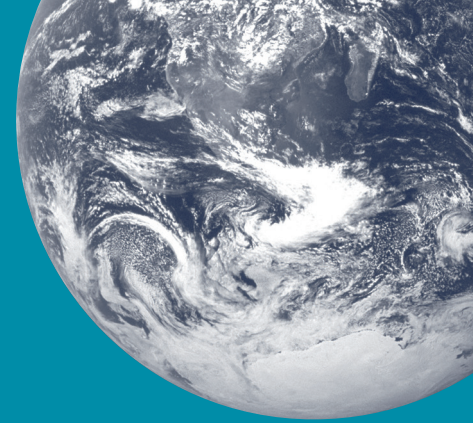




NON-HODGKIN'S LYMPHOMA IN THE WORLD: AN EPIDEMIOLOGICAL REVIEW

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Abstract – Objective: *Non-Hodgkin's Lymphoma (NHL) with a cancer burden of 3% is one of the most commonly reported malignancies worldwide. The present study aims to investigate the epidemiology and risk factors of this cancer in the world.*

Patients and Methods: *This study was conducted on published English studies by 2018 by searching in the databases of PubMed, Google Scholar and Web of Science. The search strategy included the keywords "Non-Hodgkin's Lymphoma", "Epidemiology", "Incidence", "Mortality", "Risk factors". Studies related to incidence, mortality, and causes of NHL were evaluated.*

Results: *The highest incidence rates of this malignancy were observed in North America, Australia and Europe, and the lowest ones were in Asia and the Pacific. At the same time, some studies reported that mortality rates increase in some areas. Based on previous studies, 1 out of 110 men and 1 of 161 women suffer from NHL during their life. Also, factors such as lifestyle, age and gender, occupational conditions and environmental factors, infectious agents, genetics and family history, and autoimmune diseases play an important role in the incidence of this disease.*

Conclusions: *The incidence and death rate of NHL are different in various regions. So that, the studies which show the incidence of this disease and better identification of the related factors, which are associated with these differences, can be useful.*

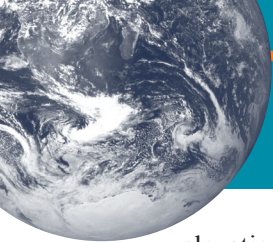
KEYWORDS: *Non-Hodgkin's lymphoma, Epidemiology, Risk factor, Incidence, Mortality.*

INTRODUCTION

Non-Hodgkin's Lymphoma (NHL) is a heterogeneous tissue and molecular malignancy that originates from B and T lymphocytes¹. It is the 10th most common cancer and 11th leading cause of cancer deaths in the world². Annually, 287,000 new cases of NHL are diagnosed worldwide³. The highest incidence of this type of lymphoma was observed in North America, Europe, the Oceania and some

African countries⁴ and the lowest incidence was in Southern Asia⁵. These geographic differences may be related to demographics, environmental dissimilarities⁴ and other factors like lifestyle, health behaviors and medical care systems⁶. NHL is a result of the combination of genetic and environmental factors⁷.

Meanwhile, the incidence and mortality rates in men are more observable than women⁴ and there is an upward trend among elderly people³. Significant



elevation in the incidence of this disease among patients over 50 years old, indicates the importance of environmental factors⁸.

Evidence suggests that this type of malignancy is associated with factors such as family history, lifestyle (cigarette, alcohol consumption, hair dying, anthropometric measurements), and autoimmune disease⁹.

Therefore, the study of the incidence and mortality of this disease in the world and its related factors is necessary. The present study was conducted with the aim of investigating the epidemiology, incidence, mortality and risk factors of NHL lymphoma in the world.

PATIENTS AND METHODS

This study was conducted on published English literature by 2018 by searching in the databases of PubMed, Google Scholar and Web of Science. The search strategy included the key words of "Non-Hodgkin's Lymphoma," "Epidemiology," "Incidence", "Mortality", "Risk factors", "World". Studies related to incidence, mortality and causes of risk of the NHL were also explored.

INCIDENCE RATE

From 1970 onward, the incidence of NHL has nearly doubled. This extension may be due to a faster diagnosis, which is indirectly caused by improved diagnosing methods and access to medical care³, or early detection of risk factors such as immune deficiencies and HIV infection¹⁰. The standardized incidence of NHL has been reported at 19.5% per 100,000 people in a year between 2016 and 2017¹¹. The highest incidence has been observed in South and Central American men and women, Uruguay, Ecuador, Peru and Colombia. However, Bolivia and Salvador have the lowest incidence⁴. This is 6, 6.3, 5.9, 5.8 and 4.7 per 100,000 people in Saudi Arabia, Oman, Qatar, Emirates and Bahrain, respectively^{12,13}.

