

**Deanship of Graduate Studies
Al-Quds University**

**Nutritional Factors and the Risk of Non-Hodgkin
Lymphoma among Palestinians**

Maram Mohammed Al-Fityani / Dahdoul

M.Sc. Thesis

Jerusalem-Palestine

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Prepared By:

Maram Mohammed Al-Fityani / Dahdoul

**B. Sc. in Pharmacy-An-Najah National University-
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Thesis submitted in partial fulfillment of the requirement of
the degree of Master of Health Policy and Management /
School of Public Health / Al-Quds University

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Al-Quds University

Deanship of Graduate Studies

Health Policy and Management / School of Public Health

Thesis Approval

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Palestinians**

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Jerusalem-Palestine

1437 / 2015

Dedication

My thesis is dedicated to my husband Waleed, my sons Kareem, Mohammed, Rayaana, and Sedra and to my parents, my brothers, my sister and to my husband's parents and to Dr. Rania Abu Seir who supported me in all my thesis steps and was a great source of motivation and inspiration.

To everyone who supported me in accomplishing this work.

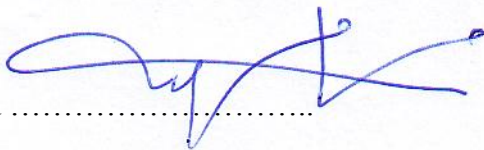
Great thanks for your support

Maram Mohammed Al-Fityani / Dahdoul

Declaration:

I certify that this thesis submitted for the degree of Master, is the result of my own research, except where otherwise acknowledged, and that this study (or any part of the same) has not been submitted for a higher degree to any other university or institution.

Signed

A handwritten signature in blue ink, consisting of several loops and strokes, positioned over a dotted line.

Maram Mohammed Al-Fityani / Dahdoul

Date:

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I would like to express my deep gratitude and appreciation to my supervisor, Dr. Rania Abu Seir, who gave me invaluable guidance and was always accessible with friendly support throughout my time at Al-Quds University.

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Nutritional Factors and the Risk of Non-Hodgkin Lymphoma among Palestinians

Prepared by: Maram Mohammed Al-Fityani / Dahdouh

Supervisor: Dr. Rania Abu Seir

Abstract:

Background: The incidence of Non-Hodgkin Lymphoma (NHL) increased worldwide during the second half of the last century and then stabilized during the nineties but subsequently increased. Environmental factors and dietary habits have been reported to play an important role in the etiology of NHL by influencing the immune system. However, no such data are available from Palestine.

Objectives: To participate in establishing a platform to study B-NHL in Palestine and further to examine the association between dietary factors and the risk of B-NHL among Palestinian B-NHL patients versus controls.

Design: Case-control study.

Methods: A case-control study was conducted between 2009-2013 including 306-histological confirmed B-NHL cases and 392 cancer-free controls among adult Palestinians recruited from three major Palestinian hospitals in the West Bank and Jerusalem which have an oncology department in addition to Hadassah Hospital in West Jerusalem. In the primary study analysis, an imbalance was encountered in the regional distribution of cases and controls in the central area. In order to correct for this imbalance, I recruited 71 controls from the primary health care centers in Jericho, Ramallah and Al-Azaria on the basis of frequency matched case-control study in terms of age and gender and region. The study participants were administered a questionnaire which is based on the international Epi-Lymph questionnaire, which focuses on demographic characteristics, types of environmental exposure and on diet and nutritional intake, specifically meat, milk, dairy, vegetables and fruits. Blood samples were also collected from participants for the purpose of DNA purification and viral serology testing.

The overall data-base was used to study the association between nutritional factors and the risk of NHL. The data was analyzed by Statistical Package for the Social

Sciences(SPSS)and associations were examined by multivariate logistic regression. For food intake analysis, the median value for each food group was calculated from overall distribution of the study population in order to use the value below the median as a reference value to detect associations by logistic regression.

Results: High consumption of meat (OR=1.8; 95% CI: 0.8-4.3) and milk (OR=1.3; 95% CI: 0.7-2.6) was found to be positively associated with the risk of B-NHL. Vegetable intake was also positively associated with the risk of B-NHL (OR=1.3; 95% CI: 0.4-4). Similarly, dairy products were significantly associated with an increased risk of B-NHL (OR=2.3; 95% CI: 1.2-4.4). In contrast, a significantly inverse association was encountered between fish consumption and B-NHL risk (OR=0.4; 95% CI: 0.2-0.8), and an inverse association was found between the consumption of fruits and B-NHL risk (OR=0.7; 95% CI: 0.2-2.1).

Conclusion:The results of this study showed that dietary intake may affect the risk of NHL as positive associations were found with meat, milk, dairy products and vegetables consumption, while an inverse association with fish and fruits consumption was encountered.

Keywords: dietary factors, non-Hodgkin lymphoma, case–control study, Palestine.

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List of abbreviations

Abbreviation	Term
AIDS	Acquired immune deficiency syndrome
B-NHL	B-cell non-Hodgkin lymphoma
BL	Burkitt lymphoma
CLL	Chronic lymphocytic leukemia
CI	Confidence interval
DLBCL	Diffuse large B-cell lymphoma
DRI	Dietary reference intake
EBV	Epstein-Barr virus
FL	Follicular lymphoma
HIV	Human immunodeficiency virus
HL	Hodgkin lymphoma
<i>H.pylori</i>	Helicobacter pylori
HTLV-1	Human T-cell leukemia/lymphoma virus
MOH	Ministry of Health
MOA	Ministry of Agriculture
NHL	Non- Hodgkin lymphoma
NK	Natural killer cells
OR	Odds ratio
SLL	Small lymphocytic lymphoma
TFAs	<i>Trans</i> fatty acids
T-NHL	T-cells Non-Hodgkin Lymphoma
WB	West bank
WHO	World health organization
RDA	Recommended daily allowance
USDA	United State Department of Agriculture

Chapter One

Introduction

1.1 Background

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of malignant neoplasms that result from the malignant transformation of lymphocytes at different developmental stages in the lymph nodes, spleen, and other organs of the immune system in the body (Alexander et al., 2007). NHL has more than 36 multiple subtypes that could arise from either B, T or natural killer cells according to new WHO classification (Jaffe, 2009) with specific molecular and clinical characteristics for each subtype (Novikova, Zotova, Dudareva, & DudarevAv, 1987). The major B-NHL subtypes are diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), Burkitt lymphoma and marginal zone B-cell (MZL) (Han et al., 2010; Schwartzkopff & Pahlitzsch, 1986).

NHL has generated increased interest internationally; incidence rates of NHL worldwide increased during the second half of the last century, stabilized during the nineties, and increased subsequently after 2000 but at lower rate (Cartwright et al., 1999; Chiu & Weisenburger, 2003; Kabat et al., 2012; Muller, Ihorst, Mertelsmann, & Engelhardt, 2005; Zheng et al., 2004). Nowadays, the incidence of NHL is among the highest in the west; for example, in the USA, 71,850 people are expected to be diagnosed with NHL and 19,790 are expected to die from this cancer (seer.cancer.gov/, 2014; Siddiqi & Rosen, 2015).

Furthermore, incidence rates have increased in Israel and some Arab countries, and according to the Middle East Cancer Consortium (MECC), in the period 1996-2001 the incidence rates of NHL per 100,000 were as the following: 15.2 for Israeli Jews, 14.2 for Egyptians, 10.2 for Israeli Arabs, 10.2 in Cyprus and 6.4 in Jordan (NCI, 2006).

In Palestine, cancer was the second-leading cause of death after cardio vascular diseases with increased incidence rate that reached 79.5 cases per 100,000 population in 2013. The four most common types of cancer were: breast, colon, lung cancer and leukemia, yet, NHL was reported to be one of the most commonly diagnosed hematological malignancies, the 8th most common cancer among women and the 11th among men with an incidence rate of 2.2 per 100,000 population in 2013. In addition, mortality from Cancer in the West Bank gradually increased from 10.3% of all deaths in 2007 to reach 13.3 % in 2013 (MOH, 2013).

Young males are diagnosed more frequently with NHL than young females, but this difference decreases with age. In addition, NHL is more common among people over 65 years and among whites than blacks (Chiu & Weisenburger, 2003; Czene, Adami, & Chang, 2007).

Several risk factors have been reported to be associated with NHL including immunodysregulation (congenital immunodeficiency, acquired immunodeficiency, and autoimmune diseases), genetic risk factors, environmental exposures (e.g. infection and occupational exposures) in addition to personal habits and lifestyle which includes dietary intake (Mozaheb, Aledavood, & Farzad, 2012). The role of dietary factors in the etiology of NHL is still largely undefined despite the fact that food is the largest single antigenic challenge to the human immune system. It is quite likely that dietary habits and lifestyle play a role in the etiology of NHL by influencing the immune system regulation, oxidative stress and hormonal pathways regulating the proliferation of lymphoid tissue (Ali, Al-Belushi, Waly, Al-Moundhri, & Burney, 2013; Mozaheb et al., 2012).

Several previous studies have reported evidence of an association between dietary patterns and the risk of several types of cancers (Davis, 1992; Donaldson, 2004). Some studies have reported a positive association between the intake of protein, meat, dairy products and fat and the risk of NHL, but some others have reported no association (Ali et al., 2013; Daniel

et al., 2012). In contrast, other studies have reported reduced risk of NHL with intake of fruits and vegetables (Kelemen et al., 2006; Ollberding et al., 2014; Thompson et al., 2010).

1.2 Study Problem

NHL is a group of blood cancers whose incidence rates worldwide has risen much over the past decades (Kabat et al., 2012; Muller et al., 2005). In fact, NHL is the 8th most common cancer among women and the 11th among men in Palestine (MOH, 2013).

The increase in the incidence of NHL has been attributed to immunodeficiency, various infections, familial aggregation, blood transfusion, genetic susceptibility, occupational and chemical exposure, as well as dietary and lifestyle factors (Hartge et al., 2006).

Dietary intake and nutritional factors have been reported to contribute to the risk of NHL (Ali et al., 2013). This association may be investigated by studying the dietary profile of B-NHL patients before their sickness as compared to the cancer-free controls.

1.3 Study Justification

- NHL is an important cause of morbidity and mortality worldwide. NHL incidence rates from 1950-2000 increased globally, tripling in people aged >65years (Chiu & Weisenburger, 2003; Kabat et al., 2012).
- In Palestine, cancer is considered to be the second leading cause of death, while NHL is currently reported to be one of the commonly diagnosed hematological malignancies, and ranks as the 8th and the 11th cancer in females and males respectively (MOH, 2013).
- There are very limited studies in Arab and neighboring countries that investigated the association between NHL and nutritional intake, for example Omani study in 2013 (Ali et al., 2013). In Palestine, the association between NHL and nutritional intake has never been investigated.

1.4 Study Goal and Specific Objectives

The study aimed to determine whether nutritional and dietary intake is associated with the risk of NHL among adult Palestinian B-NHL patients. And the specific objectives were:

- 1) Participating in establishing a platform for studying lymphomas in Palestine.
- 2) Studying the association between the B-NHL disease and the intake of some local food stuff like:
 - a. animal protein intake
 - b. milk and dairy intake
 - c. vegetable intake
 - d. fruit intake
- 3) Examining the characteristics of B-NHL among Palestinian patients in terms of average age at diagnosis, gender distribution and histological subtype frequencies.

1.5 Study Question

Does dietary intake contribute to the risk of NHL?

1.6 Study Hypothesis

This study assumed that there is no association between food intake pattern and the risk of NHL disease.

1.7 Ethical Considerations

This study was approved by the Research Review Committee at Al-Quds University. The questionnaire and the consent forms were both approved locally by the Research Review Committee at Al-Quds University and internationally by the Inter-Lymph Consortium.

An approval letter by the Ministry of Health addressed to the health directorates was secured to facilitate data and blood samples collection (Appendix 1.1).

The objectives of the study, the consent form (Appendix1.2) and the interview and blood collection procedures were all clearly explained to the selected patients and controls in a special meeting. The subjects' right to participate in the study or to withdraw from it at any point of time was emphasized; the researcher stated to the patients quite clearly that their decision whether to participate or not will have no effect on the level of medical care they receive. In addition, the researcher emphasized the confidentiality of the data to be collected.

Finally, this thesis has not been submitted for a higher degree to any other university or institution, results of my own research work that used for scientific research purposes only.

Chapter Two

Literature Review

2.1 Disease Pathogenesis

The understanding of the molecular pathogenesis of NHL has significantly improved in recent years (Czene et al., 2007). NHL is a heterogeneous group of malignant neoplasms arising from the B, T and NK cells of the immune system. B-cell lymphomas (B-NHL) arise during the different stages of B-lymphocyte development, during which DNA modifications occur, and these modifications might drive to genetic abnormalities leading to lymphoma progress (Czene et al., 2007; Nogai, Dörken, & Lenz, 2011).

B-NHL is the most common type of NHL and accounts for 80-85% of all lymphomas. Furthermore, the relative proportion of B-cell lymphoma has risen drastically over the years, from 53% in 1990 to 83% in 2012. The most common subtypes of B-NHL are: DLBCL, which accounts for 30–40%, FL, which accounts for 20–30%, Burkitt lymphoma, and marginal zone B-cell lymphoma (Cocco et al., 2013; Rodriguez-Abreu, Bordoni, & Zucca, 2007). Some types of NHL are considered to be aggressive (i.e. fast-growing), example: DLBCL and BL, and others are considered indolent (i.e. slow-growing) lymphoma, example: FL (Muller et al., 2005; Nogai et al., 2011).

2.2 Epidemiology of NHL

The incidence of NHL has greatly increased during the last several decades by 80% between 1970s and 1990s. During the 1990s, the incidence of NHL stabilized and even began to decrease between 1996-2000, this decrease was in part attributed to a decrease in the incidence of AIDS, and since 2000 the incidence of the disease has been subsequently increasing but at lower rates than before (Alexander et al., 2007; Chiu & Weisenburger, 2003; Sundewall, Lefvert, & Olsson, 1985). The epidemic of NHL has received considerable attention in many countries by various institutes and agencies such as the United States National Cancer Institute (Chen, Lv, Pang, & Liu, 2013). Figure (2.1) shows the trend of NHL incidence over the last 50 years in the UK among both genders and is considered representative of the global NHL trends.

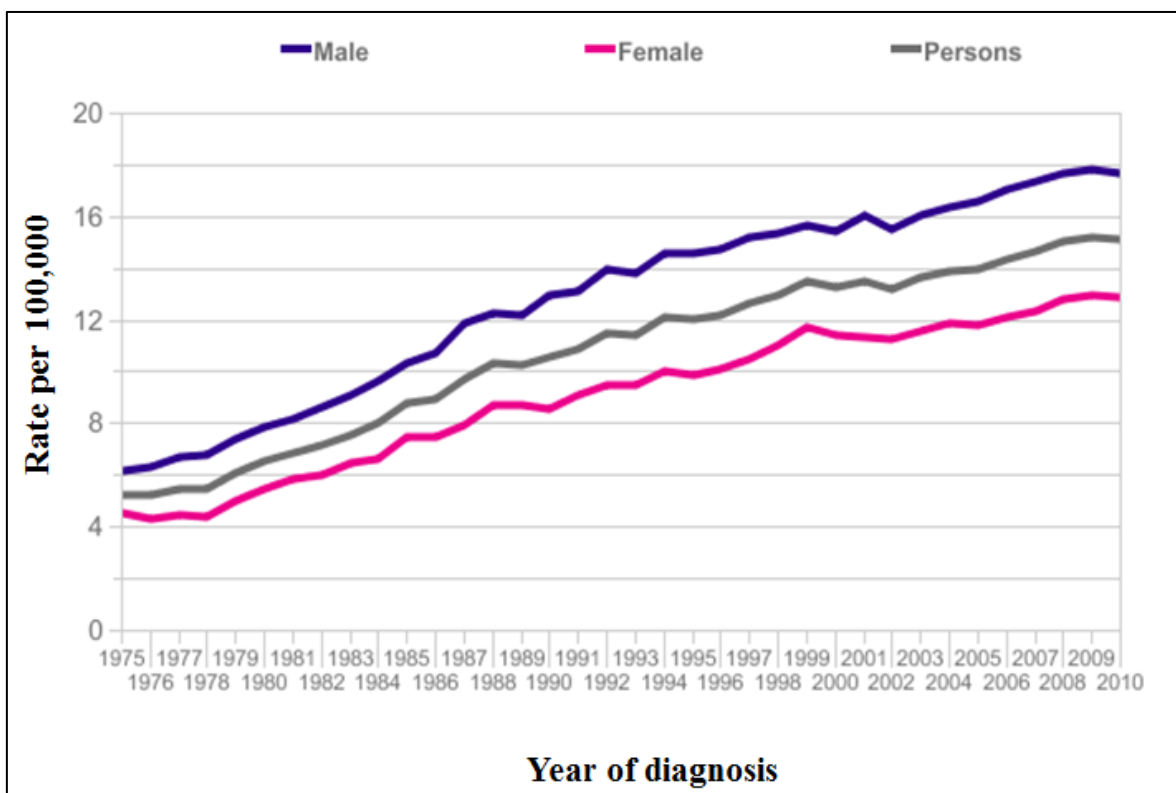


Figure (2.1): European age-standardized incidence rates of NHL, UK, 1975-2011 (<http://www.cancerresearchuk.org/>, 2014).

Globally, NHL is the 8th most commonly diagnosed cancer in men and the 11th in women. North America, Europe, Oceania have the highest incidence of NHL in the world. In addition to several African countries (Boffetta, 2011).

In the United States, NHL is the 6th most commonly diagnosed cancer in both men and women. In 2015, it is estimated that there will be 71,850 new cases of NHL and 19,790 NHL deaths with an incidence rate of 19.7 per 100,000 population (<http://www.cancerresearchuk.org/>, 2014; seer.cancer.gov/, 2014; Siddiqi & Rosen, 2015). The morbidity rate for NHL has risen by 27% in the last two decades among Jewish men and by 49% among Arab women. , in contrast, there was a moderate decrease trend among Jewish women and Arab men. In addition, Israel's morbidity rates of NHL are among the top 20 countries in the world, and ranks second in mortality rates (<http://en.cancer.org.il/>, 2015).

In the Gulf Cooperation Council (GCC) which includes Bahrain, Kuwait, Oman, Qatar, Saudi Arabia and the United Arab Emirates, NHL is the 3rd most common cancer (Ali et al., 2013), while in Egypt, NHL is the second most common cancer in adults and the incidence rates of lymphoma are among the highest in the world (Herzog et al., 2012).

In Palestine, cancer incidence rate was 79.5per100,000 population and the second leading cause of death after heart diseases causing 13.3 % from all deaths in 2013.NHL was reported to be the 8th most common cancer among women and the 11th among men with an incidence rate of 2.2 per 100,000 population (MOH, 2013).

Furthermore, the risk of NHL is strongly related to aging in both sexes. Figure (2.2) shows that age-specific incidence rates in UK rise slowly until the age of 50 years, then increases steeply over the age of 50 forming a peak in the 80-84 age group for both men and women. In addition, the figure shows that incidence rates are higher among men in all age groups (Alexander et al., 2007; Muller et al., 2005).

