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

# Occupational Determinants of B-Cell Non-Hodgkin Lymphoma: A Case-Control Study

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# Occupational Determinants of B-Cell Non-Hodgkin Lymphoma: A Case-Control Study

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## Thesis Approval

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# Dedication

To God who blessed me with your hands to hold my dreams…

To Dr. Rania, the mother, the teacher and the light…

To patients going through a journey of suffering fighting cancer…

To humanity …

I dedicate this work and all what's coming…

Nemah Mahmoud Falah Abu Khdeir

**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 ..Nemah mahmoud

Nemah Mahmoud Falah Abu Khdeir

Date: 07.05.2017

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I would like to express my sincerest thanks and my deep gratitude and appreciation to Dr. Rania Abu Seir, my supervisor, for being the mentor, the teacher, and the guiding light all the way in my journey. Her knowledge, patience, support, and encouragement, made me the person I am today. By believing in me she made it all possible.

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## Abstract

**Background:** B-cell non-Hodgkin lymphoma (B-NHL) has been raising concerns worldwide and in the Middle East for years. The global incidence of NHL has been increasing annually by 1-2% since the 1990s. Among Palestinians, the incidence of NHL in 2010 was 1 per 100,000 population. Within 5 years the incidence of NHL tripled and it became the 8$^{th}$ most common cancer with an incidence rate of 3.5 per 100,000 population. The etiology of NHL is largely unknown, but the available evidence suggests that environmental factors and industrialization are involved. In this study, occupational risk factors of B-NHL among adult Palestinians were assessed as compared to cancer-free controls. In addition, occupational exposures and their association with B-NHL were investigated.

**Methodology:** We designed a case-control study in order to investigate the risk factors of B-NHL among Palestinians. The study was conducted between 2009 and 2014 in which a total of 307 histologically confirmed B-NHL cases and 394 cancer-free controls were recruited. Cases were ascertained through three hospitals in Jerusalem and the West Bank, in addition to the Palestinian Cancer Registry and Palestinians being treated in Hadassah University Hospital. Controls were cancer-free Palestinians, ≥18 years old, recruited through the collaborating hospitals, Al-Makassed Blood Bank and 13 Ministry of Health primary health centers distributed throughout the West Bank. Data were collected using a previously validated interview-based questionnaire by International Lymphoma Epidemiology Consortium (InterLymph). The questionnaire focused on several risk factors of the disease but the current study assessed the history of the occupations that the cases were employed in compared to the controls and the exposures in each occupation. In addition, to confirm that self-reported exposures were in line with the expected exposures, we conducted a workplace walkthrough in which we compared the exposures reported by the subjects with those from the walkthrough.

**Results:** In our case-control study, the median age at diagnosis for B-NHL cases was 52 years, and the male to female ratio was 1:1. In addition, the two most common histological subtypes of NHL were diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma. The median age at recruitment for cases and controls respectively was 53 and 51 years. Approximately 68% of the controls had at least 7 years of schooling, whereas only 42% of

cases completed less than 7 years of schooling. Furthermore, 31.9% of cases were from south Palestine, 39.5% were from the middle and 24.7% were from the north. As for controls, 44.9% were from the south, 32.9% were from the middle and only 19.9% were from the north. As for residential exposures, application of pesticides indoors and contact with domestic animals were both associated with increased risk of B-NHL. Regarding the history of occupations and occupational exposures, comparison between the cases and the controls revealed several associations. Several exposures were associated with increased B-NHL risk. These exposures included: pesticides (OR=2.7, 95%CI: 1.5-4.9), glues (OR=3.5, 95%CI: 1.1-11), infections (OR=2.7, 95%CI: 1.5-4.9), hair dyes (OR=2.7, 95%CI: 0.6-11.8), radiation (OR=2.1, 95%CI: 1.3-3.3) and sunlight (OR=2.1, 95%CI: 1.3-3.4). Controversially, exposure to animals and animal products and medicine showed negative association with B-NHL risk. In addition, being involved in agricultural activities such as gardening and subsistence farming were found to increase the risk of B-NHL. Furthermore, housewives who had farming duties and used pesticides were found to be at increased risk compared to those who were not. As for occupational history, ever employment in these industries was non-significantly associated with increased B-NHL risk: agriculture industry (OR=1.7, 95%CI: 0.8-3.9), textile industry (OR=1.9, 95%CI: 0.9-4.1), protection services (OR=2.7, 95%CI: 0.8-9.1), and personal services (OR=2.5, 95%CI: 0.6-10.2). In contrast, employment in health and social work industry was associated with decreased B-NHL risk (OR=0.2, 95%CI: 0.1-0.6).

**Conclusions:** The findings of this work point to an association between the risk of B-NHL and occupational exposure to pesticides, radiation, hair dyes and infectious agents among Palestinians. Further investigations to confirm these findings and to determine their role in lymphomagenesis are required.

**Keywords:** Occupational exposure, occupational history, non-Hodgkin lymphoma, case–control study, Palestine.

**العوامل المهنية المرتبطة بالإصابة بسرطان الغدد الليمفاوية غير الهودجكن – ب: دراسة الحالات والضوابط**

**إعداد:** نعمة محمود فلاح أبو خضير

**إشراف:** د. رانية أبو سير

**ملخص:**

**خلفية الدراسة:** يعد سرطان الغدد اللمفاوية غير الهودجكن من الأمراض السرطانية التي أثارت قلق العلماء في العالم وفي الشرق الأوسط. وتشهد معدلات حدوث المرض ازدياداً سنوياً بمقدار 1–2%. أما في فلسطين فقد ازداد معدل حدوث المرض من 1 لكل 100,000 نسمة عام 2010 لتتضاعف 3 مرات خلال 5 سنوات. ويحتل سرطان الغدد الليمفاوية غير الهودجكن المرتبة الثامنة بين أكثر أنواع السرطان انتشاراً بين الفلسطينيين بمعدل حدوث مقداره 3.5 حالة لكل 100,000 نسمة. لم تتضح حتى الآن أسباب المرض، ولكنّ الدلائل الحالية تشير إلى أن العوامل البيئية والتقدم الصناعي لها دور في الإصابة بالمرض. تهدف الدراسة الحالية إلى تحديد العلاقة بين عوامل التعرض المهنية وخطر الإصابة بمرض الغدد الليمفاوية غير الهودجكن الناشئ من خلايا الدم البيضاء من النوع "ب".

