Break Cancer

A Report on the Aspects of Non-Hodgkin's Lymphoma

Madhura Manjunath[1], Anjali Shah[2], Lyn Dias[3], Neeraja Kulasingam[4]

Ardrey Kell High School[1], Ardrey Kell High School[2], Ardrey Kell High School[3], Ardrey Kell High School[4]

Corresponding author:
Dr. Lopamudra Das Roy
Questions, please reach out:
lopa@breastcancerhub.org

ABSTRACT

Non- Hodgkin's Lymphoma is a category of blood cancer that occurs in a type of white blood cell called a lymphocyte. There are more cases of NHL found in developed countries than in LMIC. This research aimed to report information on the risk factors, signs, stages, treatment, types, and other associated parts of Non-Hodgkin's lymphoma. The greater goal is to spread this information so that the general population is more aware of this type of cancer is hoped to be accomplished. The methods used to conduct this research include information gathered from articles located in the database PubMed. Other resources used to search information consist of cancer.org, mayoclinic.org, webmd.com, a government study from lymphoma-action.org.uk, ncbi.nlm.nih.gov, and census.gov. The main connections observed from this research are the following. Firstly, we have noticed that several infections are related to NHL, such as HPLV-1, EBV, HHB-8, HIV, etc. Thus, there is a correlation between having a weaker immune system and having NHL. Secondly, we observed that developed countries are more technologically advanced, in turn having more GMO's, pesticide use, and radiation. Through a relation, we have recognized that NHL is positively correlated with developed countries and their advanced infrastructures. The recommendation is for people with the interest of ending the ignorance associated with Non-Hodgkin's Lymphoma to continue spreading accurate information and aiding others who are not familiar with this topic.

RISK FACTORS[1]

- ***What is Non-Hodgkin's Lymphoma?***
- Non- Hodgkin's Lymphoma is a category of blood cancer that occurs in a type of white blood cell called a lymphocyte, which constitutes much of the lymphatic system.

Age:

Although NHL is one of the more common cancers among children and teens, as one ages the risk of developing it increases throughout life, having had more than half of its patients being 65 or older at the time of diagnosis.

Gender:

About 74,200 people (41,090 males and 33,110 females) will be diagnosed with NHL. This includes both adults and children. About 19,970 people will die from this cancer (11,510 males and 8,460 females). There are certain types of NHL that are more common in women but overall men have a high risk factor of being affected.

Race, Ethnicity, and Geography:

Whites are most likely to develop NHL in the United States and Worldwide. NHL is more common in developed countries such as the United States and Europe that have some of the highest rates of NHL diagnosis till this date. It is the fifth most common cancer in the U.S, for both men and women. **An estimated 70,800 new cases and 18,990 deaths were recorded in 2014.**

Family history:

One can develop an increased risk of NHL if they have a first degree relative (parent, child, sibling) with NHL.

Body weight and diet:

Some studies suggest that being overweight or obese, or having a diet high in fat and meats may increase your risk of NHL.

RISK FACTORS[1]

Exposure to certain chemicals and drugs:

Although research between the links of chemicals such as benzene, herbicides and insecticides is still in progress, many scientists have suggested that it could increase the risk of developing NHL.

Some drugs used during chemotherapy or during the treatment of Hodgkin Lymphoma can increase the risk of developing NHL later in life.

Drugs like methotrexate and the tumor necrosis factor (TNF) inhibitors used to treat rheumatoid arthritis (RA) may increase the risk of NHL.

Having weaker immune system:

For example, people who have received organ transplants and are treated with drugs that help suppress their immune systems to prevent it from attacking the new organ.

Since HIV (Human Immunodeficiency Virus) can weaken the immune system, people with HIV have a higher risk of NHL.

Sometimes deficient immune systems are genetically inherited such as in ataxia-telangiectasia (AT) and Wiskott-Aldrich syndrome in children.

Radiation Exposure:

Case studies about people who have survived atomic bombs and nuclear reactor accidents have shown that they had an increased risk of developing not only NHL but also other cancers such as leukemia and thyroid cancer.

