Etiology of non-Hodgkin lymphoma (C82–85, C96) in Central and South America

Maria C. Diumenjo1, Graciela Abriata2, David Forman3, Mónica S. Sierra3
1 Registro Provincial de Tumores de Mendoza, Argentina.
2 National Cancer Institute, Argentina.
3 Section of Cancer Surveillance, International Agency for Research on Cancer, France.

How to cite:

Although its etiology is poorly understood, infectious agents and immune system abnormalities have been consistently associated with an increased risk of non-Hodgkin lymphoma (NHL). Several other factors, such as a family history of lymphoma, occupational and environmental exposures, and lifestyle factors (i.e., tobacco smoking, alcohol consumption, and obesity) have also been implicated in this disease but the results across studies were inconsistent [1–7]. This section focuses on factors that are relevant for the Central and South American region.

Immunosuppression and infections

NHL strongly depends on immune function[8, 9] and declining immunity has been shown to increase the risk of NHL by approximately 100-fold [9]. Infections with HIV-1 and the Epstein-Barr virus (EBV), and chronic infection with hepatitis C virus (HCV) have been classified by the International Agency for Research on Cancer (IARC) as biological agents with sufficient evidence of causing NHL in humans [10]. IARC has also classified the following biological agents as having sufficient evidence that they cause certain subtypes of NHL in humans: T-cell lymphotrophic virus type-1 (HTLV-1) for adult T-cell leukaemia and Helicobacter pylori for mucosa-associated lymphoid tissue lymphomas (MALT) [10]. Some of the postulated mechanisms by which infections could cause NHL are: a) immunosuppression due to HIV-1 infection (indirect action); b) disruption of normal cell functions (cell proliferation, inhibition of apoptosis, genomic instability, and cell migration); c) chronic immune stimulation and persistent activation of lymphocytes; d) immortalization and transformation of T-cells; and e) oxidative stress [10, 11].

Gruulich et al. [12] evaluated the role of immune suppression among HIV-1/AIDS patients and among solid organ transplant recipients and found an increased risk of NHL compared with the general population (meta-analysis standardized incidence ratio [SIR], 76.67; 95% confidence interval [CI], 39.4–14.9 for HIV-1/AIDS in 7 cohort studies; meta-analysis SIR, 8.07; 95% CI, 6.4–10.2 for transplant recipients in 5 cohort studies). Vajdic and Leeuwen [13] described the incidence profile of NHL in solid organ transplant recipients using data from nine registry-based studies conducted in Australia, Canada, Denmark, Finland, and Sweden; the incidence of NHL 3.7–8.5 years after a kidney transplant was in the range of 3.8 to 9.9 and was remarkably high after liver (SIR, 13.9–20.8; mean follow-up, 4.5–6 years), heart/heart–lung (SIR, 26.2; mean follow-up, 5.3 years), or liver/heart/lung/pancreas...
(SIR, 37.3; mean follow-up, 3.7 years) transplants. NHL has also been reported in 2–3% of persons with AIDS, but this only accounts for a small fraction of all cases [14]. In most countries of Central and South America, the prevalence of HIV among adults (aged 15–49 years) in 2013 was < 0.6%, except for Belize and Guyana where the prevalence was 1.5% and 1.4%, respectively [15], and was much lower in this region than the global prevalence of HIV in adults (aged 15–49 years) or the prevalence in Africa (0.8% and 5.5%, respectively) [15]. These results suggest that the burden of HIV-related NHL in the Central and South American region is probably low.

Evidence has indicated an increased risk of NHL associated with primary immunodeficiency syndromes (Chediak-Higashi syndrome, ataxia telangiectasia, B-cell lymphoproliferative syndrome, Bruton agammaglobulinaemia, common variable immunodeficiency, and Wiskott-Aldrich syndrome) [16, 17]. Approximately 25% of patients with congenital (primary) immunodeficiency have been shown to develop tumours in their lifetime and, among these, 50% will develop NHL [18].