**منهجية البحث:** تم استخدام دراسة الحالات والضوابط لدراسة العوامل المهنية المسببة لسرطان الغدد الليمفاوية غير الهودجكن–ب. وقد عُقدت الدراسة بين عامي 2009 و 2014 وذلك بمشاركة 307 حالة مؤكدة التشخيص بالمرض و394 شخصاً كعينة ضابطة من الفلسطينيين. وقد تم استقطاب الحالات من ثلاثة مستشفيات رئيسية في الضفة الغربية والقدس والحالات المسجلة في مركز تسجيل الأورام الفلسطيني، بالإضافة إلى الفلسطينيين الذين يتلقون العلاج في مستشفى هداسا. أما عناصر

المجموعة الضابطة فقد تم تحديد شروط المشاركة من الفلسطيين البالغين غير المصابين بمرض السرطان. وقد تم استقطاب عناصر المجموعة الضابطة من خلال المستشفيات المذكورة، إضافة إلى بنك الدم في مستشفى المقاصد و13 من مراكز الرعاية الأولية التابعة لوزارة الصحة الفلسطينية موزعة في أرجاء الضفة الغربية. أما عن أداة الدراسة فقد قام المشاركون في الدراسة بالإجابة على استبيان تمت تعبئته خلال مقابلة. ويتناول الاستبيان عدداً من العوامل المسببة للمرض، إلا أن الدراسة الحالية ركّزت على تأثير العوامل المهنية على خطر الإصابة بالمرض. وللتحقق من أن عوامل التعرض التي قام المشاركون بالإبلاغ عنها ذاتياً متطابقة مع تلك التي يُتوقع وجودها في تلك المهن فقد تم القيام بمسوحات لمكان العمل بحيث تمت مقارنة عوامل التعرض المبلغ عنها بتلك التي وُجدت في المسح.

**النتائج:** بحسب النتائج التي ظهرت في الدراسة فقد كان العمر الوسيط للإصابة بالمرض 52 عاماً ونسبة الذكور للإناث بين الحالات 1:1. بالإضافة إلى ذلك فقد وُجد أن حوالي 68% من الضوابط حصلوا على الأقل على 7 سنوات من التعليم مقارنة بـ42% فقط بين المرضى. وقد توزع المرضى جغرافياً بحيث كان 31.9% من جنوب فلسطين و39.5% من الوسط و 24.7% من الشمال، أما الضوابط فقد كان 44.9% منهم من الجنوب، 32.9% من الوسط، و 19.9% فقط كانوا من الشمال. أما فيما يتعلق بالمخاطر المرتبطة بالسكن فقد تبيّن من الدراسة وجود علاقة بين خطر الإصابة بالمرض ورش المبيدات وتربية الحيوانات في المنزل. أما عن عوامل التعرض المهنية فقد أظهرت الدراسة وجود علاقة بين خطر الإصابة بمرض سرطان الغدد الليمفاوية غير الهودجكن–ب والتعرض للمبيدات، المواد اللاصقة، الكائنات المعدية، أصباغ الشعر، والأشعة ولا سيما أشعة الشمس. وعلى العكس، فقد كان التعرض للحيوانات ومنتجاتها والأدوية مرتبطاً بانخفاض خطر الإصابة بالمرض. إضافةً إلى ذلك، فإن الانخراط بممارسة البستنة وزراعة الكفاف تزيد من خطر الإصابة بالمرض، كما أن ربات البيوت اللواتي مارسن زراعة الكفاف وتعرضن للمبيدات زاد لديهنّ

خطر الإصابة مقارنة بربات البيوت اللاتي لم يفعلن. أما عن المهن، فإن العمل في هذه القطاعات أظهر زيادة في خطر الإصابة غير أن العلاقة لم تكن ذات دلالة إحصائية: الزراعة، النسيج، خدمات الحماية، الخدمات الشخصية. وعلى العكس، فإن العمل في قطاع الصحة والعمل الاجتماعي قد خفّض من خطورة الإصابة بالمرض.

**الاستنتاج والتوصيات:** تظهر نتائج هذه الدراسة أن التعرض للمبيدات، الأشعة، أصباغ الشعر، والكائنات المعدية كان مرتبطاً بزيادة خطر الإصابة بسرطان الغدد الليمفاوية غير الهودجكن بين الفلسطينيين. بالرغم من كون هذه النتائج بحاجة للمزيد من البحث لتأكيدها وتحديد دورها في تطور المرض، إلا أنها تُشير إلى ضرورة الاهتمام بالصحة والسلامة المهنية لوقاية صحة العاملين من تأثير التعرض للعوامل المختلفة في مكان العمل.

**الكلمات المفتاحية:** عوامل التعرض المهنية، التاريخ المهني، سرطان الغدد الليمفاوية غير الهودجكن– ب ، دراسة الحالات والضوابط، فلسطين.

