphoma (pooled OR = 1.24, 95% CI 0.80–1.93; pooled OR = 0.88, 95% CI 0.56–1.40; pooled OR = 1.28, 95% CI 0.66–2.48; pooled OR = 0.86, 95% CI 0.52–1.41 respectively). Associations between hormone therapy, NHL, DLBCL and FL were consistent across studies and study-specific ORs tended to be below one (supplementary Figure S1, available at *Annals of Oncology* online).

Five studies asked women whether they had had a hysterectomy and the pooled risk estimate for using postmenopausal hormone therapy in these five studies was similar to that for all nine studies (Table 3). For NHL overall, there was no difference in the risk associated with hormone therapy by whether women had had a hysterectomy (pooled risk estimate = 0.78, 95% CI 0.55–1.10) or not (pooled risk estimate = 0.78, 95% CI 0.58–1.03). Statistically significant decreased risks were found for DLBCL among women who had had a hysterectomy (pooled risk estimate = 0.48, 95% CI 0.30–0.77) and for FL among women who had not undergone this surgery (pooled risk estimate = 0.66, 95% CI 0.47–0.93). However, confidence limits for these subtype-specific risks overlapped with those in the other stratum.

NHL risk associated with postmenopausal hormone therapy was reduced among women of normal weight (pooled risk estimate = 0.77, 95% CI 0.62–0.96) (Table 4). Similarly for DLBCL, but not FL, risks were decreased in women who were of normal weight (pooled risk estimate = 0.57, 95% CI 0.43–0.75) and not among women who were overweight (pooled risk estimate = 0.87, 95% CI 0.63–1.20).

discussion

The nine studies from parts of North America, Europe and Japan suggested that postmenopausal women who used hormone therapy had a lower risk of NHL overall than those who had never used it. Current users were at decreased risk, but past users had risks comparable to those who had never taken hormonal therapy. Risks below one were found in all categories of duration of use and age when hormonal treatment started; no clear trends were found for either variable. Findings were similar when these analyses were restricted to current users. When hormones were started between the ages of 50–54, the decreased risk reached statistical significance. For the two most common subtypes, DLBCL and FL, findings were similar to NHL overall. Findings were consistent among population-, hospital- and clinic-based studies, in studies where case and control participation was over 70%, and when risk estimates were adjusted for socioeconomic status.

Other evidence for postmenopausal hormone therapy's role in NHL aetiology comes from five cohort [5, 7, 9, 11, 14] and two case–control studies [6, 17]. Among these further studies, one case–control study reported that hormonal therapy reduced the risk of NHL overall [6] but on the whole, cohort studies found risks to be around one. For DLBCL, two cohorts reported risks below one [5, 11] while two others found no association [7, 14]. As for FL, there has been less consistency, with one study reporting a risk below one [11], another close to one [5] and two raised [7], one of which was statistically important [14]. When we conducted a meta-analysis of cohort data, the results suggested no association with ever use for NHL, DLBCL or FL (pooled risk estimate = 1.01, 95% CI 0.89–1.14, $I^2 = 0\%$, $P_{heterogeneity} = 0.49$; pooled risk estimate = 0.87, 95% CI 0.67–1.14, $I^2 = 21\%$, $P_{heterogeneity} = 0.28$; pooled risk estimate = 1.31, 95% CI 0.70–2.45, $I^2 = 76\%$, $P_{heterogeneity} = 0.01$, respectively). However, our protective finding was among women who were using hormonal therapy 1 year before diagnosis. Current users were also at reduced risks in one cohort [5] and a case–control study [6], but not two other cohort studies [7, 14] (Figure 1). Cohort studies would have collected information on hormonal therapy many years before diagnosis. Interestingly, studies with follow-up periods that were shorter and closer to menopausal age found risks for current users more similar to ours while for longer follow-up and further from menopause, risks were closer to one (Figure 1). One cohort reported a lower risk after 7 [24] than after 13 years of follow-up [14]. In cohort studies, information may not have been available as to whether women had stopped using hormone therapy since recruitment into the cohort. One possible explanation for differences between our study and the cohorts' findings is that in cohorts, women may have been

Table 2. Associations between non-Hodgkin lymphoma, diffuse large B-cell lymphoma, follicular lymphoma and postmenopausal hormonal therapy among postmenopausal women

Hormone therapy[a]	Controls	NHL	Pooled OR[b]	95% CI	I^2 (%)	$P_{heterogeneity}$	DLBCL	Pooled OR[b]	95% CI	I^2 (%)	$P_{heterogeneity}$	FL	Pooled OR[b]	95% CI	I^2 (%)	$P_{heterogeneity}$
Hormone therapy	No. of studies = 9															
Total[c]	2731	2094					675					531				
Never used	1584	1275	1	ref			439	1	ref			299	1	ref		
Ever used	1109	772	0.79	0.69–0.90	0	0.50	217	0.66	0.54–0.80	0	0.45	218	0.82	0.66–1.01	0	0.55
Age first used (years)	No. of studies = 8[d]															
Total[c]	2519	1987					637					501				
Never used	1395	1176	1	ref			405	1	ref			273	1	ref		
<45	244	188	0.88	0.71–1.10	0	0.64	51	0.72	0.51–1.02	0	0.60	57	1.01	0.72–1.43	0	0.49
45–49	259	193	0.84	0.68–1.05	0	0.57	59	0.77	0.55–1.06	0	0.85	54	0.86	0.62–1.21	0	0.91
50–54	322	209	0.74	0.61–0.91	0	0.59	54	0.58	0.42–0.80	0	0.93	63	0.82	0.60–1.12	0	0.70
≥55	235	156	0.78	0.62–0.98	0	0.65	43	0.70	0.48–1.01	0	0.62	35	0.73	0.45–1.18	22	0.25
Trend			0.92	0.88–0.96	0	0.44		0.87	0.81–0.94	0	0.50		0.92	0.85–0.99	8	0.37
Years used	No. of studies = 9															
Total[c]	2731	2094					675					531				
Never used	1584	1275	1	ref			439	1	ref			299	1	ref		
<2	242	160	0.78	0.62–0.98	0	0.81	53	0.73	0.52–1.02	0	0.46	39	0.78	0.52–1.16	4	0.40
2 to <5	231	180	0.90	0.72–1.13	0	0.69	51	0.81	0.57–1.14	0	0.72	52	0.97	0.69–1.37	0	0.87
5 to <10	238	152	0.72	0.57–0.91	0	0.80	37	0.59	0.40–0.86	0	0.44	41	0.73	0.51–1.06	0	0.61
≥10	363	258	0.86	0.65–1.13	35	0.14	72	0.79	0.52–1.20	32	0.16	79	0.99	0.73–1.34	0	0.53
Trend			0.94	0.90–0.98	7	0.38		0.91	0.83–1.00	35	0.14		0.98	0.90–1.06	24	0.23
Years since last used	No. of studies = 6[d]															
Total[c]	2035	1647					552					418				
Never used	1237	1050	1	ref			368	1	ref			246	1	ref		
>5	153	128	1.00	0.77–1.30	0	0.47	40	0.88	0.60–1.30	0	0.67	26	0.76	0.48–1.19	0	0.99
≤5	89	80	0.97	0.69–1.35	0	0.58	23	0.84	0.50–1.40	0	0.47	25	1.05	0.64–1.71	0	0.85
Current	504	331	0.70	0.54–0.90	40	0.14	100	0.57	0.44–0.74	0	0.54	103	0.76	0.58–0.99	0	0.46
Trend			0.89	0.82–0.97	44	0.11		0.83	0.77–0.91	0	0.49		0.92	0.84–1.00	0	0.46

[a]Hormone therapy among postmenopausal women where menopause was defined as the reporting of periods that stopped naturally or due to a bilateral oopherectomy, or, in the absence of these data, women aged ≥55 years were considered postmenopausal.

[b]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.

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

[d]HERPACC2 did not collect age when hormone therapy was first used, and Mayo, Los Angeles and HERPACC2 did not collect age when hormone therapy was last used.

NHL, non-Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma.

Table 3. Associations between non-Hodgkin lymphoma, diffuse large B-cell lymphoma, follicular lymphoma and postmenopausal hormonal therapy among postmenopausal women by hysterectomy status

Hormone therapy[a]	Controls	NHL	Pooled OR[b]	95% CI	I^2	$P_{heterogeneity}$	DLBCL	Pooled OR[b]	95% CI	I^2	$P_{heterogeneity}$	FL	Pooled OR[b]	95% CI	I^2	$P_{heterogeneity}$
Studies with hysterectomy data[c]																
Total[d]	1512	1098					378					307				
Never used	696	539	1	ref			205	1	ref			150	1	ref		
Ever used	782	525	0.82	0.69–0.97	0	0.50	157	0.72	0.51–1.02	36	0.18	146	0.80	0.61–1.05	2	0.39
Missing	34	34					16					11				
No hysterectomy[e]																
Total[d]	1016	712					245					203				
Never used	579	434	1	ref			155	1	ref			129	1	ref		
Ever used	416	262	0.78	0.58–1.03	38	0.17	80	0.72	0.49–1.07	27	0.24	68	0.66	0.47–0.93	0	0.45
Missing	21	16					10					6				
Hysterectomy[e]																
Total[d]	477	373					130					101				
Never used	117	102	1	ref			50	1	ref			20	1	ref		
Ever used	353	255	0.78	0.55–1.10	0	0.80	74	0.48	0.30–0.77	0	0.87	77	1.28	0.45–3.63	50	0.09
Missing	7	16					6					4				

[a]Hormone therapy among postmenopausal women where menopause was defined as the reporting of periods that stopped naturally or due to a bilateral oopherectomy, or, in the absence of these data, women aged ≥55 years were considered postmenopausal.

[b]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.

[c]Hysterectomy data were collected in five studies (Mayo, UCSF, Los Angeles, UK and HERPACC2).

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

[e]Tests for heterogeneity between risks among women who had had a hysterectomy and those who had not were not statistically significant (NHL: $\chi^2 = 0.00$, $P = 0.99$; DLBCL: $\chi^2 = 1.90$, $P = 0.17$; FL: $\chi^2 = 1.56$, $P = 0.21$).

NHL, non-Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma.

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Table 4. Associations between non-Hodgkin lymphoma, diffuse large B-cell lymphoma, follicular lymphoma and postmenopausal hormonal therapy among postmenopausal women by normal and overweight

Hormone therapy[a]	Controls	NHL	Pooled OR[b]	95% CI	I^2	$P_{heterogeneity}$	DLBCL	Pooled OR[b]	95% CI	I^2	$P_{heterogeneity}$	FL	Pooled OR[b]	95% CI	I^2	$P_{heterogeneity}$
Studies with BMI data[c]																
Total[d]	2627	1984					632					515				
Never used	1540	1218	1	ref			413	1	ref			290	1	ref		
Ever used	1049	719	0.80	0.70–0.91	0	0.45	200	0.68	0.55–0.83	1	0.42	211	0.83	0.67–1.03	0	0.55
Missing	38	47					19					14				
Normal weight[e]																
Total[d]	1506	1050					341					276				
Never used	849	629	1	ref			223	1	ref			142	1	ref		
Ever used	634	399	0.77	0.62–0.96	20	0.27	109	0.57	0.43–0.75	0	0.63	128	0.94	0.68–1.30	12	0.34
Missing	23	22					9					6				
Overweight/obese[e]																
Total[d]	1091	909					281					233				
Never used	671	571	1	ref			184	1	ref			143	1	ref		
Ever used	407	315	0.86	0.70–1.06	0	0.91	88	0.87	0.63–1.20	0	0.80	82	0.74	0.53–1.03	0	0.99
Missing	13	23					9					8				

[a]Hormone therapy among postmenopausal women where menopause was defined as the reporting of periods that stopped naturally or due to a bilateral oopherectomy, or, in the absence of these data, women aged ≥55 years were considered postmenopausal.

[b]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.

[c]Body mass index data were collected in eight studies (Connecticut, Mayo, UCSF, British Columbia, UK, North Italy, Italy and HERPACC2).

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

[e]Tests for heterogeneity between risks among women who were normal weight (BMI < 25 kg m^{-2}) and those who were overweight or obese (BMI ≥ 25 kg m^{-2}) were statistically significant for DLBCL ($\chi^2 = 3.79$, $P = 0.05$) but not for NHL or FL (NHL: $\chi^2 = 0.78$, $P = 0.38$; FL: $\chi^2 = 0.97$, $P = 0.32$).

NHL, non-Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma.

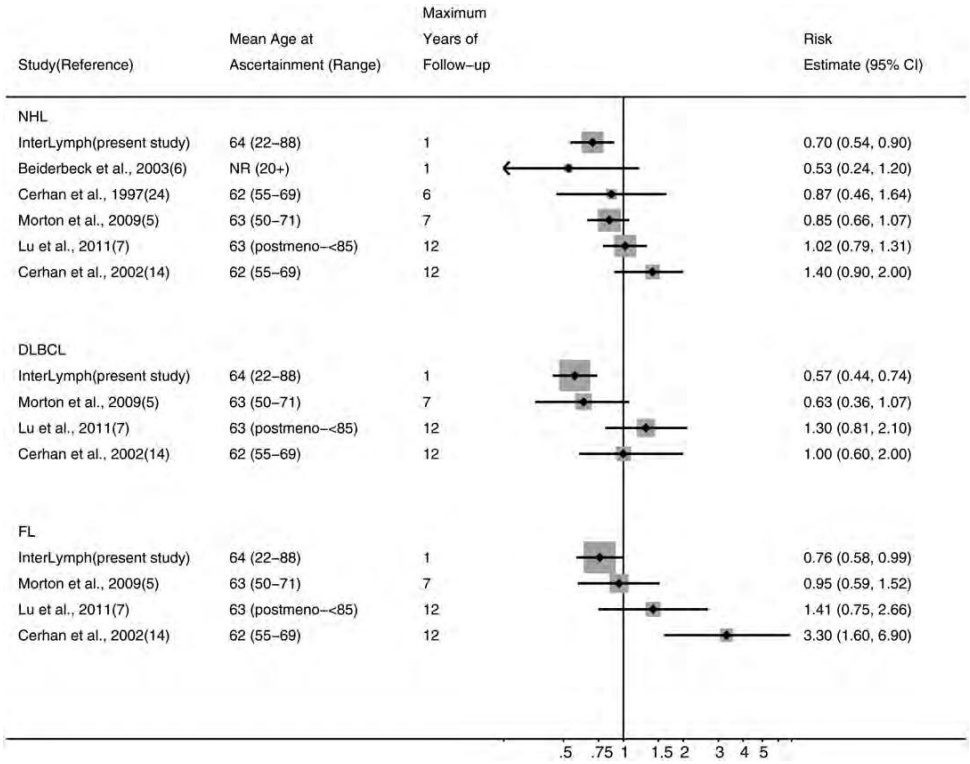

Figure 1. Associations between non-Hodgkin lymphoma, diffuse large B-cell lymphoma, follicular lymphoma and current use of postmenopausal hormonal therapy reported in published studies. Current use of hormone therapy was reported at recruitment in cohort studies and a year before diagnosis/reference date in case–control studies. Risk estimates are ordered by the maximum length of follow-up for cohort studies and latency period for case–control studies. NR, not reported; postmeno, postmenopausal. Cohort studies are Cerhan et al. [24], Morton et al. [5], Lu et al. [7] and Cerhan et al. [14]. Case–control studies are InterLymph and Beiderbeck et al. [6].

more likely to have stopped where follow-up continued further from menopausal age.

In our data, whether oestrogen only or combined oestrogen and progestin therapy contributed to the reduced risk could not be examined directly as only one study collected this information. As an alternative, we investigated whether risks were different among women who had or not had a hysterectomy since from the late 1980s, unopposed oestrogen tended to be prescribed following a hysterectomy and combined therapy to menopausal women with an intact uterus [4]. Although we found no difference for NHL overall, decreased risks of DLBCL for hormonal therapy were found among women who had had a hysterectomy in particular, but also in those who had not. For FL, risks were reduced among women with an intact uterus and not among those who did not. Findings for the two formulations have been reported in two cohorts [5, 7] and one case–control study included here [10]. No associations with either therapy were found in the cohort studies [5, 7] while reduced risks were found for both therapies in the case–control study [10]. However, some decreased risks were found in the cohort studies when hysterectomy data were considered in conjunction with treatment types [5, 7]. In the NIH-AARP cohort, women who had had a hysterectomy and were treated with unopposed oestrogen were at decreased risk of DLBCL while women with an intact uterus and on oestrogen plus progestin were not [5]. The California Teachers Study found that removal of both ovaries increased the risk of B-cell NHL possibly due to the absence of circulating hormones of ovarian origin, and when oestrogen only therapy was given to ovariectomized women, the treatment mediated the increased risk [7]. Hence, there appears to be some consistency between these findings [5, 7] and ours, but further investigation on treatment type is needed.

The mechanisms by which hormone therapy may act to reduce NHL risk among postmenopausal women are not known but may involve pro-inflammatory cytokines such as interleukins and tumour necrosis factor. As age increases, changes in immune function occur [3]. These alterations, which include increased production of pro-inflammatory cytokines, may be increased further in postmenopausal women

due to oestrogen deprivation, at least in the years soon after menopause [25]. Taking hormone therapy may normalize the immune response and decrease production of tumour necrosis factor and interleukin-6 [2, 3]. Such mechanisms may explain the lower NHL risk in postmenopausal women who take hormone therapy compared with those who are untreated, although the exact processes by which hormone therapy acts on the immune system and lymphomagenesis are unknown. We also found a reduced risk of DLBCL among hormone therapy users of normal weight, a finding that has not been reported before. Although adipose tissue is a major source of oestrogen in the postmenopausal period, being overweight may increase DLBCL risk [26, 27] and so other obesity-related alterations to immune function are likely to be involved.

Our studies, like others of similar design, have several limitations. First, the use of postmenopausal hormone therapy was self-reported, although evidence suggests that there is reasonable agreement with medical records [8, 28–31]. Secondly, the controls' hormone therapy use may not be typical of postmenopausal women in general. Data for comparison are lacking, but across case–control studies, it seems unlikely that there is systematic selection bias given that hormone therapy has also been associated with disease excess, most notably breast cancer [32]. Thirdly, we could not assess risks associated with the type of postmenopausal hormone therapy, route of administration and dose as most studies did not collect this information. Fourthly, our finding of a decreased risk with current use could be a consequence of cases stopping use as lymphoma ensues. However, 75% of cases who were using hormone therapy at 1 year before diagnosis were still using it at the time their lymphoma was diagnosed. Fifthly, some cases would have died soon after diagnosis or been too ill to be interviewed, while a minority of interviewed cases may have had another cancer before their NHL diagnosis. Whether these cases were more (or less) likely to have used hormone therapy than those who were interviewed or who did not have a previous cancer is uncertain. Sixthly, it is also not known whether cases were less likely than controls to have had menopausal symptoms or conditions such as osteoporosis which are treated with hormone therapy. Lastly, our findings may be a consequence of selection bias since our controls tended to be of higher socioeconomic status than cases. Women of higher socioeconomic status are more likely to take hormones to treat menopausal symptoms than those of lower, but nevertheless, our protective effect remained when risks were adjusted for socioeconomic status.

In this pooled analysis of individual data, we found protective associations between postmenopausal hormone therapy and NHL and its two most common subtypes, DLBCL and FL. Our findings suggest that current use may reduce NHL risk. An advantage of our data, as well as the large number of subjects, was the ability to study hormone therapy use up to the time of diagnosis. The implications of our findings are not the prevention of NHL by taking postmenopausal hormone therapy since its use can lead to the development of breast and endometrial cancers and cardiovascular disease. Rather, our study gives insight into the possible role of exogenous sex hormones on NHL aetiology.

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disclosure

The authors have declared no conflicts of interest.

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Examination of the follicular lymphoma international prognostic index (FLIPI) in the National LymphoCare study (NLCS): a prospective US patient cohort treated predominantly in community practices

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Background: Because follicular lymphoma (FL) patients have heterogeneous outcomes, the FL international prognostic index (FLIPI) was developed to risk-stratify patients and to predict survival. However, limited data exist

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Null Results in Brief

Cancer Epidemiology, Biomarkers & Prevention

A Pooled Analysis of Reproductive Factors, Exogenous Hormone Use, and Risk of Multiple Myeloma among Women in the International Multiple Myeloma Consortium

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Abstract

Background: Female sex hormones are known to have immunomodulatory effects. Therefore, reproductive factors and exogenous hormone use could influence the risk of multiple myeloma in women. However, the role of hormonal factors in multiple myeloma etiology remains unclear because previous investigations were underpowered to detect modest associations.

Methods: We conducted a pooled analysis of seven case–control studies included in the International Multiple Myeloma Consortium, with individual data on reproductive factors and exogenous hormone use from 1,072 female cases and 3,541 female controls. Study-specific odds ratios and corresponding 95% confidence intervals (CI) were estimated using logistic regression and pooled analyses were conducted using random effects meta-analyses.

Results: Multiple myeloma was not associated with reproductive factors, including ever parous [OR = 0.92; 95% confidence interval (CI), 0.68–1.25], or with hormonal contraception use (OR = 1.04; 95% CI, 0.80–1.36). Postmenopausal hormone therapy users had nonsignificantly reduced risks of multiple myeloma compared with never users, but this association differed across centers (OR = 0.65; 95% CI, 0.37–1.15, I^2 = 76.0%, $P_{heterogeneity}$ = 0.01).

Conclusions: These data do not support a role for reproductive factors or exogenous hormones in myelomagenesis.

Impact: Incidence rates of multiple myeloma are higher in men than in women, and sex hormones could influence this pattern. Associations with reproductive factors and exogenous hormone use were inconclusive despite our large sample size, suggesting that female sex hormones may not play a significant role in multiple myeloma etiology. *Cancer Epidemiol Biomarkers Prev; 25(1); 217–21. ©2015 AACR.*

Introduction

Multiple myeloma is a malignancy characterized by the accumulation of clonal plasma cells in the bone marrow, abnormal secretion of monoclonal protein, and end organ damage (1). Incidence rates are higher in men than in women (2). Because female sex hormones have immunomodulatory effects, reproductive factors, and exogenous hormone use may affect risk for

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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Table 1. Associations between reproductive factors and exogenous hormone use and multiple myeloma risk

	Co	Ca	Pooled OR (95% CI)*	*I2*	$P_{heterogeneity}$
Reproductive factors					
Age at menarche[a]					
Total	1,335	482			No. centers = 4
≤11	256	86	Ref		
12–13	717	271	1.20 (0.89–1.63)	0.0%	0.58
≥14	362	125	1.03 (0.73–1.45)	0.0%	0.57
Ever pregnant[c]					
Total	2,321	691			No. centers = 6
No	228	69	Ref		
Yes	2,093	622	0.90 (0.57–1.44)	48.2%	0.09
No of pregnancies[b]					
Total	1,494	593			No. centers = 5
None	142	64	Ref		
1	145	52	0.80 (0.39–1.64)	55.2%	0.06
2	329	134	0.83 (0.57–1.20)	0.0%	0.78
3	296	118	0.90 (0.50–1.60)	51.8%	0.08
≥4	582	225	0.91 (0.54–1.54)	50.3%	0.09
Ever parous[d]					
Total	3,075	1,007			No. centers = 7
Never	408	150	Ref		
Ever	2,667	857	0.92 (0.68–1.25)	41.8%	0.11
No of children[d]					
Total	3,075	1,007			No. centers = 7
None	408	150	Ref		
1	410	138	0.95 (0.66–1.38)	30.9%	0.19
2	802	274	0.96 (0.75–1.24)	0.0%	0.46
3	635	190	0.91 (0.60–1.37)	53.1%	0.05
≥4	820	255	0.91 (0.64–1.30)	41.3%	0.12
Age at first birth[e]					
Total	1,941	449			No. centers = 4
Nulliparous	255	64	Ref		
<20	237	66	0.97 (0.50–1.89)	54.4%	0.09
20–<25	749	167	0.99 (0.58–1.70)	56.1%	0.08
25+	700	152	0.96 (0.59–1.57)	44.8%	0.14
Age at menopause[b]					
Total	1,265	524			No. centers = 5
≤45	414	184	Ref		
45–49	313	118	1.00 (0.74–1.35)	0.0%	0.46
≥50	538	222	1.12 (0.86–1.45)	0.0%	0.58
Cause of menopause[f]					
Total	800	397			No. centers = 4
Natural	433	197	Ref		
Surgical/therapeutic	367	200	1.11 (0.80–1.54)	36.7%	0.19
Exogenous hormone use					
Ever hormonal contraception[g]					
Total	2,450	590			No. centers = 5
Never used	1,805	426	Ref		
Ever used	645	164	1.04 (0.80–1.36)	0.0%	0.66
Age at first hormonal contraception[g]					
Total	2,434	587			No. centers = 5
Never used	1,805	426	Ref		
≤25	421	101	1.07 (0.76–1.49)	0.0%	0.80
>25	208	60	1.08 (0.76–1.54)	0.0%	0.42
Year at first hormonal contraception[g]					
Total	2,434	587			No. centers = 5
Never used	1,805	426	Ref		
<1975	353	119	1.19 (0.87–1.62)	0.0%	0.87
≥1975	276	42	1.18 (0.65–2.14)	19.6%	0.29
Time since last hormonal contraception[g]					
Total	2,421	588			No. centers = 5
Never used	1,891	428	Ref		
≤20	275	70	1.22 (0.84–1.76)	0.0%	0.50
>20	255	90	1.09 (0.75–1.58)	15.2%	0.32
Years of hormonal contraception[g]					
Total	2,415	582			No. centers = 5
Never used	1,805	426	Ref		
<5	217	69	1.30 (0.92–1.83)	0.0%	0.89
≥5	393	87	0.96 (0.57–1.63)	55.6%	0.06

(Continued on the following page)

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Table 1. Associations between reproductive factors and exogenous hormone use and multiple myeloma risk (Cont'd)

	Co	Ca	Pooled OR (95% CI)*	*I2*	$P_{heterogeneity}$
Ever postmenopausal hormonal therapy[a]					
Total	1,076	432			No. centers = 4
Never used	703	307	Ref		
Ever used	373	125	0.65 (0.37–1.15)	76.0%	0.01
Age first used postmenopausal hormonal therapy[a]					
Total	1,057	425			No. centers = 4
Never used	703	307	Ref		
<50	197	72	0.60 (0.31–1.17)	71.5%	0.01
≥50	157	46	0.61 (0.41–0.90)	4.5%	0.37
Year first used postmenopausal hormonal therapy[a]					
Total	1,057	425			No. centers = 4
Never used	703	307	Ref		
<1980	143	54	0.58 (0.33–1.04)	38.9%	0.18
≥1980	211	64	0.81 (0.37–1.77)	75.3%	0.01
Time since last postmenopausal hormonal therapy consumption[a]					
Total	1,055	424			No. centers = 4
Never used	703	307	Ref		
Current	150	41	0.84 (0.30–2.38)	77.1%	<0.01
≤10	116	46	0.90 (0.37–2.16)	76.5%	0.01
>10	86	30	0.52 (0.21–1.26)	57.9%	0.07
Years of hormonal therapy use[a]					
Total	1,056	423			No. centers = 4
Never used	703	307	Ref		
<5	136	54	0.64 (0.30–1.37)	71.4%	0.01
≥5	217	62	0.56 (0.33–0.97)	57.6%	0.07

Abbreviations: Co, controls; Ca, cases.

*Adjusted for center, age (four categories), and race (white, black, and others).