Regarding NHL subtypes, DLBCL was reported to be the most common subtype worldwide and in the western countries followed by FL (Moinuddin, Dean, Vander Zwaag, & Dragutsky, 1987). In addition, a high incidence of FL and DLBCL was reported in

North America and Europe compared to a higher proportion of T-cell lymphoma in Asia(Boffetta, 2011).

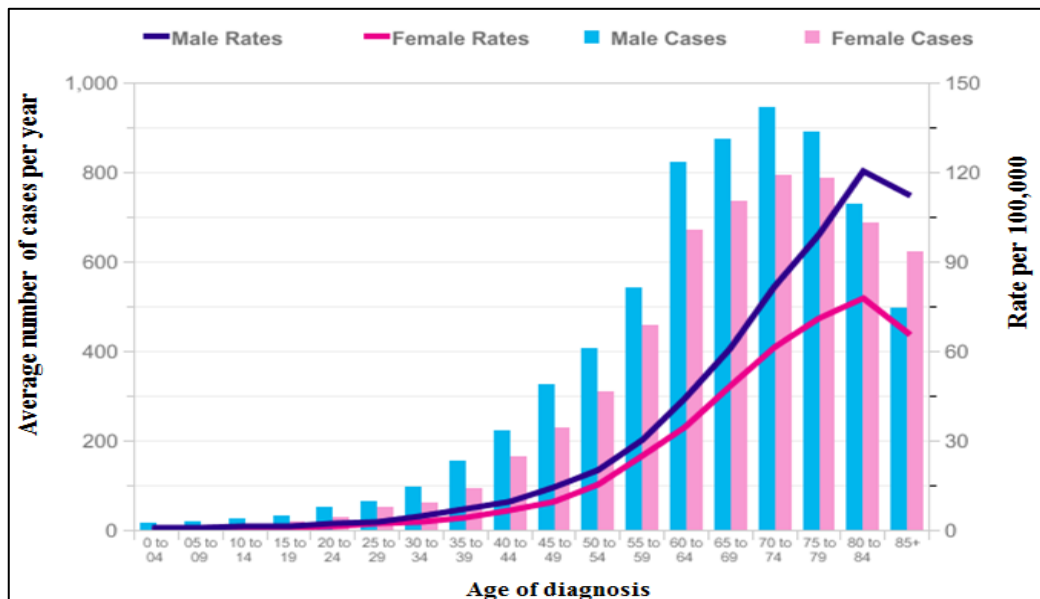


Figure (2.2): Average number of new case per year and age-specific incidence rates of NHL, UK, 2009-2011. (<http://www.cancerresearchuk.org/>, 2014)

Historically, NHL has been about 40% higher in urban than in rural areas, such trends can be attributed to the diminishing socioeconomic differences(Muller et al., 2005). Moreover, developed countries have higher incidence rates of NHL compared to developing countries (Laurini et al., 2012).

Reports have indicated a high incidence of DLBCL among Arabs, Turkish and Iranian, of FL among Kuwaiti Arabs(Ameen, Sajnani, Albassami, & Refaat, 2010), and of FL and small lymphocytic lymphoma (SLL) among Saudi Arabian patients(Akhtar et al., 2009).

Nodal lymphoma occurs when lymphoma cells develop in primary lymphoid organs, but sometimes lymphoma cells begin in other parts of the body like the stomach and skin and these types are called extra nodal lymphomas. Gastrointestinal localizations represent the most common form of extra nodal lymphoma, followed by the central nervous system and the skin(AlShemmari, Ameen, & Sajnani, 2008; Mead, 1997).

Over the past 20 years, and as a result of the AIDS epidemic and other predisposing factors, the rate of occurrence of extra-nodal disease has increased more rapidly than nodal disease(AlShemmari et al., 2008; Zucca & Cavalli, 2000). Differences in the incidence of extra-nodal lymphomas vary between countries: in the USA 24% of NHL cases are extra-nodal; while in Canada 27% are, in Israel 36%, in Denmark 37%, in Italy 48%, and in Hong Kong 29%. Little information is available about the actual incidence of extra nodal forms in developing countries(Newton, Ferlay, Beral, & Devesa, 1997), but Extra-nodal NHL was found common among patients of Arabic descent with DLBCL being the most common histological subtype(AlShemmari et al., 2008; Zucca & Cavalli, 2000) and in Lebanon it constituted 44% of cases (Newton et al., 1997), while in Kuwait 54%(Ameen et al., 2010).

2.3 Etiological Risk Factors of NHL

Several etiological risk factors have been reported to contribute in the increasing incidence of NHL worldwide. These risk factors are: immunodysregulation, genetic risk factors, infection with some viruses and bacteria, certain environmental and occupational exposures and lifestyle and dietary factors(Hartge et al., 2006).

2.3.1 Immunodysregulation:

Immunodysregulation is the strongest reported risk factor of NHL. It refers to a malfunction of immune system in the body, due to dysregulation of cytokines, which play an essential role in immune cell development and immune functions(O'Shea, Ma, & Lipsky, 2002).

2.3.1.1 Congenital immunodeficiency

Congenital immune deficiencies constitute a heterogeneous group of disorders with a variable degree of deficiency in B cell and/or T cell function. Examples of these syndromes include Wiskit–Aldrich, ataxia telangiectasia. About 25% of patients with congenital immunodeficiency develop tumors during their lifetime, and 50% of these patients have NHL. These patients seem unable to promptly eliminate respiratory and gastrointestinal pathogens and are susceptible to chronic antigen stimulation(Grulich, Vajdic, & Cozen, 2007).

2.3.1.2 Acquired immune deficiency:

2.3.1.2.1 Human immunodeficiency virus (HIV)

Infection with HIV weakens the immune system and reduces the body's ability to fight infections which may lead to certain cancer like NHL (Epeldegui, Vendrame, & Martinez-Maza, 2010). People with HIV infection were found to be at an eleven-folds increased risk of NHL compared to the general population, but the risk differ with different subtypes of NHL; the major AIDS associated NHL subtypes are: DLBCL, Burkitt lymphoma and primary lymphomas that arise in the central nervous system (Grulich et al., 2007; Vendrame et al., 2014).

2.3.1.2.2 Iatrogenic immune deficiency (immunosuppressive drugs)

Recipients of organ transplants receive a range of immune-suppressive pharmaceutical drugs. After transplantation, the relative risk of NHL was found to increase ten to fifty folds. This risk is closely correlated with the degree of immune suppressive e therapy and the organ transplanted. The risk of NHL is the highest during the first year after transplant when iatrogenic immune suppression is most intense, and patients of heart or lung transplantation have 4% higher incidence rate of NHL than other organ transplant patients (Grulich et al., 2007).

2.3.1.3 Autoimmune diseases

These include a heterogeneous group of conditions associated with a failure of the immune system to recognize self and consequent inflammatory diseases. The overactive immune system in patients of autoimmune diseases may lead to abnormal growth and division of lymphocytes; this might increase the risk of developing lymphomas. Many of the epidemiological studies that examined this association found increased risk among patients with rheumatoid arthritis, systemic lupus erythematosus, celiac spruce (Grulich et al., 2007; Muller et al., 2005).

2.3.2 Genetic Predisposition:

2.3.2.1 Family history

Studies have reported two to three-folds increase in the risk of NHL and other hematological malignancies among first degree relatives (parent, sibling or child) of NHL

(Chatterjee et al., 2004; Crump, Sundquist, Sieh, Winkleby, & Sundquist, 2012; Paltiel et al., 2000; Wang et al., 2007).

2.3.2.2 Genetic variations or single nucleotide polymorphisms (SNPs)

Several genetic variations or SNPs in different genes and pathways have been reported to modulate the risk of NHL. SNPs in pro-inflammatory cytokine genes that are involved in the regulation of immune defense mechanisms increase the risk of NHL, for example; SNPs in tumor necrosis factor (TNF) and interleukin (IL) genes (Chatterjee et al., 2004; Rothman et al., 2006). Further, SNPs in immunity genes influence lymphoma risk. The HLA region located on chromosome 6 has approximately 220 genes; Diepstra and colleagues (2005) have reported the association of these genes with lymphoid malignancies (Diepstra et al., 2005). Additionally, several epidemiologic studies in the United States, Germany and Australia have reported an increased risk of NHL associated with genetic variations in the TLR10-TLR1-TLR6 region, TLR2 and TLR4 and TRAF1, RIPK3, BAT2, MAP3K5, DUSP2, CREB1, B3GNT3, SELPLG, LSP1, FGG and ITGB3 (Edlefsen et al., 2014; Skibola, Curry, & Nieters, 2007).

Also, SNPs in genes involved in DNA double-strand break and repair, for example; mutated ATM and WRN genes that plays a crucial role in DNA double strand break repair and in other repair pathways and genes of GPX1, NOS2A, SOD2, AKR1A1, and CYBA2819165 and involved in ataxia telangiectasia (Skibola et al., 2007).

2.3.3 Environmental Exposures:

Only 5–10% of all cancer cases can be attributed to genetic factors and the remaining are mainly attributed to environmental and lifestyle factors (Diver, Teras, Gaudet, & Gapstur, 2014; Douse, Powell, Milsom, & Mitchell, 1989).

2.3.3.1 Infectious exposures:

According to the American cancer society, some infections may raise the risk of NHL through different mechanisms; for example, some viruses can directly affect the DNA of lymphocytes helping to be transformed into cancer cells by directly affecting their DNA, like HTLV-1, EBV, while other viruses act through weakening the immune system, like

HIV. A third mechanism is that the infections may cause chronic immune stimulation like *Helicobacter pylori* (*H.Pylori*) and *Chlamydia psitta*(Peveling-Oberhag, Arcaini, Hansmann, & Zeuzem, 2013; Shawki, Meshaal, El Dash, Zayed, & Hanna, 2014).

2.3.3.1.1 Human herpes virus 4 (EBV)

Herpes virus is highly prevalent worldwide. Infection with EBV is associated with a wider spectrum of NHL subtypes in the context of immunosuppressant resulting in the proliferation of transformed B-cells normally controlled by T-cell-mediated immunity. About half of DLBCL cases infected with HIV are EBV positive, whereas about 30% of Burkitt lymphoma cases are EBV associated, and nearly all cases (>95%) of endemic Burkitt lymphoma in Northern Africa are EBV positive (Muller et al., 2005). EBV has also been linked with developing nasal-type extra-nodal natural killer/ T-cell lymphoma, lymphomatoid granulomatosis (a form of B-cell lymphoma), and post-transplant lymph proliferative disorder(Teras et al., 2015).

2.3.3.1.2 Hepatitis C virus (HCV) and Hepatitis B virus (HBV)

Several epidemiological studies have demonstrated an increased NHL risk with chronic HBV or HCV infection, with potential specificity for particular NHL subtypes. B-NHL subtypes most frequently associated with HCV are marginal zone lymphoma and DLBCL (Engels, Cho, & Jee, 2010). The most important evidence for association between HCV infection and lymphoma development is the observation of B-NHL regression after HCV eradication by antiviral therapy(Peveling-Oberhag et al., 2013).

2.3.3.1.3 *Helicobacter pylori*

H.pylori is a causative agent for some types of gastric lymphomas like mucosa-associated lymphoid tissue (MALT), which is an indolent tumor arising from B cells and affecting the gastric mucosa (gastric NHLs). Some studies reported a certain proportion of patients who are *H.pylori*-positive with histological evidence of MALT lymphoma and gastric DLBCL this might be due to chronic inflammation that results in the colonization and proliferation of lymphocytes in the gastric mucosa(Suzuki et al., 2006).

2.3.3.1.4 Other infectious agents

Infection with *Chlamydia psittaci*, which can infect humans via contact with animal feces and contact with birds, and the vector borne agent *Borrelia burgdorferi*, have been

associated with rare MALT lymphomas (Muller et al., 2005). In addition, human T-cell lymphotropic virus- type I (HTLV-I) is an established cause of adult T-cell leukemia/lymphoma. There are also some bacterial infections involved in the etiology of NHL such as *Plasmodium falciparum*, and *Borrelia afzelii*(Engels et al., 2010).

2.3.3.2 Occupational exposures

The association between NHL risk and different occupations has been reported by several epidemiological studies (Alavanja et al., 2014). The evidence points that the elevated risk of NHL among farmers and agricultural workers is due to the exposure to pesticides and other agricultural chemicals such as solvents, fuels, oils, dusts, which are either potentially carcinogenic or lead to chronic antigenic stimulation .

A number of other jobs and industries, including fishing, construction, paper, wood and leather industries, metal workers, painters, electrical engineers, teachers and health care workers, have also been suggested to entail an increased risk of NHL (Alavanja et al., 2014; Boffetta & de Vocht, 2007; Schinasi & Leon, 2014).

2.3.3.3 Personal habits and lifestyle:

Lifestyle, personal habits and diet factors have been reported to play an important role in the etiology of NHL (Ali et al., 2013).

2.3.3.3.1 Smoking, alcohol consumption and hair dyes

Smoking reported in many studies to have no association with NHL, but was found to be associated with 30% increased risk of FL (Morton, Hartge, et al., 2005). On the other hand, some studies that examined the association between alcohol consumption and NHL risk have suggested that consumption of alcohol may be protective from NHL. In addition, the risk of NHL was reported to be associated with the use of hair dyes and hair coloring products in many studies, and the risk varied by the type of dye products, period of use, duration and intensity of use (Diver et al., 2014).

2.3.3.3.2 Dietary intake:

Several epidemiological studies examined the possible association between dietary intake and the risk of NHL, but results were inconsistent. The suggested mechanism of action for dietary factors include both enhancement and suppression of the immune system in the body; therefore they may increase the risk of NHL or protect against it for example, the suppressive role might be due to the effect of fat and animal proteins (Ali et al., 2013; Purdue et al., 2004; Skibola, 2007), while the protective role might be due to the antioxidant properties of vegetables and fruits that protect against the effects of free radicals (Thompson et al., 2010; Zheng et al., 2004). The role of dietary factors and the risk of NHL were found to vary also by NHL subtype.

- **Saturated fat and animal protein**

In the past, the epidemiological studies that assessed the association between dietary intake and the risk of NHL were very limited. Davis and his colleagues reported a significant increase in the risk of NHL and high consumption of liver and oil in addition to a moderate increase in consumption of meats, salami, sausages and margarine (Davis, 1992). Later, several cohort and case-control studies reported an increased risk of NHL associated with a higher consumption of animal protein, saturated fat and higher intakes of retinol, eggs, and dairy products. These studies, however, showed a reduced risk for polyunsaturated fat (Chiu et al., 2008; Zhang et al., 1999; Zheng et al., 2004). In addition, the first Omani study showed that meat intake is associated with increased risk of NHL (Ali et al., 2013). Moreover, Mozaheb and colleagues found that diets high in trans fatty acids (TFAs), high-fat dairy products and most types of meat were positively associated with the risk of NHL, while diets high in omega3- fatty acid found in plant oils, fresh fish and total seafood were inversely associated with risk of NHL (Mozaheb et al., 2012).

In a case-control study, conducted by Charbonneau and his colleagues and included 603 cases and 1,007 controls, diet was assessed with a 128-item food-frequency questionnaire. The findings showed that TFA intake was positively associated with NHL risk (OR=1.6; 95% CI: 1.2- 2.2), while intake of omega-3 fatty acids was inversely associated with NHL risk (OR=0.5; 95% CI: 0.4- 0.7) (Charbonneau et al., 2013). In contrast, a large U.S. cohort study reported no association between intake of meat or other animal products and risk of NHL (Daniel et al., 2012).

The increased risk of NHL associated with the consumption of meats and animal protein was attributed to the suppressive effect of the immune system in the body (Mallinger, Schmid, & Neu, 1987). The suppression might be due to the presence of chemicals such as haem, which is a red pigment that can irritate or damage the cells causing them to divide much more than normal to compensate for this damage and subsequently increase cancer risk (Cross, Pollock, & Bingham, 2003). Haem could also stimulate the bacteria in our guts to produce chemicals called N-nitroso compounds which are known to be carcinogens. In addition, cooking meat at high temperatures (by grilling or boiling) can produce harmful chemicals such as heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs), which are also known to be carcinogenic (Layton et al., 1995).

- **Milk and dairy products**

Many epidemiological studies in the US, Italy, Norway and other countries, from 1983 to 2007, reported a significant increase in risk of NHL associated with a high consumption of milk and dairy products like butter, margarine, cream soups, mayonnaise, mutton fat, ice cream or milkshakes, and cheese (Chiu et al., 2008; Davis, 1992). Other studies found milk consumption to be significantly associated with a higher risk of specific NHL subtypes such as DLBCL, but not associated to increased risk of other types like FL (Chiu et al., 2008). In contrast, other studies did not find any association for the consumption of milk and dairy products and the risk of NHL (Ali et al., 2013; Mozaheb et al., 2012; Skibola, 2007).

- **Fish**

Based on a number of case-control and prospective cohort studies, some evidence showed that fish intake may reduce risk for NHL (Ali et al., 2013; Fritschi, Ambrosini, Kliewer, Johnson, & Canadian Cancer Registries Epidemiologic Research, 2004). In contrast, other studies reported an increased risk for certain subtypes of NHL like FL with consumption of fish (Daniel et al., 2012; Yang et al., 2014). In consistence with a recent meta-analysis that included seven case-controls and two prospective cohort, some previous case-control studies found no association between the consumption of fish and the risk of NHL (Chang et al., 2005; Yang et al., 2014).

- **Fruits and vegetables**

Intake of fruits and vegetables is an important element of any healthy diet, and varies reflecting economic, cultural and agricultural environments among countries. It has been estimated that insufficient intake of fruit and vegetables could cause up to 14% of gastrointestinal cancer deaths(Stevens, 2009). Epidemiologic evidence suggests that intake of fruits and/or vegetables may play a role in the etiology of NHL. Several studies reported a reduced risk of NHL with higher intake of green vegetables, carrots and dietary fiber and for several fruit and vegetable items(Davis, 1992; Kelemen et al., 2006; Zheng et al., 2004). Similarly, other studies that investigated the intake of different types of vegetables and fruits separately like cruciferous vegetables, green leafy vegetables, and red vegetables, and reported a reduced NHL risk(Han et al., 2010). Furthermore, a case-control study conducted in 2012 showed that most fresh fruits like citrus, apple, melon and water melon had a protective effect against NHL, but fruit products such as compote, natural juice and commercial juice were associated with an increased risk of lymphoma(Mallinger et al., 1987). Another case-control study conducted in Oman showed that there was a significantly reduced risk of NHL associated with higher consumption of vegetables (OR=0.2; 95% CI: 0.1-0.8), though no significant association with the risk of B-NHL was detected with the consumption of fruits(Ali et al., 2013). Additionally, a meta-analysis of case-control and cohort studies conducted between 1966 - 2012 focused on fruit and vegetable consumption and the risk of different histological subtypes of B-NHL reported that vegetables intake had significant inverse association with DLBCL and FL(Chen et al., 2013). In contrast, other studies reported no association between vegetables, dark green vegetables, high-nitrate vegetables and risk of B-NHL (Chiu et al., 2008; Ollberding et al., 2014).