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## List of abbreviations

| Abbreviation | Term |
|---|---|
| AIDS | Acquired immune deficiency syndrome |
| ASR | Age standardized rate |
| AVH | Augusta Victoria Hospital |
| B-NHL | B-cell non-Hodgkin lymphoma |
| BL | Burkitt lymphoma |
| CLL | Chronic lymphocytic leukemia |
| CI | Confidence interval |
| DLBCL | Diffuse large B-cell lymphoma |
| EBV | Epstein-Barr virus |
| FL | Follicular lymphoma |
| HBV | Hepatitis B virus |
| HCV | Hepatitis C virus |
| HIV | Human immunodeficiency virus |
| *H.pylori* | *Helicobacter pylori* |
| HTLV-1 | Human T-cell leukemia/lymphoma virus |
| IARC | International Agency for Research on Cancer |
| ISCO | International Standardized Classification of Occupations |
| ISIC | International Standardized Industrial Classification of All Economic Activities |
| MALT | Mucosa associated lymphoid 6tissue |
| MCL | Mantle cell lymphoma |
| MOH | Ministry of Health |
| MZL | Marginal zone lymphoma |
| NHL | Non- Hodgkin lymphoma |
| NK | Natural killer cells |
| OR | Odds ratio |
| SLL | Small lymphocytic lymphoma |
| SNP | Single nucleotide polymorphism |
| T-NHL | T-cell non-Hodgkin lymphoma |
| WHO | World Health Organization |

# Chapter One: Introduction

This chapter focuses on the research background, research problem and study justification. In addition, this chapter demonstrates the investigated aim and study objectives of the study.

## 1.1 Background

Cancer constitutes a large scale problem worldwide being the second leading cause of mortality with about 14.1 million new cases and 8.2 million deaths reported worldwide in 2012 (Torre et al., 2015). Non-Hodgkin lymphoma (NHL) is a group of heterogeneous lymphoid malignancies that arise from B, T, or natural killer (NK) lymphocytes. Worldwide, NHL is associated with increasing morbidity; with an estimated 386,000 new cases and 200,000 deaths worldwide (Globocan, 2012).

Incidence rates of NHL in the Middle East have also been increasing (Freedman et al., 2006). NHL incidence rate in Egypt was reported to be 8.8 per 100,000 population, and rates of NHL increased 50% between 1973 and 1987 in Alexandria (Abdel-Fattah & Yassine, 2007; Ibrahim et al., 2014). In addition, among the Gulf Cooperation Council, NHL was the most commonly diagnosed cancer in both Kuwait and Saudi Arabia, while in the United Arab Emirates, NHL was the third common type of cancer, and in Oman and Qatar it was reported as the forth common cancer (Al Hamdan et al., 2009).

Among Palestinians cancer is the second leading cause of death. NHL is the 8th most common cancer with an incidence rate of 3.5 per 100,000 population (MOH, 2016). The current knowledge about the etiology of NHL couldn't explain the increasing incidence of NHL. The available evidence suggests that genetic factors, in addition to lifestyle, environmental and occupational factors and industrialization are involved. Exposure to several environmental agents such as pesticides, organic solvents, radiation, and infectious agents has been reportedly suspected to increase the risk of NHL. Occupations are sources for condensed environmental exposures, as a result, studying occupational risk factors serves as a useful tool to generate hypothesis and identify environmental agents that might cause NHL ('t Mannetje et al., 2016).

In this study, occupational risk factors of B-NHL among adult Palestinians were investigated through a case-control study. In addition, occupational exposures and their association with B-NHL were investigated.

### 1.2 Problem Statement

Among Palestinians, the incidence of NHL in 2010 was 1 per 100,000 population (MOH, 2011), a rate that has tripled by 2015. Neither the revised classification, nor the improvement in diagnostic tests could account for the rise in the rates of NHL (Kharroubi & Abu Seir, 2016; Muller et al., 2005).

Multiple occupations were postulated to contribute to the risk of NHL; therefore, the current study aimed at assessing occupational risk factors of non-Hodgkin lymphoma of B-cell origin among the Palestinian population. Up to our knowledge, this is the first study to investigate the role of occupational exposures in NHL etiology in Palestine. The study was a part of a large scale case-control study to investigate the etiological factors involved in B-cell non-Hodgkin lymphoma (B-NHL) development among Palestinians.

### 1.3 Study Justification

Non-Hodgkin lymphoma (NHL) has been associated with high morbidity and mortality worldwide. In Palestine, the incidence rates of NHL have been increasing (Figure 1.1). The etiology of NHL is largely unknown. The association between hepatitis B infection and NHL risk (Kleinstern et al., 2016), and the role of medical and lifestyle factors such as

cigarette smoking, use of hair dyes, alcohol consumption, hospitalization for infection, blood transfusion and autoimmune diseases in the etiology of NHL in Palestine have been studied (Kleinstern et al., 2017). On the other hand, occupational exposures are important part of the postulated risk factors which are not yet studied in Palestine.

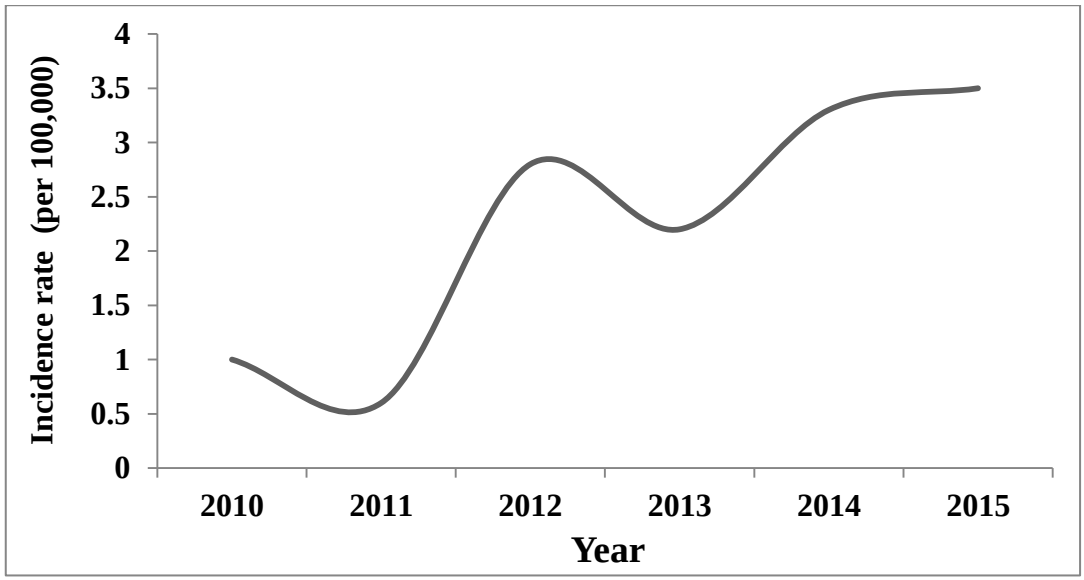


Figure 1.1: NHL incidence rates (2010-2015) in the West Bank, Palestine. (Source: Health annual report (2010-2015)).