RISK FACTORS[1]

Certain Infections:

Infection with human T-cell lymphotropic virus (HTLV-1): This increases risk certain types of T-cell Lymphoma for a person. This virus spreads through sex, contact with contaminated blood, and even to children through breast milk from an infected mother.

Infection with the Epstein-Barr virus (EBV): EBV is known to be an important risk factor in some parts of Africa for Burkitt Lymphoma.

Human herpesvirus 8 (HHV-8): HHV can lead to a rare type of lymphoma called effusion lymphoma by affecting lymphocytes.

Autoimmune diseases:

NHL has been linked to some autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, Sjogren disease, celiac disease, and others.

In autoimmune diseases, the immune system mistakenly sees the body's own tissues as foreign and attacks them, as it would a germ. This sometimes causes the immune system to overreact and might make lymphocytes grow and divide at a faster rate. This in turn increases the risk of them developing into lymphoma cells.

Infections that cause chronic immune stimulation

A person's risk of lymphoma may increase when they have been infected for a long period of time forcing their immune system to be constantly active. As more lymphocytes are produced by the immune system to fight off the infection there are greater possibilities of mutations which can lead to lymphoma.

Helicobacter pylori, It is linked to mucosa-associated lymphoid tissue (MALT) also known as lymphoma of stomach

Chlamydophila psittaci is a type of bacteria that is known to cause a lung infection called psittacosis. It has been linked to MALT lymphoma in the tissues around the eye.

COMMON LYMPHOMAS CAUSED BY B-CELLS[3]

Diffuse large B-cell lymphoma : This lymphoma caused by B-cells is the most common type of NHL in the United States with the ratio for about 1 out of every 3 lymphomas. The average given age at the time of diagnosis is somewhere near 60. Although DLBCL is an aggressive lymphoma it replies quickly to treatments, with the overall success rate of 3 out of 4 people not experiencing signs of disease after treatment.

Follicular lymphoma:. Although there are follicular lymphomas that can grow quickly, most are indolent. The average given age at the time of diagnosis is somewhere near 60. As time passes by they may turn into DLBCL making it easier to treat.

Hairy Cell Leukemia: Average age is 50, more common in men, 700 cases per year in the United States. Since it is an indolent many people do not need treatment and when people do undergo treatment its extremely effective.

Lymphoplasmacytic lymphoma: It is not a very common lymphoma (1-2% of all lymphomas) and is indolent.

Mantle Cell Lymphoma (MCL): It is more common in people older than 60 and in men than in women. Although MCL grow faster than indolent lymphomas it often doesn't respond to treatment like aggressive lymphomas making it challenging to treat. There are now newer treatments that might assure patients and offer a chance to lead long-term life.

Chronic lymphocytic leukemia (CLL) /small lymphocytic lymphoma (SLL): CLL and SLL are not the same but are very closely related. CLL and SLL both contain the same type of cancer cells known as *small lymphocytes*. The only major difference is that CLL cancer cells are mostly found in the blood and bone marrow and SLL cancer cells are found mainly in lymph nodes and spleen. They both share the same treatment although they are usually hard to cure or even incurable with standard treatments.

LYMPHOMAS CAUSED BY B-CELLS[3]

Burkitt lymphoma: This accounts for about 1-2 percent of all lymphomas found in adults . It is an aggressive lymphoma and is more common in males than in females.

Africans variety (or endemic): This lymphoma starts as a tumor in the jaw or other facial bones and most cases of it are linked to Epstein-Barr virus (EBV). Rare in the United States.

Immunodeficiency-associated: It is often related with an immune system problem.

United States (or non endemic): This lymphoma starts as a tumor in the abdomen. Also sometimes found in ovaries, testicles or other organs. This is also partly linked to EBV.

Marginal Zone Lymphomas: About 5%-10% of lymphomas are MZL. They are indolent lymphomas. There are three types of marginal zone lymphomas.

MALT: Under MALT there are gastric and non-gastric lymphomas. Gastric MALT lymphomas are linked to an infection caused by Helicobacter pylori and starts in the stomach. Non gastric MALT lymphomas can start anywhere outside of the stomach. Antibiotics is a preferred treatment by doctors since many types of MALT lymphomas are usually caused by bacteria or viruses.

Nodal marginal zone B-cell lymphoma: This is a rare disease. It starts in lymph nodes and is indolent.