Vegetables and fruits rich in antioxidant nutrients were hypothesized to be protective against many types of cancer, including NHL, and several mechanisms have been suggested; one is through reduction of reactive oxygen species responsible for oxidative DNA damage, another is through the regulation of cell survival and apoptosis pathways, in addition to protection of immune responses. Additionally, it was hypothesized that alimentary fibers may affect the dilution, absorption, and/or breakdown of fat and animal protein in the gut, either directly or indirectly, by modifying the gut micro flora(Davis, 1992; Zheng et al., 2004).

2.4 Nutritional status among Palestinians

Many studies were conducted in Palestine during both the first and the second Entifada to assess the nutritional status. In addition, Palestine is one of the three Middle Eastern countries that have national nutrition surveillance systems that have been functional since 2006 (Friedman, 2014). A study was conducted in 2003 by Abdeen and his colleagues for nutritional assessment in the West Bank and Gaza Strip for the purpose of evaluating food security. The parameters included in the study were chronic and acute malnutrition and nutrient deficiencies for critical macro and micro nutrients in pre-school age children (ages 13-59 months). The study reported that the prevalence of acute and chronic malnutrition were acceptable, yet the quality of food intake suffered from significant decline in daily intake of micro and macro nutrients compared to the defined recommended daily allowance, the nutrients assessed were energy and protein intake, vitamin A and E, folate, iron and zinc (Abdeen, Greenough, Chandran, & Qasrawi, 2007).

In 1991, a community-based cross-sectional survey conducted by the Norwegian universities' committee for development research (NUFU) assessed food consumption patterns in the West Bank and reported a high proportion of dietary energy from fat and high consumption of most animal products among the wealthiest households (Stene et al., 1999).

In addition, a cross-sectional survey that assessed the prevalence and distribution of overweight and obesity and their associations among adults in Palestine and reported that obesity and overweight are public health problems in Palestine, with adults aged 45–54 years old being more likely to be obese or overweight (Abdeen et al., 2012). Furthermore, a cross-sectional survey conducted in 2005 in Ramallah, Nablus and Hebron governorates reported that irregular meal patterns were common among Palestinian adolescents and a positive association between high standard of living index in Ramallah and increased intake of animal foods, western-style foods, dairy products, fruits and vegetables, sweets and salty snacks was found. Moreover, the study found that only 26.1 % of the students have three main meals daily, one quarter of the students drink milk daily, >70% consumes vegetables and >50% consumes fruits daily (Mikki, Abdul-Rahim, Shi, & Holmboe-Ottesen, 2010).

Another study conducted in East Jerusalem showed that 24.3% of adolescents were overweight and 9.9% were obese, while 4.8% were underweight, of which 23.3% were anemic. In addition, 55.7% of boys and 64.8% of girls had inadequate energy intake, 15.1% of boys and 43.1% of girls reported inadequate protein intake and the majority of both boys and girls met <80% of the recommended daily allowances (RDA) for most micronutrients(Jildeh et al., 2011). The findings of these studies detected a need for effective interventions to change existing dietary habits with healthy ones.

Chapter Three

Study Framework

3.1 Conceptual Framework

The conceptual framework presents the relation between the dependent variable (NHL) and the independent variables (dietary factors) and (demographics and social characteristics). Figure (3.1) shows the association between the dependent variable (NHL) and the independent variables (dietary intake, personal history of cancer, family history of cancer and demographic factors) which may increase or decrease the risk of NHL.

3.2 Study Variables

In the present study, the dependent variable is B-NHL, which is defined as a blood cancer or a heterogeneous group of malignant neoplasms that result from the malignant transformation of lymphocytes at different developmental stages in the lymph nodes, spleen, and other organs of the immune system in the body and originates from B-lymphocytes (Ansell & Armitage, 2005). The independent variables that may contribute to the risk of NHL and are included in the study are defined in Table (3.1).

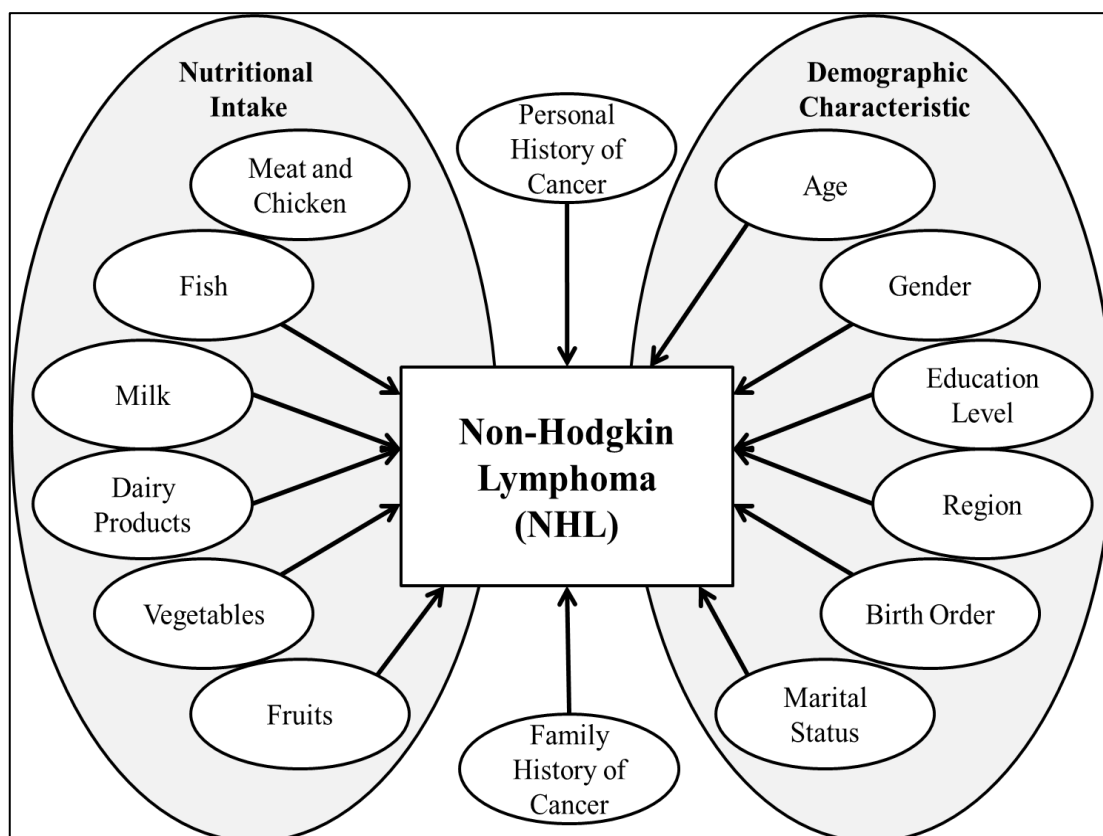


Figure (3.1): Conceptual framework of the study.

Table (3.1-a): Operational definition of study variables.

Variable	Operational Definition
Age	Age of participants at the time of interview measured in years
Gender	Gender of the participants categorized into male and female
Education level	Number of years completed in school, categorized into: <ul style="list-style-type: none"> ▪ Partial primary (< 6th grade) ▪ Primary school completed ▪ Partial secondary ▪ High school completed ▪ Diploma ▪ Bachelor degree ▪ Graduate studies
Region	Region where the participants were recruited from: <ul style="list-style-type: none"> ▪ North: Nablus, Jenin, Tubas, Qalqilya, Tulkarem, Salfit. ▪ Middle: Ramallah, Jericho and Jerusalem. ▪ South: Bethlehem, Hebron.

Table (3.1-b): Operational definition of study variables.

Variable	Operational Definition
Marital status	The social status of the participant at time of recruitment, categorized into: <ul style="list-style-type: none"> ▪ Never married ▪ Single ▪ First marriage ▪ Second marriage or more ▪ Divorced or separated ▪ Widowed
Serving (USDA, 2015)	The portion size of food depending on the type of food served: <ul style="list-style-type: none"> ▪ Fish: 30 g ▪ Meat: 30 g ▪ Milk: 240 ml ▪ Dairy products: 240 ml ▪ Vegetables: 240 g ▪ Fruits: 120 g
Meat intake	Average number of servings of red meat and chicken consumed weekly over the last six months for controls and before the diagnosis of the disease for B-NHL cases
Fish intake	Average number of servings of fish consumed weekly over the last six months for controls and before the diagnosis of the disease for B-NHL cases
Milk intake	Average number of servings of milk consumed weekly over the last six months for controls and before the diagnosis of the disease for B-NHL cases
Dairy products intake	Average number of servings of dairy products consumed weekly over the last six months for controls and before the diagnosis of the disease B-NHL cases
Vegetables intake	Average number of servings of vegetable consumed weekly over the last six months for controls and before the diagnosis of the disease B-NHL cases
Fruits intake	Average number of servings of fruit (120 g) consumed weekly during the last six months for controls and before the diagnosis of the disease B-NHL cases
Personal history of cancer	Having had a cancer in the past
Family history of cancer	Having a one or more first degree relatives (parent, sibling,, child) who had cancer

Chapter Four

Methodology

This chapter describes the methodology of the large B-NHL project that this study was a part of.

4.1 Study Design

A large case-control study of B-NHL was conducted among adult Palestinians. The study involved a questionnaire, serology and genetic analysis, which were used to study the different environmental and genetic determinants of B-NHL by comparing cases to controls. Participants were administered a standardized questionnaire-based interview and 20 ml peripheral blood was collected for the purpose of DNA purification for the genetic part of the study and serum separation to be used for viral serology analysis. Recruitment of human subjects in this study was approved by the Institutional Review Boards at the collaborating institutions. My contribution to the large case-control study was focused on recruiting controls (n=71). The whole database of the case control study was used to study the association between dietary intake and NHL risk.

4.2 Study Setting

Arab B-NHL cases were recruited in the West Bank from two major hospitals, these hospitals contain oncology departments and are supervised by the Palestinian Ministry of Health (National Hospital in Nablus and Al-Husein Hospital in Beit-Jala), in addition to Augusta Victoria Hospital, which is located in Jerusalem and supervised by Israeli Ministry of Health but all of their patients are referred from the West Bank. These are the major centers that provide treatment for hematological malignancies for Palestinians. Additionally, Arab cases treated both in Hadassah Hospital Ein-Kerem and Mount Scopus were also recruited in the study. Controls were recruited from MOH primary health care clinics or from the collaborating hospitals.

4.3 Study Population

Cases (n=306): Eligible cases were individuals aged ≥ 18 years newly diagnosed with B-NHL within < 18 months of diagnosis. Patients were recruited through four major study centers: i) in the north (National Hospital in Nablus), ii) in the south (AL-Husein Hospital in Beit-Jala) and iii) in the middle (Augusta Victoria Hospital), iv) in addition to incident B-NHL patients being treated in Hematology Day Care Centers and Clinics in Hadassah–Hebrew University Medical Center both in Mount Scopus and Ein-Kerem were also recruited. The median time from diagnosis to recruitment for the different centers was between 1-11 months which diminishes the probability of a survival bias.

Controls (n=392): Initially, 321 clinic-based cancer-free controls aged ≥ 18 years were recruited through thirteen governmental medical centers related to the Palestinian Ministry of Health (MOH) and distributed all over the West Bank (Southern Hebron, Hebron, Bethlehem, Jericho, Ramallah, Northern Ramallah, Jenin, Qalqilya, Jerusalem, Nablus, the Old City of Nablus, Salfit and Tulkarim MOH medical centers). Some controls were recruited from the collaborating hospitals: National Hospital of Nablus, Augusta Victoria Hospital, Hadassah Medical Center and the blood bank donors of Al-Makassed Charitable Hospital. These controls were cancer-free individuals accompanying other cancer patients but not first or second degree relatives or blood donors in the case of Al-Makassed Hospital. Additional 71 controls were recruited later for the purpose of correcting the regional distribution imbalance

that was found in the primary analysis, which was my contribution to the larger study. Controls were recruited from the MOH medical centers.

Inclusion-exclusion criteria: Eligible cases were individuals ≥ 18 years old, with pathologically confirmed diagnoses of B-NHL within less than 18 months. Consequently, for each case, we referred to the patient's oncologist or to the cancer registry file to fill out a pathology report (Appendix 4.1) to confirm the diagnosis. Any participant below the age of 18 years or with unconfirmed diagnosis was excluded from the study. Controls were adult cancer-free individuals who were frequency matched to the patients in terms of age and gender. Any control that was related to any of the patients was excluded from the study.

4.4 Study Tool

The questionnaire that was used from the beginning of the large project was originally formulated in English based on the questionnaire of the EpiLymph (European multicenter case-control study which is part of the International Lymphoma Epidemiology Consortium-InterLymph) (Appendix 4.2). The questionnaire was translated into Arabic (Appendix 4.3) for the purpose of conducting interviews with the target groups. Forward and back translation was performed in order to assure reliability. Further, a pilot study was conducted to check the reliability and feasibility of the questionnaire in order to make the necessary amendments and corrections. The questionnaire was administered in hospitals, outpatient clinics and Ministry of Health clinics, in a face-to-face manner. The questionnaire contains six sections including more than 500 variables collecting detailed information on a number of potential NHL risk factors. The first section focuses on socio-demographic characteristics including age, gender, marital status, education level, and family size, birth order, and attendance of day care and further it focuses on family origin of the participant, and his father, mother, grandfather and grandmother. The second section explores occupational history and the related exposures. The third section gathers information about residence properties including address, type, floor, source of water, number of peoples residing in, number of rooms, location of bathroom, and duration of residency. The fourth section investigates personal characteristics and habits (weight and height before and after illness, smoking, hair dye use, sun exposure and dietary intake). The fifth involves information about personal hobbies (physical activity, gardening, domestic use of pesticides and insecticides and hobbies that involve usage of chemicals). The sixth section focuses on medical history (history of specific infections, autoimmune diseases

or atopic conditions like asthma, eczema and hay fever, hospitalization for infection during infancy and during the life-time, vaccinations, antibiotic use, exposure to X-rays, contact with animals, medications, blood transfusion, history of cancer other than NHL, family history of cancer and autoimmune diseases.

Dietary intake was assessed using food frequency questionnaire (FFQ) which is the most common dietary assessment tool used in large epidemiologic studies of diet and health. For each food item, a commonly used portion size or unit (serving) was specified and the respondents were asked how often on average over the last months they had consumed that amount of each food item. There were 7 possible responses, ranging from 'never to 1 or more times daily.

In this study, the same previously described questionnaire was used in interviewing the newly recruited controls; blood was also collected from them for other purposes in the study. The primary focus of this study was on the part of the questionnaire which is related to food frequency where daily consumption of routine food items including red meat, chicken, fish, milk and dairy, vegetables and fruits, also intake of beverages as water, tea, and coffee, to obtain information on the frequency and amount of food items consumed during the past.

4.5 Data Collection

After getting an approval for the continuation of the project the process of recruitment was started by explaining the study and its rationale to the participants, and then they were consented. After that, the participants were administered the questionnaire in a face to face interview, blood was also collected from the participants and then transferred to the laboratory where serum was separated from plain blood, aliquoted and kept at -20°C, and also DNA was purified from EDTA blood.

Cases: The diagnosing physicians or the research assistants introduced the research project to the patients and asked for their willingness to be contacted by an interviewer. In case of a positive response, an interviewer explained the project more comprehensively and handed out written information material including informed consent. When consent was given, the interviewers administered the questionnaires in the hospital in a face to face

interview that lasted for 45-60 minutes and obtained blood. In order to confirm the pathology diagnosis for each case, we referred to the patient's oncologist to fill out a pathology report. This report specifies the subtype of lymphoma, age at diagnosis, place of diagnosis, cell markers by immune-staining or immune-histochemistry, site of biopsy, stage of disease, extra-nodal involvement, presence of B-symptoms, lactate dehydrogenase level (LDH) and the prescribed treatment.

Controls: They were approached by the interviewer and consented after getting the proper explanation about the project. All controls were administered the same questionnaire in a face to face interview within the hospital or the medical centers. The newly recruited 71 controls were from the middle regions and were distributed as the following: 23 from Jericho, 26 from Al-Azaria (Jerusalem) and 22 from Ramallah.

4.6 Validity

The EpiLymph questionnaire has been externally validated and used in several internationally published studies since 2002. Despite that, some questions suffer from low validity like the antibiotics and vaccination questions which are highly affected by recall bias; therefore they were excluded from the analysis.

4.7 Statistical Analysis

Quantitative data that were collected from participants within the questionnaires were cleaned, coded, entered and analyzed using the Statistical Package for the Social Sciences, (SPSS version 21). Descriptive analysis of food intake was dependent on the median which was used to describe the sample's intake of each food item, the use of the median provide more accurate measure to describe the subset of data given that the categories used were unequally distributed and the data was not normally distributed. Furthermore, the values below the median were used as the reference group for all comparisons.

Odds ratios (OR) and 95% confidence intervals (95% CI) were used as the measure of association between the independent variables and B-NHL. Unconditional logistic regression was used to estimate ORs and the corresponding 95% CI. In addition, a multivariate regression model that is adjusted for age in years and gender was constructed.

The sample size provided a power of >90% to detect an odds ratio of 2.2 with 15% reporting exposure among controls. The level of significance was calculated at alpha-level of 0.05.

Chapter Five

Results

This chapter presents the findings of the study including sociodemographic characteristics, disease characteristics and association between B-NHL and food intake.

5.1 Socio-demographic Characteristics

In the current study of B-NHL, a total of 306 B-NHL cases and 392 cancer-free controls were recruited. Confirmed B-NHL cases were diagnosed and recruited from different hospitals in Jerusalem and the West Bank as shown in Table (5.1); 28.3% of the cases were recruited from Augusta Victoria Hospital (Al-Mutalaa), 16.6% from the National Hospital, 13.7% from Beit-Jala Hospital (Al-Husein), 22.5% from Hadassah Hospital and 17.3% from MOH primary health care clinics. Controls also were recruited from different hospitals in Jerusalem and the West Bank as shown in Table (5.1); 10.2% of them were from Augusta Victoria Hospital, 4.2% from National Hospital, 77% from MOH primary health care clinics and 8.6% from Al-Makassed Blood Bank Volunteers.

Table 5.1: Distribution of study subjects by recruitment center.

Recruitment Center	Cases		Controls	
	(n)	%	(n)	%
Augusta Victoria Hospital	87	28.3	32	10.2
Hadassah Hospital	69	22.5	0	0
Beit-Jala Hospital	38	12.4	0	0
National Hospital	51	16.6	13	4.2
MOH clinics	53	17.3	321	77
Al-Makassed Blood Bank	0	0	27	8.6

The mean, median and SD for age at diagnosis were 50.8, 52 and 16.6 years, respectively, indicating a young age at diagnosis. On the other hand, the mean, median and SD for age at recruitment were (52.9, 53 and 16.6 years respectively) confirming the recruitment of incident cases diagnosed within less than 18months. Figure (5.1) shows the distribution of cases by age at diagnosis; a high proportion of cases were in the younger age groups (18-34 years), and as age increased, the number of cases increased, with a peak noticed in the age group 60-64 years. An almost threefold increase in the incidence of NHL with aging could be also noticed, which emphasizes the role of aging as an important risk factor in NHL.