[a]Studies with data on periods starting, ever postmenopausal hormonal therapy use, number of years postmenopausal hormonal therapy was used, years since last postmenopausal hormonal therapy consumption, and age at first post-menopausal HT use were LAMMCC, RPCI, NCI-Yale, and iMAGE. Analyses on postmenopausal hormonal therapy variables were performed among postmenopausal women.

[b]Analyses on periods stopping were performed among postmenopausal women. Analyses on number of pregnancies were performed among women aged 45 or older at reference date. Studies with data on periods stopping and number of pregnancies were LAMMCC, RPCI, NCI-Yale, iMAGE, and Utah.

[c]Among women ages 45 or older at reference date. Studies with data on ever being pregnant were LAMMCC, RPCI, NCI-Yale, iMAGE, Utah, and Epilymph.

[d]Among women ages 45 or older at reference date. All studies collected data on parity and number of children.

[e]Among women ages 45 or older at reference date. Studies with data on age at first child were RPCI, Epilymph, NCI-Yale, and iMAGE.

[f]Among postmenopausal women. Studies with data on cause of menopause were LAMMCC, RPCI, Utah, and iMAGE.

[g]Studies with data on hormonal contraception use, number of years hormonal contraception was used, years since last hormonal contraception consumption, and age at first hormonal contraception use were LAMMCC, RPCI, Epilymph, NCI-Yale, and iMAGE.

multiple myeloma. However, the role of hormonal factors in multiple myeloma etiology remains unclear. A few studies addressed possible associations between multiple myeloma risk and reproductive factors, such as parity (3–6) or use of postmenopausal hormone therapy (HT; refs. 6–8), but yielded inconsistent results as most studies were underpowered. We conducted a pooled analysis of case–control studies included in the International Multiple Myeloma Consortium (IMMC) to clarify the role of hormonal factors in the etiology of multiple myeloma.

Materials and Methods

We pooled individual-level questionnaire data from the seven IMMC case–control studies that collected information on reproductive factors among women (1,072 cases and 3,541 controls). These studies were: Los Angeles County Multiple Myeloma Case-Control Study (LAMMCC), Roswell Park Cancer Institute (RPCI), Utah, Epilymph, Fred Hutchinson Cancer Research Center (FHCRC) 1980s, National Cancer Institute (NCI)-Yale, and Molecular and Genetic Epidemiology Study (iMAGE). Enrollment period, age eligibility, study design, sample sizes, and participation rates within each study are summarized in Supplementary Table S1. Parity was defined as number of live births in NCI-Yale, iMAGE, and RCPI, and as number of children in all other studies.

Within each study, we computed ORs with corresponding 95% confidence intervals (CI) using unconditional logistic regression, adjusting for age group (four categories), race (except for Epilymph, which did not collect these data), and study center (for multicentric studies: Epilymph and FHCRC 1980s). Random-effects models were used to calculate pooled estimates using the DerSimonian and Laird method. Heterogeneity between studies was assessed using the I^2 statistic and $P_{heterogeneity}$ using the Mantel–Haenszel method. Analyses on parity and gravidity were restricted to women ages 45 or older, as they are likely to have completed their reproductive history. Analyses on hormonal therapy were restricted to postmenopausal women, defined as women who reported cessation of their menstrual periods. Wald tests were utilized to assess heterogeneity between strata.

Results

In this pooled analysis, we did not observe any statistically significant association between multiple myeloma and age at menarche or at menopause, ever pregnant, number of pregnancies, ever parous, number of children, age at first birth, or cause of menopause (Table 1). The association between multiple myeloma and ever use of hormonal contraceptives was not significant [OR = 1.04; 95% confidence interval (CI), 0.80–1.36; Table 1]. Similarly, we saw no significant associations or consistent patterns

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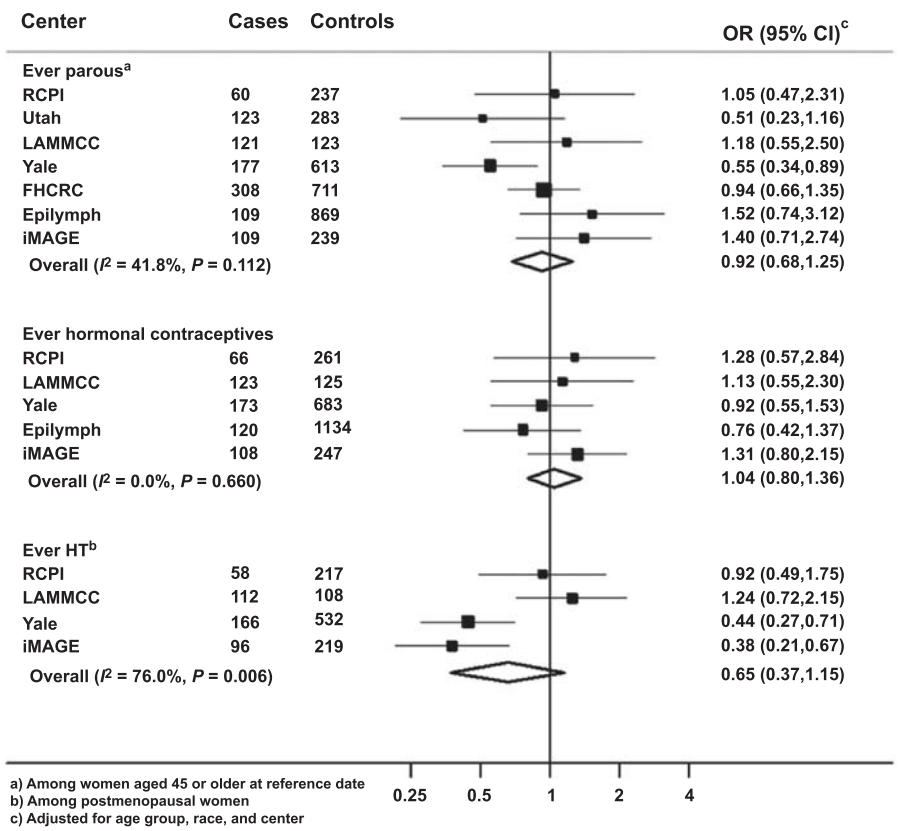

Figure 1.
Study-specific risks of multiple myeloma for ever versus never parous, hormonal contraceptives, and postmenopausal hormone therapy.

for age and year at first use, duration, or time since last hormonal contraceptive use.

Hormonal therapy use showed nonsignificant decreased risks of multiple myeloma (OR = 0.65; 95% CI, 0.37–1.15), but also showed significant heterogeneity between centers (I^2 = 76.0%; P = 0.01, Fig. 1). Further adjustment for BMI, education, tobacco, and alcohol yielded a similar risk estimate (OR = 0.70; 95% CI, 0.39–1.25). Inverse associations were observed among women taking hormonal therapy at ages 50 or older, or for more than 5 years, compared with never use (OR = 0.61; 95% CI, 0.41–0.90; and OR = 0.56; 95% CI, 0.33–0.97, respectively), although heterogeneity between centers hampered interpretation (Supplementary Fig. S1). Stratified analyses by cause of menopause, education, and BMI did not reveal statistically significant heterogeneity (data not shown).

Discussion

This large pooled analysis of 1,072 female cases and 3,541 controls yielded null associations between multiple myeloma and reproductive factors. To our knowledge, 3 case–control studies (3–5, 8) and 3 cohorts (4, 6, 7) have previously evaluated associations between reproductive factors, or exogenous hormone use and risk of multiple myeloma. Inconsistent results were observed for parity and multiple myeloma, with both significant inverse associations (5), increased risks (4), and null results (3, 6). Previously reported associations for hormonal

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contraceptives and multiple myeloma have been null (5, 6). Significant inverse associations for hormonal therapy use were observed in an Italian case–control study (8), but these associations were not corroborated in two cohort studies (6, 7). However, conclusions in these studies have been limited by small sample sizes of women using hormonal therapy.

Our study was based on a large dataset with individual-level information on reproductive factors and exogenous hormone use, yet we did not observe consistent patterns with these factors and multiple myeloma risk. We had the ability to control for a variety of potential confounders, including education, BMI, and alcohol use. Ignoring these variables may have biased previous studies of hormonal therapy and cancer, due to the potential for selection bias and a healthy user effect. We did not observe clear evidence of confounding by those variables in the present analysis, although residual confounding cannot be discarded in explaining some of our results, in particular for hormonal therapy. Also, use of controls that may not be representative of the population from which the cases arose was an inherent limitation of some of the participating studies' design. In summary, our data do not support a significant role for reproductive factors or exogenous hormones in myelomagenesis.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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ARTICLE 5

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Reproductive factors and non-Hodgkin lymphoma: A systematic review

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Contents

Abstract

Considerable efforts have been made to elucidate non-Hodgkin lymphoma's (NHL) etiology during the last decades. Some evidence points to an association with reproductive factors, as incidence rates for most NHL subtypes are usually higher in men than in women, and several

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subtypes express hormonal receptors. Although the evidence is not compelling, some studies show an inverse association with gravidity. Associations with postmenopausal hormone therapy are usually derived from unopposed estrogen use, rather than for the combination of estrogen with progestin, but these findings vary by study design. Inconsistencies in the results are likely due to the complex relationship between reproductive, biological, and sociodemographic factors, as well as to study limitations. Elucidating the role of hormonal factors should provide clues for therapeutic options and public health decisions. We provide an overview of the available evidence on reproductive factors in NHL etiology, underscoring potential sources of discrepancies and bias.

Keywords: Hormonal; Reproductive; Non-Hodgkin; Lymphoma; Etiology

1. Introduction

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of hematologic malignancies, the incidence of which has seen a rise in some western countries since the 1970s, although it seems to have reached a plateau during the last decade. Incidence rates of NHL are particularly high in western societies [1,2], and higher in men than in women for most NHL subtypes [3]. Considerable efforts have been made to elucidate the etiology of NHL. Recognized risk factors are: primary immunodeficiency disorders, HIV-infection, organ transplantation, infectious agents such as HCV and HTLV-1, autoimmune diseases such as Sjögren's syndrome and systemic lupus erythematosus, and family history of blood malignancies [4,5]. The role of other risk factors, including lifestyle and environmental factors, remains controversial. Studies tend to show that while some risk factors are common to most NHL subtypes, others are subtype-specific [6]. Therefore, continued efforts to disentangle the etiology of each entity are necessary and supported by consortia initiatives.

Emerging evidence also suggests that the effect of risk factors may differ due to sex-specific variations in the immune response [7,8]. Reproductive hormones interact with the immune system in numerous ways [9,10], and women produce a more vigorous cellular and humoral response than men [11]. Because of the complexity of the steroid metabolism, estrogens could modulate NHL risk in either direction. Some of the interactions between the immune and the endocrine systems are driven by hormone receptors. Human lymphocytes, as well as some lymphoma subtypes' cells, can express estrogen receptors (ER)α and β [12–14]. Activation of these receptors leads to opposite effects and their relative proportion determines the final effect of estrogens. Studies show that lymphoid neoplasms are likely to express and upregulate ERβ, contrary to ERα [14,15]. Furthermore, ERβ agonists strongly inhibited lymphoma and leukemia growth in mice, suggesting that these compounds may be useful in the treatment of lymphoid diseases expressing ERβ [15,16]. Therefore, despite the intrinsic complexity of interactions between the endocrine and immune systems, hormonal influences in NHL etiology seem biologically plausible.

Our aim is to provide a comprehensive review of the literature on NHL risk and reproductive factors. We evaluate here gravidity, parity, postmenopausal hormone therapy and oral contraceptives, and others less commonly assessed such as breastfeeding and abortions, with a special focus on possible sources of discrepancies in the results between studies and on potential biases.

2. Studies evaluating reproductive factors and NHL risk

We searched the PubMed database for observational studies published up to July 2013 in peer-reviewed journals reporting the association between reproductive factors and NHL incidence. We used terms related to reproductive factors ("hormonal", "reproductive", "parity", "childbearing", "breastfeeding", "menstrual", "menopause", "hormone therapy" and "contraceptives") combined with "lymphoma", "non-Hodgkin" and "cancer" terms. We included articles reporting estimates for the association between any NHL subtype (excluding multiple myeloma) and any of the following factors: parity, gravidity, breastfeeding, age at menarche, age at menopause, use of hormonal contraceptives and use of postmenopausal hormone therapy (HT). Articles were selected by screening the titles (first step), abstracts (second step), and the entire publication (third step). No publication date restrictions were imposed. Reference lists from all included studies were manually reviewed to identify potential studies not captured by our search strategy. All the reports that were finally included were in the English language. We excluded one study among women with endometriosis [17], two studies analysing lymphoma mortality rather than incidence [18,19], and one study on primary central nervous system lymphoma [20]. Finally, we excluded a cohort study where all members were HT users with no comparison group [21]. In this review we refer to reproductive characteristics affecting women at risk of NHL (usually during adulthood), and not to maternal reproductive characteristics as determinants of cancer in the offspring.

2.1. Characteristics of the studies included

We included 28 citations reporting associations for reproductive factors and NHL risk, excluding multiple myeloma

Table 1
Characteristics of studies included in the review.

Study location – study name	Related publications	Design	Sample size	Coding system; classification method	Main findings		
					Parity/gravidity	Hormonal contraception	HT
Cohort studies							
Norway	Kvale et al. (1994)	Cohort of women attending a breast cancer screening, 20 years of follow-up	427 cases; 61,774 cohort	ICD7; codes 200, 201, 205	Null associations	NA	NA
Iowa (US) – Iowa Women's Health Study	Cerhan et al. (2002a); Cerhan et al. (2002b); Cerhan et al. (1997)	Cohort of women with a driver license, 13 years of follow-up (7 years for hormonal contraceptives)	261 cases; 37,934 cohort	ICD-O-2/3; WK (modified)	Decreased risks (only significant when restricted to breastfeeding)	Null associations	Increased risks, specially FL
Denmark	Frisch et al. (1997); Frisch et al. (2006)	Population cohort based on a national register, ~20.5 years of follow-up	1573 cases; 2,024,770 cohort	ICD7; codes 200, 202	Null associations	NA	NA
North Jutland County (Denmark)	Norgaard et al. (2006)	Population cohort based on a national register, ~10 years of follow-up	350 cases; 149,132 cohort	NS; NS	NA	NA	Null associations
US – NIH-AARP Diet and Health Study	Morton et al. (2009)	Cohort of AARP members, ~5.4 years of follow-up	417 cases; 134,074 cohort	ICD-O-2/3; WHO	Null associations	Null associations overall, non-significant decreasing estimates for duration and DLBCL	Null associations overall, inverse association between ET and DLBCL
California (US) – California Teachers Study	Prescott et al. (2009); Lu et al. (2011)	Cohort of women recruited through the California State Teachers Retirement System, 11 years of follow-up	574 cases; 121,004 cohort	ICD-O-2/3; WHO	Decreased risks for gravidity and parity	Decreased risks for age at first use <25	Null associations overall, inverse association for ET among women with bilateral oophorectomy
US – Cancer Prevention Study-II Nutrition Cohort	Teras et al. (2012)	Cohort of friends, neighbors or relatives of volunteers for the American Cancer Society, ~10 years of follow-up	505 cases[a]; 67,980 cohort	ICD-O-2/3; WHO	NA	NA	Increased risks with ET use
Case–control studies							
Alberta, Manitoba and Saskatchewan (Canada)	Miller et al. (1980)	Population-based	519 cases; 11,127 controls	ICD8; codes 200–209	Null associations	NA	NA

Table 1 (*Continued*)

Study location – study name	Related publications	Design	Sample size	Coding system; classification method	Main findings		
					Parity/gravidity	Hormonal contraception	HT
Sweden	Olsson et al. (1990)	Hospital-based	79 cases; 458 controls	NS; NS	Null associations overall (late age 1st pregnancy + low parity = risk factor)	NA	NA
Los Angeles (US)	Bernstein et al. (1992)	Population-based	337 cases; 337 controls	NS; NS	NA	NA	Increased risk, significant for a longer use
Italy	La Vecchia et al. (1993)	Hospital-based	80 cases; 5619 controls	NS; NS	Null associations	NA	NA
Sweden	Adami et al. (1997)	Nested case–control, using a national register	1744 cases; 8719 controls	ICD7; codes 200, 202	Null associations	NA	NA
Northern Italy	Tavani et al. (1997); Fernandez et al. (2003); Altieri et al. (2004)[c]	Hospital-based	180 cases; 448 controls	NS; NS	Null associations	NA	Decreased risk
Los Angeles (US)	Nelson et al. (2001)[c]	Population-based	177 cases; 177 controls	NS; WK (modified)	Null associations	Decreased risks, especially before 1970	Decreased risk (non-significant)
The Netherlands	Beiderbeck et al. (2003)	Population-based, using a database with discharge and drug-dispensing records	118 cases; 469 controls	ICD9; codes 200, 202	NA	Decreased risk (non-significant)	Decreased risk (non-significant)
Connecticut (US)	Zhang et al. (2004)a[c] Zhang et al. (2004b)	Population-based	601 cases; 717 controls	ICD-O-2/3; WF	Decreased risks for gravidity and parity	Null associations	Decreased risk, significant for a longer use
California (US)	Lee et al. (2008)[c]	Population-based	581 cases; 836 controls	NS; WF	Decreased risks for gravidity (and parity only for DLBCL)	Decreased risks, especially at start <21 years old	Decreased risk, significant for a longer use, and ≤1.5 years since last use (specially DLBCL)
United Kingdom	Mildon et al. (2010)[c]	Population-based	389 cases; 394 controls	ICD-O-2/3; NS	Null associations	NA	Decreased risk, significant for FL with longer use
Europe – Epilymph	Costas et al. (2012)[c]	Population (Germany and Italy) and Hospital-based (Spain, France, Ireland and Czech Republic)	795 cases[a]; 1141 controls	ICD-O-2/3; WHO	Decreased risks for parity	Increased risks, especially for shorter use, during 1970s, and start at age >25	NA

Table 1 (*Continued*)

Study location – study name	Related publications	Design	Sample size	Coding system; classification method	Main findings		
					Parity/gravidity	Hormonal contraception	HT
North America, Europe and Asia – InterLymph	Kane et al. (2012a); Kane et al. (2012b)	Pooled analyses of case–control studies in an international consortium (InterLymph)	4263 cases; 5971 controls[b]	ICD-O-2/3; WHO	Null associations overall, decreased risks of FL for gravidity	Null associations overall, increased risk of FL, specially start after age 21, shorter use, and stop >20 years before diagnosis	Decreased risks, especially among current users and women starting use at 50 years or older

HT, postmenopausal hormone therapy; ET, estrogen therapy (unopposed); WF, working formulation; FL: follicular lymphoma; DLBCL: diffuse large B-cell lymphoma; NS, not specified; NA: not assessed.

[a] Excluding multiple myeloma.

[b] Analyses for HT use were based on 2094 cases and 2731 controls.

[c] Included in the InterLymph pooled analyses.

(Table 1). These reports are from 7 cohort studies, 12 case–control studies, and a pooled analysis from the International Lymphoma Epidemiology Consortium (InterLymph), which already include 6 of the 12 case–control studies critically assessed individually. Overall, studies included participants with age at recruitment that ranged from 15 to 96 years old, and diagnosis years from 1961 to 2007. Some studies were based on the ICD (International Classification of Diseases)-7 or 8 [22–26], or were published before 1994 [27–29] (thus suggesting they used ICD-7/8). The ICD versions-7/8 are the former coding systems used before the Revised European American Lymphoma Classification (REAL; 1994) and the World Health Organization classification (2001, updated in 2008), which both use the new ICD for Oncology (ICD-O)-2/3 systems [30,31]. Other studies were based on the (ICD-O)-2/3 systems [32–38], while the rest of studies did not specify the coding system used [39,40] or specified only that they used the Working Formulation [41,42], which is an obsolete classification method published in 1982 [43].

2.1.1. Cohort studies

We retrieved data from 7 cohort studies carried out the US [32–35], Denmark [23,40] and Norway [22]. Participation rates ranged from 9.6% (American Association of Retired Persons-AARP-cohort [33]) to 74.2% (Norwegian cohort [22]) (see Supplemental material). Participants were selected among women attending a breast cancer screening in Norway [22], women with a driver license in Iowa [32], teachers in California [34], neighbors or relatives of volunteers for the American Cancer Society [35], and members of the AARP [33], all of which may have a higher socioeconomic status than the general population. The other two cohort studies were based on population registries covering national or provincial territories [23,40]. In the latter studies [23,40], information on exposures was obtained from other demographic registers, prescription databases, or mailed questionnaires. The cohorts on which we report in this review were initiated between 1935 (Danish register [23]) and 1995 (AARP cohort [33] and California Teachers Study [34]), and follow-up length ranged from 5.4 (AARP cohort [33]) to 20.5 years (Danish register [23]). Reported losses to follow-up ranged from 7% [33] to 22% [22], including for reasons of emigration and death.

2.1.2. Case–control studies

12 case–control studies published results on reproductive factors and NHL risk. Cases were identified through national or regional cancer registries [24,25,29,36,41,42], cancer institutes, or hospital hematological departments [26–28,37–39]. Seven case–control studies [24,26,29,36,37,41,42] selected healthy controls from sources such as population registers or censuses, Medicare and Medicaid Service files, or by random digit dialing, while

3 others [27,28,39] recruited diseased controls from the same hospitals as cases. One study used a nested case–control design linking 2 nationwide registers: 5 age-matched controls were selected from the fertility register for each woman with NHL in the Cancer Register [25]. Another multi-centric study named EpiLymph used both population (2 centers) and hospital-based controls (4 centers) frequency matched to cases for sex and age [38]. The two control groups were pooled as a single group in the analysis. Eight studies reported the response rates among cases [24,27,36–39,41,42] and 7 studies among controls [27,29,36–39,41] which ranged from 45% to 98% in the former and from 47% to 96% in the latter.

In general, the description of selection processes in cohort studies at entry and at follow-up, and in case–control studies was insufficient to get a sense of the likelihood of selection bias. Some studies specified that participation referred to those subjects accepting to be interviewed among the eligible and approached [27,29,36–39,42] (see Supplemental material); however, few studies provided further details, such as specific eligibility criteria or specific reasons for non-participation [29,38,41,42].

2.1.3. InterLymph pooled case–control analysis

The InterLymph pooled analyses combined individual-data from 6 of the published case–control studies listed previously [36–39,41,42], plus 7 additional datasets in the form of case–control studies that had not previously published results on reproductive factors, but had on other type of exposures such as physical activity, pesticides or infections. The latter studies were carried out in the US [44–46], Canada [47], Italy [48] and Japan [49,50]. In these datasets, controls were selected using random digit dialing [44,45], Medicare and Medicaid Service files [44], Ministry registries [47], and convenience samples of patients not diagnosed with cancer from the same hospital as cases [46,48–50]. In total, 13 datasets were included in the individual-based pooled analyses (considering the multi-centric European Epilymph study as a single dataset). Response rates ranged from 45% to 99% in cases, and 44% to 99% in controls (see Kane et al. for more details [51,52]). Data were examined for menstrual factors (based on 8 studies/2 of them unpublished), parity (13 studies/7 unpublished), gravidity (7 studies/4 unpublished), hormonal contraception use (9 studies/4 unpublished), and HT (9 studies/4 unpublished). It is understood that in reporting results in the present review, there is an overlap in our observations between those taken from the 12 case–control studies as such and those taken from the InterLymph analysis, because InterLymph includes data from 6 of these 12 case–control studies.

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.critrevonc.2014.07.004.

3. Review of specific reproductive factors

3.1. Parity and gravidity

3.1.1. Definitions of exposures

Gravidity denotes the total number of pregnancies regardless of duration and outcome, and parity is defined as '(1) the state or fact of having borne offspring; (2) the number of times a female has given birth, counting multiple births as one, and usually including stillbirths' [53]. While the definition of gravidity includes spontaneous and voluntary abortions, parity does not. Moreover, a fetus of gestational age 20–24 weeks counts as a parous event in some countries while as an abortion in others. In the papers included in this review, a variety of definitions for parity were used: number of live-births [32,36], children [24,28,37,38,41], full-term pregnancies [22,23,34,42], or births [25,27,39], while in one study parity was not defined [33]. Two studies specified that stillbirths were not included in parity counts [23,24], and none mentioned multiple births. Adami et al. stated that for some periods of time the Swedish register took in consideration adopted and foster-children [25].

3.1.2. Main findings

The question of interest is whether a woman who experienced several pregnancies (gravidity) and/or births (parity) is at lower risk to develop NHL than a woman who never experienced pregnancy. We hypothesized that sex hormones such as estrogens could lower NHL risk, and thus partially explain why NHL incidence is higher in men than in women, as estrogen levels are higher in the latter, and dramatically increase during pregnancy.

Let us first consider gravidity results. The InterLymph pooled analysis reports that in 7 studies, out of the 13 that were analyzed, gravidity showed an association with lower follicular lymphoma (FL) risk. However, gravidity did not have a significant impact on NHL or the other subtypes [51]. The association with FL was in the form of an inverted J-shape: women with 1–2 pregnancies had higher risks than women with $\geq$4 pregnancies, but also than the nulligravid. Considering the cohort studies now; women participating in the California Teachers Study (CTS) had a significantly decreased NHL risk related to increasing pregnancies as well as increasing full-term pregnancies [34].

With respect to parity, results were mostly not significant in the CTS [34]. The Iowa cohort had non-significant inverted J-shape results [32], while 3 other cohorts had null results [22,23,33]. Similar null results for parity were observed in the InterLymph pooled analyses, and in 4 case–control studies not included in the InterLymph [24,25,27,28,51]. However, 3 of the 6 studies with previously published results on reproductive factors and included in the InterLymph had reported significant decreased NHL risks or inverted J-shaped associations for parity [36,38,41].

In summary, more studies reported protective associations when they evaluated gravidity as compared to parity.

For instance, Lee et al. assessed both factors and observed decreasing trends with increasing gravidity for all subtypes, while this was less clear for parity and only significant for DLBCL [41]. Gravidity captures the number of pregnancies including spontaneous and induced abortions, which are quite frequent (worldwide rates of ≈28 induced abortions per 1000 women aged 15–44 years [54], and spontaneous abortions range between 12 and 15% in Nordic countries [55]).

The definition of lymphoma needs to be taken into consideration when interpreting some of the results above. Most of the studies using ICD-7/8 showed null results, although the definition of NHL was heterogeneous between them and some even included non-NHL entities. Given that there is recognized etiologic heterogeneity between subtypes [6], a possible hormonal effect may be masked if different entities are mixed in the analyses. Consequently, using more homogeneous case groups and the increasing trend on reporting on NHL subtypes in recent studies, should contribute to uncover the role of hormonal factors in NHL etiology.

The evaluation of fatherhood histories can provide insights into the nature of these associations and they were investigated in two studies. A Danish cohort study unexpectedly observed a decreased NHL risk with increasing number of children among men, while in the same study, no association was found among women. On the contrary, case–control data pooled from 6 European countries did not show decreased risks with number of children for lymphoma among men, but did among women [38]. Further assessment of fatherhood histories may help uncover whether the protective associations are a consequence of sex hormones rather than lifestyle or sociodemographic characteristics that may be similar between men and women.

3.1.3. Confounders and risk modifiers

Some potential NHL risk factors, such as body mass index (BMI) and alcohol consumption, can influence hormone blood levels, and therefore could act as confounders in the association between reproductive factors and NHL risk [56].