### 1.4 Research Hypotheses

In the workplace, workers are exposed to various chemical, physical and biological agents. Several of the exposures in the workplace have been identified as either mutagenic, carcinogenic or immunomodulators, all of which can increase the risk of NHL.

$H_0$: There is no association between occupational exposures and B–NHL among Palestinians.

$H_1$: There is an association between occupational exposures and B–NHL among Palestinians.

### 1.5 Study Aim

This study aims to examine the possible association between ever held occupations and the risk of B-NHL among Palestinians, in addition to identifying possible occupational exposures associated with B-NHL.

## 1.6 Study Objectives

- To investigate the association between sociodemographic characteristics and the risk of B-NHL.
- To assess the association between lifestyle factors and B-NHL risk.
- To identify priori risk occupations that might contribute to the risk of B-NHL.
- To assess the exposures in each priori risk occupation.
- To assess the association between occupational exposures and B-NHL risk.
- To assess the association between ever employment in priori risk industries and the risk of B-NHL.

## 1.7 Study Expected Outcomes

This study describes the characteristics of NHL and investigates the etiological factors among Palestinians focusing on the occupational risk factors of the disease. Furthermore, the study describes the Palestinian workforce and sheds the light on the exposures that workers experience in different industrial settings.

## 1.8 Limitations of the Study

Upon designing and conducting the study we faced a number of limitations that might have affected the strength of the design. Regarding controls, no screening tests for NHL is available; therefore, we relied on the self-reporting to ensure the controls were cancer-free individuals. In addition, randomization in control selection might have strengthened the study, but it could not be done. Furthermore, since the cancer registry in Palestine is incomplete and computerization of health information system is still under development, it was hard ascertaining cases. Moreover, the diagnosis of NHL is not based on state-of-the-art immunostaining, as a result, misclassification of NHL subtypes is common. Finally, and as in all case-control studies, recall bias is considered to be a major limitation.

## 1.9 Summary of Thesis Chapters

This document is divided into six chapters. The first chapter describes the problem we examined, the importance of this research and the objectives of it. Chapter two focuses on the literature review regarding the research problem. As for chapter three, study framework

and variables of the study are described. Chapter four demonstrates the methodology of the study, while chapter five contains the results. In the results we started by describing the disease and demographic characteristics, family history of cancer and residential exposures. In addition, the last part, which is the focus of the study, covered aspects of occupational risk factors and B-NHL risk results. Finally, in chapter six, the findings of the study are discussed with the recommendations and the limitations.

# Chapter Two: Literature Review

In this chapter we provide an overview of the literature available on the epidemiology and etiology of NHL, focusing on the occupational risk factors postulated to be involved in lymphomagenesis.

## 2.1 Non-Hodgkin Lymphoma

Non-Hodgkin lymphomas (NHLs) are a group of heterogeneous tumors arising from lymphoid tissue. They are characterized by clonal expansion of malignant immune cells at different stages of differentiation, and varies in their cellular origin, clinical behavior (highly aggressive, aggressive or indolent), morphologic appearance, immunologic and molecular phenotypes (CancerResearchUK, 2016; FDA, 2015; Lenz & Staudt, 2010).

Lymphocytes originate from hematopoietic stem cells in the bone marrow. Precursor B-cells complete most of their development in the bone marrow, while precursor T-cells migrates to the thymus to differentiate and maturate there. Antigen specificity of lymphocytes is determined early in differentiation when gene segments from variable regions of immunoglobulins in B-lymphocytes and T-cell receptors in T-lymphocytes are assembled. Antigen affinity and specificity of receptors determines the fate of immature lymphocytes. Development of a malignant lymphoma is a multistep process, where progressive accumulation of genetic abnormalities results in clonal expansion of malignant cells. DNA rearrangements in variable regions of T- and B-lymphocytes during normal developmental stages make them genetically vulnerable to develop cancer. Mutations that result in dysregulation of cell growth, apoptosis and cell signaling pathway or

immunosuppression allows for clonal expansion (Fisher & Fisher, 2004; Janeway et al., 1997; Smedby & Hjalgrim, 2011).

Several classifications for NHL have been developed over the years; the most commonly used were the International Working Formulation (IWF), which used morphology and clinical behavior to group lymphomas. In addition, the Revised European-American (REAL) classification that used immunophenotypic and genetic characteristics to classify NHLs. Recently, the World Health Organization (WHO) established a new classification system that grouped lymphomas based on morphological, immunological, genetic and clinical features. The committee concluded that each and every subtype of lymphoma needs to be treated as a distinct entity in the course of treatment and in studying risk factors (FDA, 2015; Jaffe, 2009; Patel & Hernandez-Ilizaliturri, 2015; Vardiman, 2010).

WHO classification of NHLs divides NHLs based on their cellular origin into B-cell, T-cell, and lymphoid disorders not otherwise specified. The major and most common among these are B-cell lymphomas. Furthermore, there are 36 subtypes of NHL, 21 of which are B-cell lymphomas. Among B-NHL the major subtypes are: diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), and Burkitt lymphoma (BL) (CancerResearchUK, 2016). Other subtypes of B-NHL include mucosa associated lymphoid tissue (MALT), small lymphocytic lymphoma (SLL) / chronic lymphocytic leukemia (CLL).

Upon studying NHL, it is important to be aware to the heterogeneity of these subtypes. Moreover, in NHL studies comparative analysis has been challenging due to presence of different classification systems until the recent years. Yet, the accuracy of diagnosis and coding remains problematic for epidemiologists and pathologists, even after introducing the WHO classification, due to the need for histopathologic expertise, in addition to precise immunophenotyping, molecular and cytogenic studies, and clinical information (Huh, 2012; Smith et al., 2015).