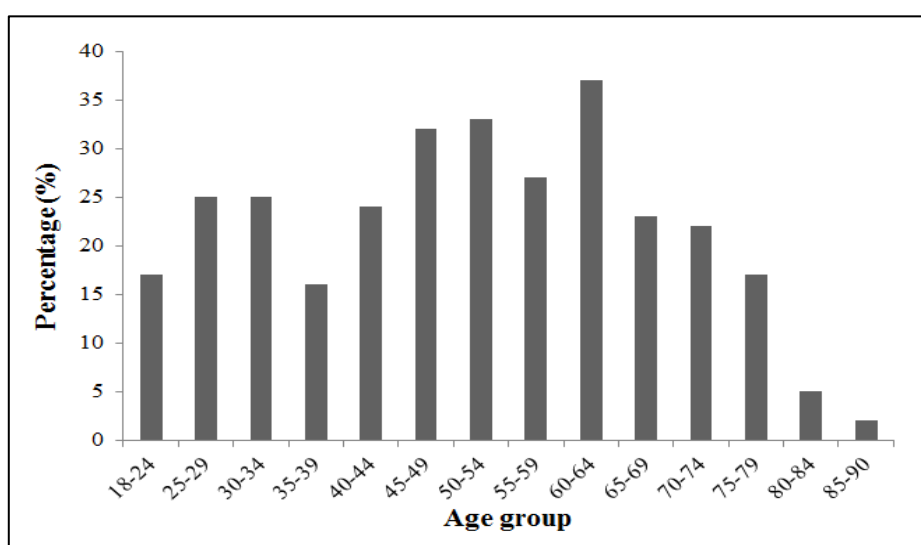


Figure 5.1: Distribution of B-NHL cases by age at diagnosis in the different age groups.

Table (5.2) demonstrates the demographic characteristics of B-NHL cases and controls including age, gender, regional distribution, educational level, marital status, birth order and recruitment centers. The controls were designed to be frequency matched with the patients in terms of mean age at recruitment, gender.

The mean age of B-NHL cases at recruitment was 52.9 with a standard deviation (SD) of 16.6 and for controls 51 years (SD=15years) for controls (Table 5.2). The distribution of both cases and controls was close in most age groups, but higher proportion of controls were recruited in two age groups, 40-44years and 45-54 years, thus confirms the matching criterion and supply a window for the matching process. Consequently, and as a result of the imbalance, our multivariate models were adjusted for age. Figure (5.2) demonstrates the distribution of cases and controls in the different age groups.

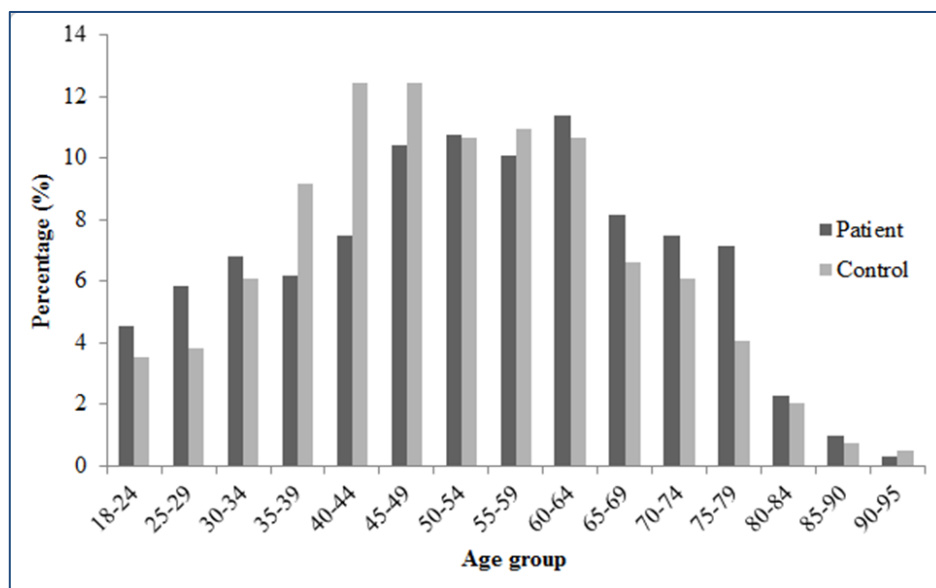


Figure (5.2): Age distribution of B-NHL cases and controls at the time of recruitment.

Among the cases, the males and females were equally represented, with a percentage of (49.5%) and (50.5%) respectively, whereas higher proportion of controls were females, therefore the multivariate models were also adjusted for sex. The cases and controls were similar with respect to the marital status (Table 5.2).

With respect to regional distribution of the participants; the regional distribution of cases was as the following: northern region contributed to 24.7% of B-NHL cases, followed by southern

region(31.9%) and then middle region(39.5%). On the other hand, the regional distribution of controls was as the following:19.9% were from the northern regions compared to 44.9% from the south and 32.9% from the middle regions (Table 5.2).

In regard to education, an equal percentage among both the cases and controls were found to be illiterate, while a higher proportion of cases (34.9%) had primary education compared to controls (23%). In contrast, almost one fourth of the controls had a first university degree (26.1%) versus only one-sixth (15.6%) among the cases (Table 5.2).

As for marital status, there was no difference between the cases and controls as most of them were currently or previously married. In regard to birth order no major differences were found between cases and controls, most of participant from both were in the second or the third order in their families (Table 5.2).

Table (5.2): Socio-demographic characteristics of B-NHL cases and controls including, age at recruitment, gender, region, educational level, marital status and birth order.

Variable	Category	Cases		Controls	
		(n)	%	(n)	%
Age at recruitment	Mean age (years \pm SD)	52.9 \pm 16.6		51.4 \pm 15.1	
Gender	Male	152	49.5	168	42.7
	Female	155	50.5	225	57.3
Region	North	75	24.7	78	19.9
	Middle	120	39.5	129	32.9
	South	97	31.9	176	44.9
	Others	12	3.9	9	2.3
Education	Illiterate	44	14.6	57	14.9
	Primary education	105	34.9	88	23
	Secondary education	92	30.6	131	34.2
	First university degree	47	15.6	100	26.1
	Others	13	4.3	7	1.8
Marital status	Never married	41	13.4	34	8.7
	Married or previously married	264	86.6	359	91.3
Birth order	1	71	23.4	68	17.8
	2 – 3	115	37.8	118	31
	4 – 5	60	19.7	100	26.2
	6 +	58	19.1	95	24.9

5.2 B-NHL Subtypes

Table (5.3) presents the relative distribution of B-NHL cases by NHL subtypes. Diffuse large B-cell lymphoma (DLBCL) was the most common NHL subtype (70.7%), followed by follicular lymphoma (FL) (14%), low grade lymphoma (4.2%), small lymphocytic lymphoma (SLL) (3.9%), mantle cell lymphoma (MCL) and mucosa-associated lymphoid tissue (MALT) each contributed to 1.3%, marginal zone lymphoma (MZL) (1%), and finally Burkitt and lymphoblastic lymphoma each contributed to (0.7%).

Table (5.3): Distribution of B-NHL cases by subtype.

B-NHL subtype	Cases	
	(n)	(%)
DLBCL	217	70.7
Follicular lymphoma	43	14.0
Low grade lymphoma	13	4.2
SLL	12	3.9
Mantle cell lymphoma	5	1.6
MALT lymphoma	4	1.3
Marginal zone lymphoma	3	1.0
Burkitt lymphoma	2	0.7
Lymphoblastic lymphoma	2	0.7
Unspecified B- NHL	5	1.6

5.3 Nutritional Intake

The results of this study showed that the median value of weekly consumption of both cases and controls for each food group was below the dietary reference intake (DRI). Table (5.4) shows the distribution of all food categories for both cases and controls, the median number of servings consumed weekly and the corresponding dietary reference intake (DRI) values provided by the USDA for each food group (USDA, 2015).

Table (5.4-a): Distribution of consumption of food groups for B-NHL cases and controls, medians and USDA'sDRI values of food groups.

Food group	Scale	Patient		Control		DRI
		n (%)	Median (servings/week)	n (%)	Median (servings/week)	
Fruits	Never	3(1)	5	5(1.3)	6	2-4 servings/day
	<1 a week	11(3.7)		14(3.6)		
	1 a week	21(7.1)		14(3.6)		
	2- 4 a week	80(26.9)		92(23.9)		
	5-6 a week	35(11.8)		43(11.2)		
	1 a day	52(17.5)		91(23.6)		
	>1 a day	95(32)		126(32.7)		
Vegetables	Never	2(0.7)	6	1(0.3)	6	3-5 servings/day
	<1 a week	5(1.7)		5(1.3)		
	1 a week	12(4)		6(1.6)		
	2- 4 a week	64(21.5)		72(18.9)		
	5-6 a week	34(11.4)		50(13.2)		
	1 a day	64(21.5)		87(22.9)		
	>1 a day	116(39.1)		159(41.8)		
Meat or chicken	Never	1(0.3)	4	3(0.8)	4	2-3 servings/day
	<1 a week	11(3.7)		15(3.9)		
	1 a week	30(10)		39(10.2)		
	2- 4 a week	180(59.8)		252(65.6)		
	5-6 a week	50(16.6)		40(10.4)		
	1 a day	29(9.6)		32(8.3)		
	>1 a day	0(0)		3(0.8)		

Table (5.4-b): Distribution of consumption of food groups for B-NHL cases and controls, medians and USDA'sDRI values of food groups.

Food group	Scale	Patient		Control		DRI
		n (%)	Median (servings/week)	n (%)	Median (servings/week)	
Fish	Never	18(6)	2	28(7.3)	2	2-4 Servings/ week
	<1 a week	180(59.8)		211(55.2)		
	1 a week	79(26.2)		112(29.3)		
	2- 4 a week	23(7.6)		30(7.9)		
	5-6 a week	1(0.3)		1(0.3)		
	1 a day	0(0)		0(0)		
	>1 a day	0(0)		0(0)		
	Subtotal	301(100)		382(100)		
Whole milk	Never	69(23)	4	128(33.8)	2	2-3 Servings/ day
	<1 a week	55(18.3)		82(21.6)		
	1/ week	14(4.7)		27(7.1)		
	2- 4 / week	54(18)		49(12.9)		
	5-6 /week	17(5.7)		14(3.7)		
	1 a day	69(23)		66(17.4)		
	>1 a day	22(7.3)		13(3.4)		
Dairy products	Never	14(4.6)	5	15(3.9)	5	2-3 servings/ day
	<1 a week	18(6)		38(9.9)		
	1 a week	23(7.6)		32(8.3)		
	2- 4 a week	76(25.2)		96(25)		
	5-6 a week	41(13.6)		67(17.4)		
	1 a day	102(33.8)		103(26.8)		
	>1 a day	28(9.3)		33(8.6)		

Fruits

The median consumption of fruits by Palestinians cases in this study was 5 servings/week) and by controls is (6 servings/week) (Table 5.4), both groups showed median intake that is below the DRI which is 2-4 servings/day. A non-significant inverse association was noticed between fruit consumption and risk of B-NHL (OR=0.7; 95% CI: 0.2-2.1) (Table 5.5), suggesting a protective effect for increased intake of fruits from the risk of B-NHL.

Table (5.5): ORs and 95% CI for B-NHL association with consumption of food groups.

Food group	OR*	95% CI
Fruits	1	Reference
	0.7	0.2 - 2.1
Vegetables	1	Reference
	1.3	0.4 - 4.0
Meat (red and white)	1	Reference
	1.8	0.8 - 4.3
Fish	1	Reference
	0.4	0.2 - 0.8
Whole milk	1	Reference
	2.3	1.2 - 4.4
Dairy products	1	Reference
	1.3	0.7 - 2.6

* ORs: Odds ratios estimated from unconditional logistic regression adjusted for age and sex.

Vegetables

Regarding vegetable intake, the median intake for both cases and controls was also much below the DRI (6 servings/week compared to 3-5 servings/day) (Table 5.4). In addition, vegetable intake was found to be positively associated with risk of B-NHL (OR=1.3; 95% CI: 0.4-4) (Table 5.5).

Meat

According to Table (5.4) the median meat intake was also found to be less than the DRI, nevertheless, a positive association between risk of B-NHL and meat intake was found although it was non-significant (OR=1.8; 95% CI: 0.8-4.3) (Table 5.5).

Fish

Fish consumption was the only one close to the DRI, though still at the lowest borders of consumption (Table 5.4). A significant inverse association between fish consumption and B-NHL risk was found (OR=0.4; 95% CI: 0.2-0.8) (Table 5.5), which means that an increased fish intake might be protective against B-NHL.

Whole milk

As for whole milk consumption, the median of weekly intake was less than the DRI as shown in Table (5.4). Yet, higher intake of milk was found to be significantly associated with increased risk of B-NHL (OR=2.3; 95% CI: 1.2-4.4) (Table 5.5).

Dairy products

As with most of rest of the other food items included in this study, the median intake of dairy products in both cases and controls participating in this study was 5servings/week, which is also far below the DRI value of (2-3 servings/day) (Table 5.4). In addition, a higher intake of dairy products was non-significantly associated with an increased risk of B-NHL (OR=1.3; 95% CI: 0.7-2.6) (Table 5.5).

5.4 Personal and Family History of Cancer and the Risk of B-NHL

A significant association between personal history of cancer and B-NHL risk was observed (OR=11.1; 95% C.I: 2.5-48.5) (Table 5.6), this means that a person with previous cancer is 11 times more likely to develop B-NHL than those without a previous history of cancer. Table (5.6) also shows that family history of cancer among first degree relatives was found to be significantly associated with increased odds of B-NHL (OR=1.7; 95% C.I: 1.2-2.5).

Table (5.6): ORs and 95% CI for B-NHL association with personal and family history of cancer.

		Case (n)	Control (n)	OR*	95% CI
Personal history of cancer	No	282	381	1	Reference
	Yes	17	2	11.1	2.5 - 48.5
Family history of cancer in the first degree relatives	No	218	299	1	Reference
	Yes	79	62	1.7	1.2 – 2.5

* ORs: Odds ratios estimated from unconditional logistic regression and adjusted for age and sex

Chapter Six

Discussion, Conclusion, Limitations and Recommendations

6.1 Discussion

Cancer is a major health problem in high, middle and low income countries, and is the second leading cause of death in the world (Al-Othman et al., 2015). Over the past several decades, a global rise in the incidence of NHL was noticed and recent studies reported that the diet may contribute to this rise (Skibola, 2007). This case-control study is the first to investigate B-NHL and dietary factor among the Palestinian population.

The results of this study add valuable information on the subject and also lead to a better understanding of dietary consumption patterns and their implications in overall health and disease. In addition, the use of face to face interview-based questionnaire conducted by trained interviewers to fill the questionnaire provided more consistency to the process of data collection increasing the reliability and reproducibility of the study. Moreover, the study provides the base to conduct more researches regarding nutritional intake and food patterns among Palestinians and the etiological factors of NHL.

6.1.1 Socio-demographic characteristics

An increase in the proportion of B-NHL cases was noticed with aging among Palestinians. Age is a major risk factor for NHL, and this result is consistent with the worldwide trends in NHL (Caimi, Barr, Berger, & Lazarus, 2010; Julius, 1987). Nevertheless, the results showed a mean age at diagnosis (years \pm SD) for B-NHL of (50.8 \pm 16.6) and a median age of 52 years, with most cases being <65 years old and a large proportion of cases (more than 20%) younger than 35 years old. The median age in this study is younger than the worldwide reported median (seer.cancer.gov/, 2014). In addition, the regional variability in the distribution of Palestinian cases might be attributed to certain environmental or genetic exposure.

In the present study, the educational level of cases was lower than that of the controls as most of cases had primary education levels while the majority of controls were either within the secondary education level or had a first university degree. The low educational level among the cases might be related to poor socio-economic status and less healthy conditions, which may contribute to the increase in the exposure to infections and consequently, may raise the risk of B-NHL. This result is in line with other studies (Allison, Daw, & Rorvik, 1987; Holly, Lele, Bracci, & McGrath, 1999), though some studies did not report a similar association (Franceschi et al., 1989; Hermann et al., 2010).

The present study showed minor differences in the distribution of B-NHL cases and controls in relation to birth order in the family. An increase in birth order was reported to be associated with increased susceptibility to infections during early development of the immune system leading in turn to an increased risk of NHL (Vineis et al., 2000). Some previous studies reported weak or non-significant associations between large sibship and the risk of NHL (Vineis et al., 2000), while other case-control studies have reported that only children and first-born children had an approximately 50% reduction in NHL risk compared with fourth or later-born children and that NHL risk increased with increasing number of older siblings, for only children OR was 0.5 (95% CI: 0.3-0.8), for first-born children (OR=0.6; 95% CI: 0.4-0.8), for second-born children (OR=0.7; 95% CI: 0.5-1.0) and for third-born children (OR=0.8; 95% CI: 0.6-1.1), however, markers of crowding later in childhood, such as bedroom and bed sharing, were not associated with risk of NHL (Grulich et al., 2005; Vineis et al., 2000). Other studies reported that a large sibship size, late birth order and childhood crowding were associated with an increase in B-NHL risk.

Effect mechanisms may be related to early age at onset and high frequency of specific infections or microbial exposure in childhood(Bracci, Dalvi, & Holly, 2006; Smedby et al., 2007).

6.1.2 Nutritional intake

Our results showed that median intake for the assessed food groups for Palestinian cases and controls were below the DRI for most food groups, which is consistent with the findings of other previous study that assessed dietary intake among Palestinians(Abdeen et al., 2007).

Regarding fruit consumption, a non-significant inverse association was found between higher intake of fruits and risk of B-NHL (OR=0.7; 95% CI: 0.2-2.1). This is in agreement with several previous studies (Davis, 1992; Holtan et al., 2012; Kelemen et al., 2006; Wang et al., 2007; Zheng et al., 2004). The protective effect of fruit intake on lowering the risk of SLL in women was reported by Purdue and his colleagues(Purdue et al., 2004). This association between fruit intake and B-NHL risk was explained by the antioxidant effect of certain components in fruits, which can prevent free radicals and inhibit nitrosation, especially of carotenoids, vitamins C, proanthocyanidins and manganese, leading in turn to the reduction of production of reactive oxygen species responsible for oxidative DNA damage, regulation of cell survival and apoptosis pathways and further improvement and protection of immune responses and immune system(Thompson et al., 2010). The protective role of fruits was also reported to be attributed to their content of folate, which prevents chromosomal breaks since it is considered an anti-carcinogenic molecule and is found mainly in fruits and vegetables(Liberski, 1987; Ollberding et al., 2012; Thompson et al., 2010). It is worth noting here that abnormal one carbon metabolism which is caused either by folate deficiency or through polymorphisms in folate metabolizing genes, may promote lymphomagenesis through mechanisms involving aberrant DNA synthesis, repair, and methylation(Chang et al., 2005; Kelemen et al., 2006; Skibola, 2007). Other studies, however, have not indicated any association between fruit intake and B-NHL risk (Ali et al., 2013; Chen et al., 2013; Ollberding et al., 2014). Similarly, no beneficial impact was found by Liberski (1987) for fruit intake, which was relate to the fact that fruit generally contains less fiber, minerals, and vitamins and more sugar and calories (Liberski, 1987).