Splenic marginal zone B-cell lymphoma: This is also a rare type of lymphoma. It doesn't need to be treated unless the symptoms

B-CELLS VS. T-CELLS

- ***There are two ways lymphoma can begin:***
- ***B-Cell:*** B-cells are known to produce antibodies that help fight infections by neutralizing foreign invaders.[2] B-cells are the cause of most Non-Hodgkin's Lymphoma. Non-Hodgkin's Lymphoma subtypes that involve B-cells are; diffuse large B-cell lymphoma, follicular lymphoma, mantle cell lymphoma and Burkitt lymphoma.[3] B-cells make up about 85% of Non-Hodgkin's Lymphoma cases in the United States. **This means these lymphomas directly affect B-cell lymphocytes.**
- ***T-Cell:*** Instead of fighting infections by neutralizing foreign invaders, T-cells directly kill these invaders.[2] They account for less than 15% of lymphomas in the United States.[4] Each one of the following has several of its own subtypes.
- ***T-lymphoblastic lymphoma/leukemia***[4]
- ***Peripheral T-cell lymphomas***[4]

SIGNS AND SYMPTOMS [5]

Swollen lymph nodes:

Abdominal pain or swelling:

This can be caused by growths in the spleen or liver and or a buildup of fluids.

Trouble breathing, persistent cough, or chest pain/pressure

Lymphoma in the lungs or the lymph nodes in the chest can press on the windpipe.

SVC Syndrome:

If Lymphoma press on the SVC(superior vena cava-a vein that carries blood), it causes blood to back up in the veins.

It causes swelling/bluish-red color in head, arms, and upper chest.

It can also cause trouble breathing and a change in consciousness if it affects the brain.

Lymphoma in the brain:

Can cause headache, trouble thinking, weakness, personality changes, and sometimes seizures

Weight loss/feeling of fullness after small amounts of food

Loss of appetite

Nausea or vomiting

Lumps on the

Fatigue

Fever

Night sweats

Easy bruising/bleeding

Severe or frequent infections

STAGES OF NHL[6]

- ***Stage I- one of these cases:***
- Lymphoma is only found in one particular area such as the tonsils, with 1 lymph nodes.

or

- The cancer itself is found in only 1 part of a particular organ outside the lymph system .

- ***Stage II- one of these case:***
- The cancer is in 2 or more groups of lymph nodes, but on the same side of the diaphragm. For example, it can't include the underarm and groin area but it can include the underarm and neck
- The lymphoma is now in a group of lymph nodes, and is in one area of a nearby organ. It is also possible for other groups on the same side of the diaphragm to be affected.

- **Bulky Disease**- characterized by big tumors in the chest and needs more intensive treatment. It is important to diagnose this by stage 2.
- ***Stage III- one of these cases:***
- The lymphoma is on both sides of the diaphragm
- The lymphoma is in the spleen and in lymph nodes above the diaphragm

- ***Stage IV- one of these cases:***
- The lymphoma has spread to at least one organ other than those in the lymph system, ie. lung, bone marrow, kidney

DIET

Good for **preventing NHL:**	Bad for **preventing NHL:**	Good **after recovery:**	Bad **after recovery:**
A higher-than-average intake of dietary fiber have a reduced risk of non-Hodgkin's lymphoma.[7]	However, If a person has a higher intake of animal protein or saturated fat have an increased risk of Non-Hodgkin's lymphoma.[7]	Consuming high intakes of green leafy vegetables and citrus fruits before getting NHL were associated with a 29% and 27% reduced risk of death.[10]	No dietary supplements (including vitamins, minerals, and herbal products) have been shown to clearly help lower the risk of lymphoma progressing or coming back.[8]
Risk reducing foods: tomatoes, broccoli, squash, cauliflower, onions, mixed lettuce salad, leeks, apples, pears, and citrus fruits.[9]	High-risk foods: dairy products, eggs, high-protein foods, and saturated fats.[9]	Eating two portions of fish a week and dairy products, especially low fat options is recommended after recovery; it is also important to have a high protein and high carb diet to promote recovery.[9]	Red meat is still linked to cancer, however, and may cause a relapse, so it is best to avoid it or limit it to 70 grams a day.[9]

Monoclonal Antibodies: Artificial antibodies that are designed to attack specific antigens. They can be used to treat Non-Hodgkin's Lymphoma by being designed to attack substances on lymphocytes.[12]

Some examples of substances on lymphocytes that monoclonal antibodies can be used to attack cancer cells are: **CD20, CD52, CD30, and CD779b.**[12]

Immune Checkpoint Inhibitors: The body's immune system's cells have "checkpoints" that have the function of preventing the cells from attacking healthy cells. Cancer cells take this to advantage by using this to prevent the immune system to attack them.