3.1.3.1. Anthropometric factors and alcohol intake. A high BMI is related to higher estradiol and estrone blood levels, probably due to the aromatase activity of the adipose tissue [56]. A high BMI is also likely to increase NHL risk, especially among women [8,57]. One cohort study and the InterLymph pooled analysis examined BMI as a confounder in the relationship between parity and gravidity and NHL risk without noting meaningful changes in the estimates [34,51]. Alcohol intake is also a predictor of estrogens blood levels [56], and may reduce NHL risk [58]. The studies just mentioned [34,51] that had examined BMI, plus the Iowa cohort [32], also examined alcohol intake and reached similar conclusions as for BMI. Based on this evidence, BMI and alcohol intake do not seem to act as confounders in the association between NHL risk and the reproductive factors parity and gravidity. These conclusions were derived from the change-in-estimate method.

3.1.3.2. Hormone receptors and genetics. ERβ is expressed by some lymphoma subtypes and not others, and this expression may differ across populations, influenced by genetic structure. The different expression of receptors may result in a different role of hormones by lymphoma subtype or between populations. Inconsistent findings in reproductive risk factors for lymphoma might relate to the different hormone receptors in lymphoid cells, as shown in breast cancer (where parity is protective if ER are expressed, while it increases risk if receptors are undetectable) [59,60] Zhu et al. observed that polymorphisms in the in Th1/Th2 pathway modified the association between hormone therapy and NHL risk [61]. It is possible that these or other related polymorphisms could modify the relationship between NHL and other reproductive factors.

3.1.4. Selection bias

An attenuated association between parity and gravidity and NHL is likely in case–control studies if participation is higher among controls of high socio-economic status (SES) groups, and low SES is a marker for high gravidity or parity, as observed in several countries [62]. Selection bias can also affect cohort studies at entry if parity itself or SES influenced participation as well as did risk factors for NHL. All case–control studies with significant associations for parity/gravidity were adjusted for SES factors but also showed that controls achieved higher level of education than cases [36,38,41]. In addition, the only cohort adjusting for SES factors reported decreased NHL risks related to parity and gravidity [34]. In order to assess the potential for selection bias in published studies, it is essential to have adequate information on the selection processes. In the studies included in this review such information was incomplete (e.g., response rates were not clearly defined) (see Supplemental material). When reported, the response rates were generally high, but difficult to interpret. No study included in this review carried out a formal sensitivity analysis for selection bias. Such an analysis could be carried out using an unbiased SES distribution (i.e., representative of the source population) to adjust the observed odds ratios [63], or adjusting for SB using hypothesized values for selection probabilities, or other related methods. See Glaser et al. for an example of weighted estimates to correct for selection bias in a case–control study of Hodgkin lymphoma (a different entity from NHL) [64].

3.2. Hormonal contraception

Hormonal contraception has substantially changed over the years. One of the major changes is the dose of hormones contained in these compounds: in most countries, preparations used in the 1960s contained high estrogen levels, and subsequent generations of contraceptives had decreased levels of estrogens and progestins, being medium-dose

preparations between 1970 and 1980 and low-dose by 1980. Similarly, new routes of administration have emerged besides oral contraception (the classical pills), such as injectable contraceptives, implants, vaginal rings, and patches. However, the studies in this review refer mostly to oral contraception, as generally women who developed NHL were exposed when the new routes were not widely used yet. Information on formulations was generally not available, as most of the studies relied essentially on self-reported data. Moreover, use of contraception occurred longer ago with respect to NHL diagnosis than some of the other studied reproductive factors, and thus may be more prone to recall bias.

Three cohort studies examined the association between oral contraception and NHL risk. Estimates were close to 1 in the Iowa study cohort [65], and AARP cohort study [33] although estimates for DLBCL were decreasing across categories of duration in the latter. Lu et al. observed that women using oral contraceptives before the age of 25 had lower NHL risk compared to non-users in the California Teachers Study [66]. However, based on 9 case–control studies from the InterLymph pooled analyses, hormonal contraception was found to increase the risk of FL, but not that of NHL. FL risks were particularly increased when use started after the age of 21, lasted less than 5 years or stopped for more than 20 years before diagnosis [51]. Models were adjusted for age and ethnicity, and results were consistent in hospital and population based studies, where participation rates were ≥70%, or adjusted for SES, smoking status, alcohol consumption, BMI or other reproductive variables [51].

3.3. Postmenopausal hormone therapy

3.3.1. Main findings

Several case–control studies have reported decreased lymphoma risk related to HT. The InterLymph pooled analyses included 9 case–control studies in the assessment of HT use and NHL risk [52]. A decreased NHL risk in postmenopausal women who ever used HT was observed, in particular in current users and in women starting use at ≥50 years. Findings were consistent across studies and across BMI strata, and all estimates tended to be below 1, although no clear trend was observed according to duration of use. Two other case–control studies not included in the InterLymph pooled studies reported results on HT use and NHL risk. Beiderbeck et al. used pharmacy records in the Netherlands and found non-significant decreased estimates for HT use and NHL risk (OR = 0.5) [26]. On the contrary, a study from Los Angeles evidenced increased risks among long-term users (>12 months) compared to non-users [29]. The protective role of HT observed in most case–control studies has not been replicated in cohort studies. Three of 5 cohorts had overall null findings [33,40,66], while 2 observed an increased NHL risk associated with HT use, especially for FL [35,67].

Selection bias through SES could lead to a protective association for HT use in case–control studies, if participation was higher among controls of high SES (or among cases of lower SES). A higher SES was associated with a higher HT use in some populations, including UK and US [68,69], and this would result in a higher HT use observed in controls compared to cases. The resulting confounding can also affect cohort studies. Four of the 5 cohort studies evaluating HT use and NHL risk [33,35,66,67], and 7 of the 9 centers from the InterLymph case–control analyses of HT [52], explored confounding by SES factors, without meaningful changes in the estimates. SES factors are complex and heterogeneous between regions, but the role of SES seems unlikely to explain all discordances between studies. It is noteworthy that there are some cohorts that have not investigated the effects of reproductive factors on NHL risk. For example, the UK Million Women Study and the US Nurses' Health Study have reported on reproductive factors and other types of neoplasms, such as breast or colorectal cancer [70,71], but not on NHL, maybe due to lack of statistical power in cohort studies for this group of neoplasms.

3.3.2. HT formulations and causes of menopause

The effects of HT may differ by formulation or cause of menopause. From the 1980s, combined therapy (estrogen + progestin) was commonly prescribed to women with an intact uterus, while estrogen alone was the norm for women with surgical menopause [72,73]. Lu et al. showed in the California Teachers cohort that bilateral oophorectomy among non-users was associated with an approximately 3-fold higher risk of NHL compared to natural menopause. Among users with a bilateral oophorectomy, estrogen therapy was related to a decreased NHL risk compared to never users [66]. However, Cerhan et al. reported no association between estrogen therapy and NHL among women with bilateral oophorectomy in the Iowa cohort [32]. Using data from the NIH-AARP cohort, Morton et al. showed a 50% risk reduction of DLBCL with estrogen therapy when they restricted analyses to women with hysterectomy [33]. On the contrary, Teras et al. observed an increased risk of FL and DLBCL related to estrogen therapy but not with combined therapy [35], although analyses stratified by hysterectomy and/or oophorectomy status were not shown. As for case–control studies, 5 studies in the InterLymph collected data on hysterectomy status, but this factor did not modify the relationship between HT use and NHL risk [52]. Using breast cancer as the paradigm for hormonal cancer, we observe that concepts related to HT have evolved, and the current understanding is that both estrogen and progesterone are needed to develop breast cancer, while estrogen alone decreases its risk [74]. Interestingly, in the reviewed studies, all associations are derived from unopposed estrogen use, while estrogen + progestin do not seem to play a significant role. Unfortunately, information on HT formulations in observational studies of NHL is still scarce. Because the formulation used and the oophorectomy/hysterectomy status are correlated, and both factors may affect NHL risk, additional work is needed to disentangle the role of each exposure.

3.3.3. Time of consumption

All cohort studies evaluated the duration of HT use (or number of prescriptions) [33,35,40,66,67], and 2 assessed the time since the last consumption [40,66], observing in general no associations with NHL risk. In the InterLymph analyses of case–control studies, Kane et al. observed decreased NHL risks among women who started HT after the age of 50. Unfortunately, none of the cohort studies assessed the age of participants at the first or last consumption to confirm this result. The decreased lymphoma risks observed in case–control studies (in particular among current HT users) could be the result of cases stopping HT use when lymphoma symptoms start. The definitions of "current use" are typically different for cohort and case–control studies, although sometimes the same words are used indistinctively. Cohort studies usually collect information on HT several years before diagnosis, and exposure is determined from study entry period or earlier. Information is available on prevalent users (current + former users), but not on incident users, unless updates of the exposures during follow-up are regularly performed. On the contrary, information on the use during the preceding years before NHL diagnosis is typically available in case–control studies.

It remains unclear if prevalent users should be excluded in prospective studies, as the inclusion of prevalent users produced bias in previous studies of cardiovascular diseases and HT use [75]. Among studies in this review, the CPS-II Nutrition Cohort updated information on HT every 2 years and follow-up response rate was 91% [35]. Risks were increased among prevalent users over 15 years of follow-up, but the risk among incident users was not assessed.

3.4. Other hormonal factors

Other hormonal factors may be relevant in NHL etiology. We briefly describe here previous findings on breastfeeding, menarche, age at the first birth and abortions. We do not provide a review of other hormonal factors as they have been too rarely assessed and based on relatively small counts for exposed NHL.

3.4.1. Breastfeeding

Cerhan et al. observed a significantly decreasing trend between NHL and number of breastfed children in the Iowa cohort. However, in the study by Prescott et al., this association was not supported, although estimates were non-significantly decreased for FL subtype [34]. If the NHL protection previously observed for gravidity is actually related to breastfeeding, it might be mediated by hormones released during lactation (mainly oxytocin and prolactin), or by a decline of maternal persistent organic pollutants, which are transferred from mother to child via breastfeeding [76]. These environmental contaminants include pesticides and PCBs, both likely to increase NHL risk [77,78]. Yet, evidence to determine the role of breastfeeding as an NHL risk factor, is scarce to date.

3.4.2. Menarche and age at the first birth

In the AARP cohort and the California Teachers cohort, women with a delayed menarche had a non-significantly lower NHL risk than women who had their first menstruation at an early age [33,34]. Neither the pooled analyses of case–control studies nor the Iowa cohort supported these findings [32,51]. Similarly, age at the first birth does not seem to strongly influence NHL risk. Frisch et al. observed that age at first childbirth was inversely associated with NHL incidence, but this finding has not been corroborated by the other cohort or case–control studies [23].

3.4.3. Abortions

Frisch et al. analyzed a subcohort of 1.2 million Danish women aged 15–44 years old. Three hundred NHL cases were included, of which 67 had had induced abortions, 24 spontaneous abortions, 8 delayed miscarriages, and 1 stillbirth; no associations with any of these factors were observed [23,79]. Likewise, Cerhan et al. observed no significant associations when they evaluated 63 NHL cases with history of miscarriages, and 5 with induced abortions in a cohort of 37,934 Iowa women [32].

4. Summary of results

Fig. 1 is a forest plot summarizing results for those articles that used the ICD-O-2/3 coding system. This selected group captures recent articles with probably more accurate definitions of NHL, while all of them have information on histologic subtypes. Results are comparable to those results described above in each section, except for parity/gravidity results where studies that used other coding systems generally reported null associations.

With respect to parity and gravidity, significantly decreased NHL risks were observed for increasing number of pregnancies and full-term pregnancies in the California Teachers Study [34], while no significant associations were found for parity in the AARP cohort or in the Iowa cohort study [32,33]. Decreased NHL risks were observed for parity in two case–control studies: the Epilymph study in Europe and the Connecticut study [36,38], but not in the UK study [37]. Zhang et al. also reported decreased NHL risks with gravidity in the Connecticut study [36]. The InterLymph pooled analyses, which included these three case–control studies, evidenced inverted J-shape associations for FL and gravidity but not with parity or for overall NHL [51].

As for use of hormonal contraceptives, estimates for NHL were close to 1 in the California Teachers Study [66], and the AARP cohort study [33]. Similarly, no associations were observed with ever use of hormonal contraceptives in the Connecticut [36] and the Epilymph case–control studies [38], although increased estimates for a short-term use (<5 years)

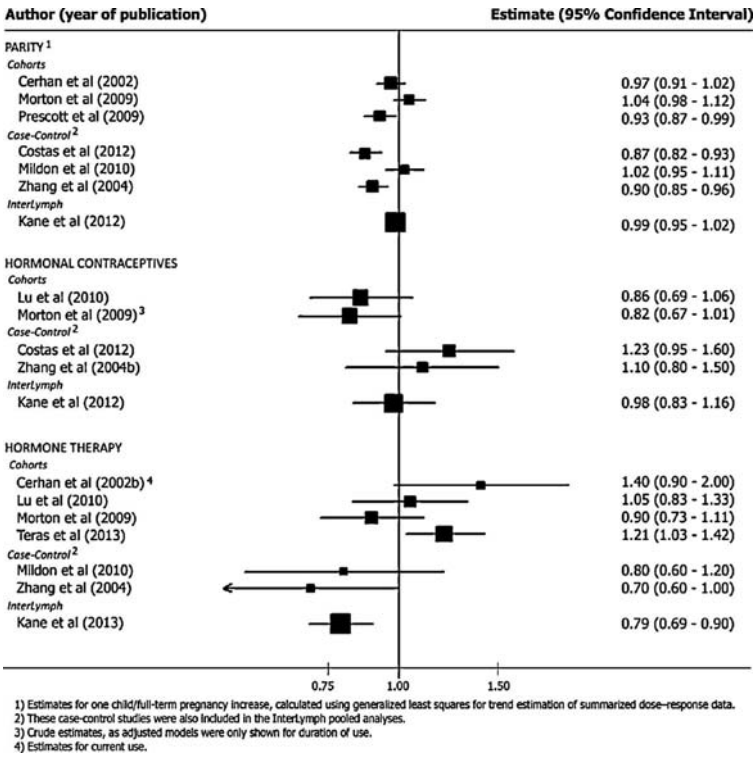

Fig. 1. Forest plot of associations between NHL and reproductive factors for articles using the ICD-O-2/3 coding systems

were observed for NHL compared with never use in the latter. These results were in concordance with the InterLymph analyses in regard to FL risk, but results for hormonal contraceptives and NHL were mostly null [51].

Concerning HT use, results varied by study design: while estimates for HT use and NHL were in general below 1 in case–control studies, cohort studies showed overall null results with some exceptions by histological subtypes, formulation, and among women with surgical menopause. Teras et al. observed increased risks of FL and DLBCL related to estrogen therapy (the most common therapy prescribed to women with surgical menopause) in the CPS-II cohort [35]. Cerhan et al. reported increased risks of FL in the Iowa cohort [67]. On the contrary, decreased risks were observed for estrogen therapy and DLBCL among women with surgical menopause in the NIH-AARP cohort [33], and for NHL in the California Teachers cohort [66].

5. Conclusions

Several facts suggest that NHL could have a hormonal influence, as this cancer is more common in men than in women, and several NHL subtypes express hormonal receptors. Previous studies suggested decreased risks related to certain hormonal exposures such as gravidity and HT, but overall the evidence for reproductive factors is not compelling. We summarize the potential sources of discrepancies on the association between NHL risk and hormonal exposures in Fig. 2. With respect to endogenous exposures, a higher proportion of studies reported protective associations when they evaluated gravidity compared to parity, usually showing a J-shaped pattern. As for HT, it probably depends on the formulation, oophorectomy status and age of consumption, which have been rarely assessed. When these data were available, associations were derived from unopposed estrogen use, rather than estrogen + progestin, although still with inconsistencies. Based on the available data, the evidence for a relationship between reproductive factors and NHL seems at best moderate. Given the complexity of reproductive factors and the neoplasms under study, hormonal-related associations need to be very robust in order to be consistently detected across studies. Weak associations will probably be masked by the NHL heterogeneity, as its subtypes may have different etiology, as well as different expression of hormone receptors. Also, results on reproductive factors have a particular potential for selection bias that, along with the unclear definitions of exposures, may contribute to the inconsistency of the existing evidence. However, the special emphasis that is being made on studying subtype-specific associations

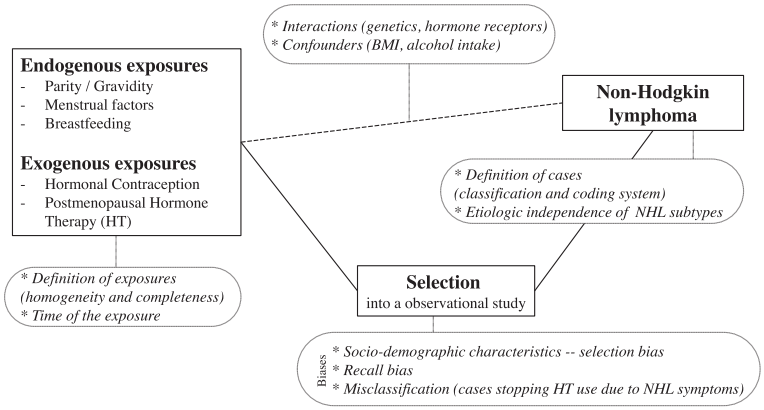

Fig. 2. Potential sources of discrepancies on the association between NHL risk and hormonal exposures (dashed line). In solid line, a potential link between exposures and selection affecting the observed associations in the selected sample. BMI, body mass index; HT, postmenopausal hormone therapy; NHL, non-Hodgkin lymphoma.

in recent and new studies will certainly contribute disentangling the potential hormonal role in lymphomagenesis. Elucidating the role of hormonal components in NHL will help understand its biology and provide some guidance for potential therapeutic options. Hormonal contraceptives and postmenopausal hormone therapy are consumed frequently in the general population, therefore clarifying their role in women's health will be valuable from a public health perspective.

Conflict of interest

None declared.

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Biography

Laura Costas obtained her M.D. in 2005 from the Autonomous University of Barcelona, Spain. In 2010, she completed her residency in Preventive Medicine and Public Health at the Hospital Clinic de Barcelona, with the End of the Medical Residency "Emili Letang" Award. During the last few years she had worked in her Ph.D. project examining the hormonal etiology of lymphoid neoplasms with Dr de Sanjosé, chief of the Unit of Infections and Cancer at the Catalan Institute of Oncology with a Rio Hortega grant from the Spanish Ministry of Economy and Competitiveness. As part of her Ph.D., she had spent one year at the Department of Epidemiology, Biostatistics and Occupational Health, at McGill University in Montreal (Canada) under the supervision of Dr Infante-Rivard. Currently, Dr Costas and Dr de Sanjosé are leading a pooling project to investigate the hormonal etiology of multiple myeloma in the International Multiple Myeloma Consortium.

ARTICLE 6

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Occupational exposure to endocrine disruptors and lymphoma risk in a multi-centric European study

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Background: Incidence rates of lymphoma are usually higher in men than in women, and oestrogens may protect against lymphoma.

Methods: We evaluated occupational exposure to endocrine disrupting chemicals (EDCs) among 2457 controls and 2178 incident lymphoma cases and subtypes from the European Epilymph study.

Results: Over 30 years of exposure to EDCs compared to no exposure was associated with a 24% increased risk of mature B-cell neoplasms (*P*-trend = 0.02). Associations were observed among men, but not women.

Conclusions: Prolonged occupational exposure to endocrine disruptors seems to be moderately associated with some lymphoma subtypes.

Incidence rates of lymphoid neoplasms are usually higher in men than in women for most subtypes, especially T-cell lymphomas, multiple myeloma (MM) and chronic lymphocytic leukaemia (CLL; Smith *et al*, 2010). Immune suppression, which is the most well-established risk factor for lymphoma, and other possible risk factors, cannot explain this gender pattern. Human lymphocytes, as well as cells from some lymphoma subtypes, including Hodgkin lymphoma, MM, and CLL, can express oestrogen receptors (ERs)

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α and β (Yakimchuk *et al*, 2013). During their lifetime, women have higher hormone levels, such as oestrogens, which have been suggested to protect against lymphoma (Glaser *et al*, 2003; Costas *et al*, 2014), possibly contributing to this pattern.

Numerous synthetic chemicals used with different purposes, such as pesticides, cosmetics, plastic additives, and flame retardants, are capable of interfering with the endocrine system (Diamanti-Kandarakis *et al*, 2009). Some polychlorinated biphenyls (PCBs), pesticides, and solvents have been associated with an increased risk of lymphoma (Alexander *et al*, 2007). However, the role of other endocrine disrupting chemicals (EDCs) with potential oestrogenic, anti-oestrogenic, or anti-androgenic effect in lymphoma aetiology is unknown. Our aim was to explore the role of occupational exposure to agents with potential endocrine disrupting activity in lymphoma risk using the Epilymph study.

MATERIALS AND METHODS

Study design and population. The Epilymph study is a multicenter case-control study carried out in six European countries (Spain, France, Germany, Italy, Ireland, and Czech Republic) from 1998 to 2004. In Germany and Italy, selection of controls was accomplished using population registers, while in the other participating countries, controls were identified in the same hospital as cases. Participants with a history of organ transplantation, cancer (other than lymphoma) or known seropositive status for HIV were not included in the analyses. Overall, we included 2457 controls and 2178 incident lymphoma cases. Cases were coded with ICD-O-3, and were classified according to the most recent World Health Organization (WHO) Classification (Swerdlow, 2008; Turner *et al*, 2010). Instead of 'B-cell non-Hodgkin lymphoma' as was customary, we refer to 'mature B-cell neoplasms' as in the WHO 2008 classification, this latter category includes MM and CLL in its definition. We mainly present results on mature B-cell neoplasm, as this is the largest lymphoma group. Secondary analyses stratified by subtype (including Hodgkin and T-cell neoplasms) can be found in the Supplementary Material. Additional details of the study design have been provided elsewhere (De Sanjosé *et al*, 2006).

Participants were interviewed face-to-face by trained interviewers using the same questionnaire in all countries. Participants listed all full-time jobs held for 1 year or longer. Industrial hygienists in each participating centre coded the occupations using the ISCO-68 coding system. Job codes were translated into the SOC 2000 coding system in order to apply a job-exposure matrix (JEM) for EDCs (Brouwers *et al*, 2009). Three experts assigned exposure probability scores for all chemical groups to each of the SOC job titles defined as 'unlikely', 'possible', and 'probable' based on their expertise and a previous bank of coded jobs (Van Tongeren *et al*, 2002). These scores refer to the probability that the occupational exposure level exceeded the background level (through diet, environment, or consumer products) in the general population (Brouwers *et al*, 2009). Supplementary Appendix 1 shows the occupational titles assigned to a possible or probable exposure to EDCs. Exposure assignment was blind to the case-control status and dichotomized into exposed (including exposures categorised as possible and probable) and unexposed. Forty-one participants did not report information on occupational exposures or the information was insufficient to classify exposure and they were excluded from these analyses. See Supplementary Appendix 2 for the most common occupations of controls and mature B-cell lymphoma according to their longest-held job. We evaluated exposure to several chemical groups with potential oestrogenic, anti-oestrogenic, or anti-androgenic effects including the following: polycyclic aromatic hydrocarbons, polychlorinated organic compounds (including PCBs), pesticides (organochlorines, carbamates, organophosphates, pyrethroids, and other pesticides), solvents (ethylene glycol ethers, styrene, toluene, xylene, trichloroethylene, and perchloroethylene), bisphenol-A, alkylphenolic compounds, brominated flame retardants, metals (arsenic, cadmium, copper, lead, and mercury), and a miscellaneous group (parabens, siloxans, and benzophenones).

Statistical analyses. Odds ratios (ORs) for lymphoma were computed as estimates of relative risk using unconditional logistic regression. All models were adjusted for age, sex, education, and country. Potential confounding effects of number of children, body mass index (BMI), ever smoking, regular intake of alcoholic beverages, and ever using hair dyes were examined, but none of them altered the estimates for mature B-cell neoplasms by more than 10%. Because occupational exposure to solvents has been previously associated with lymphoma, we analysed associations among the unexposed to solvents, and we included ever exposure to organic solvents as a covariate in the regression models evaluating specific groups of chemicals. Duration, age at first exposure, and time since last exposure were calculated based on the years at start and stop reported for each job. Data were missing for $<5\%$ of subjects for all variables, except for BMI, which reached 9% because its measure was introduced at a later stage in the study. We used generalised additive models to inspect the linearity of associations on duration of exposures. We used the MC-SIMEX method to correct estimates for measurement error of the exposure (Küchenhoff *et al*, 2006) fitting a quadratic regression to extrapolate the SIMEX OR estimate with no measurement error; a non-differential arbitrary sensitivity and specificity of 85% for binary exposures measured with the JEM were postulated as the misclassification probabilities.

RESULTS

Compared with controls, cases were less likely to report high BMI, and to have a lower parity (among women; Supplementary Table S1). Overall, we did not observe associations between lymphoma and ever workplace exposure to EDCs (Table 1 and Supplementary Table S2). Subjects occupationally exposed to any EDC at the time of interview (i.e., currently exposed) had a modestly elevated risk of mature B-cell lymphoma (OR = 1.29, 95% confidence interval (CI) = 1.04–1.60, Table 1). Age at first exposure did not affect lymphoma risk. Duration of exposure to EDCs (i.e., years of work in jobs with exposure to EDCs) showed an upward trend in risk for mature B-cell lymphoma (OR = 1.24, 95% CI = 1.01–1.51 for >30 years of exposure; P-trend = 0.02, Table 1). Estimates for associations on duration of the exposure among the unexposed to solvents were of the same magnitude, although CIs were wide. Among the unexposed to pesticides, increased risks seemed to occur mainly after an exposure period of 10–30 years (Figure 1 and Supplementary Table S3). Among currently exposed workers, associations were observed for those exposed for 10 years or longer (OR = 1.35, 95% CI = 1.08–1.70), but not those exposed for less than 10 years (OR = 0.97, 95% CI = 0.62–1.53; data not shown). Correcting for misclassification of exposure yielded an OR = 1.32 (95% CI = 1.04–1.68) for >10 years of exposure (Supplementary Table S4).