A positive association between increased vegetable intake and the risk of B-NHL was found in this study (OR=1.3; 95% CI: 0.4-4). Although an increased risk for SLL have been previously reported to be associated to higher intake of vegetables(Lazar, Hodin, Darling, & Chin, 1988), but no similar positive association with vegetables, vegetable fat, dark green vegetables or high-nitrate vegetables and the risk of NHL was reported(Chiu et al., 1996, 2008; Ollberding et al., 2014). In contrast, most previous case-control and cohort studies reported an inverse association between intake of vegetables and the risk of NHL, an association that was explained by their anti-oxidant properties which cause reduction of reactive oxygen species which contributes in oxidative DNA damage, regulation of cell survival and apoptosis pathway, and protection of immune responses(Ali et al., 2013; Kelemen et al., 2006). Furthermore, dietary fibers was found to be inversely associated with risk of NHL and inhibit lymphoma development by suppressing inflammation that was indicated by serum levels of C-reactive protein, a clinical marker of inflammation(King, Egan, & Geesey, 2003; Zheng et al., 2004). In addition, the association between vegetable intake and lymphoma was found to differ by lymphoma subtype; Chiu et al (2011) reported that higher intake of cruciferous vegetables and green leafy vegetables was associated with a lower risk of NHL and in particular DLBCL (OR=0.4; 95% CI: 0.2-0.8), while green leafy vegetable intake was associated with a lower risk of FL (OR=0.5; 95% CI: 0.3-0.8) and DLBCL (OR=0.5; 95% CI: 0.3-0.9)(Chiu et al., 2011).

The positive association between vegetable intake and the risk of B-NHL found here could be attributed to the misuse of pesticides among Palestinian farmers and the lack of safety precautions(Alavanja et al., 2014; Schinasi & Leon, 2014), or to the increasing use of wastewater in agriculture in Palestine. In fact, most agricultural land in the Palestinian National Authority is used for food production where vegetables, orchards, and dry land crops are planted, and the problem of agricultural pesticides in Palestine, in addition to Arab countries, is not only about uncontrolled use, but also attached to the unsafe handling, misuse and disposal of unwanted pesticides. In Palestine this effect is even amplified by the undeveloped national laws and regulations in regard to potential fate and the impact of residuals of pesticides on groundwater, food safety and public health (Bashour, 2008). Furthermore, the sale and handling of pesticides are not regulated and that accredited labs for pesticide residue analysis are not available(DeWaal & Robert, 2005). Further, the shortage of reliable data has alerted the scientific community and, to some extent, the

general public, to the need for facts on potential health hazards of pesticides through their indiscriminate use (Samhan & PWA, 2008). Moreover, most Palestinian agricultural workers have low level of knowledge regarding pesticide use, safety precautions and the protective measures; Al-Sa'ed and his colleagues assessed the knowledge of Palestinians about pesticide use and reported that 86.3% of respondents were not able to read instructions on pesticides' labels as most of them are either in Hebrew or English, in addition to 95.4% that were found to rely on their own experience for the dose amount and calibration (Al-Sa'ed, Ramlawi, & Salah, 2011). The misuse of these pesticides was reported in other studies to cause intoxication among exposed persons (Zyoud et al., 2010) and was also reported to be associated with increased NHL risk (Alavanja et al., 2014; Hohenadel et al., 2011; Sundewall et al., 1985).

The existing condition of wastewater is considered to be disastrous for Palestinians as reported in other studies. Wastewater that seeps and infiltrates down from the individual cesspools to the groundwater aquifers causing groundwater pollution as well as spring pollution. In addition, some farmers use the raw sewage to irrigate their vegetables, such as DeirSharaf's farmers in Nablus area and Obedia's farmers in Bethlehem area. This wastewater flows over soil surface and causes salt accumulation as well as suspended solids which is known to destroy the texture and the structure of the soil and might cause some diseases for human beings (Sbeih, 1996). A previous study reported that a long term exposure to elevated nitrate levels in drinking water may contribute to the risk of NHL (Ward et al., 1996), and another one conducted in China in 2012 reported that protecting groundwater from nitrogen contamination is an important public-health concern and a major national environmental issue (Halwani, Baroudi, & Wartel, 1998). The existing evidence suggest that the use of wastewater in crop irrigation increases their content of nitrates, and since nitrates and nitrites are precursors in the endogenous formation of N-nitroso compounds, which are potent animal carcinogens, their increased intake might entail an increase in the risk of NHL among other serious health effects (Mousavi, Balali-Mood, Riahi-Zanjani, & Sadeghi, 2013; Ward et al., 2010).

Furthermore, a positive association between B-NHL risk and an increased meat intake was found (OR=1.8;95% CI: 0.8-4.3), a finding that is consistent with previous case-control and cohort studies that reported a positive association between a high-meat diet and high animal fat intake and the risk of B-NHL, although meat consumption among Palestinians

was shown to be less than DRI(Ali et al., 2013; Ollberding et al., 2014; Purdue et al., 2004; Skibola, 2007; Zhang et al., 1999). Excessive meat intake, which is high in saturated fat, animal protein and calories, might lead to increased chronic antigen stimulation and altered immunocompetence and immune system impairment, it might also amplify the effect of certain viruses or genetic susceptibility(Morton, Hartge, et al., 2005), which in turn may lead to the development of lymphoma (Davis, 1992; Zheng et al., 2004). The suppressive effect of meat consumption to the immune system might be due to the presence of chemicals such as haem, which can damage the cells causing them to divide much more than normal to compensate for this damage and subsequently increase cancer risk (Cross et al., 2003). Haem could also stimulate the bacteria in the gut to produce N-nitroso compounds which are known carcinogens. Furthermore, consumption of cooked meat, either fried, grilled, or boiled, may influence NHL development through the generation of immunotoxic heterocyclic amines and other polycyclic aromatic (Layton et al., 1995). Saturated fats can also increase the risk of NHL and its subtypes by promoting inflammation via the cyclooxygenase and lipoxygenase pathways (Zheng et al., 2004). Moreover, a positive association between the intake of fried red meat in particular and NHL risk was reported with no association between red or white meat intake and the risk of NHL(Chang et al., 2005).In contrast, no association between the consumption of meat, fat or chicken and NHL risk was reported in other studies(Daniel et al., 2012; Hansen, Casaburi, Cooper, & Wasserman, 1988; Rohrmann et al., 2011).

Concerning fish consumption, a significant inverse association between fish consumption and B-NHL risk was found with an odds ratio of 0.4 (95% CI: 0.2-0.8). This finding is consistent with several case-control and cohort studies(Ali et al., 2013; Fritschi et al., 2004; Hinrichs, Gaab, Feistner, Lorenz, & Dorfmueller, 1989; Skibola, 2007). In fact, fish oils have been used successfully in the management of several inflammatory and autoimmune diseases, which are risk factors of B-NHL(Kelley, 2001). On the other hand, a previous meta-analysis and a case-control study detected no association between consumption of fish and the risk of NHL(Chang et al., 2005; Yang et al., 2014). In contrast, other studies showed a positive association between the consumption of fish intake and B-NHL risk(Daniel et al., 2012; Yang et al., 2014), which was attributed to the high content of organochlorine pesticides and PCBs in some fish(Skibola, 2007).

A significant positive association between milk intake and B-NHL risk was found in this study (OR=2.3; 95% CI: 1.2-4.4). This is consistent with several previous studies (Chiu et al., 2008; Davis, 1992). Other studies reported a positive association between milk intake and DLBCL but not FL (Chiu et al., 2008). Moreover, milk types were reported to have varied effects on NHL risk; i.e. low fat milk was found to have a protective impact while fatty milk was a risk factor (Mallinger et al., 1987). An increased risk of NHL associated with a high fat diet may lead to altered immunocompetence, and immune system impairment by acting on the lipoxygenase, cycloxygenase, cytochrome P-450 pathways or its direct effects on cell membrane function and structure, which lead to alteration in lymphocytes, and as a result, impaired immune function (Calder & Kew, 2002; Zheng et al., 2004). On the other hand, a beneficial effect for the milk pattern on SLL in women was reported (Purdue et al., 2004). In addition, skim milk was inversely associated with NHL risk and SLL. However, other studies found no association with NHL risk (Chiu et al., 1996; Ward et al., 1994).

With regard to the association between the consumption of dairy products and B-NHL, a positive association between consumption of dairy products and the risk of B-NHL was found (OR=1.3; 95% CI: 0.7-2.6) and this result is in agreement with several previous studies (Skibola, 2007; Talamini et al., 2006). The proposed mechanism of action for dairy products is through increased chronic antigen stimulation and altered immunocompetence and immune system impairment (Morton, Zheng, et al., 2005). Another mechanism could involve inhibition of 1,25(OH)₂D production, which is the biologically active form of vitamin D and considered an anti-carcinogen because it promotes differentiation and apoptosis and inhibits cell growth in neoplastic cells. This inhibition occurs due to the calcium in dairy products. In addition, contamination of dairy fat with significant levels of organochlorines such as dioxins and polychlorinated biphenyls which are considered carcinogens and immunotoxins that can alter normal B-cell responses; positive associations between organochlorines and NHL suggest a role of dairy fat in lymphomagenesis (Skibola, 2007). In contrast, other studies reported no association between dairy consumption and B-NHL risk (Chiu et al., 1996; Ursin, Bjelke, Heuch, & Vollset, 1990).

6.1.3 Personal and family history of cancer

An elevated significant positive association was found between personal history of cancer and B-NHL risk (OR=11.1; 95% CI: 2.5-48.5). This result is consistent with several

previous studies(Crump et al., 2012; Paltiel et al., 2000; Wang et al., 2007); for example, a previous study reported that women with endometriosis were at an increased risk of hematopoietic malignancies, especially B-NHL. In addition, other studies reported an increase in the incidence of lymphomas in patients with gastric tumors (Rothman et al., 2006; Skibola et al., 2007). Moreover, liver cancer, breast cancer and kidney cancer were all reported to be associated with increased NHL risk(Linet et al., 2014; Negri et al., 2006; Skibola et al., 2014).

The association between the risk of B-NHL and first degree relatives' history of cancer was found to be significantly increased in this study. A multicenter U.S.-based case-control study of NHL was conducted to evaluate familial aggregation of NHL with various hematolymphoproliferative and other cancers, reported that a positive family history of NHL was associated with a 2-fold increased risk of NHL(Chatterjee et al., 2004; Linet & Pottern, 1992). Other studies reported that a familial history of NHL is significantly associated with increased risk for NHL and B-NHL subtypes like DLBCL and FL. In addition, NHL was found to have a stronger familial association among men than among women, and siblings were also a more strong marker of personal risk of NHL than is history of NHL in a parent(Altieri, Bermejo, & Hemminki, 2005; Wang et al., 2007; Zhu et al., 1998).

6.2Conclusion

This study affirmed the role of aging in the etiology of NHL, which is consistent with the worldwide trends of NHL. Further, the findings of this study supports a possible contribution for dietary intake and nutritional factors in the process of lymphomagenesis; high consumption of meat, dairy products, milk and vegetables were all found to be associated with an increased risk of B-NHL, while fruit intake was found to reduce the risk of B-NHL. In addition, a significant protective effect of fish consumption and B-NHL risk was found. These findings need further investigation to be confirmed in larger studies, but they provide a base to study NHL in Palestine and the Arab region.

6.3Limitations

Despite the fact that this study is the first to investigate NHL in Palestine and one of few in the Arab world, and all the efforts provided to strengthen the design and outcomes of it; there remain some limitations that may affect the outcomes and the generalizability of this study.

The most apparent limitation is the retrospective case-control design which is affected by recall bias. In addition, relying on self-reported consumption data and family history of cancer may result in a misclassification bias. The use of standardized face-to-face interview-based questionnaire for data collection by trained interviewers with both cases and controls limit the probability of differential bias, still the findings might suffer from non-differential bias that may lead to underestimation of the associations.

Furthermore, in this study we were unable to evaluate the association between dietary intake and NHL subtypes due to the limited sample size in each subcategory. Moreover, the pathological diagnosis in the West Bank is not based on the state-of art immunostaining.

6.4 Recommendations

Based on the findings of the study, further investigation regarding dietary factors patterns and the role in lymphoma risk using larger samples, more detailed questionnaires such as the 36 or 72-item FFQ, or 24-hour recall questionnaire, in addition to details regarding methods of food preparation which might also be a factor associated with NHL risk and is not investigated in this study. Further, it is worthy to investigate the postulated association for pesticide misuse, the use of untreated wastewater in agriculture, vegetable intake and the association with the risk of NHL.

Public health efforts are recommended strongly to be directed towards developing better dietary habits that meets the recommended RDIs through public awareness programs for food safety and prevention of nutritional-associated health problems that include cancer, which is a shared responsibility between the Ministry of Health and the Ministry of Agriculture.

Controlling and monitoring for agricultural practices such as the use of pesticides for crops and livestock and the use of untreated wastewater for irrigation, which could be achieved through development of legislations and regulations and training programs for farmers to ensure safety of workers and consumers.

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Appendices

Appendix 1.1

Approval letter by the Ministry of Health

تحية طيبة وبعد ...

حضرة مدير صحة بيت لحم المحترم الموضوع: المشاركة في دراسة علمية حول ورم الغدد الليمفاوية غير الهودجكن

يسعدنا إعلامكم أن جامعة القدس تقوم باستكمال بحث يتعلق بدراسة وبائية وجينية لمرضى ورم الغدد الليمفاوية غير الهودجكن والذي تم سابقا بالتعاون بين جامعة القدس ووزارة الصحة بالتنسيق بين د اسعد الرملاوي واقسام المختبرات في PHC حيث أن الطالبة مرام محمد الفتياي ستكون مسؤولة عن تأمين خمسين شخص كجزء من المجموعة الضابطة في رسالتها البحثية في الماجستير تحت عنوان

(Nutritional risk factors of Non-Hodgkin Lymphoma)

نرجو من حضرتكم المساعدة في التنسيق ما بين الطالبة مرام ومدير المهن الصحية الاستاذ نبيل ابو ريان في اجراء عملية سحب الدم من هذه المجموعة علما بان الطالبة مرام بدأت بالترتيب لهذا الموضوع منذ 2014 /1/7 وتجهيز المواد (التي ستؤمن لها بالكامل من قبل القائمين على المشروع) وان عملها على المشروع سيتم خلال يومها الدراسي الاثنين او تديبه مع يوم اخر حسب الحاجة والتنسيق مع مختبرات المدن والقرى التابعة للرعاية الصحية الاولى.

الرجاء مساعدتها على استقطاب المجموعة الضابطة وسحب عينات الدم منهم حسب البروتوكول المخصص لذلك .

شاكرين لكم حسن تعاونكم

تفضلوا مع فائق الاحترام والتقدير

د.زياد عابدين



دائرة العلوم الطبية المخبرية
Medical Laboratory Science Dept.



Appendix 1.2

Informed consent form in Arabic language

الموافقة عن علم للمشاركة في دراسة

ورم الغدد الليمفاوية

لقد طلب مني المشاركة في دراسة تبحث في أسباب الورم الليمفاوي غير الهودجكن، حيث سأشارك كحالة (مريض الذي شُخصَ بهذا المرض) ، أو كمجموعة ضابطة (شخص سليم لا يعاني من هذا المرض ، ولكن لديه صديق أو أحد افراد عائلته يعالجون في هذا المستشفى) . هذه الدراسة سوف تقارن المعطيات الشخصية ، والتاريخ الطبي ، وسبل التعرض. وذلك للناس المصابين والغير مصابين بالمرض. هذه الدراسة لديها القدرة على اكتشاف معلومات هامة عن أسباب هذا المرض.

سوف يطلب مني الإجابة على أسئلة تتعلق بنفسي ، و تفاصيلي الطبية ، والعلاج في المستشفى بالماضي ، و عائلتي ، وأين عشت ، ووظائفي التي عملت بها ، جميع المعلومات في هذا الاستبيان ستحتفظ بطابع من السرية. المقابلة ستدوم حوالي 30 دقيقة أو أقل.

أيضا سيطلب مني تقديم عينة دم (حوالي "15cc"). الدم سوف يفحص من أجل بعض الخصائص الجينية التي قد تتعلق بورم الغدد الليمفاوية وأيضا سيتم فحصه لإصابات فيروسية سابقة والمعروف بأن لها علاقة بورم الغدد الليمفاوية. المعلومات من هذا الفحص ستبقى سرية أيضا . قد يكون هناك الشعور بعدم الراحة نتيجة أخذ عينات الدم. ولا يوجد هناك أي آثار جانبية أخرى متوقعة من المشاركة في هذه الدراسة.