In general, the highest incidence rates for this malignancy are in North America, Australia and Europe, and the lowest ones are in Asia and the Pacific¹⁴. Approximately 1000 new items are detected annually in Finland¹⁵. The standardized incidence rates for Indian men and women were 2.9 and 1.5 per 100,000, respectively⁵, while these statistics were reported to be 32.5 - 58.9 and 24.3-43.7 among Canadian males and females¹⁶. Generally, the incidence of this disease is different based on the geographical area, which is due to the distribution of genetic, environmental factors and lifestyle.

MORTALITY RATE

The death rate from NHL is rising, with an estimated 143,000 deaths in 1990 to 210,000 deaths in 2010¹⁷. The highest mortality rate has been reported from NHL in New Zealand and Canada⁴. The death rate from NHL in the United States was estimated to be 1910 in 2018¹¹ and 3,125 in Canada in the years 1984-2014¹⁶. Also, 52100 deaths due to this malignancy (32,700 among men and 19400 in women) were estimated in China in 2015¹⁸. Finnish men and women with 5 and 7 deaths per 100000 were at the highest rates¹³.

The highest mortality rates in South and Central America were found in Uruguay and Costa Rica, with the lowest observed death rate in Guatemala, El Salvador⁴. The death rate from this malignancy increased by 2.5% every year from 1991 to 1975, while there was a downward trend during the years 1991-1997 (1.6% per year); then, in the period 2006-2011, NHL fell by 3.1%¹⁹.

RISK FACTORS

Related Factors (Risk factor, Protective or Controversial factor) according to Host or non-modifiable factors and Environmental or modifiable factors to NHL are summarized in Table 1.

GENETIC AND FAMILY HISTORY

The Tumor Necrosis Factor (TNF) gene increases the risk of NHL and is associated with T lymphoma and Mantle Cell Lymphoma (MCL) cells. Interleukin 10 (IL-10) is a cytokine that causes the prolonged survival and proliferation of B cells. Some of the gene polymorphisms (IL-10) are associated with an increased risk of diffuse large B-cell lymphoma (DLBCL) and MCL⁷.

AUTOIMMUNE DISEASE

Patients with rheumatoid arthritis, celiac disease, systemic lupus erythematosus, and Sjogren are more likely to get NHL²⁰. In a meta-analysis study was reported that the risk of NHL in patients with lupus, rheumatoid arthritis and Sjogren was 3.9, 7.4 and 18.8%, respectively, more than those without the above-mentioned illnesses²¹.

INFECTIOUS FACTORS

The epidemiological studies indicate that the risk of NHL, in the case of hepatitis B virus, is 2 to 3 times higher than others²². Also, *Helicobacter py-*

TABLE 1. Related factor to NHL

Variable		Risk factor	Protective	Controversial
Host or non-modifiable factors	Family history	*		
	Age	*		
	Sex	*		
	Autoimmune diseases	*		
	Infectious agents	*		
	Drugs	Phenytoin	*	
	Radiotherapy	*		
	Chemotherapy	*		
Environmental or modifiable factors	Occupational exposure	Dioxin	*	
		Phenoxy	*	
	Lifestyle	Blond tobacco	*	
		black tobacco		*
		High-fat diet	*	
		Alcohol		*
		Smoking	*	
		Marijuana		*
		blood transfusion		*

lori, *Chlamydia psittaci*, Hepatitis C²³, EBV, and HIV²⁴ are associated with the risk of NHL. Infectious agents cause NHL with DNA damage, proliferation of inflammatory cells and cytokine release²³. It should be mention here that EBV is associated with burkitt lymphoma that is a native disease for African regions. Additionally, Human T-cell leukemia virus type 1 (HTLV-I) activates T-helper cells, which are native to the center of Japan and the Caribbean; meanwhile, hepatitis C virus cells with B cells, have more risk factors for NHL²⁵.

OCCUPATIONAL AND ENVIRONMENTAL CONDITION OR DRUG

Exposure to environmental factors or drugs such as phenytoin, dioxin, phenoxy herbicide, radiotherapy, and chemotherapy, increases the risk of NHL.