### 2.2 Epidemiology of NHL

The incidence of NHL has been showing increased rates. In the 1970s and 1980s NHL incidence rate increased at an annual rate of 3-4% and during the 1990s NHL stabilized for

few years. Since then NHL rates have been increasing by a rate of 1-2% each year (Alexander et al., 2007; Muller et al., 2005).

NHL is most commonly diagnosed among white males, >55 years old (Muller et al., 2005). According to the WHO, in 2012, there was an estimated 386 thousand new cases and 200 thousand deaths of NHL worldwide (Globocan, 2012), it was the 8$^{th}$ most frequently diagnosed cancer among men and the 10$^{th}$ among women worldwide (Jemal et al., 2011). Between 2002 and 2008 the 5-year relative survival for NHL patients was 69% and the 10-year relative survival was 58% according to the National Cancer Institute's SEER database (http://www.cancer.org/).

B-NHLs constitute 85-90% of NHL cases and the rest of the cases originates from either T or natural killer (NK)-lymphocytes (Shankland et al., 2012). Moreover, 60% of NHL cases are high-grade lymphomas. DLBCL, an aggressive subtype of NHL, is the most common (~30%). Other aggressive NHL subtypes include BL, lymphoblastic lymphoma, central nervous system lymphoma, MCL and acquired immunodeficiency syndrome (AIDS) associated lymphoma. FL is the most common subtype of indolent (low grade) NHLs, accounting for 20-25% of NHL cases. MZL, cutaneous T-cell lymphoma, MALT, and SLL/CLL are types of low-grade lymphomas (LLS, 2013).

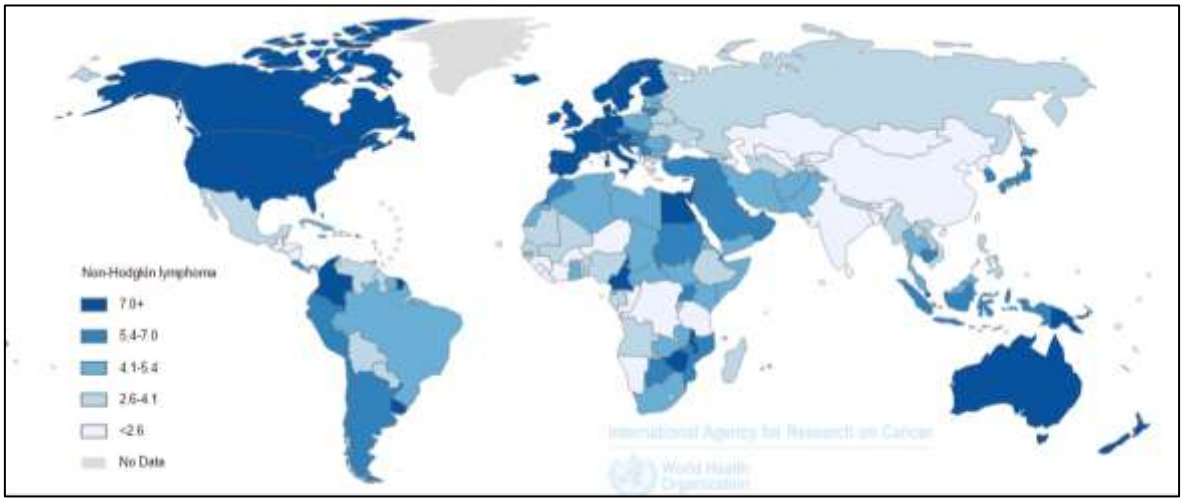


Figure 2.1: World map of the estimated age-standardized incidence (ASR) rates (per 100,000 WHO world standard population) of non-Hodgkin lymphoma. Source: (Globocan, 2012).

NHL is considered as a disease of industrialization; it is found to be more frequent in the developed countries except for regions of Africa where endemic Burkitt lymphoma is

common (Figure 2.1). In fact, the resemblance between the world GDP per capita map and lymphoma map demonstrates the correlation with economic development. Economic development is linked to changes in dietary patterns, hygiene, family size, lifestyle, access to healthcare, and industrialization. Europe, North America, and Australia have the highest rates in the world, while the lowest rates are seen in Eastern and South Central Asia (Ekstrom-Smedby, 2006; Huh, 2012; Muller et al., 2005).

The distribution of NHL subtypes varies by race, age, gender and geographic location. While DLBCL is the worldwide most common subtype of NHL is more frequent in middle age men, FL is distributed equally in both sexes, being twice more common among whites than blacks and more frequent in Western Europe and North America, constituting approximately 30% of all NHL cases in North America, London and Capetown as compared to less than 20% in other regions. On the other hand, peripheral T-NHL is the only subtype that has higher incidence in blacks, and thyroid lymphoma has the higher rates in females. Rare T-NHLs are found to be more common in Asia than other areas (Alexander et al., 2007; Ekstrom-Smedby, 2006; Evans & Hancock, 2003; Muller et al., 2005; Shankland et al., 2012).

### 2.2.1NHL in the developing countries and the Arab world

In the third world countries (developing countries), 80% of NHL cases are of B-cell type and 18% are of T-cell. DLBCL constitutes about one third of all NHL cases, and in some region is even more frequent. FL constitutes ~15%, and precursor T-cell lymphoblastic lymphoma forms 6-7% of all NHL cases with >90% males, being the predominant T-NHL, mostly observed during the first two decades of life (median age = 16 years) and accounting for 32% of all NHL cases among pediatrics. In addition, 25% of pediatric NHL is DLBCL, and 11% are Burkitt lymphoma (Naresh et al., 2004).