الإسم: _____

وافق على اجراء المقابلة (التوقيع) _____

وافق على إعطاء عينة الدم (التوقيع) _____

وافق على أن تخزن عينة الدم التي سحبت مني وأن تستخدم في دراسات لاحقة (التوقيع) _____

التاريخ : _____

Appendix 4.1

Pathology questionnaire

Pathology questionnaire:

Patient Name: _____

Patient Code: _____

1. **Date of Diagnosis:** ___/___/___
2. **Age at Diagnosis (years) :** _____
3. **Date of last follow up:** ___/___/_____
4. **Hospital of diagnosis:**

1. Augusta Victoria 2. Nablus (National)
3. Cancer Registry 4. Beit Jala 5. other: _____

5. Histological diagnosis:

1. DLBCL (large cell)	6. SLL	11. Mycosis fungoides
2. Follicular	7. Lymphoblastic	12. NHL
3. MALT	8. Low grade lymphoma	13. Hodgkin lymphoma
4. MANTLE	9. B-cell NHL	14. others: _____
5. Burkitt	10. T-cell lymphoma	

6. Immunostain: A. T cell B. Bcell C. unspecified.

<p><u>1.</u> IHC (P-Positive N- Negative)</p> <p><u>2.</u> CD20 (P-Positive N- Negative)</p> <p><u>3.</u> CD10 (P-Positive N- Negative)</p> <p><u>4.</u> BCL6 (P-Positive N- Negative)</p> <p><u>5.</u> BCL2 (P-Positive N- Negative)</p> <p><u>6.</u> CD43 (P-Positive N- Negative)</p> <p><u>7.</u> CD79A (P-Positive N- Negative)</p> <p><u>8.</u> CD5 (P-Positive N- Negative)</p> <p><u>9.</u> CD23 (P-Positive N- Negative)</p> <p><u>10.</u> kappa (P-Positive N- Negative)</p>	<p><u>11.</u> lambda (P-Positive N- Negative)</p> <p><u>12.</u> CD22 (P-Positive N- Negative)</p> <p><u>13.</u> CD19 (P-Positive N- Negative)</p> <p><u>14.</u> CD30 (P-Positive N- Negative)</p> <p><u>15.</u> CLA (P-Positive N- Negative)</p> <p><u>16.</u> ALK (P-Positive N- Negative)</p> <p><u>17.</u> CD3 (P-Positive N- Negative)</p> <p><u>18.</u> CD2 (P-Positive N- Negative)</p>
--	---

7. Site of biopsy:

<p>1. Lymph Nodes (LN):</p> <p>1.1. Cervical LN</p> <p>1.2. Axillary LN</p> <p>1.3. Mediastinal & Hylum</p> <p>1.4. Para aortic LN</p> <p>1.5. Abdominal LN</p> <p>1.6. Inguinal LN</p> <p>1.7. Submandibular LN</p> <p>1.8. Other LN: _____</p>	<p>3. Organs:</p> <p>3.1. Nasopharynx</p> <p>3.2. Oropharynx</p> <p>3.3. Thyroid</p> <p>3.4. Lungs</p> <p>3.5. Breast</p> <p>3.6. Stomach</p> <p>3.7. Colon</p> <p>3.8. Small Intestine</p> <p>3.9. Pancreas</p> <p>3.10. testes</p> <p>3.11. Ovaries</p> <p>3.12. skin</p> <p>3.13. Brain</p> <p>3.14. Bone Marrow</p> <p>3.15. Others organs:</p>
<p>2. Lymphoid Organs:</p> <p>1. Tonsils</p> <p>2. Spleen</p>	

8. Spread of disease:

1. Nodal 2. Extra nodal 3. Undefined

9. Stage :

1. I 2. II 3. III 4. IV

10. Presence of B-symptoms (fever, weight loss, night sweat)

1. Yes 2. No 3. Unknown

11. Treatment received:

1. CHOP
2. Rituximab
3. Other Chemotherapy: _____
4. Radiotherapy
5. Surgery
6. Transplantation: 6.1. Autologous 6.2. Allogenic

12. LDH at diagnosis: _____

Appendix 4.2

Study questionnaire in English

Non-Hodgkin Lymphoma

Interviewer name: _____

Code

Date of Interview: ____/____/____

Time Started ____: ____

Finished at ____: ____

Site of Interview: 1. Home 2. Hospital _____ 3. Clinic 4. others

Part I: Demographic Information

I would like to ask you about your sociodemographic information including your marital status, education, place of birth, and others

Q1) ID Number

--	--	--	--	--	--	--	--	--	--

Q2) Interviewee Name:

--

Q3) Gender: 1. Male 2. Female

Q4) Date of Birth	Year	Month	Day
	_ _	_	_

Q5) Marital status:

- 1. Single
- 2. First marriage
- 3. Second marriage or more
- 4. Divorced or separated
- 5. Widowed

Q6) How many births did you have? (including all living and dead)

--

Q7) How many are alive?

--

Q8) What were the causes of death

--

Q9) I would like to ask about the sex and birthdates of your children?

Child Number	Sex	Date of Birth Day/Month/Year
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		

1.Male 2.Female

Q10) How many siblings do you have?

Q11) What is your birth order in the family

Q12) What is your religion?

- 1. Muslim
- 2. Jewish
- 3. Christian
- 4. others

Q13) How many years did you complete in school?

Q14) Before kindergarten did you go to:

- 1. Day care
- 2. Nursery school
- 3. Baby sitter who takes care of more than one child
- 4. Baby sitter at home
- 5. Mother stayed home

Q15) Did you go to kindergarten?

- 1. Yes
- 2. No

Q16) What is your highest diploma?

1. Never went to school <input type="checkbox"/>	2. Partial Primary (< 6 th grade) <input type="checkbox"/>	3. Primary school completed <input type="checkbox"/>
4. Partial Secondary <input type="checkbox"/>	5. High school completed <input type="checkbox"/>	6. Diploma <input type="checkbox"/>
7. Bachelor degree <input type="checkbox"/>	8. Higher research degrees <input type="checkbox"/>	

Primary school: 1st grade-6th grade, **Secondary school:** 7th grade-12th grade)

2. Teacher					
3. Textile					
4. Wood industry					
5. Flour workers					
6. Dry cleaning					
7. Chemical Industry					
8. Gasoline/ petroleum workers					
9. Lab technicians					
10. Health care provider a. doctors b. nurses c. physiotherapist					
11. Photoimager					
12. Veterinary					
13. Air crew					
14. Butcher					
15. Hair dresser					
16. Asbestos worker					
17. Leather worker					
18. Construction Workers					
19. Cleaners					
20. House wives					
21. others:					

Exposures codes:

1. Pesticides 2. Meat products 3. Organic solvents 4. inorganic Solvents 5. Gasoline 6. UV radiation
7. Cosmic radiation 8. Ionizing radiation 9. electromagnetic radiation 10. Infectious agents /
microorganisms 11. Animals 12. Antibiotics 13. Paints 14. Hair dyes 15. Asbestos 16. animal skin
17. Glues 18. sunlight 19. medicines (pharmaceuticals) 20 flour dust 21 cleaning materials 22.
wood dust 23. Others

Part III: Housing

I would like to have some information about your current and previous residences

Q23) What type of residence have you lived in?

(do not include residence of less than 3 years)

Addresses	Type of settlement	House type	Which storey did you live on	Water source	# of persons residing in the house	# of rooms	Bathroom	From what year to what year?
Current Residence								
Previous								
1.								
2.								
3.								
4.								
5.								

➤ **Type of settlement** :1. City >100000 persons 2.Town 20000-99999 persons 3.Small town 5000-19999 persons 4.village<5000 persons 5.agricultural settlement 6.private farm or rural dwelling 7. Other

➤ **House type**:1. a private house 2. A multifamily (10 families) house 3.an apartment building (>10 families) 4. tent 5.agricultural settlement

➤ **Storey**:1. ground floor 2. second floor 3.third floor 4. higher floor

➤ **Drinking water source**:1. pipes 2. a well 3. cisterns 4. mineral water 5. don't know

➤ **Bathroom**:1. indoors 2. outdoors

Part IV: Habits

I would like to ask you about some of your personal characteristics as your measurements, and other habits as smoking, hair dyeing, sun exposure, and your diet

Q24) What are your measurements?

Parameter	Measurement	Measurement(before 10yrs)
Height		
Weight		

1:the same 2: much higher 3:somewhat higher (<10%) 4:much lower somewhat lower(10%)

Q25) Have you ever smoked? (if never, go to Q31)

- 1. Cigarettes
- 2. Nargilah
- 3. Pipes
- 4. Tobacco
- 5. Never smoked

Q26) Are you a smoker now?

- 1. Yes
- 2. No

Q27) Have you stopped smoking?

- 1. Yes
- 2. No

Q28) How many years did you smoke?

Q29) How many cigarettes do (did) you smoke per day?

Period of time	Number of cigarettes
Average of smoking before illness	
Current level of smoking	

1: less than 10 2: 11-20 3: 21-40 4:more than 40

Q30) What is the average of your smoking, before illness and currently?

Period if time	Nargilah	pipes	Tobacco
Before illness			
Currently			

1: everyday 2: more than once/week 3: less than once/week

Q31) Did you ever dye your hair?(if No go to37)

- 1. Yes
- 2. No

Q32) Do you dye your hair regularly?

- 1. Yes
- 2. No

Q33) At what age did you begin to dye your hair?

#	Physical Activities	1. Don't do this activity	2. 2-3 times a month or more seldom	About once a week	2 times a week or more
1	Football, handball, basketball, tennis, hockey or other ball games				
2	Athletics, gymnastics				
3	Aerobics / fitness club exercise/Trade mill at home				
4	Jogging, running				
5	Karate, Judo taekwondo				
6	Wrestling				
7	Boxing/Kick boxing				
8	Weightlifting/Weight-training				
9	Dancing (disco, techno, folkdance, line dance, ballet)				
10	Camping				
11	Swimming				
12	Cycling				
13	Climbing				
14	skateboarding, roller skating				
15	Hiking, fishing				
16	Water activities (sailing, surfing, water-skiing)				

Q55) Do you keep a garden as a hobby? (if not, go to Q64)

1. Yes 2. No

Q56) What type of gardening do you perform?

1. Indoor 2. Outdoor

Q57) How many years have you practiced gardening?

Q58) How many hours per week did you practice gardening?

1. less than 10 hours/week
 2. 10-20 hours/week
 3. more than 20 hours/week

Q59) Do (did) you grow fruits and vegetables?

1. For your own use
 2. For sale
 3. Do not grow fruits and vegetables

Q60) Do (did) you use pesticides? (if not, go to Q64)

1. Yes 2. No

Q61) Do (did) you wear protective gloves and wearing when you use pesticides?

- 1.all the time 2.most of the time 3. sometime 4. never

Q62) Do (did) you wash your hands after using pesticides?

- 1.all the time 2.most of the time 3. sometime 4. never

Q63) Your pesticides are (were) against:

1. weeds 2. insects 3. fungus 4. don't know

Q64) Do (did) you spray insecticides in your house?

1. ≥1time/week 2.<1time/week-1time/month 3. few times/year 4. never

Q65) Do you remember the name of the pesticide(s) whether being used in the house or in gardening? (if No go to 67)

1. Yes 2. No

Q66) What is(are) the name of the pesticide(s) did you use?

Name of Pesticide

Q67) When you were a baby or a small child, did you go to the agricultural field with your parents or older siblings?

1. Yes 2. No

Q68) Do (did) you practice art as a hobby? (if not, go to Q75)

1. Yes 2. No

Q69) What type of art do (did) you practice?

1. painting
2. sculpture
3. pottery and ceramics
4. glasswork
5. lithography and prints
6. iron work
7. Model making

Q70) In your hobbies were (are) you exposed to any of the following chemicals?

1. oil paints
2. acrylic paints
3. other paints
4. Solvents (as turpentine, kerosene, glues, dust, lead)_____

Q71) How many years did you practice this art?

Q72) At what age did you start practicing this art?

Q73) At what age did you stop practicing this art?

Q74) How many hours per week did you practice this art?

1. less than 10 hours/week
2. 10-20 hours/week
3. more than 20 hours/week

Q75) Do (did) you have other hobbies that involve the use of chemicals? (if not, go to Q80)

1. Yes
2. No

Q76) What is this hobby?

Q77) What type of chemical is involved in this hobby?

Q78) At what age did you practice this hobby?

Q79) How many hours per week do (did) you practice this hobby?

1. less than 10 hours/week
2. 10-20 hours/week
3. more than 20 hours/week

Part V: Health

Now I am going to ask you about your health

Q80) Have you ever suffered form diarrhea lasting more than two days? (if not, go to Q82)

1. Yes 2. No 3. Don't remember

Q81) Did you have any serious diarrhea from any of the following agents:

Causative agent	Number of times	When was your last infection
1. Salmonella <input type="checkbox"/>		
2. Shigella <input type="checkbox"/>		
3. Campylobacter <input type="checkbox"/>		
4. Yersinia <input type="checkbox"/>		
5. Strongiloidosis <input type="checkbox"/>		
6. Ameba <input type="checkbox"/>		
7. Other parasitic infection <input type="checkbox"/>		
8. E.coli <input type="checkbox"/>		
9. I was told it was a viral infection <input type="checkbox"/>		
10. They did not find the causative agent <input type="checkbox"/>		
11. They didn't check <input type="checkbox"/>		
12. Other <input type="checkbox"/>		

Q82) Did you have a serious infection that required hospitalization during infancy (before the first year of age)?

1. Yes 2. No

Q83) Did you ever have any other serious infections that required hospitalization (like pneumonia)?(if no go to Q86)

1. Yes 2. No

Q84) How many times were you hospitalized for infections and at what age?

Age	# of times	Type of infection
1. more than 40 yrs		
2. 21-40yrs		
3. 11-20 yrs		
4. 1-10 yrs		
5. less than 1yr		

Infection codes

1. sinusitis 2. bronchitis 3. enteritis 4. gall bladder infection
 5. urinary tract infection 6. prostatitis (men only) 7. anal infection 8. dermatitis 9. gynecologic infection (women only) 10: meningitis 11. appendicitis
 12. other

Q85) Apart from infections requiring hospitalization, did you suffer from any of the following disease(s)? If yes, when?

Disease	Yes	No	Don't remember	Age
1. Hepatitis A				
2. Hepatitis B				
3. Hepatitis C				
4. Herpes: lips, nose, ear, other				
5. Infectious Mononucleosis				
6. Asthma				
7. Eczema				
8. Tonsillitis				
9. Measles				
10. Mumps				
11. Rubella				
12. Rheumatic fever				
13. Arthritis				
14. Tuberculosis				
15. Brucellosis				
16. Sinusitis				
17. Enteritis				
18. Polio				
19. Typhus				
20. Ulcer				
21. Allergy				
22. other				

Infection time code:

1. more than 40yrs 2. 21-40yrs 3. > 11-20yrs 4. 1-10yrs 5. less than 1yr

Q86) Did you receive vaccinations to the following microorganisms?

Disease	Yes	No	Don't remember	Age of the first vaccination	Age of the last vaccination
1. Tetanus					
2. Small Pox					
3. Typhoid					
4. measles					
5. Mumps					
6. Rubella					
7. Whooping cough					
8. Polio injection					
9. Polio drinking					
10. TB/BCG					
11. Yellow Fever					
12. Viral meningitis					
13. Cholera					
14. Hepatitis A					
15. Hepatitis B					
16. Hemophilus					
17. Pneumococcus					
18. Influenza					
19. others					

Q87) Did you undergo tonsillectomy? (if not, go to Q89)

1. Yes 2. No

Q88) At what age ?

Q89) Were (have) you ever administered antibiotics ? (if not, go to Q91)

1. Yes 2. No 3. Don't know

Q90) On average, how many times per year were you administered antibiotics and at what age?

Age	# of times
1. more than 40 yrs	
2. 21-40yrs	
3. 11-20 yrs	
4. 1-10 yrs	
5. less than 1yr	

Q91) Did you ever have an X-ray?

1. Yes 2. No 3. don't remember

Q92) Why did you perform an X-ray?

X-ray	# of times	Age
1. dental x-rays		
2. Chest x-rays		
3. Mammography (women)		
4. Bone x-rays		
5. Other		

1. >40yrs 2. 21-40yrs 3. > 11-20yrs 4. 1-10yrs 5. less than 1yr

Q93) Which one of the following sentences describes your childhood the best up to 18?

1. I was sick more often than my friends
2. I was away from school more than my friends
3. I got more medications than my brothers and sisters
4. I was a healthy child other than the normal childhood diseases
5. I was sick much less often than my siblings and friends

Q94) Did you have pets or large animals at home or on the grounds of your home? (if not, go to Q96)

1. Yes 2. No

Q95) What type of animal (do) did you have?

1. cat
2. dog
3. bird
4. horse
5. cow
6. camel
7. goat
8. sheep
9. donkey
10. pig
11. others

Q96) Have (were) you ever prescribed any of the following medications? if yes, at what age and how many times?

1. Yes 2. No 3. Don't Know

Medication	Never	Occasional <1/wk	Regular	
			Year started	Year ended
1. Steroids				
2. Contraceptives				
3. Hormone replacement therapy				
4. Other hormones				
5. Antifungal (oral)				
6. Non-steroidal anti-inflammatory				
7. Paracetamols				
8. Antidepressants				
9. Anti-parasitic				
10. Anti-anxiety				
11. Antiviral				
12. antihistamines				
13. B-Blockers				
14. Diuretics				
15. Anti-hypertensive drugs				
16. Thyroid replacement				
17. Anticoagulants				
18. Aspirin				
19. Chemotherapy				
20. Others				

Q97) Were you ever transfused with blood?

1. Yes 2. No 3. Don't know

Q98) Prior to your current illness, did you ever have cancer? (if not, go to Q100)

1. Yes 2. No

Q99) What was the treatment you received?

1. Chemotherapy
 2. Surgery
 3. Radiotherapy
 4. Don't know

Q100) Did any of your first degree relatives have cancer? If yes, what was the cancer type and who was that?

1. Yes 2. No 3. Don't Know

Cancer type	Siblings	Mother	Father	Child 1	Child 2	Child 3
1. Any Cancer						
2. Non Hodgkins Lymphoma						
3. Hodgkins Lymphoma						
4. CLL						
5. ALL						
6. Multiple Myeloma						
7. Acute Myeloid Leukemia (AML)						
8. CML						
9. Blood cancer						
10. Other blood problems						

Q101) Did any of your second degree relatives have cancer? If yes, what was the cancer type and who was that?

1. Yes 2. No 3. Don't Know

Cancer type	GM/m	GF/m	GM/f	GF/f	Uncles	aunts	cousins/n ephew	Nieces
1. Any Cancer								
2. Non Hodgkins Lymphoma								
3. Hodgkins Lymphoma								
4. CLL								
5. ALL								
6. Multiple Myeloma								
7. Acute Myeloid Leukemia (AML)								
8. CML								
9. Blood cancer								
10. Other blood problems								

GM(m): grandmother on mother's side
mother's side

GM(f): grandmother on father's side
side

GF(m): grandfather on

GF(f): grandfather on father's

Q102) Did any of your first degree relatives suffer from any of the following diseases? (If yes, who was that)

1. Yes 2. No 3. Don't Know

Disease	Siblings	Mother	Father	Child 1	Child 2	Child 3
1. Frequent Infection						
2. Allergy						
3. Rheumatoid Arthritis						
4. Autoimmune diseases						
5. Other immune problems						

Q103) Did any of your second degree relatives suffered from any of the following diseases? (If yes, who was that?)

1. Yes 2. No 3. Don't Know

Disease	GM/m	GF/m	GM/f	GF/f	uncles	aunts	cousins/n ephew	Nieces
1. Frequent Infection								
2. Allergy								
3. Arthritis								
4. Autoimmune diseases								
5. Other immune problems								

GM(m): grandmother on mother's side

GF(m): grandfather on mother's side

GM(f): grandmother on father's side

GF(f): grandfather on father's side

Q104) How often do you go to the dentist?

1. For regular check-ups (at least once a year)
2. For regular check-ups (less than once a year)
3. Only when I have a toothache or other problem
4. Never

Q105) Do you own a car?

1. Yes 2. No

Q106) How did you get to the hospital today?

1. Walk 2. Private car 3. Taxi 4. Public Transportation
5. Other

Q107) When is your next visit?

Thank you very much for you co-operation.