Table 2 shows associations between mature B-cell neoplasms and a 10 years increase in exposure to individual chemicals. Significant associations were observed for each component in the pesticide group, as well as for ethylene glycol ethers, alkylphenolic ethoxylates, and copper. However, independent effects were difficult to assess due to the correlation between exposures (Supplementary Table S5 and Supplementary Figure S1). Increasing risks by duration of exposure were mostly observed among

Table 1. Associations of occupational exposures to endocrine disruptors and risk of mature B-cell neoplasms

	Overall			Men			Women			
	Controls ($n=2457$)	Cases ($n=1720$)	OR (95% CI)	Controls ($n=1317$)	Cases ($n=962$)	OR (95% CI)	Controls ($n=1140$)	Cases ($n=758$)	OR (95% CI)	p-interaction
Ever held a job with exposure to any endocrine disruptor										
Unlikely[a]	901	588	Ref	358	247	Ref	543	341	Ref	
Possible (never probable)	591	438	1.11 (0.93,1.32)	386	286	1.16 (0.92,1.46)	205	152	1.03 (0.79,1.34)	*0.89*
Probable	838	633	1.07 (0.91,1.26)	551	415	1.10 (0.87,1.39)	287	218	1.04 (0.82,1.33)	
Never worked[b]	115	51	0.72 (0.50,1.03)	15	6	1.05 (0.39,2.82)	100	45	0.67 (0.45,1.00)	
Age at first exposure[c]										
<15	466	379	1.12 (0.92,1.36)	307	254	1.19 (0.91,1.55)	159	125	1.04 (0.77,1.40)	*0.96*
15–19	576	421	1.12 (0.94,1.34)	393	280	1.15 (0.91,1.46)	183	141	1.09 (0.83,1.43)	
20+	383	269	1.05 (0.87,1.28)	235	166	1.06 (0.81,1.38)	148	103	1.04 (0.78,1.39)	
P-trend[d]			0.50			0.51			0.78	
Time since last exposure[c]										
Current	338	237	1.29 (1.04,1.60)*	262	189	1.39 (1.06,1.83)*	76	48	1.12 (0.75,1.66)	*0.91*
<14	428	319	1.12 (0.92,1.36)	321	241	1.13 (0.88,1.45)	107	78	1.11 (0.79,1.55)	
15+	658	512	1.01 (0.86,1.20)	351	270	0.99 (0.78,1.27)	307	242	1.02 (0.80,1.31)	
P-trend[d]			0.01			0.01			0.50	
Total years of exposure to endocrine disruptors[c]										
<10	551	341	0.98 (0.82,1.18)	297	170	0.97 (0.75,1.26)	254	171	0.97 (0.76,1.25)	*0.38*
10–29	460	352	1.17 (0.97,1.41)	302	213	1.13 (0.87,1.46)	158	139	1.23 (0.93,1.64)	
30+	409	374	1.24 (1.01,1.51)*	332	317	1.32 (1.03,1.70)*	77	57	0.98 (0.67,1.45)	
P-trend			0.02			0.02			0.46	

Abbreviations: CI = confidence interval; OR = odds ratio. *$P<0.05$.
[a]Reference category for all comparisons. All models were adjusted for age, education, sex, and country.
[b]Participants who uniquely held occupations described as unemployment, retirement, student, family work (housewifes), or illness.
[c]Probable and possible exposures to endocrine disruptors are combined.
[d]Among exposed.

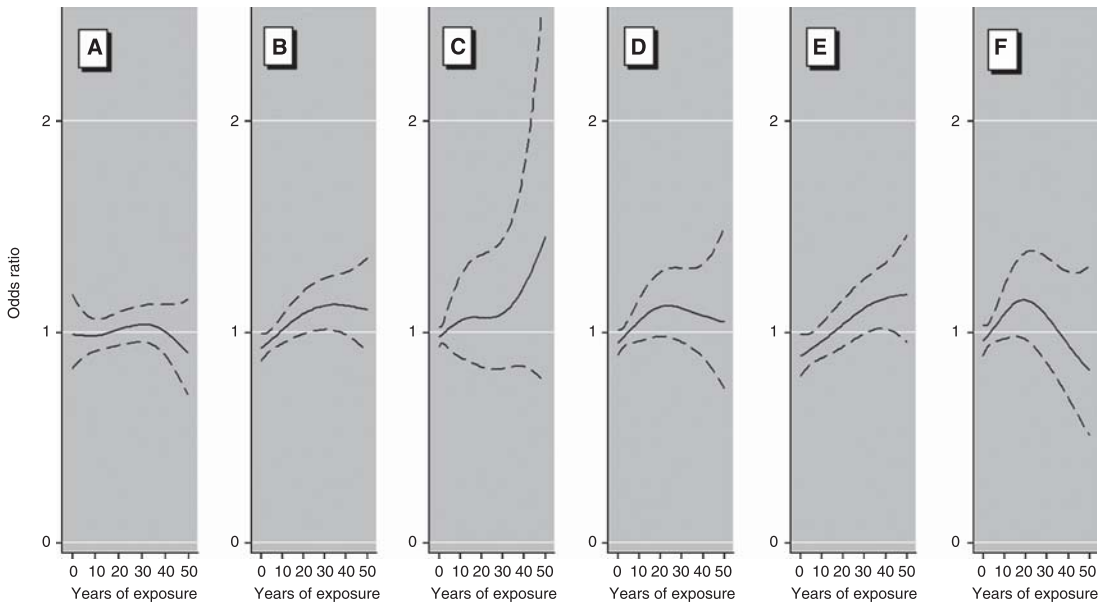

Figure 1. Smooth splines for the effect duration of occupational exposure to endocrine disruptors in generalised additive models with two cutpoints for mature B-cell lymphoma. Model adjusted for age, sex, country, and education level. Smooth estimates are represented in solid lines and 95% confidence intervals in dashed lines. Years of exposure >50 have been omitted from the graph (3.4% of exposed participants). (**A**) Jobs without exposure to EDCs. (**B**) Jobs with exposure to any EDC. (**C**) Jobs with exposure to any EDC, excluding those participants exposed to solvents. (**D**) Jobs with exposure to any EDC, excluding those participants exposed to pesticides. (**E**) Jobs with exposure to any EDC, among males. (**F**) Jobs with exposure to any EDC, among females.

men, while associations were null among women; however, no significant interaction was detected between sex and exposure to EDCs (Tables 1 and 2). Analyses by lymphoma subtype showed associations with EDCs mainly among MM and CLL (Supplementary Tables S6 and S7). Mature T-cell neoplasms and Hodgkin lymphoma also showed associations with certain EDCs,

Table 2. Duration of exposures to endocrine disruptors and risk of mature B-cell neoplasms. Estimates for 10 years increase of occupational exposure to endocrine disruptors

	Overall			Men			Women			
Total years of exposure to	Controls	Cases	OR[a] (95% CI)	Controls	Cases	OR[a] (95% CI)	Controls	Cases	OR[a] (95% CI)	p-interaction
Unexposed[a]	901	588	Ref	358	247	Ref	543	341	Ref	
Pesticides										
Organochlorines	442	347	1.10 (1.00,1.20)*	275	227	1.13 (1.02,1.26)*	167	120	1.00 (0.85,1.17)	*0.13*
Carbamates/pyrethroids	507	391	1.11 (1.02,1.21)*	337	268	1.15 (1.04,1.27)**	170	123	0.99 (0.84,1.16)	*0.11*
Organophosphates	467	366	1.10 (1.01,1.20)*	297	245	1.14 (1.03,1.26)*	170	121	1.00 (0.85,1.17)	*0.11*
Organic Solvents										
Ethylene glycol ethers	943	719	1.06 (1.00,1.12)*	595	454	1.08 (1.01,1.16)*	348	265	1.01 (0.92,1.12)	*0.34*
Styrene	38	33	0.96 (0.67,1.39)	27	21	1.05 (0.65,1.70)	11	12	0.90 (0.49,1.62)	*0.74*
Toluene/xylene	735	565	1.05 (0.99,1.11)	504	389	1.08 (1.00,1.16)*	231	176	0.97 (0.87,1.09)	*0.18*
Trichloroethylene	320	222	1.00 (0.90,1.11)	262	181	1.01 (0.90,1.14)	58	41	0.97 (0.71,1.34)	*0.94*
Perchloroethylene	315	223	1.00 (0.90,1.12)	254	175	1.01 (0.89,1.14)	61	48	1.04 (0.76,1.43)	*0.73*
Alkylphenolic compounds										
Alkylphenolic ethoxylates	736	578	1.07 (1.00,1.15)*	393	298	1.11 (1.02,1.22)*	343	280	1.01 (0.90,1.13)	*0.40*
Alkylphenols	466	379	1.06 (0.98,1.16)	285	238	1.12 (1.01,1.24)*	181	141	0.94 (0.81,1.10)	*0.12*
Metals										
Cadmium	108	77	0.90 (0.69,1.19)	62	64	0.89 (0.66,1.20)	16	13	0.89 (0.35,2.25)	*0.67*
Arsenic	78	80	1.06 (0.87,1.30)	99	72	1.05 (0.85,1.29)	9	8	2.10 (0.61,7.20)	*0.27*
Copper	824	617	1.07 (1.00,1.14)*	583	433	1.10 (1.02,1.19)*	241	184	0.97 (0.84,1.11)	*0.14*
Lead	508	383	1.03 (0.95,1.12)	432	336	1.06 (0.97,1.16)	76	51	0.77 (0.55,1.08)	*0.09*
Mercury	14	6	1.27 (0.84,1.93)	6	5	1.25 (0.77,2.02)	4	1	1.15 (0.47,2.79)	*0.72*

Abbreviations: CI = confidence interval; OR = odds ratio. *$P<0.05$; **$P<0.01$.
[a]Reference category for all comparisons. All models were adjusted for age, education, sex, country and ever exposure to organic solvents (except for estimates on organic solvents).

such as alkylphenolic compounds (Supplementary Tables S2 and S7), while no significant associations were observed for FL or DLBCL.

DISCUSSION

In this large case-control study, we observed an increase in the risk for specific mature B-cell lymphoma subtypes with recent and prolonged occupational exposure to endocrine disruptors. Increased risks were observed among men, and associations were null among women, which could contribute to explaining the differences in lymphoma incidence between gender. Significant associations were observed for exposures to EDCs that lasted 30 years or more, while associations were null for exposures that lasted <10 years. Also, recent exposures were associated with an increased risk, while null risks were observed 15 years after the exposure. Associations with current exposures could reflect a better performance of the JEM for recent exposures. However, we would expect that the association with a recent + short exposure to EDCS would also be positive, whereas this association was null. This suggests that prolonged exposures may increase risk although this risk may decrease with increasing years after cessation of exposure. Reproductive hormones interact with lymphoid cells in several ways, and women produce a more vigorous cellular and humoral response than men (Bouman *et al*, 2005). Some lymphoma subtypes express ERs (Yakimchuk *et al*, 2013), and certain endocrine disruptors have been previously reported as lymphoma risk factors (Alexander *et al*, 2007). We observed associations with exposures to organic solvents, pesticides, certain metals, brominated flame retardants, and alkylphenolic compounds.

Among the EDCs included in the JEM that we applied, associations with lymphoma risk have been previously reported for PCBs, solvents, and pesticides, although with inconsistencies as some of the reports have been negative (Alexander *et al*, 2007). As only 11 subjects were classified as exposed to PCBs, our study was underpowered to explore the association with lymphoma risk. Our results partially overlap with a previous evaluation of occupational exposure to pesticides and solvents (including others than EDCs) and lymphoma risk, using the assessment of industrial hygienists (Cocco *et al*, 2010, 2013). They are significant and concordant with these former results, and other published papers (Alexander *et al*, 2007).

Other potential EDCs have rarely been assessed. The few human studies have been negative, inconsistent or too small to show an association with brominated flame retardants or with polycyclic aromatic hydrocarbons (Hardell *et al*, 1998; Cross *et al*, 2006; Yang *et al*, 2014). We observed significant associations with alkylphenolic compounds, which have been widely used in occupational settings as surfactant in cleaning agents, as well as in emulsion polymerisation, and textile and leather auxiliaries. Apart from oestrogenic and weak anti-androgenic activities (Kochukov *et al*, 2009; Luccio-Camelo and Prins, 2011), alkylphenols can interact with the immune system, increasing interleukin (IL)-4 and TNF-α, and suppressing IL-10, IFN-α and IFN-β (Hung *et al*, 2013). Alkylphenolic compounds have been detected in blood or urine in approximately half of the adult population (Gyllenhammar *et al*, 2012), but their role in human health, including their carcinogenicity, is largely unknown. Our results also showed increased risks with increasing duration of exposure to metals, in particular for CLL. Some studies have suggested that working in metal-related jobs might increase risk of lymphoma (Band *et al*, 2004; Mester *et al*, 2006; 't Mannetje *et al*, 2008). However, some of these occupations have concomitant exposure to solvents, and previous studies have not determined whether associations were driven by solvents.

Our associations were consistent with the reported ER interaction scores of the different chemicals evaluated. ER interaction scores are constructed to reflect both potency and efficacy of EDCs in regard to their potential to interfere with the ER signalling pathway (Rotroff *et al*, 2014). ER interaction scores were higher for bisphenol-A (for which our study was underpowered), and alkylphenolic compounds (ER interaction

score = 52 and 51, respectively), and some of the pesticides, such as organochlorines (ER interaction score = 37), while other chemicals had lower scores (Rotroff *et al*, 2014). However, our associations were moderate in magnitude, and other carcinogenic pathways may explain them. Apart from endocrine disruption, oxidative stress, DNA methylation, disruption of methyltransferases activity, and reduction of S-adenosyl-methionine, among others, have also been proposed for chemicals such as pesticides (Collotta *et al*, 2013). The main limitation of this study is the potential for misclassification of the exposure. However, in case of truly positive associations, this would result in the attenuation of estimates for binary and continuous exposures (Pearce *et al*, 2007), which would strengthen our conclusions, as supported by our sensitivity analyses with MC-SIMEX. Some of the reported associations may be due to chance because we have performed multiple comparisons. Also, independent effects were difficult to assess, as the exposures to different chemicals were correlated. Other routes of exposures, such as diet, might contribute to the EDCs intake, but we did not have dietary information. Strengths of our study include the large sample size that allowed us to analyse exposures using an updated classification of lymphoma subtypes. Also, we have evaluated a large number of chemicals not previously assessed as lymphoma risk factors, exploring new hypotheses on possible aetiological mechanism of lymphoma development.

In conclusion, this is, to our knowledge, the first comprehensive study assessing the occupational exposure to EDCs and lymphoma risk. We assessed exposure to chemicals with potential endocrine disrupting properties, using a large sample size and accurate information on histological subtypes. We observed associations with some lymphoma subtypes for recent and prolonged exposures to several EDCs. Studies using a more detailed exposure assessment are warranted.

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CONFLICT OF INTEREST

PB provided expert testimony and consulted with government and private organizations on lymphoma risk and exposure to potential endocrine disruptors, including solvents and PCB. The remaining authors declared no conflict of interest.

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ARTICLE 7

Martín-Bustamante MT, Oliete-Canela A, Diéguez M, Benavente Y, Casabonne D, Alguacil J, Kogevinas M, de Sanjosé S, **Costas L**. A job-exposure matrix for the assessment of alkylphenolic compounds. Occup Environ Med. 2016 Epub: Aug 18. pii: oemed-2016-103614

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ORIGINAL ARTICLE

Job-exposure matrix for the assessment of alkylphenolic compounds

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ABSTRACT

Objectives Our aim was to develop a job-exposure matrix (JEM) to assess occupational exposure to alkylphenolic compounds in epidemiological research, considering changes in their use over time, and including exposure probabilities in the assessments.

Methods We consulted multiple sources of information, and performed interviews with 9 key people from industry and academia. 3 hygienists coded frequency (minority or majority of workers involved) and intensity of exposure (including dispersive processes, with shaking, or aerosol generation, or otherwise) to alkylphenolic compounds for all the 390 International Standard Classification of Occupations (ISCO)-88 job titles by period of time. Intensity and frequency of exposure were combined in a single score as follows: unlikely=0, occasionally+low intensity=1, occasionally +high intensity=2, frequent+low intensity=2, and frequent+high intensity=3.

Results We identified 54 (13.8%) of the 390 ISCO-88 job titles with potential exposure to alkylphenolic compounds. In 6 of jobs deemed as exposed, exposure depended on the economic sector of the occupation. Nonylphenol ethoxylates were the compounds most commonly involved (30 job titles, 55.6% of the exposed). Variations in alkylphenolic compounds use varied greatly over time; while they are still used in the plastic and rubber industry, in domestic cleaning agents their use began to decline before 1995.

Conclusions We built a JEM to assess exposure to alkylphenolic compounds, taking into account changes in use over time, different types of alkylphenolic compounds and different scenarios of exposure, which can be a valuable tool for exposure assessment in epidemiological research on the health effects of these chemicals.

What this paper adds

- Alkylphenolic compounds are ubiquitous environmental pollutants with endocrine disrupting properties used in a wide range of industrial applications.
- Epidemiological studies are hampered by limitations on the available tests, which are not sensitive enough and too susceptible to contamination, and previous JEMs did not consider relevant changes in use over time.
- A new JEM was developed considering time windows of exposure and different types of alkylphenolic compounds.
- The present JEM could be a valuable tool for exposure assessment in epidemiological research on the health effects of these compounds.

INTRODUCTION

Alkylphenols are organic chemicals obtained through alkylation of phenols, produced generally for the manufacture of alkylphenolic ethoxylates. Alkylphenolic ethoxylates are composed of a polyethoxy chain and an alkyl radical connected to a phenolic ring, and they are mainly used as nonionic surfactants, as well as in a wide range of applications. There are numerous types of alkylphenolic compounds, and nonylphenol and octylphenol and their ethoxylates are the most common ones.[1] Butylphenol, decylphenol and dodecylphenol are other alkylphenols less frequently used in the industry. Uses of alkylphenolic compounds are summarised in table 1. Occupational exposure can take place during their production or with exposure to detergents, specialty paints, pesticides, cosmetics and hair dyes among others.

Owing to the toxicity and bioaccumulation of alkylphenolic compounds in marine organisms, the European Union (EU) limited the marketing of nonylphenol and nonylphenol ethoxylates in 2003.[2] Indeed, long-chain alkylphenolic ethoxylates can degrade to metabolites like short-chain alkylphenolic ethoxylates and alkylphenols, which can bioaccumulate in soils, plants and animals.[3] Alkylphenols are ubiquitous, and they have been detected in rivers and bottled water,[4–6] as well as in human fluids or tissues, such as urine,[7] blood,[8] placenta,[9] breast milk[10] and adipose tissue.[11] These compounds have the capacity to interact with the endocrine system, especially in aquatic organisms and among humans. Alkylphenols and short-chain alkylphenolic ethoxylates are considered endocrine disruptors in animals and humans, mainly because of their oestrogenic effects mediated by oestrogen receptors.[12–15] In 2012, the WHO expressed concern about the potential effects of exposure to endocrine disruptors, such as female reproductive disorders and hormonal cancers, and considered a research priority to improve the assessment of exposure to these chemicals.[16]

Given the great variations of use of alkylphenols over time in industry, the study of the potential

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Table 1 Types of alkylphenolic compounds and their industrial uses

Chemical	Uses
Nonylphenol	Production of nonylphenol ethoxylate, lubricant oils, others: antioxidants for plastic and rubber production
Octylphenol	Production of phenol formaldehyde resin, production of octylphenol ethoxylate
Nonylphenol ethoxylate	Mainly detergent, others: cosmetics, pesticides and resin additives
Octylphenol ethoxylate	Mainly detergent, others: cosmetics, pesticides and resin additives
Butylphenol	For chemical synthesis in general, polycarbonate resins and phenolic resins
Dodecylphenol	Intermediary in the preparation of lubricants for vehicles, and gas tank cleansers. Monomer for hair dyes and phenolic resins

effects of alkylphenolic compounds on chronic diseases requires development of retrospective exposure assessment tools. The half-lives of these compounds in blood are likely to be short,[17 18] and their detection most likely reflect recent exposures. Available tests measuring alkylphenolic compounds in sera or plasma are generally not sensitive enough and often too susceptible to contamination.[19]

Job-exposure matrices (JEM) are a widely used tool for retrospective exposure assessments in occupational studies, and they have the benefit of being more efficient than expert assessment.[20] Although JEM estimates may be affected by misclassification of exposure,[21] they perform better than self-reported occupational exposures in large population-based studies.[22] JEMs are based on job titles, which suffer less from differential recall bias than self-reported chemical exposures.

We aimed to develop a comprehensive JEM for estimating lifetime exposure to alkylphenolic compounds considering relevant changes in their use over time. The JEM could then be used as a tool for exposure assessment in epidemiological research on the health effects of these compounds regardless of the latency period of the disease under study.

METHODOLOGY

We originally developed this JEM to apply it to the MCC-Spain study,[23] which included more than 10 000 participants in Spain. Population controls and cases of breast, prostate, stomach, colon cancer and chronic lymphocytic leukaemia were enrolled and they were asked for their occupational histories, among others. Lifetime occupational history was assessed for all jobs held for at least 1 year, and in total 26 149 job registries were registered in this study. Occupational histories in this study spanned a period of time from 1931 to 2014. Each occupation was coded with the national codes of occupation Clasificación Nacional de Ocupaciones (CNO)-94, which is the Spanish adaptation of the International Standard Classification of Occupations (ISCO)-88.

To identify potential occupational uses of alkylphenolic compounds, different sources of information were consulted, including PubMed, official webpages from different governments, including safety and health at work agencies from local governments, doctoral dissertation databases, databases on importation and usage from the Spanish Tax Agency, newspaper libraries, web pages from international organisations (the WHO, Occupational Safety and Health Administration Europe). The main key words for search were alkylphenol, nonylphenol, octylphenol, butylphenol, dodecylphenol, surfactant, tensioactive, occupation, job-exposure matrix, endocrine disruptor, resin, formaldehyde and epoxy resin.

Three industrial hygienists independently coded exposure to alkylphenolic compounds in a first step for each of the CNO-94 occupational codes, as follows: (1) ever exposure, (2) never exposure and (3) insufficient information. In 29.8% of occasions, the three hygienists did not agree on the ever/never classification, or at least one of them considered that there was insufficient information to classify exposure. This first classification helps the hygienists in order to obtain further information to fill these knowledge gaps. For instance, there were disagreements or insufficient information in regard to specific uses in the livestock and pharmaceutical industry, the industrial processes in certain sectors—involving closed methods or not—changes in work practices over time, as well as specific questions about the dates that use changed due to potential industry voluntary restrictions. This specific information was searched on specialised libraries (Chemist Faculty of Barcelona University, Science library from Autonomous University of Barcelona, Polytechnic University of Catalonia—Terrassa Campus, Spanish National Institute for Safety and Health at Work, and Statistical Institute of Catalonia), newspaper libraries, doctoral dissertation databases, and databases on importation and usage from the Spanish Tax Agency.

Furthermore, nine key people from five industries in Spain using alkylphenolic compounds in sectors such as textile, detergent, paints, plastic additives and cosmetic industries, and from universities and other agencies were contacted and personally interviewed. They were asked for usage of alkylphenolic compounds over time in the specific areas where they had worked. All relevant information on the industrial uses of alkylphenolic compounds obtained in each interview and literature review was gathered and summarised and this reference material served as a tool for the expert assessment. An example to illustrate the flow of information and consequent decisions is the following case from the textile industry. The Spanish Ministry of Environment[24] published a document specifying that the use of alkylphenol ethoxylates was still common in the textile industry in 2004 (after the European regulation). This was further confirmed by the consulted key expert in this sector. This information, along with the decline in importation of alkylphenolic compounds over time observed using other sources, such as the Spanish Tax Agency, helped the hygienists assign a specific key time point in this sector. The interviews also helped understand specific changes in work practices over time. For example, closed-system methods were encouraged from 2000 onwards in the phenolic resins industry in order to decrease exposure to formaldehyde. Consequently, workers' exposure to alkylphenolic compounds also decreased in this specific industry and period of time.

A temporal axis was created taking into account the calendar years that alkylphenolic compounds were used for each of the occupations. The exposure probability scores were assigned by means of consensus discussions by the three hygienists. Two external hygienists, who previously reviewed all reference material from the literature review and interviews, were also invited to the discussion meetings to help the three main hygienists assign the scores. The intensity of exposure for each occupation and each period of time was coded as high or low, and the frequency as occasionally or frequent. Owing to the low volatility of alkylphenolic compounds, in general we considered that the intensity of exposure was 'low' if it involved a non-dispersive process, a generally closed production process, with

manipulation of alkylphenolic compounds in a solid status, at ambient temperature, or other matrices with difficult migrations. We considered that the intensity of exposure was 'high' in dispersive processes, with shaking or stirring, aerosols generation, at high temperatures, or in a liquid status. Frequency of exposure was coded as 'occasional' if only a minority of workers is usually involved in tasks with alkylphenolic compounds, in very specific tasks and a short time of exposure compared with the annual amount of work, and 'frequent' otherwise. We combined intensity and frequency of exposure in a single score as follows: unlikely=0, occasionally+low intensity=1, occasionally+high intensity=2, frequent+low intensity=2, and frequent+high intensity=3. We identified those job titles in which exposure depended on the economic sector. We used the Statistical Classification of Economic Activities in the European Community (NACE) to list these economic sectors.

We considered two routes of exposure (dermal and inhalation) with no distinction between them. The main types of alkylphenolic compounds used were identified (octylphenol, nonylphenol and nonylphenol ethoxylates) for some occupations, while others involved a mixture of alkylphenols or alkylphenolic ethoxylates. We grouped the job codes under the following scenarios of exposure: (a) manufacture and use of plastic and rubber products, (b) use of industrial tensioactives, (c) manufacture and use of paints and lubricants, (d) use of domestic tensioactives, (e) use of cosmetic and hair products, and personal hygiene products and (f) use of pesticides. The JEM was finally translated to ISCO-88, which is more commonly used in other countries than Spain.

RESULTS

Several key time points in alkylphenolic compounds use were identified in order to define time windows of exposure. These time points were related to the first estimated use of alkylphenolic compounds, the internationalisation of producing companies, the first concerns on their effects, the voluntary agreements on reduction or elimination of alkylphenolic compounds in domestic and industrial detergents, and the EU regulations on nonylphenol (table 2). However, use greatly varied over time by scenario; for example, decreases in alkylphenolic compounds use on domestic detergents occurred in 1995 voluntarily in Spain in industries after a European agreement,[25] while alkylphenolic compounds are still used in the production of plastics and rubber.

Out of 390 job titles, we identified 54 potentially exposed to alkylphenolic compounds (13.8%; see online supplementary table S1). In six of these exposed titles, exposure was dependent on the economic sector of the occupation. Those economic sectors with potential exposure to alkylphenolic compounds among these six job titles are specified in online supplementary table S2. These are related to manufacture of textiles, leather, paper, chemicals (including dyes and pigments, plastics, synthetic rubber, pesticides, paints, varnishes, printing ink and mastics, soap and detergents, cleaning and polishing preparations, and perfumes), and pharmaceutical preparations. For five job titles (1.3%), there was not enough information to assign a level of exposure, and they were treated as unknown exposure level.

Of the 54 job titles classified as exposed, 30 were classified as mainly exposed to nonylphenol ethoxylates (55.6% of the exposed), 12 as exposed to a mixture of alkylphenolic compounds (22.2%), 10 as exposed to alkylphenolic ethoxylates (18.5%), and 2 to octylphenol or octylphenol+nonylphenol (3.7%; table 3). Manufacture and use of paints and lubricants was the scenario with more job titles involved (20 job titles), followed by use of industrial tensioactives and use of pesticides (10 job titles each), manufacture and use of plastic and rubber products (6 job titles), and domestic tensioactives (5 job titles), while cosmetics was the scenario with less job titles involved (3 job titles).

The structure of the JEM is shown in table 4. Briefly, one axis contains all 390 ISCO-88 titles, and the other contains the exposure scores for all the time periods, the scenarios and compounds involved, as well as a column to identify those titles with exposure dependent on the economic sector. 'Fibre-preparing-, spinning- and winding-machine operators' is a job title classified under the industrial tensioactives scenario, and coded as frequent and high intensity of exposure from 1960 to 1998. From 1999, alkylphenolic compounds use in this specific occupation became less frequent and probable, and from 2008 it is coded as unlikely. The job title 'Rubber-products machine operators' from the plastic and rubber scenario is coded as unlikely before 1979, frequent and high intensity of exposure from 1979 to 2000, while the exposure is coded as probable or frequent from 2001 onwards. 'Computer equipment operators' is an example of a job title for which exposure to alkylphenolic compounds is classified as unlikely. In the job title 'Chemical engineering technicians', exposure is considered depending on the industry sector of economic activities involved (see online supplementary table S2 to see the sectors to be considered in the assignment of exposure for these selected job titles).