NHL rates are showing high rates in the surrounding countries too. In Jordan the incidence of NHL was reported to be 8.6 per 100,000 people (Almasri et al., 2004). Furthermore, in 2012, NHL was reported to be the $10^{th}$ most common cancer among Palestinians in the West Bank and climbed up to become the $8^{th}$ by 2015. The incidence rate of NHL was 2.8 case per 100,000, comprising 3.7% from all new cancer cases, and increased to become 3.5 per 100,000 population. Moreover, NHL ranked the $3^{rd}$ among children after leukemia and brain and nervous system malignancies (MOH, 2013, 2016).

## 2.3 Etiological factors of NHL

Neither the revised classification, nor the improvement in diagnostic and therapeutic strategies, or the HIV pandemic could explain the increased incidence of NHL worldwide. This increase is thought to be due to increased exposure to existing risk factors, or that new etiological factors are emerging (Muller et al., 2005; Weir, 2001).

### 2.3.1 Immune modulation

#### 2.3.1.1 Immunosuppression

Both congenital and acquired immunodeficiency disorders are the best described risk factors of NHL. among immunosuppressed persons, the relative risk measures of NHL varied between 10-100 folds or more (Grulich & Vajdic, 2005). NHL is the most commonly diagnosed malignancy in patients with immunosuppression disorders such as ataxia-telangiectasia, common variable immunodeficiency, Wiskott-Aldrich syndrome (WAS) and severe combined immunodeficiency (SCID) accounting for 48.6% of cancer cases (Kersey et al., 1988; Vajdic et al., 2010).

Furthermore, NHL is considered as the defining illnesses of AIDS (Biggar, 2001), where it accounts for 23-30% of AIDS-related mortality (Nolen et al., 2014). The increase in NHL incidence in the 1970s-1980s has been partially linked to the AIDS epidemic, especially in developed countries (Aboulafia, 1998). The pathogenesis of AIDS related cancers was related to immunosuppression rather than HIV infection (Hooper et al., 2001; Muller et al., 2005; Nolen et al., 2014).

Moreover, treatment with immunosuppressive drugs, especially after organ transplantation to prevent graft rejection was found to increase the risk of NHL, the intensity of the regimen is an important variable in the process. Basically, this association is explained by the inadequate host response to transforming pathogens such as Epstein–Barr virus (EBV) infection in the immunologically disordered individuals (Aboulafia, 1998; Grulich et al., 2007).

#### 2.3.1.2 Autoimmune diseases

Autoimmune diseases are a range of conditions characterized by dysregulation of immune response leading to loss of tolerance to self-antigens. The chronic immune stimulation and

treatment with immunosuppressive drugs, in addition to shared genetic and environmental factors are plausible explanations of interaction between NHL and autoimmune diseases (Fallah et al., 2014; Mellemkjaer et al., 2008). Epidemiological studies reported significant increase in the risk of NHL in people with autoimmune diseases, this association was found for subtypes of autoimmune diseases such as rheumatoid fever, Sjögren disease, celiac disease, systemic lupus erythematosus (SLE), rheumatoid arthritis, systemic sclerosis, Hashimoto/hypothyroidism, psoriasis and hemolytic anemia (Ekstrom Smedby et al., 2008; Fallah et al., 2014; Grulich et al., 2007; Mellemkjaer et al., 2008; Morton et al., 2014).

### 2.3.2 Genetic predisposition

Family history provides an evidence of genetic factors' role in the etiology of NHL. Increased risk of NHL was reported to be associated with family history of hematological malignancies; the odds ratio increased by about 50% for history of lymphoma (Mensah et al., 2007).

Moreover, several single nucleotide polymorphisms (SNPs) were identified by epidemiologic studies to be associated with risk of NHL. The SNPs associated with NHL were in genes involved in the metabolism and homeostasis in the body, DNA synthesis and methylation, production and trafficking of cytokines, immune and inflammatory response and immune pathways (Alexander et al., 2007; Cerhan & Slager, 2015; Gemmati et al., 2004; Lan et al., 2006; Lightfoot et al., 2005; Lincz et al., 2003; Rothman et al., 2006; Skibola et al., 2004; Soucek et al., 2002; Willett et al., 2005).

In light of the current knowledge, it is reasonable to hypothesize that the association between NHL and environmental factors will differ with the presence of gene susceptibility to the disease, relatively few studies examined this interaction, and increased risk was found in some studies (Alexander et al., 2007; Chiu et al., 2004; Vineis et al., 2007; Zhu et al., 2001).

### 2.3.3 Lifestyle and medical history factors

2.3.3.1 Medical history

Cancer treatments have negative effects on the body caused by radiation and chemotherapy including immunosuppression, therefore history of cancer is considered a risk factor of

NHL. Additionally, the inherited susceptibility to malignancy and exposure to agents associated with risk of both cancers are possible explanations of the increased risk of developing NHL as a secondary malignancy, especially with history of another hematopoietic malignancy (Alexander et al., 2007; C. H. Lu et al., 2013; Tanaka et al., 2001; Wassberg et al., 1996).

Findings regarding the association between NHL risk and blood transfusion have been inconsistent. It is hypothesized that blood transfusion causes NHL through inducing immunosuppression, or engraftment of lymphoma cells from donor with asymptomatic NHL, or transferring oncogenic viruses from donor to recipient (Castillo et al., 2010; Chow & Holly, 2002; Zhang et al., 2004).

2.3.3.2 Lifestyle factors

Tobacco is known as a human carcinogen for about 15 cancer sites, and also to contain components known to affect the immune system such as benzene, lead and polonium (Diver et al., 2014; Fernberg et al., 2006). Results have been inconsistent regarding a causal association for tobacco smoking with NHL. The contradiction might be in part related to difference in design, size, type, and subjects of studies (Besson et al., 2003; Bracci & Holly, 2005; Diver et al., 2012; Fernberg et al., 2006; Lu et al., 2011; Morton et al., 2014; Schollkopf et al., 2005; Talamini et al., 2005; Wong et al., 2010).