Immune checkpoint inhibitors block these checkpoints so that cancer cells can be targeted.[12]

Chimeric Antigen Receptor (CAR) T-Cell Therapy:

- T-cells are taken from the patient into the lab.
- Chimeric antigen receptors (CARs) are placed on the cells by altering them. These receptors are able to attach to lymphoma cells and cause an immune system action against them.
- The cells are multiplied and added back to the patient to kill lymphoma cells.[12]

- **IMMUNOTHERAPY-** A type of cancer treatment in which **a patient's immune system is used to fight against cancer.** Can be done by either stimulating a person's immune system to act smarter or harder to kill cancer cells or giving components to a person's immune system to fight the cancer cells.[11]

CHEMOTHERAPY

Chemotherapy: Works by targeting cells at different stages of the cell cycle, which is different with each drug**. Is effective because it can target cells throughout the entire patient's body, which also kills metastasized cancer cells.** The negative side is that chemo drugs have the potential to damage a patient's healthy cells.[13]

Intrathecal Chemo- Since chemo given through IV or the mouth are unable to reach lymphomas in the brain and cord, this special type of chemo is **given in the cerebrospinal fluid**. [14]

Tumor Lysis Syndrome- In fast growing lymphomas, . The cancerous cells' contents spill into the blood, so the minerals get built up. The kidneys are unable to filter out the contents so quick .This **can cause kidney failure, heart, and nervous system problems.**[14]

Chemotherapy drugs are grouped by how they work. The most common drugs are :

Alkylating Agents- Damage the cell's DNA, so that it cannot reproduce. Can work in all phases of the cell cycle. Side effects are that it can also damage bone marrow cells, which makes it a risk for developing leukemia.[15]

Corticosteroids: They can also be used to prevent nausea, vomiting, and severe allergic reactions as a result of chemo.[15]

Anti-metabolites: Works during the synthesis phase of the cell cycle. They **substitute the normal building blocks of RNA and DNA** when DNA is being replicated, which damages the cell.[15]

PEDIATRIC NON-HODGKIN'S LYMPHOMA IN DEVELOPING COUNTRIES[16]

NHL Cases in children in the United States younger than 20 years of age is 10 cases per million which is around 7% of all pediatric cancers.

Most common Pediatric NHL in the United States:

- Burkitt lymphoma- 40%
- Lymphoblastic lymphoma- 25%
- Diffuse large B-cell lymphoma- 10%
- Anaplastic large lymphoma- 10%

However in parts of the world the following are the unusual increased Burkitt lymphoma rates:

- Sub-Saharan Africa: 10- to 20- fold higher
- Guatemala: 2- to 4- fold higher

LMIC also known as low and middle income countries account for over 80% of pediatric cancers.

5 year survival rate has increased from 45% to 87% in children younger than 15 and 48% to 82% for those between 15-19 years of age, in the **United States** between the years 1975 and 2010.

Despite this steady change occurring in the United States, **low and middle income countries are still struggling to improve their survival of pediatric NHL.**

ANALYSIS ON OCCURRENCE OF PEDIATRIC NHL IN DEVELOPING COUNTRIES[16]

Problems during diagnosis and staging that occur:

In many LMIC clinical confirmation of diseases and cancers such as NHL, proper practices are not widely performed causing the patients of NHL to be less aware about the symptoms and the disease itself.

1. Lack of correct anatomical location and ability to do proper surgery to take tissue samples from the patient for diagnoses.
2. When patients come to the doctor, they have a poor medical state.
3. There is not much technology that is required to diagnose NHL, such as tissue processing and staining.
4. There is a lack of money to buy the equipment and technology needed for a proper diagnosis.