The incidence of nasal type extranodal natural killer/T-cell lymphoma (ENKTL) is higher in Brazil, Guatemala, Mexico, and Peru than in the USA (as cited in [19]). In Peru, a study of 28 cases of nasal type ENKTL revealed that 96% were positive for EBV [20]. In a study of 1028 cases of NHL from five countries of the Central and South American region (Argentina, Brazil, Chile, Guatemala, and Peru), Laurini et al. [21] found a higher overall prevalence of ENKTL (nasal type) than in North America (2.9% vs 0%; \( P < 0.05 \)), with the highest frequency observed in Guatemala (7.8%), Peru (2.9%), and Chile (2.6%). A high frequency of ENKTL has also been reported in Asians and Asian-Americans [7, 20]. Laurini et al. [21] suggested that the Asian ancestry of populations in the countries located along the west coast of the Central and South American region corresponds with the high frequency of ENKTL. However, little information is available on the prevalence of EBV and ENKTL in the region.

Dal Maso and Franceschi [22] reported a 2.5-fold increase in the risk of NHL among HCV-infected patients compared with controls (pooled relative risk [RR], 2.5; 95% CI, 2.1–3.1 in 15 case–control studies; RR, 2.0; 95% CI, 1.8–2.2 in 3 cohort studies). They also estimated that approximately 10% of NHL cases were attributable to HCV in countries where the prevalence of HCV-seropositivity in the general population was high (i.e., Italy) and less than 1% of cases in countries where the prevalence was very low (< 1%). In Argentina, Brazil, Mexico, Peru, and Venezuela, the estimated prevalence of HCV in the adult population ranged from 1.4% to 2.5% in 2010 (1.5% for all ages) [23], which was much lower than that reported among controls by Dal Maso and Franceschi [22] (i.e., prevalence of > 20% in Egypt and 5–10% in Italy). Even in a high-risk population (drug users) from Maracaibo-Venezuela, the HCV prevalence was still low (1%) [24].

Compelling evidence indicates that \( H. pylori \) infection causes low-grade gastric MALT lymphomas [7], with approximately 85–90% of the cases infected [25]. In the classification study of 1028 NHL cases from the Central and South American region, Laurini et al. [21] found that the overall frequency of MALT-type lymphomas in these countries was 6.9% which was similar to the frequency in North America (6.2%). The highest prevalence was observed in Chile (10.4%) and Brazil (9.4%) and the lowest in Guatemala and Peru (~4%). This is particularly relevant since the prevalence of \( H. pylori \) infection is lower in these regions.
In some parts of Africa (Central and West), the Caribbean Basin, Japan, and South America, adult T-cell leukaemia/lymphoma has been reported to be endemic and accounts from more than 50% of all NHL cases [14]. Moreover, HTLV-I infection is also endemic in populations of African ancestry from the Caribbean islands as well as in some areas in Brazil, Colombia, French Guyana, Guyana, Nicaragua, Panama, and Suriname, where the prevalence of the infection is between 1% and 5% [28]. Carneiro et al. [29] reported a similar prevalence of HTLV-1 across all 13 countries in the South American region (ranging from < 0.1% to 5%), and described the presence of HTLV-1 infection among Amerindian populations in Argentina, central and southern Bolivia, northern and southern Chile, southern Colombia, Paraguay, and south-eastern Peru. The study of 1028 NHL cases from Central and South America revealed that the frequency of adult T-cell leukaemia/lymphoma was higher in this region than in North America (1.1% vs 0%; \( P < 0.05 \)), with the highest frequency observed in Peru (5.5%) [21].

**Autoimmune disorders, diabetes, and blood transfusions**

A growing body of evidence has linked some autoimmune disorders with an increased risk of developing NHL [30, 31]. In a meta-analysis of 12 case–control studies conducted in Europe and North America, Ekstrom-Smedby et al. [31] showed that people who reported a personal history of Sjögren syndrome, systemic lupus erythematosus, or haemolytic anaemia had an increased risk of NHL (pooled RR, 6.56; 95% CI, 3.10–13.9 in 8 studies; pooled RR, 2.69; 95% CI, 1.68–4.30 in 11 studies; pooled RR, 2.57; 95% CI, 1.27–5.21 in 5 studies; although heterogeneity was found between studies). However, they did not observe an association between NHL and a wide range of other autoimmune diseases.