Alcohol consumption is responsible for approximately 3.3 million deaths annually worldwide, constituting 5.9% of the overall mortality. Statistics shows that 12.5% of these deaths are cancer related (WHO, 2014). Evaluation of cellular and humoral immune responses has so far shown that moderate consumption of alcoholic beverages might be beneficial, particularly those containing antioxidants (e.g. red wine), and therefore considered protectors against immune cell damage (Diaz et al., 2002). Nieters and his colleagues reported risk of lymphoma to be 53% lower among men who consumed alcohol compared to men who drank rarely or never during the last 10 years before interview (Nieters et al., 2006). Further, a pooled analysis of 9 studies on alcohol consumption and risk of NHL found that drinkers had lower risk than non-drinkers (OR=0·8, 95% CI=0·8–0·9), and current drinkers OR was lower than former drinkers (0·7 vs 1, respectively) (Morton et al., 2005).

Regarding dietary intake, increased risk has been linked to increased intake of proteins and fats of animal sources, while fruits and vegetables have been linked to risk reduction (Blinder et al., 2008), but findings were inconsistent. Several studies examined the association between NHL and nutritional patterns by examining energy intake, intake of animal proteins, consumption of milk and dairy products, high intake of fruits and vegetable, fat intake, and carbohydrate intake (Ali et al., 2013; Chang, Smedby, Zhang, et al., 2005; Daniel et al., 2012; Purdue et al., 2004; Zheng et al., 2004). A positive association between the risk of NHL and intake of animal proteins, consumption of milk, fat intake and carbohydrate intake was observed by Zheng and his colleagues. On the other hand, a reduction in the risk was associated with high intake of fruits and vegetables (Zheng et al., 2004). Furthermore, in Oman, Ali and his colleagues reported increased association between risk of NHL and increased energy intake, meat consumption and carbohydrate intake, while consumption of dairy products was not associated with NHL and intake of fruit and vegetables significantly reduced NHL risk (Ali et al., 2013).

Overweight and obesity have been linked to NHL risk and several studies have examined this association. Obesity is a global major health issue since it is related highly to morbidity and mortality. Obesity is linked to chronic, low-grade inflammation and some immune alteration that may alter immune responses. In addition, dysregulation of leptin, or obesity associated hormone that is released from adipocytes, was found to be associated to breast cancer, thyroid, endometrial cancer and gastrointestinal cancer and to influence pro-inflammatory responses. *In vitro* studies showed that leptin suppressed apoptosis and promoted proliferation of DLBCL (Bassig et al., 2012; Dutta et al., 2012; Fernberg et al., 2006; Han & Wang, 2015). Several studies examined the association between obesity and NHL (Ali et al., 2013; Kelly et al., 2012; Morton et al., 2014; Pan et al., 2005; Troy et al., 2010; Wong et al., 2010).

Exercise was found to affect the immune status. The type of influence depends on intensity and duration of activity relative to fitness level. Moderate training increases NK activity, while hard training decreases it; therefore, moderate training is hypothesized to enhance resistance against tumors and protects against certain types (Kelly et al., 2012; Pan et al., 2005).

### 2.3.4 Environmental and occupational exposures

The continuing global and unexplained increase in NHL incidence and mortality, along with the different patterns seen in different regions of the world suggests a possible partial role for environmental and occupational exposures (Zheng et al., 2002).

#### 2.3.4.1 Environmental exposures

Various environmental exposures have been found to influence the risk of NHL; these exposures might occur at different settings and at different stages of life and might be physical, chemical or biological.

Among physical environmental exposures, it is hypothesized that increased exposure to sunlight results in DNA damage, which triggers immunosuppression that plays a role in the etiology of NHL (Blinder et al., 2008). The epidemiologic evidence regarding such an association between exposure to sunlight and NHL has been weak and indirect, it is even suggesting protective association between recreational sun exposure and NHL (Armstrong & Kricker, 2007; Bassig et al., 2012; Soni et al., 2007; Weir, 2001).

The health effects associated with contamination of ground water with nitrates from the misuse of fertilizers are becoming a growing problem. Nitrates are reduced to nitrites, and with further reaction in the body system, N-nitroso carcinogenic compounds are produced. Weisenburger conducted an ecological study in Nebraska and found that contamination of water by nitrate was associated with increased incidence of NHL (Weisenburger, 1993). On the other hand, there were other studies that haven't found such an association (Cocco et al., 2003; Ward et al., 2006; Weyer et al., 2001).

Regarding infectious agents, 18% of global cancer burden have been attributed to specific chronic infections including HBV, HCV, human papilloma virus and *H. pylori* (WHO, 2011). Apart from HIV infection, several infectious agents have been reported to increase risk of NHL such as EBV infection (Alexander et al., 2007; De Roos et al., 2013), but the exact role of EBV in common types of NHL (e.g. DLBCL and FL) is still not clear. Seemingly, reduced immune function (in its more mild forms; i.e. psychological stress and aging) can reactivate the latent virus and increase the risk of NHL (Teras et al., 2015).

Furthermore, hepatitis C virus (HCV) infection constitutes a major global public health problem. Its prevalence was estimated by about 170 million people worldwide, with geographic variability in the prevalence estimates of the infection ranging from 1-2% in developed countries to 5-10% in other countries such as Japan, Italy, Egypt (Alexander et al., 2007; de Sanjose et al., 2008; Gisbert et al., 2003). The virus's role in inducing immune mediated processes including hematologic disorders suggested a link with lympho-proliferative diseases and lymphomagenesis; the replication of the virus in the peripheral blood mononuclear cells and the E2 membrane protein has been suggested to explain its implication (Alexander et al., 2007; de Sanjose et al., 2008; Ekstrom-Smedby, 2006; Gisbert et al., 2003).

Other infectious agents have also been hypothesized to play a role in the etiology of NHL; other viruses such as hepatitis B Virus (HBV), human herpes virus 8 (HHV8), in addition to human T-cell lymphotropic virus- type I (HTLV-I), which is the established cause of adult T-cell leukemia/lymphoma. There are also some bacterial infections involved in the etiology of NHL such as *Plasmodium falciparum*, *Helicobacter pylori* and *Borrelia afzelii* (Engels, 2007; Kleinstern et al., 2016).