Table 2 Key chronological events identified in relation to the use of alkylphenolic compounds in Europe

Year	Observations
1944	First use of alkylphenolic compounds detected in the UK
1959	Spanish Plan of Stabilization, opening to international markets*
1970	First concerns on the effects of alkylphenolic compounds
1986	Voluntary agreements on reduction or elimination of alkylphenolic compounds in domestic detergents
1992	Voluntary agreements on reduction or elimination of alkylphenolic compounds in industrial detergents
2002	EU regulations on nonylphenol

*This key time point is specific of Spain.
EU, European Union.

DISCUSSION

We constructed a new JEM for estimating occupational exposure to alkylphenolic compounds in epidemiological studies. We considered changes in their use over time, included exposure probabilities in the assessments, and refined some of the scores of specific job titles by using an industrial–occupational coding, which altogether allow the assignment of more accurate exposure estimates. Alkylphenolic compounds are ubiquitous compounds commonly detected in food, drinking water,[4–6 8] as well as in human fluids or tissues.[7 8 10 11] Alkylphenols, such as nonylphenol, mainly derive from the environmental degradation of alkylphenolic ethoxylates. Alkylphenolic ethoxylates are used as detergents, cleaners, emulsifiers and a variety of other applications such as plastics and pesticides. They were regulated in 2003 in the EU due to their large toxicity on aquatic organisms due to endocrine disruption. The effects of these compounds on human health are mostly unknown. Literature on the subject is scarce and limitations exist due to difficulties in measuring

Table 3 Compounds and scenarios involved in the JEM

	Total			AP/APE*		APE		NPE		OP/NP†	
	Job titles	Per cent‡	Percentage of all titles	Job titles	Per cent‡	Job titles	Per cent‡	Job titles	Per cent‡	Job titles	Per cent‡
All ISCO-88 job titles	390	–	–	–		–		–		–	
Exposed to alkylphenolic compounds	54	100	13.8	12	22.2	10	18.5	30	55.6	2	3.7
By exposure scenario											
Manufacture and use of plastic and rubber products	6	11.1	1.5	4	7.4	0	0.0	0	0.0	2	3.7
Use of industrial tensioactives	10	18.5	2.6	1	1.9	0	0.0	9	16.7	0	0.0
Manufacture and use of paints and lubricants	20	37.0	5.1	7	13.0	10	18.5	3	5.6	0	0.0
Use of domestic tensioactives	5	9.3	1.3	0	0.0	0	0.0	5	9.3	0	0.0
Use of cosmetic and hair products, and personal hygiene products	3	5.6	0.8	0	0.0	0	0.0	3	5.6	0	0.0
Use of pesticides	10	18.5	2.6	0	0.0	0	0.0	10	18.5	0	0.0

*This category includes those job titles involving a mixture of alkylphenols and alkylphenolic ethoxylates.
†One job title was coded as exposed to OP, and another as exposed to both OP and NP.
‡Percentage of exposed job titles.
AP, alkylphenols; APE, alkylphenolic ethoxylates; ISCO-88, International Standard Classification of Occupations-88; JEM, job-exposure matrix; NPE, nonylphenol ethoxylates; OP/NP, octylphenol/nonylphenol.

alkylphenolic compounds in epidemiological studies. Occupational studies represent an opportunity to explore the role of these compounds.

Fifty-four (13.8%) job titles out of a total number of 390 listed in ISCO-88 were considered to be exposed to alkylphenolic compounds in the present JEM. Windows of exposure, which reflect changes in production and use over time, varied greatly depending on the considered scenario of exposure. For instance, alkylphenolic compounds are still used in the plastic and rubber industry, as well as in special paints, nowadays. In contrast, job titles under the domestic tensioactives scenario were coded as unlikely from 2004 onwards, due to voluntary restrictions in its use from the industry and the subsequent EU regulation on nonylphenol in 2003.[2] Nonylphenol ethoxylates were the compounds most often linked to an occupation in the JEM; however, only two occupations (both related to the plastic and rubber industry) scored as exposed to octylphenol or nonylphenol. This low number of titles may imply a low prevalence of exposure, and thus a power issue, when evaluating exposure to octylphenol/nonylphenol. Twelve other job titles involving alkylphenols actually involved a mixture of alkylphenols and alkylphenolic ethoxylates, and therefore we did not assign a more specific category of compound. These 12 occupations were in general related to the manufacture of alkylphenolic compounds and to the use of plastic and rubber products.

For simplicity, we grouped job titles by scenarios, which had similar windows of exposure. However, for more accuracy, the assignment was done independently for each of the job titles, therefore allowing for certain variations on the scores within the scenario. The inclusion of scenarios allows stratified analyses as sensitivity analyses to account for other chemicals that can occur concomitantly to alkylphenolic compounds. Scenarios may help interpret results in regard to the potential overlap with exposure to other agents. For example, when evaluating associations with alkylphenolic compounds in epidemiological studies using this JEM, positive associations observed in the scenario 'Use of pesticides' but not in the rest of the scenarios may imply that associations could be driven by pesticides but not by alkylphenolic compounds.

There is a scarcity of epidemiological studies evaluating the effect of these compounds in human health. To the best of our knowledge, alkylphenolic compounds have been linked to certain maternal exposures leading to health outcomes in their offspring,[26–29] congenital heart defects,[30 31] male infertility[32] and certain types of neoplasms[33–36] in epidemiological studies among humans. Studies have usually evaluated exposure to alkylphenols in urine samples[26–28 32 35–37] or through occupational studies using JEMs.[29–31 33 34] The evaluation of alkylphenolic compounds in epidemiological studies is hampered by limitations on the available laboratory tests to assess levels on blood serum or plasma samples, which are generally collected in epidemiological studies. Determination by gas chromatography coupled with mass spectrometric detection is the most commonly applied analytical technique to detect these compounds in biological samples. However, a step to increase volatility (termed derivatization) is usually needed to improve sensitivity, but this step increases the risk of contamination from the environmental background and it is time-consuming. Other techniques, such as hybrid solid phase extraction, are still being developed to test alkylphenol levels in difficult biological matrices and they might be future candidates to help reduce these drawbacks.[19] Biopsies of adipose tissue are more reliable matrices to evaluate alkylphenols due to the affinity of these compounds for the lipid fraction.[11] Measurements in adipose tissue could better reflect past exposures, although biopsies are less suitable for epidemiological studies due to the invasiveness of this procedure. However, their toxicokinetic behaviour among humans is not completely understood. Müller *et al*[17] assessed the kinetics of nonylphenol after oral and intravenous exposures among two healthy volunteers. The authors observed that the half-life of nonylphenol in blood was short (2–3 hours) after oral or intravenous application, in accordance with studies among rats,[38 39] and that only 11.5% of the oral dose was recovered in the urine and faeces during the study. This could mean that the remainder may be exhaled or taken up by the lipid compartment, but the literature is too scarce to draw conclusions on the toxicokinetics of nonylphenol as well as of other alkylphenolic compounds.[40]

We identified two previous matrices evaluating occupational exposure to alkylphenolic compounds. In a publication from the National Institute for Occupational Safety and Health (NIOSH)[41] in 1981–1983, the estimated numbers of employees

Table 4 Examples of entries in the job-exposure matrix

ISCO-88 code	Job title	Scenario	Exposure	Sector	Compounds	Scores by windows of exposure*								
						<1960	1960–1970	1971–1978	1979–1998	1999–2000	2001–2003	2004	2005–2007	2008–2009	>2009
8261	Fibre-preparing-, spinning- and winding-machine operators	Use of industrial tensioactives	Yes		NPE	0	3	3	3	2	2	2	1	0	0
8231	Rubber-products machine operators	Manufacture and use of plastic and rubber products	Yes		OP	0	0	0	3	3	2	2	2	2	2
5141	Hairdressers, barbers, beauticians and related workers	Use of cosmetic and hair products, and personal hygiene products	Yes		NPE	0	2	2	2	0	0	0	0	0	0
9133	Hand-launderers and pressers	Use of domestic tensioactives	Yes		NPE	0	3	3	3	2	2	2	0	0	0
3116	Chemical engineering technicians	Manufacture and use of paints and lubricants	Yes	Specific	APE	0	2	2	2	2	2	2	1	1	0
6111	Field crop and vegetable growers	Use of pesticides	Yes		NPE	0	0	3	3	3	3	1	1	1	0
7232	Computer equipment operators	–	No		–										

*0=unlikely; 1=occasionally+low intensity; 2=occasionally+high intensity or frequent+low intensity; 3=frequent+high intensity.
AP, alkylphenols; APE, alkylphenolic ethoxylates; ISCO-88, International Standard Classification of Occupations-88; NPE, nonylphenol ethoxylates; OP, octylphenol.

potentially exposed to different agents in their survey were provided by occupation. The JEM for endocrine disruptors by Van Tongeren *et al* and updated by Brouwers *et al*[21 42] provided the probability of exposure to alkylphenols and alkylphenolic ethoxylates in two categories, 'unlikely' versus 'possible' exposure, as none of the job titles scored as 'probable' exposure. Previous JEMs were aimed at assessing recent exposures, and therefore none of them considered changes in use over time, while this has dramatically fluctuated over the years due to the start of commercialisation, the concerns on their impact and consequent regulations.

The NIOSH study was based on the Classification by the Bureau of the Census 1980, and 148 job titles of the 503 (29.4%) were classified as having one or more employees potentially exposed to alkylphenolic compounds. This prevalence of use seem to be higher than that observed in our study, maybe due to the higher sensitivity rather than specificity of the NIOSH method, although comparisons with our JEM are difficult to assess because of the different methodologies used. In the JEM by Brouwers *et al*, which was based on the UK Standard Occupational Classification 2000 (SOC2000) coding system, 19 (5.4%) job titles out of a total of 353 were classified as exposed, while 13 job titles (3.7%) were classified as unknown. The lower prevalence of exposure in this JEM compared with our JEM is probably due to the fact that it assessed a short period of time (1996–2006) when use of alkylphenolic compounds was lower. For instance, some of the job titles involving cleaning activities were classified as unexposed by Brouwers *et al*,[21] but as exposed in the previous version of this JEM by Van Tongeren *et al*.[42] A specific difference with the JEM by Brouwers *et al*, which also contributes to our higher prevalence of use, is that we considered that exposure to alkylphenolic compounds was likely among job titles involving lubricants and cutting oils. We considered that exposure was likely in these occupations, such as 'Motor vehicle mechanics and fitters', because nonylphenol ethoxylates are used in metal degreasing and cutting oils may contain nonylphenol as an emulsifier.[43 44] We have applied the present JEM using data from 4098 controls participating in the MCC-Spain study, and observed that 25.1% of this population has been ever exposed to alkylphenolic compounds. This prevalence is higher than that observed in the list of 390 ISCO codes (13.8%), because some exposed job titles (for instance, cleaners) are over-represented in the general population, while some non-exposed titles (such as legislators) are less represented. As well, a same person can have several job titles over time, increasing the probability to be classified as ever exposed.

We included three key features that have been shown to improve the performance of a JEM in order to obtain more accurate exposure estimates, as demonstrated by Dosemeci *et al*.[45] First, we accounted for differences in exposures over time considering periods of predominant use; second, we included both intensity and frequency of exposures in the assessments (instead of a dichotomous exposure score—yes/no); and third, we refined some of the scores of specific job titles by considering the industry sectors of economic activities involved in specific occupations, allowing a better assessment of the exposure than the job title alone in these particular occupations. The main limitation in the construction of this JEM was the limited availability of data, which on occasions was scarce, especially for periods referring to a long time ago. Therefore, we were not able to assign approximate prevalences of exposed workers for each job title by scenario and by time period.

We originally developed this JEM to be applied to the Spanish population, and therefore we mainly considered

relevant changes in use over time in Spain. However, it can be applicable to other populations, especially from European countries, modifying specific key time points that may vary by country. In particular, the second key time point in our JEM (1959, Spanish Plan of Stabilization) should not be considered in other countries because these compounds were not available in Spain until the 1960s, when they started to be imported from other countries. Therefore, in other countries, exposure can be considered from the first identified use, typically in the 1940s (eg, 1944 in the UK[46]). Also, specific variations in alkylphenolic compounds use or limitations by country should be considered. For example, an European agreement was signed in 1992[25] to limit use of alkylphenolic ethoxylates in cleaning products, but the year of limitation may slightly vary in each specific country. In summary, we developed a JEM to assess retrospective exposure to alkylphenolic compounds considering relevant changes in their use over time that can be a valuable tool for exposure assessment in epidemiological research on the health effects of these endocrine disrupting chemicals.

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GENERAL DISCUSSION

In the next section, a global discussion of the main results generated by the project is presented. The discussion is organized in two major sections: 1) Reproductive factors and exogenous hormone use in lymphoid neoplasms etiology, and 2) Occupational exposure to endocrine disruptors in lymphoid neoplasms risk. A summary of potential limitations, strengths and future research directions is also given.

Reproductive factors and exogenous hormone use in lymphoid neoplasms etiology.

We have evaluated the role of reproductive factors and exogenous hormone use in lymphoid neoplasms etiology using the largest series of cases and controls from the multicentric European EpiLymph study and two international consortia: the InterLymph and the IMMC. Our conclusions for the role of reproductive factors and exogenous hormone use in lymphoma excluding myelomas are discussed in the article 5 ("*Reproductive factors and non-Hodgkin lymphoma: A systematic review*"). In this paper, we concluded that the evidence for a relationship between reproductive factors and lymphoma seems at best moderate.

Overall, we observed inconsistent associations for the role of reproductive factors in lymphoid neoplasms. While parity was protective against CLL/SLL, DLBCL, and T-cell lymphoma in the EpiLymph study, associations were null in the InterLymph consortium, except for follicular lymphoma. The IMMC also yielded null results for parity and MM. Considering all the published literature, we observed a higher proportion of studies reporting protective associations for NHL when they evaluated gravidity (i.e. number of pregnancies) compared to parity (i.e. number of children or full-term pregnancies), usually showing a J-shaped pattern. Overall, this suggests that the association between reproductive factors and lymphoma, if any, it is not strong enough to be consistently detected across studies, given the heterogeneity of definitions of reproductive factors, and the potential heterogeneity in etiology of lymphoma subtypes.

Similarly, associations with hormonal contraception were also heterogeneous by study and lymphoma subtype. We observed in the EpiLymph study increased risks of NHL with a short use (<5 years) of hormonal contraception, after the age of 25, stopped for >10 years before diagnosis, or before the 1980s. These associations were observed for CLL/SLL, DLBCL and follicular lymphoma. Similar associations were observed in the InterLymph pooled analyses (which included EpiLymph) for follicular lymphoma, but not for DLBCL. However, three individual case-control studies [69–71] (two of them included in the InterLymph analyses [70,71]) showed inverse associations with hormonal contraception and NHL or its subtypes. We observed null associations for MM and hormonal contraception in the IMMC. Cohort studies have found in general null or inverse associations with hormonal contraception and NHL or its subtypes. Overall, results on hormonal contraceptives are too heterogeneous between studies and subtypes, suggesting that they may not play a strong role in lymphomagenesis. In accordance to these conclusions, we have performed analyses on CLL/SLL using the MCC-Spain study (**Appendix 1**), a population-based case control study in Spain, among 790 female population controls and 223 female CLL/SLL cases, and we observed non-significant inverse associations for ever use of hormonal contraceptives.

Conclusions for the role of HT in lymphoma etiology differ by study design. In the InterLymph pooled analyses we observed inverse associations between NHL and HT use, especially when the age of start was 50 years or older and among current users. Similarly, we observed, decreased risks of MM with HT use, although results were heterogeneous by center. The protective role of HT has not been replicated in cohort studies, and some of them even observed increased risks. Furthermore, HT role could be very different depending on the formulation, and oophorectomy / hysterectomy status, which are correlated, but have been rarely assessed in NHL risk.

Results on HT have a particular potential for selection bias that previously affected conclusions for breast cancer and cardiovascular disease in observational studies. Several observational studies had shown that women who took HT had lower risk of cardiovascular disease. However, in 2002, the WHI showed in a clinical trial that HT users were actually at higher risk of cardiovascular disease [72].

The reasons for such discrepancy included the "healthy user bias": women who consumed HT had different characteristics than non-users, for example, they were thinner, and they exercised more, among others. In addition, a protective effect of HT was evident in studies that did not control for socioeconomic status, but not in studies that did, as a higher socioeconomic position is associated with both more frequent use of HT and lower risk of coronary heart disease.

We had the opportunity to adjust for several potential confounding factors, including socioeconomic status, in the EpiLymph, InterLymph, and IMMC analyses, although the potential for residual confounding cannot be discarded. Using population controls from the MCC-Spain study we have described characteristics of hormonal contraceptives and HT users and non-users [73] (**Appendix 2**). We observed that several variables were associated with hormonal contraceptives and HT use, including age, education, BMI, smoking, parity, cause of menopause, and occupational characteristics, such as shifts. Although we did not have data on occupational shifts in EpiLymph/InterLymph/IMMC, we evaluated the rest of potential confounders, suggesting that our results were not due to confounding. However, the associations on HT use and NHL from the InterLymph analyses could be the result of cases stopping these hormonal drugs when lymphoma symptoms start, as reduced risks were mostly observed among current users, but not former users.

Since the publication of our systematic review (article 5), which summarizes our conclusions for objective 1, three other articles have been published on the subject:

a) Our pooled analysis on reproductive factors and exogenous hormone use and MM in the IMMC, in which as stated above, we observed null results for reproductive factors and MM, and decreased associations for HT, although results were heterogeneous by center.

b) A prospective study examining an association between parity and risk of death from NHL among 1,292,462 Taiwanese primiparous women [74]. Nulliparous women were not included in this study. In this population, 412 NHL deaths were registered in a follow-up that comprised a period from the first childbirth to 21/12/2009. Results showed an association between increasing parity and decreased NHL mortality, as well as an association between older age at first birth and risk of death from NHL. Although these results support the hypothesis of hormonal factors protecting against lymphoma, studies based on mortality data have inherent limitations, as they may not reflect only etiological factors, but also prognostic factors.

c) Interestingly, Kato et al [75] published in 2016 the first study examining associations between HT and NHL incidence in a randomized clinical trial setting. This epidemiologic design has the benefit of eliminating the potential confounding from observational studies, as treatments are randomly assigned to women independently of their risk factors for NHL. The analyses were based on the WHI Health Initiative trials where conjugated equine estrogens plus medroxyprogesterone acetate or conjugated equine estrogens alone were tested against placebo 27,229 women were randomized to treatments, and 383 incident NHL cases were identified during the 13 years of follow-up. In this study, incidence of NHL was similar in the treatment and placebo groups, although there was an initial decrease in the

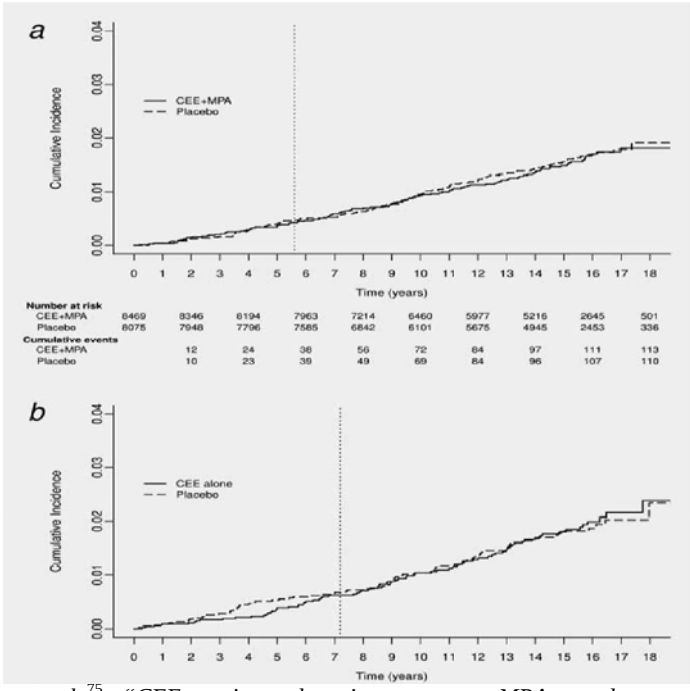
incidence of NHL in the conjugated equine estrogens alone treatment arm (**Figure 9**). By subtypes, a marginally decreased risk of MM (HR= 0.53, 95% CI 0.27–1.03) was observed in the conjugated equine estrogens alone group, suggesting that this subtype could be the most susceptible to hormonal exposures.

We previously hypothesized that MM could be one of the subtypes most susceptible to the hormonal action, as this is one of the subtypes with greater male:female sex incidence ratio, and previous studies have showed that myeloma cells can express hormonal receptors. Accordingly, a potential benefit of 2-methoxyestradiol and tamoxifen, two hormonal compounds, have been suggested in the treatment of MM [76,77].

Our pooled analyses of HT and MM in the IMMC revealed heterogeneous results by center: null associations were observed in 2 study centers (Yale and iMAGE), while inverse associations in 2 others (RCPI and LAMMCC). One of the reasons that could explain this discrepancy would be that in Yale and iMAGE centers, there was generally more prescription of combined therapy (which showed null associations in the WHI trial) than estrogen alone therapy. Unfortunately, we did not have this baseline information and thus we have difficulties in explaining whether these differences are not random findings. However, the cause of menopause (natural vs hysterectomy) is a proxy for HT composition: estrogen alone therapy is usually prescribed among women without uterus while women with an intact uterus are likely to be prescribed combined estrogen–progestogen therapy. We performed stratified analyses by cause of menopause without significant differences between strata, supporting random findings rather than composition-driven associations.

The observations from the WHI trial, which are less prone to bias due to the randomized design, suggest that MM could be a subtype susceptible to the hormonal action. Similarly, the associations observed between EDCs in the EpiLymph were more pronounced for MM than for the rest of the subtypes. However, our associations on HT and MM in the IMMC were marginal and heterogeneous between centers. Further evaluation in studies with detailed data on HT composition could shed light on this topic.

Figure 9: Kaplan-Meier curves for cumulative incidence of NHL by treatment assignment in the Women's Health Initiative



From Kato et al [75]: "CEE=conjugated equine estrogens. MPA= medroxyprogesterone acetate. 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)".

As stated above, we originally expected associations with hormonal factors and lymphoma etiology to be greater in those subtypes with a greater male:female incidence rate ratio, such as MM, CLL/SLL, and T-cell lymphoma. However, associations in the InterLymph analyses were mostly derived from follicular lymphoma, which has a male:female incidence rate ratio around 0.9 [13].

It is noteworthy that in the subsequent analyses of the "InterLymph Non-Hodgkin Lymphoma Subtypes Project", where all potential risk factors were systematically evaluated for each lymphoma subtype [17], neither use of oral contraceptives nor use of HT was linked with follicular lymphoma risk [16,78]. It is possible that different statistical methods (e.g. one vs two-stage, inclusion vs exclusion of postmenopausal women), as well as

a slightly different number of studies contribute to the different conclusions obtained using a relatively similar dataset.

Overall, the discrepancies between studies suggest that the effect of reproductive factors and exogenous hormone use in lymphoma etiology is most likely due to artefacts because of study variability and/or random associations.

Occupational exposure to endocrine disruptors in lymphoid neoplasms risk.

Exploring occupational lifetime exposure to EDCs can give hints on the potential role of environmental hormonal exposures in lymphoma etiology. We evaluated occupational exposure to EDCs in the EpiLymph European study using 2,457 controls and 2,178 lymphoma cases. We used a JEM that captures occupational exposure to EDCs when this contributes significantly to an individual's body burden in comparison to other sources of exposure such as diet, environment and consumer products. Diet is probably the most important source of EDCs for the general population. Other sources such as cosmetics and other consumer products also contribute to the burden of EDCs. The tool that we used is useful to explore potential associations between EDCs and health outcomes as it assesses the probability that the occupational exposure level exceeds the background level from other sources.

We could not identify an association between lymphoma and holding a job with exposure to EDCs, but we observed associations with the length of the exposure. Over 30 years of exposure to EDCs compared with never exposure was associated with a 24% increased odds ratio (OR) of mature B-cell neoplasms. A similar finding was seen for the subtype CLL/SLL. An unexpected finding was that, although sample size allowed detecting potential associations among women, associations were mostly observed among men. A different impact of EDCs by sex is biologically plausible given the well-known sex-specific variations in immune response. Women produce a more vigorous cellular and humoral response than men, and suffer more often from autoimmune diseases [56]. Ansell et al noticed different associations on NHL and autoimmune diseases in analyses stratified by sex in a case–control study in UK, and

suggested that future studies should analyze data for men and women separately, in order to gain further mechanistic insight into these complex diseases. We consequently performed stratified analyses by sex also observing a difference in risk, although the interaction was not statistically significant. If confirmed in other studies, the fact that we observed associations between NHL and exposure to EDCs restricted to men could contribute to the higher lymphoma incidence ratios observed among men than women.

To further explore whether these associations were driven by a particular compound we performed analyses by type of chemical. We identified associations with several lymphoma subtypes and duration of occupational exposure to pesticides, organic solvents, alkylphenolic compounds, and metals.

Some organic solvents have been reported to increase lymphoma risk, including benzene, toluene and xylene, although with inconsistencies [14,46,79,80]. We also observed increased mature B-cell lymphoma risks for toluene, xylene and ethylene glycol ethers, but we did not evaluate benzene, as this was not included in the JEM that we used. Occupational exposure to organic solvents is frequent as they have a wide range of applications, for example they are contained in fuels, glues and paints. We observed null associations for solvents such as styrene, trichloroethylene and perchloroethylene (tetrachloroethylene). In accordance with our results, the evidence from a systematic review does not support a causal relationship between styrene and lymphoma [81]. However, our null results on perchloroethylene are conflicting with suggestive evidence of its carcinogenicity observed in another systematic review reporting on bladder cancer, MM and NHL [82]. As well, while we observed null results with occupational exposure to trichloroethylene, a pooled analysis from the InterLymph observed increased risks for follicular lymphoma, but not NHL overall [83].

The interpretation of these results is hampered by the correlation of exposures frequently observed in these studies. It is very common that workers are exposed to many and not only to a specific chemical, and it is difficult to assess which one/s is/are driving the associations. Independent effects of the different compounds in the EpiLymph were difficult to assess due to the correlation between exposures. For example, the correlation coefficient for duration of

exposures between metals and organic solvents was 0.79 (Supplemental material – article 6).

Some studies [46–49], but not all [43–45] have suggested that working in metal related jobs, such as metal platers and sheet metal workers, might increase risk of NHL. However, some of these occupations have concomitant exposure to solvents, —for example those that involve metal degreasing. Our results showed increased mature B-cell neoplasms risks with increasing duration of exposure to metals, in particular for CLL/SLL also when we restricted the analyses among those unexposed to solvents. As we cannot rule out the possibility of residual confounding, further assessment possibly testing metals in biological samples might help to understand the nature of the observed associations. A study based on biomarkers published in 2013, after the initiation of this thesis, evaluated blood erythrocyte concentrations of cadmium and lead in a nested case-control study. It revealed sex-specific associations: increased risks of B-cell NHL were observed with high levels of cadmium only among females. In this study, associations with lead were null [84]. In this regard, we are collaborating in the evaluation of metals in nail samples from CLL/SLL cases and population controls that Dr Pérez-Gómez from the Institute of Health Carlos III is performing in the framework of the MCC-Spain study, and will be helpful to corroborate these associations, as well as to evaluate the potential sex-specific role of these compounds.