Q108) Interviewer rating of interview

1. Highly reliable
2. Somewhat reliable
3. Somewhat unreliable
4. Unreliable

Appendix 4.3

Study questionnaire in Arabic

الورم الليمفاوي الغير هودجكن Non-Hodgkin Lymphoma

الشخص الذي أجرى المقابلة: _____

كود الشخص الذي أجرى المقابلة : _____

- هل تم؟ توقيع الموافقة عن علم للمشاركة
- إصاق رقم الشخص المشارك على الاستبيان
- إصاق رقم الشخص المشارك على أنابيب الدم
- إصاق رقم الشخص المشارك على الاستبيان الباثولوجي
- سحب ثلاث أنابيب حمر وانبوبين بنفسجين

اسم الشخص المشارك: _____

رقم الشخص المشارك: _____

رقم الهاتف: _____

رقم الخلوي: _____

اسم الطبيب المعالج: _____

معلومات المقابلة-

تاريخ المقابلة: ____/____/____

وقت بداية المقابلة: _____:

وقت نهاية المقابلة: _____:

مكان المقابلة

1. المنزل
2. المستشفى
3. العيادة
4. في مكان آخر
- _____
- _____

القسم الأول : المعلومات السكانية

للمجموعة الضابطة فقط:

هل أنت مرافق (لمريض لمفوما/ لمريض آخر)?

ما هي صلة قرابتك للمريض

أود أن أسألك حول معلوماتك الديموغرافية والتي تتضمن الحالة الاجتماعية ، التعليم ، مكان الولادة و معلومات أخرى.

س (1) رقم الشخص المشارك

س (2) الأحرف الأولى من اسم الشخص المشارك

س (3) الجنس : 1. ذكر 2. أنثى

س (4) تاريخ الميلاد				اليوم		الشهر		السنة	

س (5) الحالة الاجتماعية :

1. أعزب
2. متزوج لمرة واحدة
3. متزوج لمرتين أو أكثر
4. مطلق أو منفصل
5. أرمل

س(6) كم مولود لديك ؟ (يتضمن الأحياء منهم والمتوفون و لا يشمل الإجهاض)

س (7) كم عدد الأحياء؟

س (8) ما هي أسباب الوفاة ؟

س 9) أود أن أسألك حول تواريخ ميلاد أطفالك وجنسهم ؟

تاريخ الميلاد			الجنس	رقم الطفل
سنة	شهر	يوم		
				1
				2
				3
				4
				5
				6
				7
				8
				9
				10

*** 1.ذكر 2. أنثى

س 10) كم عدد الأشقاء عندك؟

س 11) ما هو ترتيبك في العائلة ؟

س 12) ما هو دينك؟

1. مسلم
2. مسيحي
3. آخر

س 13) كم عدد سنوات الدراسة في المدرسة ؟

س 14) قبل الروضة هل ذهبت إلى :

1. مركز الرعاية اليومية
2. الحضانة
3. حاضنة أطفال والتي تعتني بأكثر من طفل واحد
4. حاضنة أطفال في البيت
5. البقاء مع الأم في المنزل

س 15) هل ذهبت إلى الروضة؟

1. نعم
2. لا

س 16) ما هي أعلى شهادة علمية حصلت عليها ؟

<input type="checkbox"/>	3.أكملت الدراسة الأساسية	<input type="checkbox"/>	2. أساسي جزئي (> الصف السادس)	<input type="checkbox"/>	1.لم أذهب إلى المدرسة
<input type="checkbox"/>	6. دبلوم	<input type="checkbox"/>	5.أكملت الدراسة الثانوية	<input type="checkbox"/>	4.ثانوي جزئي
<input type="checkbox"/>	9. درجة أكاديمية جزئية	<input type="checkbox"/>	8. درجات عليا	<input type="checkbox"/>	7. درجة البكالوريوس

المرحلة الأساسية : الصف الأول – الصف السادس ، المرحلة الثانوية : الصف السابع – الصف الثاني عشر

س17) هل تلقيت تدريباً تقنياً ؟ (إذا كانت الإجابة " لا " ، أذهبا إلى س 20)

1.نعم 2. لا

س 18) كم كانت مدة التدريب ؟ _____

س 19) ما هي المهنة التي تدرّبت عليها؟ _____

آباؤك و أجدادك

س 20) أين ولدت و أين ولد آباؤك وأين ولد أجدادك؟

المدينة	الدولة	القريب
		الشخص المقابل
		الأم
		الأب
		الجد (من جهة الأب)
		الجدّة (من جهة الأب)
		الجد (من جهة الأم)
		الجدّة (من جهة الأم)

القسم الثاني : المعلومات الوظيفية

أود أن أسألك حول عملك السابق وعملك الحالي ، ما هي العناصر/الأشياء التي تعرضت (تتعرض) لها خلال عملك؟ (لا تشمل الوظائف التي عملت فيها لمدة تقل عن ستة أشهر . رجاءً أبلغنا فيما إذا غيرت موقعك داخل العمل نفسه . رجاءً أبلغنا عن فترات البطالة ، وفترات الانقطاع عن العمل ، وإجازة الأمومة الخ).

س 21) هل لديك وظيفة حالياً؟

1.نعم 2. لا

س 22) قبل مرضك ، هل كان عندك عمل منتظم؟

1.نعم 2. لا

العمل	تاريخ البداية	تاريخ الانتهاء	فترات الانقطاع	المكان	التعرض لـ
1) ما هو عملك الحالي؟ _____					
2) ما هي وظائفك السابقة؟					
أ.					
ب.					
ج.					
د.					
3) هل سبق لك أن عملت في إحدى المجالات الآتية؟					
1. الزراعة والبستنة					
2. التعليم					
3. النسيج					
4. صناعة الخشب					
5. عمال طحين					
6. التنظيف الجاف					
7. الصناعة الكيماوية					
8. البنزين / عمال نפט					
9. فنيو المختبر					
10. مقدم خدمات الرعاية الصحية					
أ. الأطباء					
ب. الممرضين					
1. فنيو العلاج الطبيعي					
11. فنيو الأشعة					
12. طبيب بيطري					
13. الملاحين والاطمق الجوية					
14. الجزار (اللحم)					
15. مزين الشعر (الكوافير / الكوافيرة)					
16. عمال الأسبست					
17. عمال الجلود					
18. عمال البناء					
19. عمال التنظيفات					
20. ربة البيت					
21. أخرى					

***رموز التعرض :

1. المبيدات الحشرية	2. منتجات اللحوم	3. المذيبات العضوية	4. المذيبات غير العضوية
5. البنزين و النقط ومشتقاته	6. الأشعة فوق البنفسجية	7. الإشعاع الكوني	8. الإشعاع الناتج عن التأيين
9. الموجات المغناطيسية	10. الميكروبات / الكائنات الدقيقة	11. الحيوانات	12. المضادات الحيوية
13. الأظلية/الدهان	14. أصباغ الشعر	15. الأسبستوس	16. جلد
17. الأصماغ	18. ضوء الشمس	19. الأدوية	20. غبار الطحين
21. مواد التنظيف	22. غبار الخشب	23. أخرى	

القسم الثالث : السكن

أود أن أسألك حول سكنك الحالي والسابق (لا تشمل الإقامة في سكن لمدة تقل عن 3 سنوات)

س (23) ما نوع السكن الذي عشت فيه؟

العنوان	تصنيف المكان	نوع المنزل	الطابق الذي تعيش فيه	مصدر ماء الشرب	عدد الأشخاص المقيمين في المنزل	عدد الغرف	مكان الحمام	الفترة الزمنية
الحالي: الشارع: _____ المدينة (البلدة): _____								
السابق: 1. الشارع: _____ المدينة (البلدة): _____								
2. الشارع: _____ المدينة (البلدة): _____								
3. الشارع: _____ المدينة (البلدة): _____								
4. الشارع: _____ المدينة (البلدة): _____								
5. الشارع: _____ المدينة (البلدة): _____								

***مبنى

➤ نوع المنزل: 1. منزل خاص 2. مبنى سكني (اقل من 10 عائلات) 3. مبنى سكني (أكثر من 10 عائلات)

4. خيمة 5. سكن في مزرعة 6. أخرى

➤ الطابق : 1 طابق أرضي 2. طابق ثاني 3. طابق ثالث 4. طابق أعلى 5. أخرى

➤ مصدر الماء: 1. أنابيب 2. بئر 3. صهاريج 4. مياه معدنية 5. لا أعرف 6. أخرى

➤ الحمام : 1. في الداخل 2. في الخارج 3. أخرى

القسم الرابع : العادات

أود أن أسألك حول بعض خصائصك الشخصية كقياساتك الجسمية ، وبعض عاداتك كالتدخين ، تزيين الشعر ، التعرض للشمس ، والحمية الغذائية و أخرى:

س (24) ما هي قياساتك الجسمية؟

المؤشرات	القياس عند المرض	القياس 6 اشهر قبل المرض
الطول		
الوزن		

- ***
1. نفس الشيء
 2. أعلى بكثير
 3. أعلى بقليل (حتى 10%)
 4. أقل بكثير
 5. أقل بقليل (حتى 10%)

س (25) هل سبق لك أن دخنت (إذا لم تدخن أبدا ، اذهب إلى س31) ؟

1. السجائر
2. النرجيلة
3. الغليون
4. التبغ
5. لم أدخن أبدا

س (26) هل أنت مدخن حاليا؟

1. نعم
2. لا

س (27) هل أقلعت عن التدخين؟

1. نعم
2. لا

س (28) كم سنة دخنت ؟

س (29) كم عدد السجائر التي تدخنها (دخنتها) في اليوم ؟

عدد السجائر	الفترة الزمنية
	معدل التدخين قبل المرض
	المستوى الحالي للتدخين

1:10 سجائر أو أقل 2: 11-20 3: 21-40 4: أكثر من 40 سيجارة

س 30 ما هو معدل تدخينك (للنرجيلة أو الغليون أو التبغ) ، قبل المرض و حاليا ؟

الفترة الزمنية	النرجيلة	الغليون	التبغ
معدل التدخين قبل المرض			
المستوى الحالي للتدخين			

***1. كل يوم 2 : أكثر من مرة في الأسبوع 3 : أقل من مرة في الأسبوع

س 31 هل سبق لك أن صبغت شعرك؟؟ (إذا كانت الإجابة " لا " ، أذهباى س 37)

1.نعم 2. لا

س 32 هل تصبغين (تصبغ) شعرك بانتظام ؟

1.نعم 2. لا

س 33 (في أي عمر بدأت بصباغة شعرك؟

س 34 بالمعدل ، كم مرة تصبغين (تصبغ) شعرك؟

1. أقل من مرة/سنة 2. 1-3 مرات/سنة 3. 4-6 مرات/سنة 4. أكثر من 7 مرات في السنة

س 35 أي لون تستخدمين (تستخدم) في العادة؟

1. الأسود 2. البني 3. الأشقر 4. لون الحناء 5. ألوان أخرى

س 36 هل الصبغة التي تستخدمها اصطناعية؟

1.نعم 2. لا

س 37 هل تعرضت للإصابة بحروق شمس حادة في طفولتك؟

1.نعم 2. لا 3. لا أذكر

س 38 كم ساعة في الأسبوع تتعرض (تعرضت) لضوء الشمس في الخارج ، خارج ساعات عملك (اشمل تعرضك خلال أوقات فراغك و ذهابك ورجوعك من العمل)

س 39 عندما تكون في الخارج ، هل يكون رأسك مغطى ؟

1. دائما 2.معظم الوقت 3. أحيانا 4. أبدا

س 40) عندما تكون في الخارج ، هل تلبس أكمام طويلة ؟

1. دائما 2.معظم الوقت 3. أحيانا 4. أبدا

س 41) هل تستخدم واقي شمس عندما تخرج في الشمس؟

1. دائما 2.معظم الوقت 3. أحيانا 4. أبدا

س 42) هل تلقيت رضاعة طبيعية؟

- 1.نعم 2. لا 3. لا أدري

س 43) هل أنت نباتي (لا تأكل أي نوع من اللحوم)؟ (إذا كانت الإجابة لا ، اذهب إلى س 45)

- 1.نعم 2. لا

س 44) كم سنة كنت نباتي؟

س 45) هل تتناول اللحوم بانتظام؟ (لحوم حمراء أو بيضاء) (إذا كانت الإجابة لا ، انتقل إلى سؤال 47)

- 1.نعم 2. لا

س 46) كم مرة في الأسبوع تأكل اللحوم؟

س 47) ما هو معدل حبات الفاكهة التي تتناولها يوميا؟

- 1) ولا مرة 2) 3-1 3) 7-4 4) أكثر من 7

س 48) ما هو معدل حبات الخضار التي تتناولها يوميا؟

- 1) ولا مرة 2) 3-1 3) 7-4 4) أكثر من 7

س 49) أي نوع من الزيوت تستخدمه / تستخدمينها في الطهي والقلي بشكل أساسي؟

- 1) الزيتون 2) الصويا 3) الذرة 4) عباد الشمس 5) أخرى _____

س 50) عادة كم مرة تأكل أو تشرب الأصناف التالية:

8	7	6	5	4	3	2	1	
الكمية في اليوم	أكثر من مرة واحدة في كل يوم	مرة واحدة في كل يوم	5-6 أيام في الأسبوع	2-4 أيام في الأسبوع	مرة في الأسبوع	أقل من مرة في الأسبوع	ولا مرة	
_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	1-فواكه
_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	2-خضراوات
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	3-لحوم أو دجاج
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	4-سمك
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	5-حليب كامل / قليل الدسم
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	6-منتجات الحليب (مثل اللبن أو الجبن أو الشكولاتة بالحليب)
أكواب _____								7-شرب الماء فقط
أكواب _____								8-مشروبات أخرى غير كحولية (ساخنة وباردة)
أكواب _____								9-مشروبات كحولية

القسم الخامس : الهوايات

أود أن أسألك حول هواياتك كالجهد البدني الذي تمارسه ، الفنون ، وأخرى.

س 51) أثناء السنوات العشر الأخيرة ، هل مارست أي جهد بدني منتظم ؟ (إذا كانت الإجابة " لا " ، أذهب إلى س 55)

1.نعم 2.لا

س 52) ما هو نوع الجهد الذي مارسته؟

1. شاق (كالركض)
2. متوسط (كالمشي)
3. خفيف (كالبيستنة)

س 53) في أغلب الأحيان، كم مرة مارست الجهد البدني؟

1. ثلاث مرات في الأسبوع أو أكثر
2. مرتين في الأسبوع
3. مرة واحدة أسبوعياً
4. أقل من ذلك

س 54) هل مارست أي من النشاطات البدنية الآتية ، وكم مرة عادة؟

#	النشاطات البدنية	1. لا أقوم بهذا النشاط	2. مرتين - ثلاث مرات بالشهر	3. مرة بالأسبوع	4. مرتين بالأسبوع أو أكثر
1	كرة قدم ، يد ، تنس ، سلة، الهوكي ، ألعاب كرة أخرى	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2	ألعاب رياضية (ألعاب قوى) ، جمباز	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3	تمارين لياقة بدنية، اشتراك في نادي لياقة بدنية ، جهاز ركض بيتي	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4	المشي السريع والركض	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5	الكاراتيه ، جودو ، تاكوندو	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6	المصارعة	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7	الملاكمة	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8	رفع الأثقال	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9	الرقص والدبكة	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10	الكشافة	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
11	السباحة	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
12	ركوب الدراجات الهوائية	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
13	تسلق الجبال	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
14	التزلج والتزحلق	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
15	المشي الطويل وصيد الأسماك	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
16	الأنشطة المائية (الإبحار ، ركوب الأمواج ، والتزحلق على الماء)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

س 55) هل تعني بالحديقة كهواية؟ (إذا كانت الإجابة " لا " ، اذهبيلى س 64)

1. نعم 2. لا

س 56) أي نوع من البستنة تؤدي؟

1. في الداخل 2. في الخارج

س 57) كم سنة مارست البستنة ؟

س 58) كم ساعة في الأسبوع مارست البستنة ؟

1. أقل من 10 ساعات في الأسبوع

2. 10-20 ساعة في الأسبوع

3. أكثر من 20 ساعة في الأسبوع

س 59) هل تزرع (زرعت) الخضار والفواكه ؟

1. لك شخصيا
2. للبيع
3. لا أزرع الخضار والفواكه

س 60) هل تستعمل أو (استعملت) المبيدات الحشرية ؟ (إذا كانت الإجابة " لا " ، اذهبي إلى س 64)

1. نعم
2. لا
3. لا أعرف

س 61) هل ترتدي (ارتديت) قفازات وقائية عندما تستخدم المبيدات الحشرية؟

1. في جميع الأوقات
2. في معظم الأوقات
3. أحيانا
4. أبدا

س 62) هل تغسل (غسلت) يديك بعد استخدام المبيدات؟

1. في جميع الأوقات
2. في معظم الأوقات
3. أحيانا
4. أبدا

س 63) المبيدات الحشرية التي تستخدمها أو استخدمتها هي ضد :

1. الأعشاب
2. الحشرات
3. الفطريات
4. لا أعرف

س 64) هل ترش (رشيت) مبيدات حشرية داخل منزلك؟

1. مرة أو أكثر في الأسبوع
2. أقل من مرة في الأسبوع – مرة في الشهر
3. بعض المرات في السنة
4. أبدا

س 65) هل تذكر اسم المبيد (المبيدات) الحشرية (التي استخدمتها في البستنة أو في منزلك) ؟ (إذا كانت الإجابة " لا " ، اذهب إلى س 67)

1. نعم
2. لا

س 66) ما هو اسم (أسماء) المبيد (المبيدات) الحشرية التي استعملتها؟

اسم المبيد

س 67) عندما كنت رضيع أو طفل صغير ، هل كنت تذهب إلى الحقل الزراعي مع والديك أو أشقائك الأكبر منك سناً ؟

1. نعم 2. لا 3. لا أذكر

س 68) هل الأشغال اليدوية (كانت) وما زالت من أحد هواياتك؟ (إذا كانت الإجابة " لا " ، اذهب إلى 75)

1. نعم 2. لا 3. لا أذكر

س 69) أي نوع من الأشغال مارست (أو تمارس حالياً)؟

1. التلوين
2. النحت
3. الفخاريات والسيراميك
4. الزُجَاجِيَّات
5. الطباعة والطباعة على الحجر
6. العمل الحديدي
7. فن تشكيلي
8. غيرها

س 70) خلال ممارستك للأشغال اليدوية ، هل تعرضت (تعرض) للمواد الكيماوية التالية:

1. ألوان زيتية
2. أظلية سائلة (أكريلية)
3. دهانات أخرى
4. مذيبات (التربينتين ، الكاز)
5. الأصماغ
6. الغبار
7. الرصاص
8. غيرها

س 71) كم عدد السنوات التي مارست فيهم الأشغال اليدوية ؟

س 72) كم كان عمرك عندما بدأت بممارسة الأشغال اليدوية ؟

س 73) كم كان عمرك عندما توقفت عن ممارسة الأشغال اليدوية ؟

س 74) كم ساعة في الأسبوع تمارس (مارست) الأشغال اليدوية ؟

1. أقل من 10 ساعات في الأسبوع
2. 10-20 ساعة في الأسبوع
3. أكثر من 20 ساعة في الأسبوع

س 75) هل عندك هوايات أخرى والتي تتضمن استخدام الكيماويات؟ (إذا كانت الإجابة " لا " ، اذهب إلى س 80)