This disease is observed more often in veterinarians, miners who work with uranium, women workers in textile factories, farmers, chemists, people who deal with asbestos, rubber, wood, and petrol²⁶. The results of 26 cohort studies in the United States, England, Canada, Australia, Italy, and Finland indicate that among the workers involved in petroleum products, a relative risk of 0.90 (95% CI: 0.82–0.98) of mortality has been observed in these workers²⁰.

LIFESTYLE

Tobacco consumption is likely to be controversial in increasing the incidence of NHL. In a case-control study in Italy, long-term consumption of white

tobacco elevates the risk of NHL, while there was no such relationship with black tobacco²⁷. Smoking exposure during pregnancy may increase the risk of developing this malignancy^{28,29}.

High-fat diet^{30,31}, animal fat and milk consumption are a potential danger to NHL³², while alcohol consumption³³, marijuana³⁴, and blood transfusions³⁵ have an inverse relationship with the disease. On the other hand, the use of women's hair dye expands the chance of lymphoid malignancies by 2.3 times³⁶.

In addition, the prevalence of obesity has been associated with the incidence of NHL³⁷ and there has also been a positive correlation between consumption of red meat and the incidence of NHL in some cases²⁰.

Furthermore, the survival rate in patients with lower education and income, or living alone is much lower than that of others. It was reported to be 48% and 58% for those with basic or high school education. Instead, it was 58% and 65% among higher educated people³⁸.

AGE AND GENDER

Approximately 4 to 5% of all cancers in men and women are NHL³⁹. About 74,680 new cases of NHL have been diagnosed in 2018, of which 41,730 were in men and 32,950 in women. The incidence rate in men in all age groups is higher than in women, with an incidence of 7.3%, which is the third most common cancer in children, adolescents and young people under the age of 20. On the other hand, with increasing age, there is an upward trend in the in-



TABLE 2. Related factor to NHL

Aggressive lymphomas	Indolent
Diffuse large B-cell lymphoma (DLBCL)	Cutaneous T-cell lymphoma (mycosis fungoides and Sézary syndrome)
Mantle cell lymphoma (MCL) Peripheral T-cell lymphoma (PTCL)	Follicular lymphoma (FL) Lymphoplasmacytic lymphoma/Waldenström macroglobulinemia
Transformed follicular and transformed mucosa-associated lymphoid tissue (MALT) lymphomas	Marginal zone B-cell lymphoma
Burkitt lymphoma	Gastric mucosa-associated lymphoid tissue (MALT) lymphoma
Central nervous system (CNS) lymphoma	Chronic lymphocytic leukemia/small-cell lymphocytic lymphoma (CLL/SLL)
Acquired immune deficiency syndrome (AIDS)-associated lymphoma	

cidence of NHL, which is observable from 2.6% in the age group of 20-24 years old to 43.8% in the age group of 60-64 and 119.7 in the 100000 in the age group of 80-84 years old¹¹.

NHL SUBTYPES

NHL Subtypes of NHL were summarized in Table 2. NHL is divided into two groups of aggressive and non-aggressive (indolent) subtypes, and the indolent tumor growth is very slow⁴⁰.

The most common types of aggressive and non-aggressive subtypes are diffuse large B cell lymphoma (DLBCL) and follicular lymphoma (FL), respectively⁴¹. Chronic lymphocytic leukemia (CLL) is also a stage of small lymphocytic lymphoma (SLL), which is a type of B-cell lymphoma. DLBCL, FL and CLL/SLL are three of the largest subtypes B-cell lymphoma, responsible for 85% of NHLs⁴¹.

According to the American Cancer Society, 72,000 children and adults in 2017 had Hodgkin's Lymphoma, 60% of the patients had advanced neoplasms, the most common type of which is DLBCL⁴².

CONCLUSIONS

This study investigated the incidence and mortality of NHL in the world and the relationship between its risk factors and the occurrence of this type of malignancy. The incidence and mortality of this disease around the world are estimated 461000 (95% UI, 428000-482000 and 240000, 95%UI, 221000-248000, respectively). So that 1 out of 110 men and 1 out of 161 women suffer from NHL during their lifetime⁴³. It is noticeable that the incidence and mortality of the disease vary in different regions,

which can be due to the distribution of risk factors in different countries. Other factors such as life-style, age and sex, occupational and environmental factors, infectious agents, genetics and family history, and autoimmune disorders are also associated with this disease.

CONFLICT OF INTEREST:

The Authors declare that they have no conflict of interests.

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