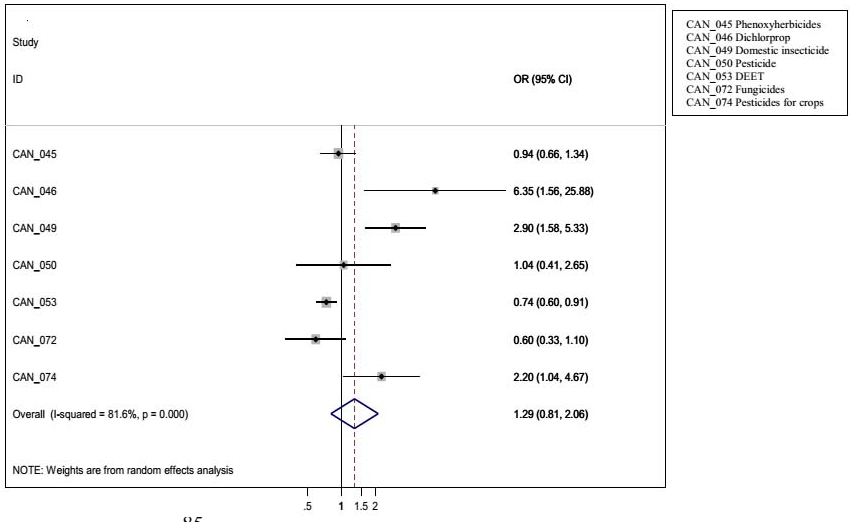
As only 11 subjects were classified as occupationally exposed to PCBs, our study was underpowered to explore the association with lymphoma risk. On the other hand, based on the current epidemiological and experimental evidence, the IARC has classified PCBs as Group 1 human carcinogens [24]. However, the evidence for their role in lymphomagenesis has been considered limited because of contradictory findings [24].

Pesticides have been previously linked to lymphoma, although with inconsistencies, as some reports have been negative [14]. A systematic review on pesticides and health effects was published by the European Food Safety Authority in 2013 [85]. The authors could not make firm conclusions for the majority of the studied outcomes, due to design limitations and the heterogeneity of data. An exemption

was childhood leukemia and Parkinson's disease, for which they found positive significant associations with pesticides.

Seven studies were summarized in this review in regard to Hodgkin lymphoma and pesticide exposure with heterogeneous results (**Figure 10**) [85].

Figure 10: **Random effects meta-analysis keeping the Agricultural Health Study analysis with the largest sample size.**



From Ntzani et al [85].

Concerning NHL and pesticides, the authors of the review by the European Food Safety Authority noted that a very wide variety of definitions of lymphomas was used in 44 studies. They only reported on results from seven of those studies, which examined associations with biomarkers of organochlorine pesticides: only 6 out of 35 analyses had significant positive results, without any firm evidence for associations [85].

A systematic review of occupational exposure to agricultural pesticides and NHL was published by Schinasi et al in 2014, after the initiation of this thesis. In this review, several pesticide types, including phenoxy herbicides, carbamate insecticides, organophosphorus insecticides and lindane, most of which have endocrine disrupting properties were positively associated with

NHL [86]. However, no clear conclusions could be made for lymphoma subtypes, as only few reported associations of pesticides with NHL subtypes.

Our study included several correlated chemicals that overall suggested an increased risk of lymphoma. However, different ways of action other than endocrine disruption may explain our results, such as oxidative stress, DNA methylation, disruption of ethyltransferases activity, and reduction of S-adenosyl-methionine, among others [87]. This thesis is based on questionnaire data, and we could not evaluate the way of action of the different chemicals. In order to explore whether the associations observed are due to the endocrine disruption pathway, an analysis of the total effective xenoestrogen burden (TEXB) among cases and controls could be useful. TEXB is a biomarker of estrogenic effect, firstly developed in adipose tissue [88] and human placenta samples [89], and currently being adapted to serum samples [90], although it requires a large amount of sample (4 mL). TEXB assesses the overall estrogenicity in 2 fractions: 1) the fraction largely attributable to environmental organohalogenated xenoestrogens (TEXB-α), and 2) the fraction mostly due to endogenous estrogens and more polar xenoestrogens, such as alkylphenols and bisphenols (TEXB-β). TEXB-α has been linked to breast cancer [91,92], however, no data exists in regard to lymphoid neoplasms and TEXB to date, which could help understanding the role of these compounds in lymphoma etiology.

Since the publication of our article on EDCs and lymphoma, we have detected 2 related articles:

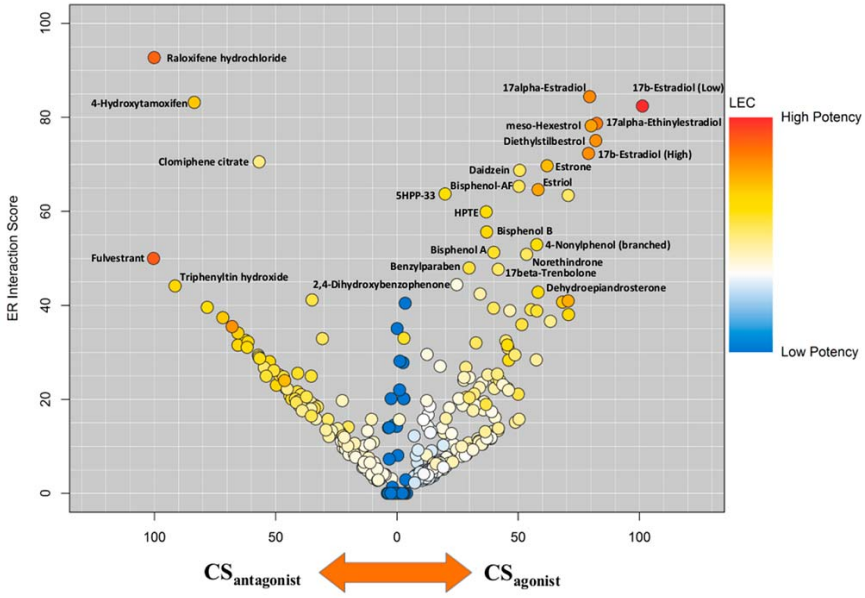
a) An evaluation of the relationship between residential carpet dust PAH concentrations and NHL risk in the National Cancer Institute Surveillance Epidemiology and End Results multicenter case–control study (NCI-SEER), among 676 cases and 511 controls [93]. These analyses suggested a potential association between PAH exposure and risk of T-cell lymphoma. Although we had a small sample size in regard to T-cell lymphoma occupationally exposed to PAH (22 cases), we did not observe suggestive associations (Supplemental material – article 6).

b) In the same study (NCI-SEER), an analysis of environmental chemical mixtures and NHL was performed using weighted quantile sum regression in 27 correlated chemicals measured in house dust from 672 cases and 508 controls [94]. They evaluated 5 PCBs, 7 PAHs, and 15 pesticides, and observed that the most highly weighted chemicals for predicting risk were PCB congener 180 and propoxur (a carbamate insecticide), although highly weighted chemicals varied by study site.

We observed novel associations with duration of exposure to alkylphenolic compounds in the EpiLymph study. While bisphenol A have received most of the attention in regard to endocrine disruption in both the society and the scientific community [95], alkylphenolic compounds have shown to have comparable endocrine disrupting properties [96] (**Figure 11**), specially nonylphenol branched, which is the most commonly used alkylphenol. Interaction scores are constructed to reflect both potency and efficacy of EDCs in regard to their potential to interfere with the ER signaling pathway. Interaction scores are higher for natural and synthetic hormones, selective estrogen receptor modulators, followed by other chemicals such as bisphenols and alkylphenols (**Figure 11**).

The role of alkylphenolic compounds in human health is largely unknown. In regard to cancer, occupational exposure to these chemicals has been associated with increased risk of breast cancer among males in a multi-centric European case-control study using the same JEM that we used in the EpiLymph [97]. Also, higher levels of nonylphenol and octylphenol in urine among patients with uterine leiomyoma than among controls were observed in two case-control studies in China [98,99].

Figure 11: Volcano plot of agonist and antagonist activity for 1814 chemicals



From Rotroff et al [96]: "Agonist and antagonist Composite Score (CS) values were plotted as a function of the ER Interaction Score on the y-axis and or $CS_{agonist}$ and $CS_{antagonist}$ on the x-axis. Chemicals with high ER Interaction Scores and high $CS_{agonist}$ fall to the upper right quadrant, whereas chemicals with high ER Interaction Scores and high $CS_{antagonist}$ are located in the upper left quadrant. The colors are determined by the potency of the LEC value. The chemicals in the middle of the x-axis with ER Interaction Score > 0 had no significant activity in either the agonist or antagonist groups but were active in the binding assay group".

To further explore the role of alkylphenolic compounds, we considered measuring levels of these compounds in serum or plasma samples from CLL/SLL cases and controls enrolled in the MCC-Study. We contacted different laboratories, however, we learned that the available tests are not sensitive enough and too susceptible to laboratory contamination among these types of samples [100]. Also, half-lives in blood seem to be short for nonylphenol [101], while for other alkylphenolic compounds this is unknown. The levels of these compounds in human fluids are likely to fluctuate over time, representing a challenge to study diseases of long latency periods, (like lymphoma or CLL/SLL), since biomonitoring short-lived chemicals data would reflect recent but

not past exposures. For these reasons, an occupational study may be more suitable to explore the role of these compounds in CLL/SLL etiology. Given that the MCC-study involved 26,149 job registries, an individual expert assessment would have represented a massive task to perform. JEMs are more cost-efficient than expert assessment, and since they are based on job titles, estimates of exposure are usually less influenced by recall bias than specific chemical exposures asked in questionnaires.

The JEM that we used in the EpiLymph study was aimed to assess recent exposures and it did not take into account when alkylphenolic compounds were first used or relevant modifications in their use over time, while use of alkylphenols in the industry has greatly varied over the years. This fact probably produces significant misclassification of the exposure. In order to obtain more accurate exposure estimates, we developed a new JEM to further evaluate the role of these compounds in CLL/SLL etiology in the MCC-Spain study. Dosemeci et al showed that JEM performance can be improved by 1) accounting differences in exposures over time, 2) including exposure probabilities in the assessments (instead of yes/no), and 3) using a specific industrial-occupational coding system [102]. We included these 3 characteristics in the development of the new JEM. Apart from its forthcoming use in the MCC-Spain study (where we will evaluate associations with CLL/SLL, breast and prostate cancer), the JEM that we developed can be a valuable tool for exposure assessment in other epidemiologic studies on the health effects of these chemicals and contribute clarifying their role in human health.

Strengths and limitations

The studies used in this thesis contain the largest number of subjects evaluated to date to study associations on hormonal factors and lymphoid neoplasms. We relied on the large multicentric EpiLymph study and on international collaborative efforts (InterLymph and IMMC) to elucidate the hormonal role of myelomas and lymphomas, as well as on a systematic review, which provides a higher grade of evidence, compared with individual observational studies, case-series, and expert opinions. Because of the large sample size, we were able to evaluate the role of hormonal factors by histological subtypes, which may have different etiology. For

instance, the EpiLymph study counted with accurate information on histological subtypes, and a random subsample of diagnosis reviewed by a central panel of pathologists.

We relied on self-reported questionnaire data. However, reproductive factors such as parity and gravidity are relatively reliable questions: women usually report their number of descendants reliably independently of the case status or the time since the exposure. Although more prone to recall bias, responses to questions on contraceptive use have been shown to be comparable to medical records [103]. Agreement was ≥90% for self-reported parity, oral contraceptives, and HT in a test-retest study [104]. However, we lacked relevant information in the evaluation of hormonal factors in lymphoma etiology, such as the composition of the hormonal drugs, and breastfeeding variables, among others. Occupational data was also self-reported. Interviews on occupational history have shown good quality in terms of agreement with census data or employment records, with agreement for job titles and dates ranging from 83 to 100% [105,106].

We did not perform mechanistic studies or evaluated biological markers. For example, presence of hormonal receptors in cancer cells from participants, or germline genetic variations, could explain previous discrepancies on reproductive factors and lymphoma risk. As well, the analysis of the total effective xenoestrogen burden (TEXB) among cases and controls could be useful to understand the endocrine disruption as a mechanism for lymphomagenesis. The evaluation of biomarkers could help understanding the mechanisms of carcinogenesis and could avoid some of the previous limitations and potential biases. However, the evaluation of certain biomarkers may have other limitations, for instance excessive variability over time for short-live chemicals reflecting recent but not past exposures. To avoid this limitation, occupational studies may be a good option for exploratory analyses. Since JEMs are prone to misclassification issues, we tried to minimize them in our improved JEM for alkylphenolic compounds by considering changes over time, among others.

Contribution to the knowledge of cancer and future research directions

This thesis provides the most comprehensive data on the role of reproductive and exogenous hormone use in the etiology of lymphomas. The analyses from Kato et al [75] using the WHI randomized clinical trial have provided further valuable insights on the associations of HT and NHL. While the role of these factors in lymphoma in general seems to be limited, the marginal associations observed with HT and MM in both observational and interventional settings warrant further evaluation.

Lymphoma incidence has increased over time among men and women, although it has reached a plateau during the last decade. We hypothesized that the decreased parity observed in some developed countries could help explaining this increase among women. Based on our findings, reproductive factors do not seem to substantially contribute to this increase. However, associations with EDCs could partially explain the increase among men. The study of the role of EDCs in lymphoma etiology, though, probably has a longer way to go through compared with reproductive factors. Studies on EDCs and lymphoma have usually been retrospective and based on occupational settings, which have misclassification issues as well as correlation of exposures that hamper the understanding of their actual role. Studies using more accurate tools to study EDCs and lymphoma are warranted.

We provided novel data on alkylphenols and metals carcinogenicity potential. We also contributed with an improved tool for the study of alkylphenolic compounds that can be used in other studies of cancer. Using the MCC-Spain study and the JEM that we developed in this thesis, we will further contribute to uncover the role of these chemicals on CLL/SLL, breast and prostate cancer. In the same study, the biomarkers-based analyses on metals and CLL/SLL proposed within the MCC-Spain will probably provide relevant insights on the role of metals in cancer.

Epidemiological assessment of potential causality for parity, HT and EDCs in lymphoma etiology

Criterion	Parity	HT use	EDCs	References
1. Strength	Range of ORs for 1 child increase= 0.87-1.04	Range of ORs for HT use= 0.70-1.40	Range of ORs= 0.27-3.94	Article 5 (Figure 1) and 6 (Suppl S2).
2. Consistency	Associations are not consistent across studies	Associations are not usually observed in cohort studies	Associations are not consistent across studies	Article 5. Alexander 2007 [14].
3. Specificity	Associations are not consistent across subtypes	Associations observed for all subtypes	Associations usually observed for CLL/SLL and MM	Article 5, article 3 and article 6, respectively.
4. Temporality	Male:female incidence ratios are greater during the pre-menopausal period than the post-menopausal period, suggesting that endogenous hormones may protect against lymphoma	For NHL decreased risks were observed among current users; while for MM decreased risk was observed at > time since last use	Increased risks are observed among currently exposed workers	Hedström 2015[107], Article 2, article 3, article 4 and article 6.
5. Biological gradient	In some studies, risk decreases through categories of parity in a dose-response manner	Not clearly observed	Associations are observed with increasing duration of exposure	Article 5, article 3 and article 6, respectively.
6. Plausibility	Lymphoid cells express ERβ and hormones interact with the immune system	Lymphoid cells express ERβ and hormones interact with the immune system	Lymphoid cells express ERβ and EDCs interact with the immune system	Pierdominici 2010 [64], Cutolo 2010 [54], Shim 2006 [66].
7. Coherence	Although some reports are null, the direction in both epidemiologic and experimental data is estrogens as protective factors against lymphoma	The direction in both case-control (but not cohort) studies and experimental data is estrogens as protective factors against lymphoma	Both experimental and epidemiologic data suggest that EDCs are risk factors of lymphoma, although experimental data suggest that other ways of action than endocrine disruption could be involved	Article 5, Hasni 2016 [67], Talaber 2016 [68], Lauby-Secretan 2013 [24], Guha 2012 [29], Collotta 2013 [87].
8. Experiment	Experimental data in mice show that estrogenic compounds have an influence on tumor growth and prognosis	Experimental data in mice show that estrogenic compounds have an influence on tumor growth and prognosis	Some EDCs have shown genotoxic effects, immune suppression, and inflammatory responses. Some EDCs (organic solvents) induced tumors of haemopoietic system in rats and mice	Yakimchuk 2011,2012 [108], Hasni 2016 [67], Talaber 2016 [68], Lauby-Secretan 2013 [24], Guha 2012 [29].
9. Analogy	Hormones are involved in other carcinogenic processes of other types of cancer, such as breast and ovarian cancers	Hormones are involved in other carcinogenic processes of other types of cancer, such as breast and ovarian cancers	Hormones are involved in other carcinogenic processes of other types of cancer, such as breast and ovarian cancers	IARC [19].

CONCLUSIONS

1. **Reproductive factors and exogenous hormone use**

➔ Reproductive factors and exogenous hormone use are unlikely to play a role in lymphomagenesis.

- Using the largest datasets evaluated to date, we observed heterogeneous results between studies and lymphoma subtypes for reproductive factors and hormonal contraception; implying that an association is not probable.
- Based on the observations from our systematic review, inverse associations with HT and NHL, and its subtypes, were mostly observed in case-control studies. These findings were not corroborated by cohort studies or the WHI trial, suggesting that bias may have produced inverse associations.
- We observed marginal inverse associations for HT and MM in the IMMC. Previous cohort studies were underpowered, and the WHI trial observed a marginally decreased risk of MM in the estrogen, but not estrogen+progestogen, group. Since data on HT composition was not available in the IMMC, further investigation in large studies considering HT formulations is warranted.

2. **Occupational exposure to EDCs**

➔ The associations between occupational exposure to EDCs and lymphoma require further evaluation in studies using a more detailed exposure assessment.

- We observed novel associations with prolonged occupational exposure to certain endocrine disrupting chemicals, including alkylphenolic compounds and certain metals. However, individual exposures were correlated and exposure estimates were susceptible to

misclassification; therefore, confirmation in other studies overcoming these limitations is warranted.

- In order to minimize sources of misclassification, we built a new JEM to assess occupational exposure to alkylphenolic compounds, accounting for changes over time, which can be used for further evaluation of these chemicals.

RESUM EN CATALÀ

Les neoplàsies limfoides són un grup heterogeni de càncers caracteritzats per la proliferació neoplàsica o clonal de cèl·lules limfoides en diverses etapes de diferenciació. La taxa d'incidència d'aquestes neoplàsies ha vist un augment en alguns països occidentals des de la dècada dels 1970 i sembla haver assolit un altiplà durant l'última dècada. Les taxes d'incidència són més altes en els homes que en les dones per a la majoria dels subtipus de linfoma. No obstant, les causes que expliquen aquestes diferències per sexe són desconeguts. Vam hipotetitzar que els factors hormonals podrien tenir un paper en l'etiologia limfoma.

Aquesta tesi avalua el risc de neoplàsies limfoides en relació amb els factors reproductius i l'exposició ocupacional als disruptors endocrins. Vam utilitzar diferents estudis i poblacions per avaluar la nostra hipòtesi: l'estudi EpiLymph, el consorci InterLymph, el Consorci Internacional del Mieloma Múltiple, i una revisió sistemàtica. A més, vam desenvolupar una nova eina per estimar l'exposició ocupacional a un tipus específic de disruptors endocrins.

Els resultats en relació a l'associació entre els limfomes i la paritat, així com els anticonceptius hormonals, van ser contradictoris entre estudis i subtipus de limfoma. Vam observar associacions invertides entre la teràpia hormonal postmenopàusica i el limfoma, encara que a la nostra revisió sistemàtica vam veure que els estudis de cohorts generalment trobaven associacions nules. Vam observar associacions amb limfoma i l'exposició ocupacional als disruptors endocrins de ≥30 anys, en particular per al mieloma múltiple i la leucèmia limfàtica crònica. Les associacions es van observar entre el limfoma i l'exposició perllongada als dissolvents orgànics, pesticides, retardants de flama bromats, compostos alquilfenòlics, i metalls. Vam desenvolupar una matriu d'exposició considerant finestres temporals per avaluar més a fons les associacions amb els compostos alquilfenòlics.

En conclusió, els nostres resultats indiquen que és poc probable que els factors reproductius i l'ús d'hormones exògenes juguin un paper en la limfomagènesi. Les associacions entre l'exposició ocupacional a disruptors endocrins i el limfoma s'han d'estudiar amb més profunditat en estudis que utilitzin una avaluació de l'exposició més detallada.

SPECIFIC TASKS PERFORMED BY THE PHD STUDENT

The PhD student (Laura Costas) has participated in the following tasks:

1. Preparation of grant applications.
2. Participation in the follow-up of the grants obtained, by performing several activities such as regular interim and final reports for the activities performed.
3. Fieldwork of the MCC-Spain study/CLL node:
    a. Contacting participants, explaining the study, obtaining consent forms
    b. Collection of biological samples (hair, nails, blood, saliva)
    c. Coordination of interviewers and contact with hematologists
    d. Process of some samples in the laboratory (aliquotation)
    e. Design of clinical form and clinical data collection
    f. Participation in the different working groups, especially the Endocrine Working Group
    g. Data cleaning of hormonal compounds for all the cancer types and controls (N>10.000)
4. Coordination of the study of reproductive factors in the International Multiple Myeloma Consortium:
    a. Identification of studies with reproductive data
    b. Contact with PIs of each center
    c. Data Transfer Agreements coordination
    d. Data Harmonization
5. Statistical analyses of articles 1, 4, 5, 6 and 7.
6. Manuscript writing of articles 1, 4, 5, 6 and 7.
7. Dissemination of results:
    a. Participation in international congresses and meetings
    b. Coordination of blog for the general public (http://mejorsincancer.org)
    c. Contact with journalists (articles 4 and 6)

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PI14/01219 – Funds from the Health Ministry of Spain. Project: "Molecular profile of aging in the pathogenesis and prognosis of Chronic Lymphocytic Leukemia". 2015-2017

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SUPPLEMENTARY MATERIAL:

ARTICLE 1

Online Resource 1: Risk estimates and 95% confidence intervals for the association between fathering factors in men and mature B-cell and T-cell neoplasms, and Hodgkin lymphoma risk.

Online Resource 1A: Mature B-cell neoplasms, Hodgkin lymphoma and Mature T-cell neoplasms risk overall.

		Mature B-cell neoplasms			Hodgkin Lymphoma			Mature T-cell neoplasms [c]		
	Controls (n=1318) [a]	Cases (n=1019) [a]	OR	95% CI	Cases (n=164) [a]	OR	95% CI	Cases (n=76) [a]	OR	95% CI
N° Children [b]										
0	281	157	0.92	[0.69,1.23]	83	1.26	[0.73,2.17]	12	0.52	[0.22,1.20]
1	221	164	Ref	-	24	Ref	-	14	Ref	-
2	447	366	1.08	[0.84,1.39]	40	1.10	[0.63,1.93]	27	0.96	[0.49,1.90]
3	206	179	1.10	[0.82,1.47]	9	0.71	[0.31,1.63]	11	0.75	[0.33,1.73]
>=4	159	146	1.09	[0.79,1.49]	7	1.02	[0.41,2.57]	9	0.81	[0.33,2.00]
		p-trend(fathers)=		0.21	p-trend(fathers)=		0.31	p-trend(fathers)=		0.56

OR: Odds Ratio

[a] Numbers do not always add to the total because of missing values

[b] Adjusted for age (continuous), center (country) and education (low, medium and high categories)

[c] Mature T-cell neoplasms = Angioimmunoblastic T-cell lymphoma (n=7), Anaplastic large cell lymphoma T-cell or null-cell type (n=6), NK/T-cell lymphoma, nasal type/ aggressive NK-cell leukemia (n=3), T-cell large granular lymphocytic leukemia (n=4), Peripheral T-cell lymphoma, NOS (n=26), Precursor (n=4), Mycosis fungoides/Sézary syndrome (n=24), Hepatosplenic T-cell lymphoma (n=2), Enteropathy-type T-cell lymphoma (n=3), Prolymphocytic T-cell leukemia (n=1)

Online Resource 1B: Mature B-cell neoplasms risk, by subtypes.

