ELSEVIER

Critical Reviews in Oncology/Hematology 92 (2014) 181–193

CRITICAL REVIEWS IN
Oncology
Hematology
Incorporating Geriatric Oncology

www.elsevier.com/locate/critrevonc

Reproductive factors and non-Hodgkin lymphoma: A systematic review

Laura Costas [a,b,c,d,*], Silvia de Sanjosé [a,b,c], Claire Infante-Rivard [d]

[a] *Unit of Infections and Cancer, Cancer Epidemiology Research Programme, IDIBELL, Catalan Institute of Oncology, Barcelona, Spain*
[b] *Department of Medicine, University of Barcelona, Barcelona, Spain*
[c] *CIBER Epidemiologia y Salud Pública (CIBERESP), Madrid, Spain*
[d] *Department of Epidemiology, Biostatistics and Occupational Health, Faculty of Medicine, McGill University, Montreal, Canada*

Accepted 23 July 2014

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

* Corresponding author at: Unit of Infections and Cancer, Cancer Epidemiology Research Programme, Institut Català d'Oncologia, Av. Gran Via de l'Hospitalet 199-203, 08908 L'Hospitalet de Llobregat, Spain. Tel.: +34 93 260 7812; fax: +34 932607787.
E-mail addresses: laura.costas.ico@gmail.com, lcostas@iconcologia.net (L. Costas).

http://dx.doi.org/10.1016/j.critrevonc.2014.07.004

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