A growing body of evidence has also linked type-2 diabetes with an increased risk of developing NHL [32, 33]. In a recent meta-analysis of 21 studies conducted in Asia, Europe, and the USA, Castillo et al. [33] found that individuals with type-2 diabetes had a 21–24% higher risk of developing NHL (RR, 1.21; 95% CI, 1.02–1.45 in 11 cohort studies; RR, 1.24; 95% CI, 1.03–1.49 in 10 case–control studies; heterogeneity was found between the studies).

Several case–control and cohort studies have shown an association between blood transfusions and NHL. In a meta-analysis of 14 studies, Castillo et al. [34] showed that the risk of developing NHL increased by 20% (95% CI, 7–35%) in patients who received allogeneic red blood cell transfusions and the effects were stronger in the meta-analysis of the cohort studies (RR, 1.34; 95% CI, 1.15–1.55) than in that of the
case–control studies (RR, 1.05; 95% CI, 0.89–1.25). A subsequent sub-analysis revealed that, after receiving blood transfusions, the risk of developing chronic lymphocytic leukaemia/small lymphocytic lymphoma was higher (RR, 1.66; 95% CI, 1.08–2.56) than that of developing any other NHL subtypes (RR, 1.02 for follicular lymphoma; RR, 1.06 for diffuse B-cell lymphoma) [34]. The study of 1028 NHL cases conducted in the Central and South American region showed that the frequency of low-grade B-cell NHL, particularly follicular and chronic lymphocytic leukaemia, was lower in Guatemala and Peru than in North America [21].

**Occupational and environmental exposures**

Occupational and environmental exposures to malathion and diazinon (insecticides) and glyphosate (herbicide) have been positively associated with an increased risk of NHL; thus, IARC concluded that these agents are probably carcinogenic to humans [35]. Recent results from the Agricultural Health Study revealed that occupational exposure to dichlorodiphenyltrichloroethane, a pesticide, increased the risk of NHL [36]. In a meta-analysis of 44 occupational studies including 80 active ingredients and 21 pesticides, Schinasi and Leon [37] found positive associations between pesticides and specific subtypes of NHL, between glyphosate and B lymphoma, and between NHL and the following agents: phenoxy herbicides, carbamate insecticides, organophosphorus insecticides, and the active ingredient lindane, an organochlorine insecticide. In a separate meta-analysis of 10 occupational studies, Karami et al. [38] found that exposure to trichloroethylene was positively associated with an increased risk of NHL. These studies were conducted in the developed world, and no information on the impact of these substances in the Central and South American region is available. Pesticides are extensively used for farming purposes in the region, but little is known about their impact on health due to the lack of structured reporting and surveillance mechanisms in most countries [39].

**Family history and genetic factors**

Persons with a family history of NHL have an increased risk of developing NHL [14]. Several epidemiologic studies and genome-wide association studies have identified several candidate loci involved in the immune function which were associated with an increased risk of NHL, specifically diffuse large B-cell lymphoma, the most common NHL type [40–43].

**Other factors**

Immunosuppressive drugs, such as azathioprine and cyclosporine, have been classified as having sufficient evidence of causing NHL [44]; exposure to hair dyes has been evaluated in several studies with mixed results for an association with NHL [45, 46]; and there is limited evidence to suggest that exposure to X- or gamma-radiation is related to an increased risk of NHL [44].

Some studies have suggested that obesity and increased body weight may increase the risk of NHL and other lymphoid and haemopoietic malignancies. Obesity produces inflammation and alters immune responses and is thought to influence lymphoid and haemopoietic cell function [6]. Some studies have investigated the role of diet in the risk of NHL. The consumption of products such as milk, dairy, and meat...
has been related to an increased risk of NHL while the intake of fruit and vegetables has been related to a decreased risk of NHL [6]. However, further research is needed for a better understanding of such associations. Current evidence suggests a lack of carcinogenicity for tobacco smoking and alcohol consumption in NHL, but these two factors have been found to cause other cancers (i.e., lung, oesophagus, and breast among others) [47].

Acknowledgements

This work was undertaken during the tenure of a Postdoctoral Fellowship by Dr Mónica S. Sierra from the International Agency for Research on Cancer, partially supported by the European Commission FP7 Marie Curie Actions – People – Co-funding of regional, national and international programmes (COFUND). The authors also wish to thank Dr Tracy Lightfoot for her valuable comments.
References