		Mature B-cell neoplasms														
		CLL/SLL			DLBCL			Follicular Lymphoma			Multiple Myeloma			Other Mature B-cell Neoplasms [c]		
	Controls (n=1318) [a]	Cases (n=262) [a]	OR	95% CI	Cases (n=276) [a]	OR	95% CI	Cases (n=115) [a]	OR	95% CI	Cases (n=157) [a]	OR	95% CI	Cases (n=209) [a]	OR	95% CI
N° Children [b]																
0	281	28	0.69	[0.41,1.17]	57	1.09	[0.69,1.73]	20	1.15	[0.55,2.40]	19	0.68	[0.36,1.27]	34	1.05	[0.61,1.79]
1	221	46	Ref	-	41	Ref	-	14	Ref	-	30	Ref	-	33	Ref	-
2	447	95	1.00	[0.67,1.49]	92	1.07	[0.71,1.60]	47	1.77	[0.95,3.31]	57	0.95	[0.59,1.54]	75	1.11	[0.71,1.73]
3	206	51	1.05	[0.67,1.66]	44	1.15	[0.71,1.85]	20	1.65	[0.80,3.40]	28	0.88	[0.50,1.54]	36	1.08	[0.64,1.81]
>=4	159	42	1.02	[0.62,1.67]	38	1.20	[0.72,2.01]	13	1.47	[0.65,3.34]	23	0.83	[0.45,1.53]	31	1.11	[0.63,1.94]
		p-trend(fathers)=		0.21	p-trend(fathers)=		0.60	p-trend(fathers)=		0.22	p-trend(fathers)=		0.78	p-trend(fathers)=		0.77

OR: Odds Ratio, CLL/SLL: chronic lymphocytic leukaemia/ small lymphocytic lymphoma, DLBCL: diffuse large B-cell lymphoma

[a] Numbers do not always add to the total because of missing values

[b] Adjusted for age (continuous), center (country) and education (low, medium and high categories)

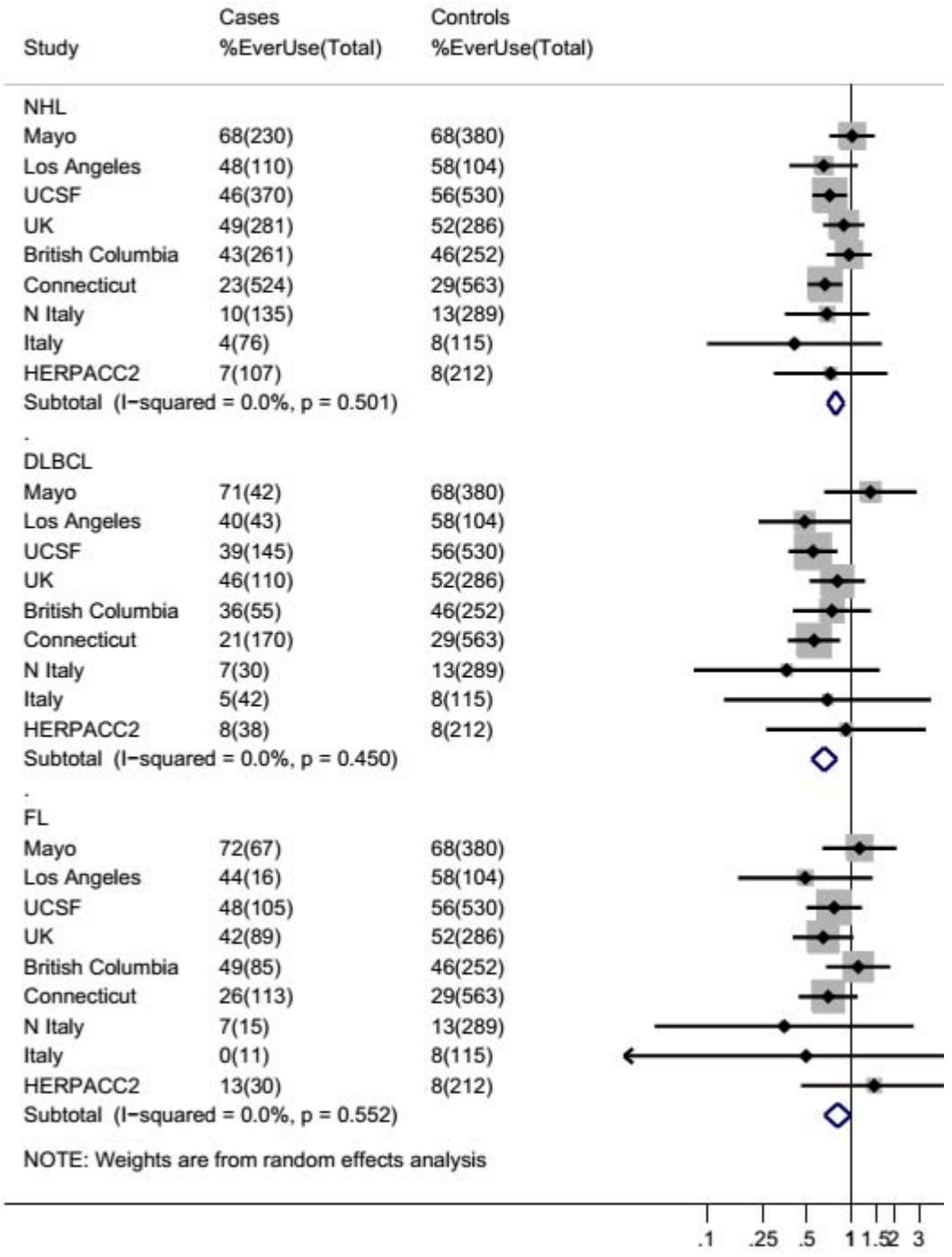
[c] Other mature B-cell neoplasms= Lymphoplasmacytic lymphoma (n=28), Mucosa-associated lymphoid tissue lymphoma (n=51), Splenic Marginal Zone lymphoma (n=17), Mantle Cell lymphoma (n=48), Hairy Cell leukemia (n=14) and B-cell lymphoma – unclassifiable (n=51)

Online Resource 2: Odds Ratios and 95% confidence intervals for the association between reproductive factors and hormonal contraceptive use and non-Hodgkin lymphoma for comparison with previous studies (combining all T-cell and B-cell subtypes, and excluding Multiple Myeloma)

		Non-Hodgkin lymphoma		
	Controls (n=1141) [a]	Cases (n=751) [a]	OR	95% CI
REPRODUCTIVE HISTORY				
Pregnant Ever [b]				
No	207	119	Ref	-
Yes	933	629	0.99	[0.76,1.29]
p-heterogeneity=				0.94
Parity [b]				
Nulliparous [c]	207	119	0.85	[0.61,1.19]
1	176	138	Ref	-
2	313	250	1.02	[0.77,1.35]
3	184	123	0.79	[0.57,1.10]
>=4	220	100	0.49*	[0.34,0.69]
p-trend (in parous)[d]=				<0.0001
Age at first child (years) [e]				
<20	107	70	Ref	-
20-24	404	272	0.96	[0.68,1.36]
25-29	237	174	1.03	[0.70,1.51]
>=30	133	89	0.88	[0.57,1.37]
p-trend (in parous) =				0.76
Age at last child (years) [e]				
<25	158	101	Ref	-
25-29	236	190	1.43*	[1.03,1.97]
30-34	242	180	1.39	[0.99,1.95]
>=35	237	133	1.11	[0.76,1.62]
p-trend (in parous) =				0.84
HORMONAL CONTRACEPTIVE USE				
Use of contraceptives [e]				
Never used [f]	863	566	Ref	-
Ever used	271	175	1.24	[0.96,1.61]
p-heterogeneity=				0.11
Duration of use (years) [e]				
<5	78	71	1.88*	[1.29,2.75]
5-9	67	37	1.12	[0.71,1.77]
>=10	115	60	0.91	[0.63,1.31]
p-trend (in users) =				0.0001
Age at first use (years) [e]				
<20	111	46	0.82	[0.54,1.26]
20-24	75	48	1.23	[0.81,1.86]
>=25	79	76	1.53*	[1.08,2.16]
p-trend (in users) =				0.03
Time since last use (years) [e]				
Current	73	17	0.49*	[0.27,0.89]
1-9	73	34	0.88	[0.55,1.41]
10-19	49	52	1.84*	[1.19,2.83]
>=20	68	67	1.57*	[1.08,2.28]
p-trend (in users) =				0.0002
Calendar year of first use [e]				
<1970	31	24	1.15	[0.66,2.01]
1970-1979	80	75	1.65*	[1.15,2.36]
>=1980	154	71	0.92	[0.64,1.33]
p-trend (in users) =				0.27

[a] Numbers do not always add to the total because of missing values
[b] Adjusted for age (continuous), center (country) and education (low, medium and high categories)
[c] Women who had experienced abortions or pregnancy losses are excluded from this category
[d] As a continuous variable in parous women
[e] Adjusted for age (continuous), center (country), education (low, medium and high categories) and number of children (0, 1+2 and >=3 categories)
[f] Referent category for all analyses on contraceptive use
* p<0.05

ARTICLE 3


Study
Cases %EverUse(Total)
Controls %EverUse(Total)
NHL
Mayo 68(230) 68(380)
Los Angeles 48(110) 58(104)
UCSF 46(370) 56(530)
UK 49(281) 52(286)
British Columbia 43(261) 46(252)
Connecticut 23(524) 29(563)
N Italy 10(135) 13(289)
Italy 4(76) 8(115)
HERPACC2 7(107) 8(212)
Subtotal (I-squared = 0.0%, p = 0.501)
DLBCL
Mayo 71(42) 68(380)
Los Angeles 40(43) 58(104)
UCSF 39(145) 56(530)
UK 46(110) 52(286)
British Columbia 36(55) 46(252)
Connecticut 21(170) 29(563)
N Italy 7(30) 13(289)
Italy 5(42) 8(115)
HERPACC2 8(38) 8(212)
Subtotal (I-squared = 0.0%, p = 0.450)
FL
Mayo 72(67) 68(380)
Los Angeles 44(16) 58(104)
UCSF 48(105) 56(530)
UK 42(89) 52(286)
British Columbia 49(85) 46(252)
Connecticut 26(113) 29(563)
N Italy 7(15) 13(289)
Italy 0(11) 8(115)
HERPACC2 13(30) 8(212)
Subtotal (I-squared = 0.0%, p = 0.552)
NOTE: Weights are from random effects analysis
.1
.25
.5
1
1.5
2
3

ARTICLE 4

Supplemental Table 1. Characteristics of the studies included in the analysis of reproductive factors, exogenous hormone use, and risk of multiple myeloma.

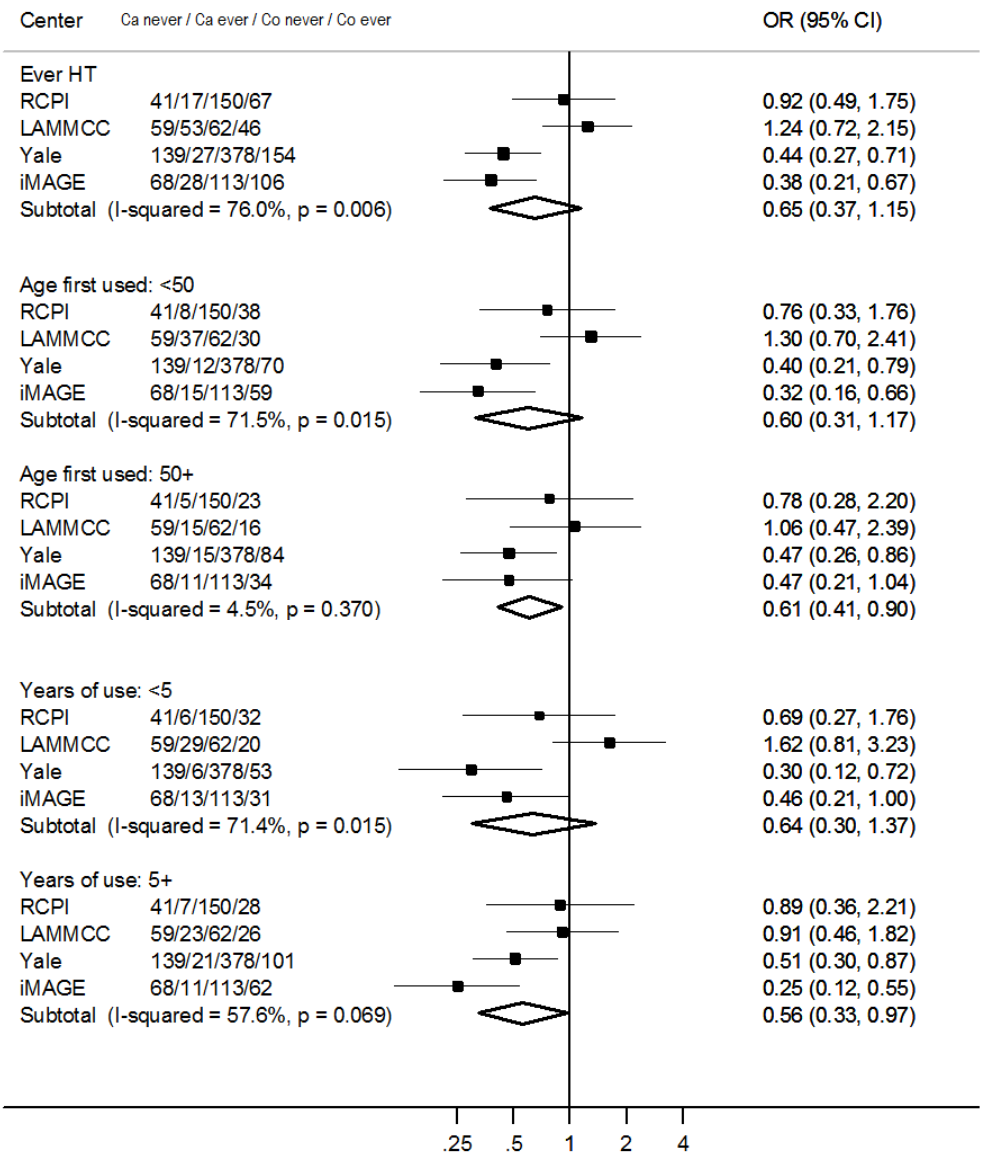
Case-control studies [a]	Location	Enrollment period	Age elegibility	Study design [b]	Female controls	Female cases
Los Angeles County Multiple Myeloma Case-Control Study (LAMMCC) (1)	Los Angeles County (US)	1985–1992	18-75	Population	126	126
Roswell Park Cancer Institute (RPCI) (2)	Buffalo (US)	1982–1998	>=20	Hospital	264	66
Utah	Salt Lake City (US)	2008–	>=18	Population	295	134
Epilymph (3)		1998–2004	>=17		1141	120
	Spain			Hospital	*302*	*40*
	France			Hospital	*139*	*18*
	German			Population	*320*	*33*
	Italy			Population	*158*	*6*
	Ireland			Hospital	*84*	*7*
	Czech Republic			Hospital	*138*	*16*
Fred Hutchinson Cancer Research Center (FHCRC) 1980s (4)		1977-1981	<82		747	326
	Washington (US)			Population	*73*	*79*
	Utah (US)			Population	*102*	*37*
	Michigan (US)			Population	*510*	*166*
	Georgia (US)			Population	*62*	*44*
National Cancer Institute (NCI) – Yale (5)	Connecticut (US)	1996-2002	21-84	Population	*716*	*183*
Molecular and Genetic Epidemiology Study (iMAGE)	Alabama (US)	2009-2013	≥21	Population	252	117

[a] More details on methods from some of the studies can be found in the following publications:

1. Wang SS, Voutsinas J, Chang ET, et al. Cancer Causes Control. 2013;24:1279–89.
2. Moysich KB, Bonner MR, Beehler GP, et al. Leuk Res. 2007;31:547–51.
3. Costas L, Casabonne D, Benavente Y, et al. Cancer Causes Control. 2012;23:195–206.
4. Koepsell TD, Daling JR, Weiss NS, et al. Am J Epidemiol. 1987;126:1051–62.
5. Koutros S, Baris D, Bell E, et al. Occup Environ Med. 2009;66:68–70.

[b] Based on source of controls

Supplemental Figure 1. Study-specific risks of multiple myeloma for postmenopausal hormone therapy (HT), age at first HT use and years of HT use.



Among post-menopausal women. Adjusted for age group, race, and center.
Ca: cases; Co: controls; OR: Odds Ratio; CI: Confidence Interval; HT: postmenopausal hormone therapy; LAMMCC: Los Angeles County Multiple Myeloma Case-Control Study; RPCI: Roswell Park Cancer Institute; FHCRC: Fred Hutchinson Cancer Research Center; iMAGE: Molecular and Genetic Epidemiology Study.

ARTICLE 5

Supplemental material: Participation rates.

First author, year of publication (Study Name)	PR (%)		Definition of Participation Rate (PR)
Cohort studies	***Baseline***	***Follow-up***	
Kvale et al, 1994	74	78[a]	Interviewed people from those who attended the screening program in Norway. 2.1% of women were excluded due to lacking information on parity. Follow-up rate is computed based on permanent emigrations registered during follow-up and deaths.
Cerhan et al, 2002; Cerhan et al, 2002b; Cerhan et al, 1997 (Iowa Women's Health Study)	43	NA	Randomly selected women having a valid Iowa driver's licence who returned a mailed questionnaire. For follow-up rates, the authors specified: "*Out migration has been estimated at 1%/year*". Censoring for deaths were not specified.
Frisch et al 1997; Frisch et al, 2006	NA	NA	Based on a national register (the Civil Registration System, a national database that keeps track of all demographic changes in Denmark)
Norgaard et al. 2006	NA	NA	Based on a national register and a prescription database that covered all pharmacies in North Jutland County, in Denmark.
Morton et al, 2009 (NIH-AARP Diet and Health Study)	10[a]	93[a]	PR at baseline includes men. PR is computed as AARP members, who satisfactorily completed a 1st questionnaire (16.2%), and further completed a 2nd questionnaire of reproductive factors (59.1% of first respondents). Of those, they excluded men, proxy respondents, women with a previous history of cancer, and women for whom all MHT data were missing (overall 8.7% of women excluded). Follow-up rate is computed based on the participants that moved out of a registry catchment area, deaths, and diagnosis of a non-lymphoid hematopoietic neoplasm.
Prescott et al, 2009; Lu et al 2011 (California Teachers Study)	40[a]	83[a]	Not defined. PR at baseline and follow-up have been extracted from one of their references (Bernstein et al 2002). Respondents were defined as women who returned a completed questionnaire and provided identifying and contact information. PR at follow-up considered response to either biennial questionnaire nº1 or nº2. Exclusions for each exposure are detailed in Prescott et al. and Lu et al.
Teras et al, 2012 (Cancer Prevention Study-II Nutrition Cohort)	51[a]	91	PR at baseline was not defined. It was computed based on figures provided by Calle et al. The authors further excluded 15% of women due to missing values or situations such as: "*history of both unopposed estrogen and estrogen plus progestin use, report of unopposed oral progesterone or vaginal estrogen cream, and report of contraindicated hormone use (estrogen-only users with intact uterus, estrogen plus progestin users after hysterectomy".*
Case Control studies	***Cases***	***Controls***	
Miller et al, 1980	92/90/69[b]	NA	For cases, it was defined as "*the percentage of patients on whom parity information was obtained*", and for controls they mentioned "*the response rate from the controls would have been virtually 100%, since all were legally required to respond to the census survey*".
Olsson et al, 1990	NA	NA	Not defined. They specified "*no patients were excluded from interview*".
Bernstein et al 1992	45[a]	76	Eligibility was defined for cases as all cases who were English speaking and were diagnosed between 1979 and 1982. 742 cases (including men) were not interview because of death, illness, moving out, or permission denied from physicians. They identified controls "*by walking a predetermined algorithm through an obligatory sequence of residences beginning with a residence that had a specific geographical relationship to that of the case".* "*On average, 21 household units were contacted to identify a consenting matched neighborhood control. For 76% of the cases, the first eligible control agreed to be interviewed*"
La Vecchia et al, 1993	96	96	Eligible subjects who accepted to be interviewed. Cases and controls with missing information for reproductive factors were excluded from the analyses (the extent of the missingness is not specified).
Adami et al, 1997	NA	NA	Based on a linkage from the Swedish Cancer Register, and the Swedish Fertility Register. The authors specify "*The major part of the lack of reproductive information is from non-Swedish citizens that are on record only in the Cancer Register*".
Tavani et al, 1997; Altieri et al, 2004; Fernandez et al, 2003	98	96	PRs refer to the proportion of participants who did not refuse to be interviewed (Altieri et al 2004).
Nelson et al, 2001	45	69[a]	Eligibility was defined for cases as all cases who were English- or Spanish-speaking , diagnosed between 1989 and 1992, resident of Los Angeles County and diagnosed with high- or intermediate-grade tumors. PR for controls has been extracted from another citation that the authors provided (Nelson et al. 1997). 448 cases were not interview due to death, illness, refusal, or others. For controls they mentioned "*We canvassed each housing unit until a woman who matched the case subject on the matching criteria was located and interviewed*." 26 pairs of matched cases and controls were further excluded because of missing information (not included in PR calculation).
Beiderbeck et al, 2003	NA	NA	Based on a database from community pharmacies of a population approximately 300.000 residents in the Netherlands
Zhang et al, 2004a Zhang et al, 2004b	72	69/47[c]	They specified that potential participants were approached by letter and/or by phone, and those who consented were interviewed. They specified PRs stratified by age, as participants below 65 were approached by random digit dialing methods and those 65 or above by using Centers for Medicare and Medicaid Service files.
Lee et al, 2008	72	78	They mentioned that controls were identified by random digit dialing and that eligibility criteria for controls were the same as those for cases.
Mildon et al, 2010	74	71	PRs were defined as the proportion of cases and controls participating among those eligible subjects approached.
Costas et al, 2012 (Epilymph)	88	69	Denominators used in the calculation of participation rates were the numbers of cases or controls approached to participate in the study. For cases, it was all consecutive incident cases including deceased subjects diagnosed in each center during the study period; for controls, it was the number of persons randomly selected from among newly hospitalized patients or the general population.

PR: Participation rate; NA: Not Available

[a] The authors of this review computed or extracted the corresponding PR, based on their data or their references.

[b] For the three Canadian provinces evaluated (Alberta, Saskatchewan, and Manitoba, respectively).

[c] For participants below age 65, and 65 or above, respectively.

ARTICLE 6

Table S1: Descriptive statistics of cases and controls in the EpiLymph study

	Controls *(n=2,457)*		Cases *(n=2,178)*		
	No. [b]	**(%)**	**No.** [b]	**(%)**	**p-value**
Age at recruitment					
<60	1255	51.1	1080	49.6	0.31
60+	1202	48.9	1098	50.4	
Education level					
Low	1121	45.6	1003	46.1	0.89
Medium	998	40.6	870	39.9	
High	338	13.8	305	14	
Smoking					
Never	1095	44.6	948	43.6	0.50
Ever	1361	55.4	1227	56.4	
Regular alcohol consumption					
Never	937	38.2	854	39.3	0.45
Ever	1515	61.8	1319	60.7	
Body mass index					
<25	939	41.1	910	47.2	<0.01
25-30	904	39.5	724	37.5	
30+	443	19.4	295	15.3	
Gender					
Male	1317	53.6	1217	55.9	0.12
Female	1140	43.4	961	44.1	
Parity [a]					
0	525	21.4	453	20.9	0.03[a]
1-2	1157	47.2	1104	50.9	
3+	769	31.4	613	28.2	
Country					
Spain	629	25.6	542	24.9	0.12
France	272	11.1	281	12.9	
Germany	710	28.9	663	30.4	
Italy	336	13.7	253	11.6	
Ireland	207	8.4	171	7.9	
Czech republic	303	12.3	268	12.3	

[a] For male participants, parity refers to the number of children they had fathered; for females parity is defined as the number of children they had. P-value for this variable differs by sex (0.96 for men and <0.01 for women).

[b] Numbers do not always add to the total because of missing values

Table S2: Ever exposure to groups of endocrine disruptors and risk of lymphoma

	Mature B-cell neoplasms														
	Overall			*MM*		*FL*		*DLBCL*		*CLL*		*Mature T-cell neoplasms*		*Hodgkin lymphoma*	
	Co	***Ca***	***OR a (95% CI)***	***Ca***	***OR a (95% CI)***	***Ca***	***OR a (95% CI)***	***Ca***	***OR a (95% CI)***	***Ca***	***OR a (95% CI)***	***Ca***	***OR a (95% CI)***	***Ca***	***OR a (95% CI)***
Unexposed	901	588	Ref	85	Ref	102	Ref	196	Ref	119	Ref	39	Ref	128	Ref
Ever exposed to:															
Polycyclic aromatic hydrocarbons	438	309	1.02 (0.76,1.37)	48	0.89 (0.48,1.66)	37	1.02 (0.56,1.89)	85	1.00 (0.65,1.54)	77	0.93 (0.53,1.62)	22	1.04 (0.47,2.32)	53	0.81 (0.48,1.38)
Polychlorinated organic compounds	58	30	0.71 (0.37,1.35)	7	1.10 (0.36,3.34)	3	0.34 (0.05,2.60)	7	0.57 (0.19,1.67)	7	0.56 (0.16,1.93)	5	1.38 (0.30,6.39)	8	1.52 (0.47,4.86)
Pesticides	528	406	1.19 (0.64,2.21)	82	2.36 (0.84,6.63)	46	1.19 (0.34,4.08)	89	0.77 (0.26,2.26)	127	1.66 (0.60,4.59)	33	0.75 (0.10,5.82)	40	0.81 (0.23,2.90)
Organic solvents	1111	844	1.08 (0.92,1.26)	151	1.16 (0.85,1.59)	102	0.96 (0.69,1.34)	239	1.11 (0.88,1.41)	223	1.17 (0.89,1.53)	62	1.01 (0.63,1.61)	116	1.12 (0.80,1.55)
Bisphenol A	17	19	1.55 (0.78,3.08)	3	1.36 (0.37,4.99)	3	1.92 (0.53,6.95)	7	1.85 (0.73,4.68)	4	1.12 (0.35,3.57)	0	-	3	1.46 (0.36,5.89)
Alkylphenolic compounds	745	583	1.21 (0.74,1.98)	110	1.00 (0.38,2.66)	67	0.82 (0.24,2.74)	155	1.03 (0.47,2.29)	155	0.96 (0.39,2.38)	47	**3.33* (1.27,8.74)**	63	1.53 (0.49,4.79)
Brominated flame retardants	87	73	1.22 (0.67,2.21)	10	0.27 (0.04,2.03)	10	1.28 (0.37,4.46)	21	0.89 (0.33,2.39)	18	1.14 (0.41,3.14)	7	**3.94* (1.33,11.66)**	10	0.67 (0.08,5.58)
Metals	946	726	1.21 (0.93,1.59)	121	0.60 (0.30,1.20)	89	1.33 (0.78,2.27)	185	1.23 (0.82,1.84)	202	1.43 (0.92,2.23)	54	0.93 (0.41,2.09)	98	1.25 (0.76,2.07)
Miscellaneous	41	42	1.54 (0.98,2.42)	6	1.26 (0.51,3.13)	6	1.47 (0.59,3.65)	15	1.70 (0.91,3.19)	11	1.79 (0.86,3.74)	3	1.57 (0.45,5.52)	10	2.20 (0.95,5.10)

a All models were adjusted for age, education, sex, country and ever exposure to organic solvents (except for estimates on organic solvents). Probable and possible exposures are combined.

MM = Multiple Myeloma; FL= Follicular Lymphoma, DLBCL= Diffuse Large B-Cell Lymphoma; CLL= Chronic Lymphocytic Leukemia

Co= Controls / Ca= Cases

* $p<0.05$

Table S3: Duration of exposures to endocrine disruptors and risk of selected lymphoma subtypes, among the unexposed to solvents and pesticides. Estimates for 10 years increase of occupational exposure to endocrine disruptors.

	Unexposed to solvents			*Unexposed to pesticides*		
	Controls *(n=1,346)*	**Cases** *(n=876)*	**OR (95% CI)**	**Controls** *(n=1,917)*	**Cases** *(n=1,306)*	**OR (95% CI)**
Ever held a job with exposure to any endocrine disruptor						
Unlikely [a]	901	588	Ref	901	588	Ref
Possible (never probable)	199	154	1.18 (0.92,1.52)	564	415	1.11 (0.93,1.33)
Probable	119	73	1.02 (0.74,1.40)	337	250	1.17 (0.95,1.45)
Never worked [b]	115	51	0.67 (0.46,0.97)	115	51	0.70 (0.49,1.01)
Age at first exposure [c]						
<15	40	41	1.56 (0.98,2.48)	198	169	1.27 (0.99,1.64)
15-19	129	85	1.12 (0.82,1.53)	407	296	1.17 (0.96,1.43)
20+	149	101	1.03 (0.77,1.37)	296	199	1.04 (0.84,1.29)
p-trend [d]			*0.09*			*0.16*
Time since last exposure [c]						
Current	93	49	0.98 (0.67,1.44)	223	137	1.22 (0.94,1.59)
<15	100	76	1.25 (0.90,1.75)	267	199	1.21 (0.97,1.52)
15+	124	101	1.13 (0.84,1.51)	408	327	1.09 (0.90,1.32)
p-trend [d]			*0.95*			*0.13*
Total years of exposure to endocrine disruptors [c]						
<10	157	100	1.11 (0.84,1.47)	420	282	1.10 (0.91,1.33)
10-29	98	67	1.07 (0.76,1.51)	270	208	1.22 (0.98,1.52)
30+	62	59	1.27 (0.85,1.88)	206	172	1.15 (0.90,1.48)
p-trend			*0.23*			*0.10*

a Reference category for all comparisons. All models were adjusted for age, education, sex and country.

b Participants who uniquely held occupations described as unemployment, student, family work (housewifes), or illness.

c Probable and possible exposures to endocrine disruptors are combined.

d Among exposed.

Table S4: Corrected estimates for misclassification of the exposure using MC-SIMEX.

	Mature B-cell neoplasms	
	OR (95% CI)	**% bias**
Ever held a job with exposure to any endocrine disruptor		
Unlikely a	Ref	
Possible or probable	1.16 (0.94,1.42)	-0.04
Time since last exposure		
Current	1.42 (1.01-2.00)	-0.14
Age at first exposure		
<15	1.16 (0.85,1.58)	-0.06
Total years of exposure to endocrine disruptors		
10+	1.32 (1.04,1.68)	-0.09

a Reference category for all comparisons. All models were adjusted for age, education, and sex.

Table S5: Concordance and correlation coefficients between exposures among controls. Cohen's Kappa coefficients are computed for binary variables (ever/never). Correlation coefficients are computed for duration of exposures in years.