Additionally, many LMIC centers lack access to cancer treatments such as radiation therapy, immunotherapy, and oncological surgery.

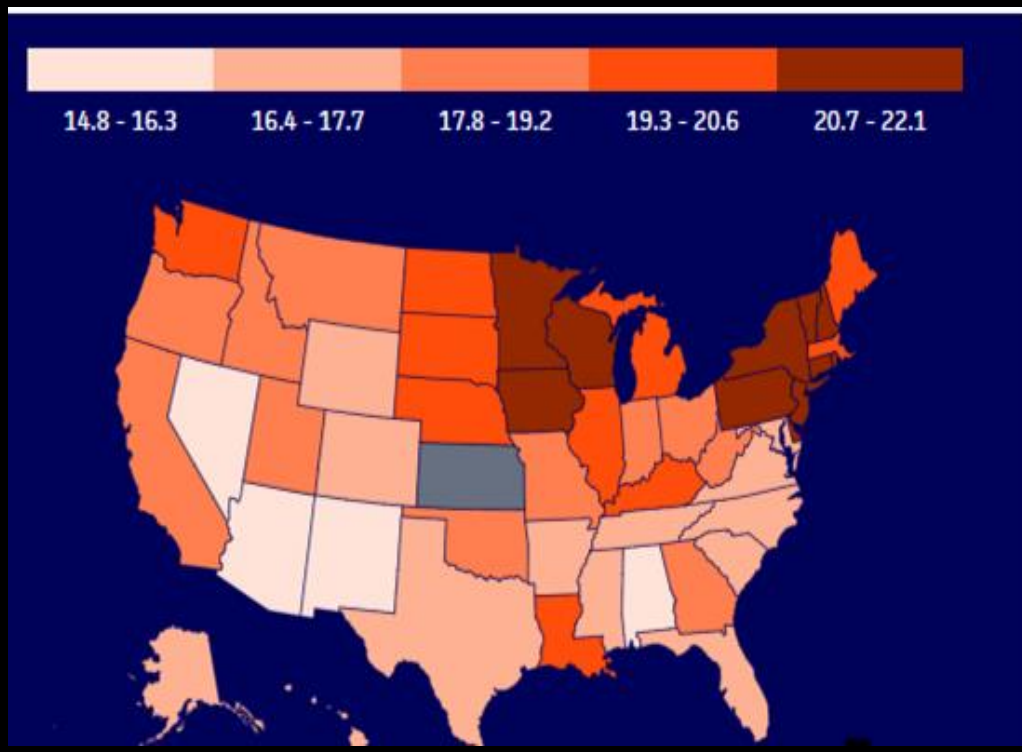
These problems were clearly shown in a report from Kenya, where as many as 25% of patients were not able to have a full staging or diagnosis of a certain disease.

Many developing countries have improved their facilities and treatments for cancer patients. For example, in Guatemala, the drug methotrexate has been started to used for chemotherapy for cancer patients. Additionally, the survival rate has increased to be 83%, although the survival rate is still low for stage IV cancer patients.

Analysis

State	Percentage of the Population being of the White Race
Minnesota	**84.1%**[18]
Iowa	**90.7%**[18]
Wisconsin	**87.1%**[18]
Florida	**77.3%**[18]
Texas	**78.8%**[18]
Alabama	**69.1%**[19]
South Carolina	**68.5%**[19]

Incidents rates of NHL from 2011- 2015[17]



https://cancerstatisticscenter.cancer.org/#!/cancer-site/Non-Hodgkin%20lymphoma

In the US, whites are more likely than African Americans and Asian Americans to develop NHL. **Northern states such as Minnesota, Iowa, Wisconsin, that consist of a higher population of the white ethnicity have higher rates of incidents**, thus proving a correlation between race and the occurrence of NHL in a specific region. Adding on, developed countries such as United States, and Europe have higher rates of NHL diagnosis than developing countries such as India, Brazil and China that have much lower rates. This shows that race plays an important role as a risk factor in developing NHL. There is not enough data from developing countries on NHL but it is know that countries like the United States and Europe have the highest rates from available data.

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