1. نعم 2. لا

س 76) ما هي الهواية؟

س 77) ما هو نوع المادة الكيماوية المستخدمة في هذه الهواية؟

س 78) كم كان عمرك عندما مارست هذه الهواية؟

- س 79) كم ساعة في الأسبوع تمارس (مارست) هذه الهواية؟
1. أقل من 10 ساعات في الأسبوع
2. 10-20 ساعة في الأسبوع
3. أكثر من 20 ساعة في الأسبوع

القسم السادس: الصحة

الآن ، أريد أن أسألك حول حالتك الصحية قبل المرض

س 80) قبل المرض، هل سبق لك أن عانيت من إسهال دام لأكثر من يومين؟ (إذا كانت الإجابة " لا " ، اذهب إلى س 82)

1. نعم
2. لا
3. لا أذكر

س 81) كم مرة عانيت من هذا إسهال خلال السنوات العشر الأخيرة قبل المرض و هل كان الإسهال الحاد نتيجة أحد المسببات الآتية :

المسبب	عدد المرات	متى كانت آخر عدوى
1. Salmonella (السالمونيلا)	<input type="checkbox"/>	
2. Shigella (شيغيلا)	<input type="checkbox"/>	
3. Campylobacter (الكامبيلوبكتر)	<input type="checkbox"/>	
4. Yersinia (اليرسينييا)	<input type="checkbox"/>	
5. Strongiloidosis (الأسطونيات)	<input type="checkbox"/>	
6. الأميبا	<input type="checkbox"/>	
7. عدوى طفيلية أخرى	<input type="checkbox"/>	
8. E.coli (اي كولاي)	<input type="checkbox"/>	
9. أعلمت بأن المسبب فايروس	<input type="checkbox"/>	
10. لم يجدوا المسبب	<input type="checkbox"/>	
11. لم يتم الفحص	<input type="checkbox"/>	
12. أخرى	<input type="checkbox"/>	

س 82) هل عانيت من أي مرض و الذي تطلب العلاج في المستشفى خلال السنة الأولى من عمرك؟

1. نعم
2. لا
3. لا أعرف

ما هو هذا المرض؟

س 83) هل عانيت من أي التهاب حاد والذي تطلب العلاج في المستشفى ؟ (إذا كانت الإجابة " لا " ، اذهب إلى س 85)

1. نعم
2. لا
3. لا أذكر

س 84) ما هو هذا الالتهاب، وكم مرة دخلت المستشفى نتيجة الالتهاب وفي أي عمر؟

العمر	عدد المرات	نوع العدوى
1. أكثر من 40 سنة		
2. 40 – 21 سنة		
3. 20-11 سنة		
4. 10-1 سنوات		
5. أقل من سنة		

***رموز العدوى :

1. التهاب الجيوب
2. التهاب الشعب الهوائية
3. التهاب معوي
4. عدوى المرارة
5. عدوى المسالك البولية
6. التهاب البروستات
7. العدوى الشرجية
8. التهاب الجلد
9. عدوى في الجهاز التناسلي الأنثوي (للنساء فقط)
10. التهاب السحايا
11. التهاب الزائدة لدودية
12. أخرى

س 85) بغض النظر عن الالتهابات التي تطلبت العلاج في المستشفيات ، هل عانيت من أي من الأمراض الآتية ؟ إذا كان الجواب نعم، متى؟ (استخدم رمز زمن العدوى الموجود تحت الجدول لتحديد العمر)

العمر	لا أذكر	لا	نعم	المرض
				1. التهاب الكبد A
				2. التهاب الكبد B
				3. التهاب الكبد C
				4. Herpes (القوباء): الشفتين، الأنف ، الأذن ، أخرى
				5. Infectious Mononucleosis Epstein Bar Virus (حمى)
				6. Asthma (الربو)
				7. Eczema (الأكزيما)
				8. Tonsillitis (التهاب اللوزتين)
				9. Measles (الحصبة)
				10. Mumps (النكاف)
				11. Rubella (الحصبة الألمانية)
				12. Rheumatic fever حمى الروماتزم
				13. Rheumatoid arthritis التهاب المفاصل
				14. السل
				15. Brucellosis (الحمى الماطية)
				16. التهاب الجيوب
				17. التهاب معوي
				18. شلل الأطفال
				19. التيفوس
				20. القرحة
				21. الحساسية
				22. الالتهابات المعوية (مثل حساسية القمح او الجلوتين)
				23. الصدفية
				24. الأمراض المناعية الذاتية
				25. الأمراض المناعية الأخرى
				26. أمراض أخرى

***رمز الجيل:

1. أكثر من 40 سنة 2. 40 – سنة 3. 20-11 سنة 4. 10-1 سنوات 5. أقل من سنة

س 86) هل تلقيت التطعيمات ضد الأمراض التالية؟

العمر عند التطعيم	العمر عند التطعيم الأول	لا أذكر	لا	نعم	المرض
					1.داء الكزاز
					2.الجدري
					3.التيفوئيد
					4.الحصبة
					5.النكاف
					6.الحصبة الألمانية
					7.السعال الديكي
					8. شلل الأطفال (تطعيم بالحقن)
					9.شلل الأطفال (تطعيم سائل بالفم)
					10. السل
					11. الحمى الصفراء
					12. التهاب السحايا الفيروسي
					13. الكوليرا
					14.التهاب الكبد الحاد (أ)
					15. التهاب الكبد (ب)
					16. بكتيريا الهيموفيلس
					17.نيوموكوكس (البكتيريا المكورة الدورية)
					18.فايروس الانفلونزا
					19.الخناق
					20.أخرى

س 87) هل خضعت لاستئصال اللوزتين؟ (إذا كانت الإجابة " لا " ، اذهب إلى س 89)

1.نعم 2. لا

س 88) كم كان عمرك ؟

س 89) هل سبق لك أن تعاطيت مضادات حيوية ؟ (إذا كانت الإجابة " لا " ، اذهب إلى س 91)

1.نعم 2. لا

س 90) بالمعدل ، كم مرة في السنة تناولت المضادات الحيوية ، وفي أي سن؟

العمر	معدل عدد المرات في السنة
1. أكثر من 40 سنة	
2. 40 – 21 سنة	
3. 20-11 سنة	
4. 10-1 سنوات	
5. أقل من سنة	

س 91) هل سبق لك أن تعرضت للأشعة قبل مرضك ؟

1. نعم
2. لا
3. لا أذكر

س 92) لماذا قمت بعمل الأشعة؟

السنة	عدد المرات	أشعة X
		1. أشعة أسنان
		2. أشعة صدر
		3. تصوير الثدي (للنساء)
		4. أشعة عظام
		5. أخرى

***رمز الجيل:

1. أكثر من 40 سنة 2. 21-40 سنة 3. 11-20 سنة 4. 1-10 سنوات
5. أقل من سنة

س 93) أي من الجمل التالية تصف طفولتك حتى سن 18؟

1. كنت أمرض في أغلب الأحيان أكثر من أصدقائي
2. تغيبت عن المدرسة أكثر من أصدقائي
3. حصلت على أدوية أكثر من أخوتي وأخواتي
4. كنت طفلاً
5. كنت أمرض ولكن أقل بكثير من أصدقائي وأشقائي

س 94) هل لديك حيوانات أليفة أو حيوانات كبيرة في منزلك أو في حدائق منزلك ؟ (إذا كانت الإجابة " لا "،
أذهب إلى س 96)

1. نعم
2. لا

س 95) ما نوع الحيوانات عندك (كان عندك)؟

1. قط
2. كلب
3. طيور
4. حصان
5. بقرة
6. جمل
7. ماعز
8. أغنام
9. حمار
10. أخرى

س 96) هل سبق لك أن تناولت أي من الأدوية الآتية بوصفة طبية؟ إذا كانت الإجابة نعم، في أي عمر، وكم مرة؟

بشكل منتظم		أحياناً	أبداً	الأدوية
سنة الابتداء	سنة الانتهاء			
				1. الستيرويدات (الكورتيزون و مشتقاته)
				2. موانع الحمل الهرمونية
				3. علاج بديل هرموني في سن اليأس (استروجين)
				4. الهرمونات الأخرى _____
				5. مضاد الفطريات (فموي)
				6. NSAIDs (الأدوية الغير إستيرودية المضادة للإلتهاب)
				7. خافضات الحرارة
				8. مضادات الاكتئاب
				9. مضادات الطفيليات
				10. مضادات القلق
				11. مُضادات الفيروسات
				12. مضادات الهيستامين
				13. مثبطات بيتا
				14. مدررات البول
				15. الأدوية الخافضة لضغط الدم
				16. Thyroid replacement (البديل الدرقي)
				17. أدوية تميع الدم
				18. الأسبرين
				19. العلاج الكيماوي
				20. أخرى _____

س 97) هل سبق وأن نقل إليك دم قبل مرضك؟

1. نعم 2. لا 3. لا أعرف

س 98) قبل مرضك الحالي، هل سبق لك أن أصبت بالسرطان؟ (إذا كانت الإجابة "لا"، أذهبي إلى س 100)

1. نعم 2. لا

س 99) ما هو العلاج الذي تلقينته؟

1. العلاج الكيماوي
2. الجراحة
3. العلاج بالأشعة
4. لا أعرف

س 100) هل احد اقربائك من الدرجة الأولى مصاب بالسرطان؟ (إذا كانت الإجابة نعم ، فمن هو وما اسمه الثلاثي)

1.نعم 2. لا 3.لا أعرف

الطفل 3	الطفل 2	الطفل 1	الأب	الأم	الأشقاء	نوع السرطان
						1.أي سرطان (نوعه)
						2.الأورام الليمفاوية الغير هودجكن Non Hodgkin's Lymphoma
						3.الأورام الليمفاوية الهودجكن Hodgkin's Lymphoma
						4. سرطان الدم اللمفاوي المزمن Chronic lymphocytic leukemia
						5. سرطان الدم اللمفاوي الحاد Acute lymphocytic leukemia
						6. السرطان النخاعي المتعدد Multiple Myeloma
						7. سرطان الدم الحبيبي الحاد Acute Myeloid Leukemia
						8. سرطان الدم الحبيبي المزمن Chronic Myeloid Leukemia
						9.سرطان الدم
						10.أمراض الدم الأخرى

س 101) هل أحد اقربائك من الدرجة الثانية مصاب بالسرطان ؟ (إذا كانت الإجابة نعم ، فمن هو) 1.نعم 2. لا 3.لا أعرف

ابن الأخ أو الأخت/ أبنة الأخ أو الأخت	ابن أو ابنة العم أو الخال	العمة أو الخالة	العم أو الخال	الجدّة من جهة (الأب)	الجدّة من جهة (الأب)	الجد من جهة (الأم)	الجدّة من جهة (الأم)	نوع السرطان
								1.أي سرطان (نوعه)
								2.الأورام الليمفاوية الغير هودجكن Non Hodgkin's Lymphoma
								3.الأورام الليمفاوية الهودجكن Hodgkin's Lymphoma
								4. سرطان الدم اللمفاوي المزمن Chronic lymphocytic leukemia
								5. سرطان الدم اللمفاوي الحاد Acute lymphocytic leukemia
								6. السرطان النخاعي المتعدد Multiple Myeloma
								7. سرطان الدم الحبيبي الحاد Acute Myeloid Leukemia
								8. سرطان الدم الحبيبي المزمن Chronic Myeloid Leukemia
								9.سرطان الدم
								10.أمراض الدم الأخرى

س 102) هل أحد أقربائك من الدرجة الأولى كان يعاني أي من الأمراض الآتية؟ إذا كانت الإجابة نعم، فمن هو؟
1. نعم
2. لا
3. لا أعرف

الأمراض	الأشقاء	الأم	الأب	الطفل 1	الطفل 2	الطفل 3
1. العدوى المتكررة						
2. الحساسية						
3. التهاب المفاصل (الروماتزم)						
4. الأمراض المناعية الذاتية (Autoimmune Diseases)						
5. الأمراض المناعية الأخرى						

س 103) هل أحد أقربائك من الدرجة الثانية كان يعاني أي من الأمراض الآتية؟ إذا كانت الإجابة نعم، فمن هو؟
1. نعم
2. لا
3. لا أعرف

الامراض	الجددة من جهة (الأم)	الجد من جهة (الأم)	الجددة من جهة (الأب)	الجد من جهة (الأب)	الجددة من جهة (الأب)	العم أو الخال	العمة أو الخالة	ابن أو ابنة العم أو الخال	ابن الأخ أو الأخت/ أبنة الأخ أو الأخت
1. العدوى المتكررة									
2. الحساسية									
3. التهاب المفاصل (الروماتزم)									
4. الأمراض المناعية الذاتية (Autoimmune Diseases)									
5. الأمراض المناعية الأخرى									

س 104) كم مرة تذهب إلى طبيب الأسنان؟
1. للفحوصات المنتظمة (مرة أو أكثر في السنة)
2. للفحوصات المنتظمة (أقل من مرة كل سنة)
3. فقط عندما يكون عندي وجع أسنان أو مشكلة أخرى
4. أبدا

س 105) هل تمتلك سيارة؟
1. نعم
2. لا

س 106) كيف وصلت إلى المستشفى اليوم؟
1. مشيا على الأقدام
2. سيارة خاصة
3. تاكسي
4. النقل العام
5. أخرى

س 107) متى زيارتك القادمة للمستشفى أو العيادة؟

شكرا جزيلا لتعاونك

س 108) تقييمات المقابلة

1. معتمد جدا
2. معتمد إلى حد ما
3. غير معتمد إلى حد ما
4. غير معتمد

العوامل الغذائية ومخاطرها على الإصابة بمرض الورم الليمفاوي غير الهودجكن بين الفلسطينيين

إعداد: مرام محمد شاكر الفتياني / دحدول

إشراف: د. رانيا أبو سير

ملخص:

مقدمة: في النصف الثاني من القرن العشرين ازدادت نسبة الإصابة بمرض الورم الليمفاوي غير الهودجكن حول العالم ثم استقرت في التسعينات لتعود إلى الارتفاع فيما بعد. وقد تبين أن العوامل البيئية وعادات النظام الغذائي تلعب دوراً هاماً في التسبب بمرض الورم الليمفاوي غير الهودجكن من خلال التأثير على نظام المناعة. وقد تبين لنا أنه لا تتوفر معلومات حول الإصابة بمرض الورم الليمفاوي غير الهودجكن في فلسطين.

الأهداف: المشاركة في إنشاء منصة لدراسة مرض الورم الليمفاوي غير الهودجكن "ب" في فلسطين بالإضافة إلى دراسة العلاقة بين العوامل الغذائية وخطر الإصابة بهذا المرض بين المرضى الفلسطينيين المصابين بمرض الورم الليمفاوي غير الهودجكن "ب" والمجموعة الضابطة.

تصميم البحث: دراسة الحالة والمجموعة الضابطة (case-control study)

منهج البحث: أجريت دراسة الحالة المرضية مقارنة بالمجموعة الضابطة بين 2009 - 2013 على 306 حالة مصابة بمرض الورم الليمفاوي غير الهودجكن "ب" التي تم تشخيصها و392 حالة ضابطة من غير المصابين بالمرض من الفلسطينيين البالغين. وقد تم اختيار هؤلاء من ثلاثة

مستشفيات رئيسية في الضفة الغربية التي لديها قسم للأورام بالإضافة إلى مستشفى هداسا في القدس الغربية. وقد أظهر التحليل الأولي أن هناك خللاً في التوزيع الجغرافي للحالات والضوابط من المنطقة الوسطى. ولإصلاح هذا الخلل قامت الباحثة باستقطاب 71 حالة ضابطة من مراكز الرعاية الصحية في أريحا، ورام الله والعيزرية. وقد تم اختيار عناصر المجموعة الضابطة بحيث تتناسب مع عينة المرضى من حيث العمر والجنس والتوزيع الجغرافي (frequency matched controls). و قد قام المشاركون في الدراسة بالإجابة على استبانة تعتمد على استبانة Epi-Lymph الدولية، التي تركز على الخصائص الديمغرافية والعوامل البيئية ومن ضمنها النظام الغذائي ومعدل الاستهلاك من المجموعات الغذائية: اللحوم والحليب ومنتجات الألبان والخضراوات والفاكهة. إضافة إلى ذلك فقد تم جمع عينات من الدم من المشاركين بهدف تحليلها للكشف عن الإصابات الفيروسية وتحليل الجينات.

التحليل الإحصائي: لقد تم استخدام قاعدة البيانات لدراسة العلاقة بين العوامل الغذائية وخطرا لإصابة بمرض الورم الليمفاوي غير الهودجكن"ب". وتم تحليل البيانات باستخدام برنامج الحزمة الإحصائية للعلوم الاجتماعية SPSS وفحص الارتباط باستخدام الانحدار اللوجستي المتعدد المتغيرات. وتحليل الاستهلاك الغذائي، تم احتساب القيمة المتوسطة لكل مجموعة من المواد الغذائية من التوزيع العامل مجتمع الدراسة من أجل إيجاد قيمة ممثلة لمجتمع الدراسة بشكل أقرب من المتوسط واستخدامها كقيمة مرجعية في المقارنات بين مجموعة المرضى والمجموعة الضابطة.

النتائج: أظهرت الدراسة أن الاستهلاك العالي لكل من اللحوم (OR=1.8; 95%CI: 0.8-4.3) والحليب (OR=1.3; 95%CI: 0.7-2.6) مرتبط بشكل إيجابي مع خطرا لإصابة بمرض الورم الليمفاوي غير الهودجكن"ب"، كما وقد تبين أيضاً في هذه الدراسة أن استهلاك الخضراوات يرتبط

ارتباطاً إيجابياً بخطر الإصابة بهذا المرض (OR=1.3; 95%CI: 0.4-4). كذلك فقد وجد أن منتجات الألبان ترتبط بعلاقة ذات دلالة إحصائية بارتفاع خطورة الإصابة بهذا المرض (OR=2.3; 95%CI: 1.2-4). وفي المقابل، بينت الدراسة وجود علاقة عكسية بين استهلاك الأسماك (OR=0.4; 95%CI: 0.2-0.8) والفاكهة (OR=0.7; 95%CI: 0.2-2.1) وخطراً للإصابة بمرض الورم الليمفاوي غير الهودجكن "ب" كمواد تحمي من الإصابة بهذا المرض.

الاستنتاج: تظهر نتائج هذه الدراسة أن الاستهلاك الغذائي يلعب دوراً في الإصابة بمرض الورم الليمفاوي غير الهودجكن "ب"، وقد يؤثر استهلاك اللحوم والحليب ومنتجات الألبان والخضراوات سلباً ويؤدي لزيادة خطر الإصابة بمرض الورم الليمفاوي غير الهودجكن، كما قد يلعب استهلاك الفاكهة والأسماك دوراً في الحماية من الإصابة بالمرض.

الكلمات المفتاحية: العوامل الغذائية، مرض الورم الليمفاوي غير الهودجكن "ب"، دراسة الحالة والمجموعة الضابطة، فلسطين.