	Polycyclic aromatic hydrocarbons		Polychlorinated organic compounds		Pesticides		Phthalates		Organic Solvents		Alkylphenolic compounds		Brominated flame retardants	
	Kappa	**Correlation**	**Kappa**	**Correlation**	**Kappa**	**Correlation**	**Kappa**	**Correlation**	**Kappa**	**Correlation**	**Kappa**	**Correlation**	**Kappa**	**Correlation**
Polychlorinated organic	0.09	0.67												
Pesticides	0.04	0.01	0.01	-0.22										
Phthalates	0.12	0.15	0.07	0.56	0.84	0.95								
Organic Solvents	0.14	0.15	0.00	-0.05	0.46	0.81	0.54	0.84						
Alkylphenolic compounds	0.04	-0.04	0.06	0.60	0.64	0.89	0.66	0.87	0.63	0.87				
Brominated flame retardants	0.10	0.55	0.16	0.81	0.02	0.01	0.12	0.54	0.04	0.32	0.11	0.63		
Metals	0.10	0.01	0.04	0.45	0.56	0.86	0.57	0.85	0.60	0.79	0.47	0.78	0.09	0.65

Table S6: Associations of occupational exposures to endocrine disruptors and risk of lymphoma, stratified by lymphoma subtype.

		Mature B-cell neoplasms								Mature T-cell neoplasms		Hodgkin lymphoma	
		MM		FL		DLBCL		CLL					
	Co	Ca	OR (95% CI)	Ca	OR (95% CI)	Ca	OR (95% CI)	Ca	OR (95% CI)	Ca	OR (95% CI)	Ca	OR (95% CI)
Ever held a job with exposure to any endocrine disruptor													
Unlikely [a]	901	85	Ref	102	Ref	196	Ref	119	Ref	39	Ref	128	Ref
Possible (never probable)	591	63	0.99 (0.69,1.42)	60	1.03 (0.72,1.47)	149	1.25 (0.97,1.61)	95	1.12 (0.83,1.52)	33	1.11 (0.67,1.83)	81	1.06 (0.75,1.49)
Probable	838	119	1.19 (0.85,1.65)	75	0.97 (0.69,1.38)	161	0.97 (0.76,1.26)	179	1.27 (0.95,1.68)	46	0.96 (0.59,1.56)	87	1.04 (0.74,1.46)
Never worked [b]	115	8	0.89 (0.41,1.94)	11	0.94 (0.48,1.84)	11	0.45 (0.24,0.87)	17	1.28 (0.72,2.29)	6	1.04 (0.42,2.58)	32	1.19 (0.71,1.98)
Age at first exposure [c]													
<15	466	71	1.21 (0.82,1.78)	41	0.99 (0.64,1.53)	87	1.00 (0.73,1.37)	110	1.24 (0.89,1.72)	31	1.12 (0.64,1.97)	33	1.22 (0.75,1.97)
15-19	576	74	1.19 (0.84,1.70)	62	1.13 (0.79,1.63)	126	1.12 (0.85,1.46)	101	1.25 (0.92,1.71)	31	1.07 (0.63,1.80)	83	1.04 (0.73,1.47)
20+	383	36	0.92 (0.60,1.40)	32	0.86 (0.56,1.31)	96	1.20 (0.91,1.59)	63	1.12 (0.80,1.58)	17	0.92 (0.50,1.67)	52	1.10 (0.75,1.61)
p-trend [d]			*0.18*		*0.65*		*0.51*		*0.56*		*0.49*		*0.7*
Time since last exposure [c]													
Current	338	46	**1.68 (1.10,2.57)**	32	1.17 (0.74,1.84)	72	1.18 (0.85,1.63)	48	1.36 (0.91,2.01)	22	1.14 (0.63,2.08)	80	1.23 (0.85,1.76)
<15	428	43	0.90 (0.59,1.37)	40	1.04 (0.69,1.58)	95	1.16 (0.86,1.56)	93	**1.39 (1.00,1.93)**	22	0.93 (0.52,1.66)	55	0.99 (0.67,1.45)
15+	658	92	1.04 (0.74,1.46)	62	0.90 (0.62,1.30)	142	1.07 (0.82,1.39)	133	1.09 (0.82,1.46)	35	1.05 (0.63,1.76)	33	1.01 (0.64,1.59)
p-trend [d]			*0.07*		*0.20*		*0.44*		*0.16*		*0.99*		*0.12*
Total years of exposure to endocrine disruptors [c]													
<10	551	52	0.96 (0.66,1.40)	45	0.81 (0.56,1.19)	122	1.11 (0.86,1.45)	71	1.04 (0.75,1.44)	24	0.86 (0.50,1.49)	93	0.99 (0.71,1.38)
10-29	460	61	1.23 (0.85,1.79)	49	1.18 (0.80,1.74)	110	1.23 (0.93,1.63)	88	1.28 (0.93,1.76)	26	1.09 (0.63,1.89)	55	1.27 (0.86,1.87)
30+	409	68	1.24 (0.84,1.84)	40	1.16 (0.75,1.81)	76	0.94 (0.68,1.31)	115	**1.39 (1.00,1.93)**	28	1.33 (0.74,2.39)	20	1.22 (0.69,2.16)
p-trend			*0.18*		*0.35*		*0.80*		***0.03***		*0.32*		*0.27*

a Reference category for all comparisons. All models were adjusted for age, education, sex and country.

b Participants who uniquely held occupations described as unemployment, retirement, student, family work (housewifes), or illness.

c Probable and possible exposures to endocrine disruptors are combined.

d Among exposed.

Co= Controls / Ca= cases

MM = Multiple Myeloma; FL= Follicular Lymphoma, DLBCL= Diffuse Large B-Cell Lymphoma; CLL= Chronic Lymphocytic Leukemia

Table S7: Duration of exposures to endocrine disruptors and risk of lymphoma, stratified by lymphoma subtype. Estimates for 10 years increase of occupational exposure to endocrine disruptors.

Total years of exposure to:		Mature B-cell neoplasms								Mature T-cell neoplasms		Hodgkin Lymphoma	
		MM		FL		DLBCL		CLL					
	Co	Ca	OR a (95% CI)	Ca	OR a (95% CI)	Ca	OR a (95% CI)	Ca	OR a (95% CI)	Ca	OR a (95% CI)	Ca	OR a (95% CI)
Unexposed [a]	901	85	Ref	102	Ref	196	Ref	119	Ref	39	Ref	128	Ref
Pesticides													
Organochlorines	442	67	**1.18 (1.02,1.37)**	35	0.96 (0.77,1.21)	74	1.04 (0.89,1.21)	112	1.06 (0.94,1.20)	27	1.06 (0.84,1.35)	31	1.03 (0.77,1.39)
Carbamates / Pyrethroids	507	78	**1.19 (1.04,1.37)**	40	0.98 (0.79,1.22)	85	1.00 (0.87,1.16)	127	1.11 (0.99,1.25)	32	1.11 (0.90,1.38)	38	1.14 (0.89,1.47)
Organophosphates	467	72	**1.22 (1.06,1.41)**	38	0.97 (0.78,1.21)	78	1.02 (0.88,1.19)	117	1.06 (0.94,1.20)	28	1.10 (0.88,1.39)	34	1.04 (0.78,1.38)
Organic Solvents													
Ethylene glycol ethers	943	133	**1.14 (1.04,1.26)**	79	0.94 (0.82,1.08)	193	1.00 (0.91,1.10)	195	1.08 (0.99,1.17)	54	1.07 (0.91,1.25)	82	1.12 (0.95,1.33)
Styrene	38	5	0.62 (0.21,1.78)	4	0.84 (0.33,2.13)	9	0.95 (0.53,1.70)	10	1.10 (0.66,1.84)	0	-	7	0.85 (0.24,2.96)
Toluene / Xylene	735	104	**1.11 (1.00,1.23)**	71	1.04 (0.91,1.18)	140	0.96 (0.86,1.06)	168	1.06 (0.97,1.16)	42	1.06 (0.90,1.26)	76	1.13 (0.94,1.35)
Trichloroethylene	320	40	0.98 (0.80,1.21)	29	0.93 (0.72,1.22)	59	1.02 (0.86,1.21)	54	0.93 (0.78,1.12)	19	1.05 (0.78,1.41)	32	0.83 (0.57,1.21)
Perchloroethylene	315	41	0.97 (0.79,1.20)	28	0.93 (0.71,1.21)	62	1.01 (0.85,1.20)	54	0.96 (0.80,1.15)	19	1.05 (0.78,1.41)	28	0.83 (0.56,1.21)
Alkylphenolic compounds													
Alkylphenolic ethoxylates	736	109	**1.16 (1.03,1.31)**	66	0.91 (0.75,1.10)	152	0.92 (0.81,1.04)	155	**1.11 (1.00,1.24)**	46	1.13 (0.93,1.36)	63	**1.29 (1.06,1.58)**
Alkylphenols	466	73	**1.17 (1.01,1.35)**	40	0.89 (0.71,1.12)	85	0.98 (0.84,1.14)	118	1.07 (0.95,1.21)	30	1.03 (0.82,1.30)	40	1.15 (0.89,1.48)
Metals													
Cadmium	78	15	0.93 (0.58,1.52)	10	1.26 (0.75,2.10)	22	0.79 (0.48,1.30)	15	0.67 (0.38,1.19)	1	2.85 (0.42,19.21)	9	1.58 (0.87,2.90)
Arsenic	108	16	1.05 (0.73,1.52)	8	1.40 (0.91,2.16)	21	0.82 (0.56,1.21)	20	1.21 (0.90,1.64)	5	1.32 (0.78,2.22)	11	**1.57 (1.02,2.41)**
Copper	824	107	1.09 (0.96,1.23)	66	1.02 (0.87,1.20)	155	1.01 (0.90,1.13)	179	1.09 (0.99,1.20)	52	1.14 (0.95,1.36)	76	1.08 (0.88,1.32)
Lead	508	56	0.91 (0.76,1.10)	53	1.16 (0.97,1.38)	110	1.03 (0.90,1.18)	92	1.03 (0.90,1.19)	22	1.08 (0.83,1.40)	66	1.05 (0.83,1.33)
Mercury	14	0	-	0		1	1.08 (0.55,2.09)	4	**1.72 (1.05,2.79)**	1	0.90 (0.17,4.62)	2	-

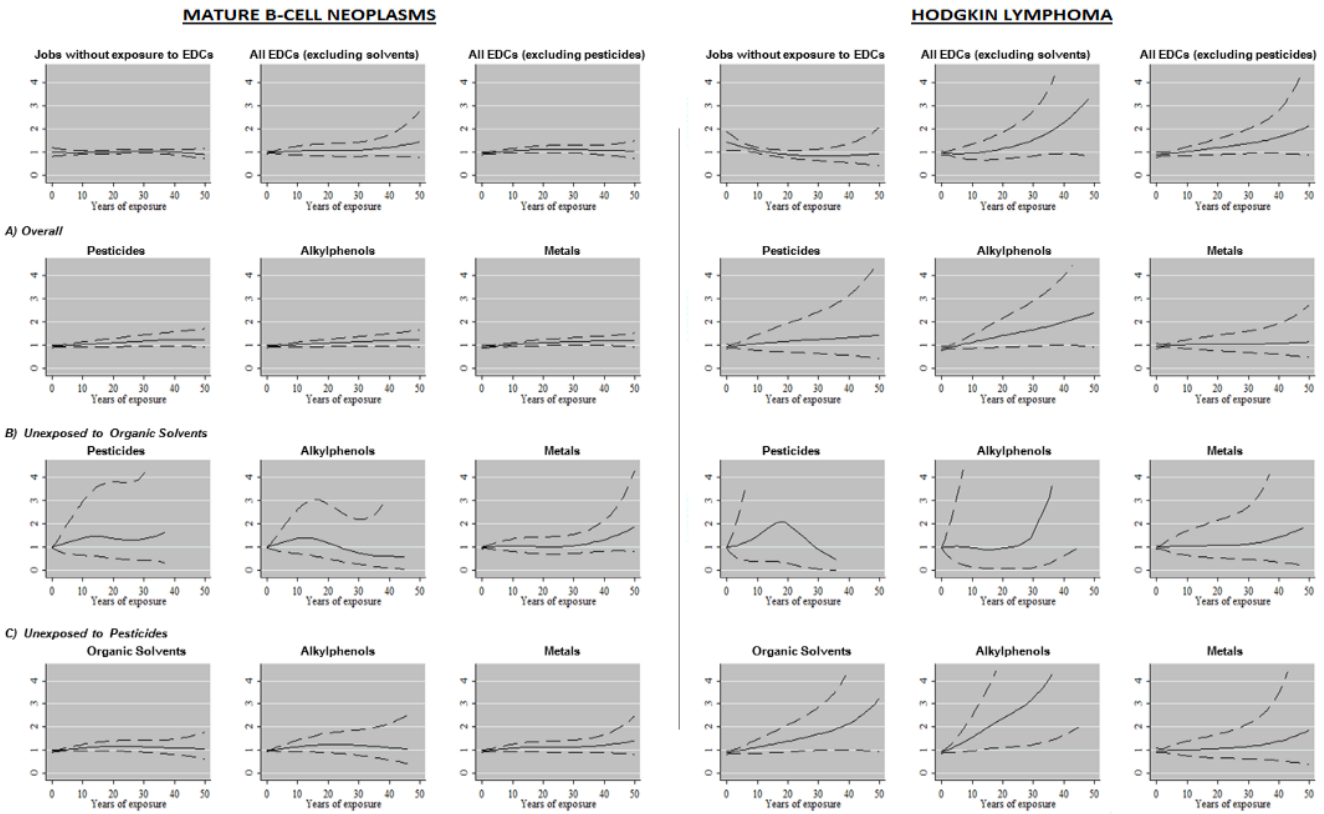
a Reference category for all comparisons. All models were adjusted for age, education, sex, country and ever exposure to organic solvents (except for estimates on organic solvents).

* p<0.05; ** p<0.01

Co= Controls / Ca= Cases

MM = Multiple Myeloma; FL= Follicular Lymphoma, DLBCL= Diffuse Large B-Cell Lymphoma; CLL= Chronic Lymphocytic Leukemia

Figure S1: Smooth splines for the effect duration of occupational exposure to endocrine disruptors in generalized additive models with two cutpoints for mature B-cell lymphoma and Hodgkin lymphoma. Models adjusted for age, sex, country and education level. Smooth estimates are represented in solid lines and 95% confidence intervals in dashed lines.



Appendix from Article 6

Appendix 1. List of occupational titles assigned to a possible or probable exposure to EDCs.

Agricultural and fishing trades n.e.c.
Agricultural machinery drivers
Air transport operatives
Ambulance staff (excluding paramedics)
Animal care occupations n.e.c.
Artists
Assemblers (electrical products)
Assemblers (vehicles and metal goods)
Auto electricians
Bar staff
Beauticians and related occupations
Bookbinders and print finishers
Bus and coach drivers
Car park attendants
Carpenters and joiners
Chemists
Cleaners, domestics
Conservation and environmental protection officers
Countryside and park rangers
Dental nurses
Dental practitioners
Driving instructors
Electrical/electronics engineers n.e.c.
Electrical/electronics technicians
Electricians, electrical fitters
Electroplaters
Farm managers
Farm workers
Farmers
Fire service officers (leading fire officer and below)
Fishing and agriculture related occupations n.e.c.
Floorers and wall tilers
Fork-lift truck drivers
Furniture makers, other craft woodworkers
Gardeners and groundsmen/groundswomen
Glass and ceramics makers, decorators and finishers
Glass and ceramics process operatives
Glaziers, window fabricators and fitters
Goldsmiths, silversmiths, precious stone workers
Hairdressers, barbers
Hairdressing and beauty salon managers and proprietors
Heavy goods vehicle drivers
Horticultural trades
Industrial cleaning process occupations
Laboratory technicians
Labourers in foundries
Launderers, dry cleaners, pressers
Leather and related trades
Lines repairers and cable jointers,
Managers in animal husbandry, forestry and fishing n.e.c.
Medical and dental technicians
Metal machining setters and setter-operators
Metal making and treating process operatives
Metal plate workers, shipwrights, riveters

Metal working machine operatives
Metal working production and maintenance fitters
Mobile machine drivers and operatives n.e.c.
Motor mechanics, auto engineers
Moulders, core makers, die casters
Musical instrument makers and tuners
Natural environment and conservation managers
NCOs and other ranks
Officers in armed forces
Painters and decorators
Paper and wood machine operatives
Paramedics
Pest control officers
Photographers and audio-visual equipment operators
Pipe fitters
Plastics process operatives
Plumbers, heating and ventilating engineers
Police officers (sergeant and below)
Postal workers, mail sorters, messengers, couriers
Precision instrument makers and repairers
Printers
Printing machine minders and assistants
Publicans and managers of licensed premises
Refuse and salvage occupations
Road construction operatives
Road sweepers
Roofers, roof tilers and slaters
Roundsmen/women and van salespersons
Routine laboratory testers
Rubber process operatives
School crossing patrol attendants
Screen printers
Sheet metal workers
Smiths and forge workers
Taxi, cab drivers and chauffeurs
Textile process operatives
Textiles, garments and related trades n.e.c.
Tool makers, tool fitters and markers-out
Traffic wardens
Transport operatives n.e.c.
Tyre, exhaust and windscreen fitters
Upholsterers
Van drivers
Vehicle body builders and repairers
Vehicle spray painters
Veterinarians
Veterinary nurses and assistants
Waiters, waitresses
Welding trades

Appendix from Article 6

Appendix 2. List of the 20 most common occupations of controls and mature B-cell lymphoma according to their longest-held job.

Controls			*Mature B-cell neoplasms*		
Job description	*N*	*%*	*Job description*	*N*	*%*
Personal assistants & other secretaries	103	4%	Farmers	84	4%
Shelf fillers	99	4%	Personal assistants & other secretaries	76	3%
Farmers	79	3%	Shelf fillers	66	3%
Cleaners, domestics	78	3%	Cleaners, domestics	64	3%
Nurses	68	3%	Farm workers	62	3%
Financial & accounting technicians	62	3%	Metal working production & maintenance f	41	2%
Kitchen & catering assistants	61	2%	Kitchen & catering assistants	40	2%
Farm workers	59	2%	Financial & accounting technicians	38	2%
General office assistants/clerks	53	2%	Metal working machine operatives	32	1%
Bricklayers, masons	49	2%	Gardeners & groundsmen/groundswomen	30	1%
Metal working production & maintenance f	48	2%	Bricklayers, masons	29	1%
Sewing machinists	43	2%	General office assistants/clerks	29	1%
Gardeners & groundsmen/groundswomen	41	2%	Bar staff	28	1%
Secondary education teaching professiona	41	2%	Nurses	27	1%
Bar staff	40	2%	Secondary education teaching professiona	27	1%
Sales related occupations n.e.c	37	2%	Sewing machinists	27	1%
Taxi, cab drivers & chauffeurs	36	1%	Shopkeepers & wholesale/retail dealers	25	1%
Chefs, cooks	33	1%	Chefs, cooks	23	1%
Metal working machine operatives	33	1%	Primary & nursery education teaching pro	23	1%
Primary & nursery education teaching pro	32	1%	Sales related occupations n.e.c	22	1%

APPENDIX

Appendix 1. Preliminary analises on reproductive factors and exogenous hormone use and CLL/SLL in the MCC-Spain study.

	CONTROL n (%)	CLL/SLL n (%)	OR[1] 95% CI
Have you ever been pregnant?			
No	98 (12)	15 (7)	REF
Yes	624 (79)	198 (89)	1.73 (0.95- 3.15)
Number children			
One	115 (15)	33 (15)	REF
Nulliparous	98 (12)	15 (7)	0.52 (0.26- 1.05)
Two	281 (36)	88 (39)	0.93 (0.57- 1.52)
2+	213 (27)	73 (33)	0.82 (0.49- 1.39)
Age at first child			
<=26	308 (39)	96 (43)	REF
26+	296 (37)	97 (43)	1.00 (0.70- 1.43)
Age at last child			
<=32	338 (43)	106 (48)	REF
32+	265 (34)	86 (39)	0.97 (0.69- 1.38)
Menopausal Status			
Menopause or post	638 (81)	199 (89)	
Natural	439 (69)	141 (71)	REF
Hysterectomy and/or ovariectomy	90 (14)	37 (19)	1.21 (0.78- 1.90)
other	12 (2)	10 (5)	3.14 (1.22- 8.09)
Pre-menopause	144 (18)	14 (6)	0.52 (0.24- 1.15)
Age at menarque			
<=13	483 (61)	130 (58)	REF
13+	233 (29)	80 (36)	1.11 (0.79- 1.57)
Age at menopause			
<=50	317 (40)	108 (48)	REF
50+	206 (26)	75 (34)	1.07 (0.74- 1.54)
Hormonal contraceptives (HC)			
Never	414 (52)	131 (59)	REF
Ever	375 (47)	82 (37)	0.80 (0.56- 1.15)
Oral	337 (43)	74 (33)	0.80 (0.56- 1.17)
No oral	8 (1)	2 (1)	0.99 (0.19- 5.16)
Both	28 (4)	2 (1)	0.30 (0.07- 1.34)
Duration of HC (years)			
<2	76 (10)	20 (9)	0.93 (0.53- 1.66)
2-8	113 (14)	31 (14)	0.98 (0.60- 1.61)
>=8	116 (15)	19 (9)	0.57 (0.32- 1.03)
p-trend			0.1
Ever HT (among post-menopausal women)			
Never	562 (88)	178 (89)	REF
Ever	38 (6)	14 (7)	1.12 (0.57- 2.17)
Duration of HT (years)			
<2	6 (1)	1 (1)	0.43 (0.05- 3.74)
2-4	16 (3)	4 (2)	0.79 (0.25- 2.49)
>=5	14 (2)	8 (4)	1.70 (0.68- 4.27)
p-trend			0.2

[1]Basic model: age (five groups), sex, region (5 categories) and educational level (3 groups)

Appendix 2. Selected characteristics of hormonal contraception and hormone therapy users in the Multi Case-Control Spain study.

TABLE. *Selected characteristics of hormonal contraception and hormone therapy users in the Multi Case-Control Spain study*

	Hormonal contraception				Postmenopausal hormone therapy[a]			
	Total (n)	Ever use (%)[b]	Age-adjusted PR (95% CI)	Fully adjusted PR (95% CI)[c]	Total (n)	Ever use (%)[b]	Age-adjusted PR (95% CI)	Fully adjusted PR (95% CI)[c]
Overall	1,954	48.5			1,381	9.8		
Sociodemographics								
Region								
Barcelona	385	53.0	Ref	Ref	300	7.3	Ref	Ref
Madrid	361	53.7	0.86 (0.76-0.98)[d]	0.85 (0.75-0.97)[d]	233	10.7	1.52 (0.88-2.63)	1.48 (0.87-2.54)
Gipuzkoa	253	51.8	0.87 (0.75-1.00)[d]	0.82 (0.71-0.94)[e]	177	17.5	2.47 (1.49-4.09)[f]	2.73 (1.67-4.47)[f]
León	199	39.2	0.69 (0.57-0.82)[f]	0.78 (0.64-0.94)[e]	139	7.2	1.06 (0.52-2.15)	1.25 (0.61-2.55)
Others	756	45.1	0.75 (0.67-0.84)[f]	0.79 (0.70-0.89)[f]	532	9.0	1.25 (0.77-2.02)	1.44 (0.89-2.33)
Age at recruitment								
≤45 y	350	72.3	Ref	Ref	18	11.1	Ref	Ref
46-55 y	454	65.9	0.91 (0.83-1.00)[d]	0.88 (0.80-0.97)[e]	276	5.4	0.49 (0.12-1.98)	0.70 (0.14-3.36)
56-70 y	685	45.5	0.63 (0.57-0.70)[f]	0.69 (0.61-0.79)[f]	645	14.6	1.31 (0.35-4.91)	1.92 (0.41-8.99)
>70 y	465	18.1	0.25 (0.20-0.31)[f]	0.33 (0.26-0.42)[f]	442	5.7	0.51 (0.13-1.99)	0.92 (0.19-4.48)
High education level of partner	935	59.9	1.28 (1.15-1.41)[f]	1.13 (1.02-1.26)[d]	614	12.7	1.70 (1.18-2.43)[e]	1.48 (0.97-2.26)
High education level	1,010	60.8	1.25 (1.13-1.39)[f]	1.13 (1.02-1.26)[d]	583	11.7	1.39 (1.00-1.93)	1.04 (0.72-1.50)
Lifestyle								
Body mass index								
Normal weight	868	56.7	Ref	Ref	536	11.6	Ref	Ref
Underweight	38	57.9	0.98 (0.77-1.25)	1.05 (0.83-1.32)	20	5.0	0.43 (0.07-2.88)	0.64 (0.09-4.49)
Overweight	577	47.0	0.98 (0.89-1.08)	1.02 (0.92-1.12)	444	10.6	0.90 (0.63-1.29)	1.00 (0.71-1.41)
Obesity	318	37.1	0.79 (0.68-0.92)[e]	0.86 (0.74-1.00)[d]	252	7.1	0.60 (0.36-0.98)[d]	0.73 (0.44-1.20)
Ever smoker	773	66.5	1.38 (1.26-1.51)[f]	1.28 (1.17-1.41)[f]	479	11.7	1.28 (0.91-1.81)	1.14 (0.81-1.61)
Reproductive history								
Parity								
1 child	359	39.6	Ref	Ref	203	11.8	Ref	Ref
Nulliparous	296	59.5	0.69 (0.59-0.80)[f]	0.73 (0.62-0.86)[f]	176	9.7	1.18 (0.66-2.10)	1.45 (0.73-2.85)
2 children	760	52.4	0.97 (0.88-1.08)	1.00 (0.90-1.11)	538	10.2	0.98 (0.59-1.63)	0.98 (0.59-1.64)
≥3 children	535	42.8	1.05 (0.92-1.20)	1.14 (0.99-1.30)	463	8.6	0.80 (0.46-1.39)	0.88 (0.50-1.56)
Cause of menopause								
Natural	1,101	39.2	Ref	Ref	1,045	7.8	Ref	Ref
Surgical	192	42.2	1.03 (0.87-1.22)	1.03 (0.87-1.22)	184	23.4	2.90 (2.07-4.05)[f]	3.05 (2.18-4.25)[f]
Others	27	40.7	1.01 (0.68-1.48)	0.93 (0.68-1.28)	25	20.0	2.59 (1.19-5.60)[d]	2.48 (1.21-5.08)[d]
Occupation								
Employment status at interview								
Working/employee	749	65.7	Ref	Ref	355	9.9	Ref	Ref
Unemployed	131	74.0	1.13 (1.02-1.27)[d]	1.09 (0.97-1.21)	74	6.8	0.67 (0.27-1.67)	0.67 (0.26-1.72)
Housewife	244	27.0	0.65 (0.53-0.80)[f]	0.71 (0.57-0.88)[e]	207	7.7	0.88 (0.50-1.56)	1.03 (0.57-1.84)
Retired	813	34.9	0.83 (0.74-0.95)[e]	0.86 (0.76-0.97)[d]	730	10.5	1.05 (0.71-1.56)	1.11 (0.74-1.65)
Shift								
Ever permanent day	1,312	51.8	Ref	Ref	913	9.7	Ref	Ref
Ever permanent night	39	66.7	1.11 (0.91-1.37)	1.10 (0.88-1.37)	15	20.0	2.27 (0.78-6.65)	2.18 (0.69-6.89)
Rotating	253	56.1	1.00 (0.89-1.12)	1.04 (0.93-1.17)	154	14.9	1.50 (0.99-2.29)	1.62 (1.07-2.47)[d]

From Costas et al [73]. PR: prevalence ratio. Ref: Reference. a) Among postmenopausal women. b) Row percentages. c) Fully adjusted models included age, region, and variables that were statistically significant in age-adjusted models (education level, education level of partner, body mass index, usual duration of sleep, and cause of menopause). d) p< 0.05. e) p<0.01 f) p<0.001

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