#### 2.3.4.2 Occupational exposures

Many occupational exposures have been defined as either confirmed or possible carcinogens to humans. Exposures occupationally experienced are generally more intense than those experienced by the general population. Several studies focused on finding occupational agents that contribute to the etiology and risk of NHL.

##### 2.3.4.2.1 Chemical agents

Exposure to carcinogenic, immunotoxic and mutagenic chemicals in many occupations has been addressed in occupational health and safety programs as a priority. Evidence has suggested that exposure to pesticides is potentially linked to increased risk of lymphoma (Jones et al., 2014). Specific families of pesticides have attracted researchers such as phenoxy acids, triazine, organochlorines, organophosphate pesticides and carbamates (Dreiher & Kordysh, 2006; Hoar Zahm et al., 1993; Wiklund et al., 1988).

Organic solvents are a wide group of chemicals that are suspected to exert immunotoxicity in the human body (Vineis et al., 2007). Organic solvents have various uses in a wide

number of industries. Occupations that entail the risk of exposure to organic solvents include those in the chemical industries, benzene related occupations, printing industry, wood industries and carpenters, cleaners, painters, rubber and plastic industries, shoe workers, drivers, mechanics, electrical and electronic repairs, petroleum refining industry, chemists, dry cleaners, highway workers and hairdressers. Furthermore, solvent containing agents and organic solvents include styrene, trichloroethylene, perchloroethylene, benzene, chlorophenols and phenoxy acids, lacquers and varnishes, engine exhaust fumes, dyes, paints and paint aerosols, gasoline, glues, benzene, toluene, xylene, fuels, petroleum products (Orsi et al., 2010; Rego, 1998; Vineis et al., 2007).

Furthermore, polychlorinated biphenyls (PCBs) are organochlorines that started to be used since the 1930s in various industries until their use was banned in 1977, 36 out of the possible 209 congeners were found of potential importance to public health and animal studies supported a carcinogenic effect (Engel et al., 2007). PCB118, 138, 153, 156, 170, 180, and 194 were most reportable with significant associations in the literature (Kramer et al., 2012). Capacitor manufacturing workers and electric utility workers are examples of occupationally exposed people to PCBs (Engel et al., 2007).

Other chemical exposures have carcinogenic effect, therefore suggested to contribute to the risk of hematopoietic disorders. Cancer was reported as the leading cause of female chemists in the US with a mortality odds ratio of 1.5 (95%CI=1.1-2.1), with increased risk of death from lymphohematopoietic malignancies (MOR=2.2, 95%CI=1.2-4.5) (Walrath et al., 1985). Moreover, some studies found increased risk associated with exposure to heavy metals such as arsenic, nickel, cadmium, lead, chromium, and mercury in welders and solderers ('t Mannetje et al., 2008; Band et al., 2004; Karunanayake, McDuffie, Dosman, Spinelli, & Pahwa, 2008; Zheng et al., 2002), miners (Band et al., 2004), technicians, mechanists and electricians (Band et al., 2004; Karunanayake et al., 2008). In addition, those exposed to fumes and gases (Karunanayake et al., 2008), dyes and hair permanent solutions in hairdressers ('t Mannetje et al., 2008; Karunanayake et al., 2008), leather (Amadori et al., 1995; Scherr et al., 1992), and rubber and plastic production (Miligi et al., 1999). Increased risk of NHL was also found in those working in construction and engineering ('t Mannetje et al., 2008), cleaners and drycleaners , painters and decorators ('t Mannetje et al., 2008; Band et al., 2004; Scherr et al., 1992), wood workers (Boffetta & de Vocht, 2007), publishing and printers (Band et al., 2004; Boffetta & de Vocht, 2007), and

food industry (La Vecchia et al., 1989); therefore many chemical substances have been associated to increased risk of NHL.

2.3.4.2.2 Physical agents

Occupational exposure to radiation and electromagnetic fields, whether ionizing or non-ionizing, has been hypothesized to cause cancer, therefore, its role in etiology of NHL has been suggested and investigated, but results were inconsistent and not strong enough to support such evidence (Band et al., 2004; Freedman et al., 1997).

2.3.4.2.3 Biological agents

Continuous exposure to prolonged antigenic stimulation may act in combination with other factors to induce cancer of lymphoid tissue. Exposure to animal proteins and grains, in livestock farmers, animal breeders, meat processing workers in industrial plants, slaughterhouses, butchers, and dairy workers may entail such risk ('t Mannetje et al., 2008; Boffetta & de Vocht, 2007).

Several infections have been associated to increased risk of NHL; therefore, occupations that increase the susceptibility to such infections were suggested as factors contributing to the etiology of NHL. Additionally, exposure to zoonotic oncogenic viruses has also been under investigation. Workers that interact with the public (Svec et al., 2005), such as teachers (Boffetta & de Vocht, 2007; Zheng et al., 2002), especially of primary levels ('t Mannetje et al., 2008), health and social workers (Band et al., 2004), salesmen and secretaries (Linet et al., 1993), hairdressers and cosmetologists (Lamba et al., 2001; Svec et al., 2005) were found at increased risk. Also workers who reported exposure to animals or animal products were found in several studies to be at increased risk of NHL (Svec et al., 2005).

## 2.4 Occupation and Cancer

Studying how work affects morbidity and mortality in the population is defined as occupational epidemiology. The main objective of occupational epidemiology is identifying health outcomes of occupational exposures for prevention both in occupational and community settings (ILO, 2017). The beginning of occupational epidemiology and occupational medicine goes back to the Italian physician Bernardino Ramazzini in the early 17$^{th}$ century, whose work led to identifying several health hazards encountered by

workers. After that , Pott came in the late 1700s with his findings on the association between cancer of scrotum and exposure to soot among chimney sweepers (Herr, 2011). Since then many occupational exposures have been linked to carcinogenesis (ILO, 2017).

Since then, the International Agency for Research on Cancer (IARC) has so far identified 119 agents as carcinogenic to humans (Group 1), examples are benzene and asbestos. Furthermore, 81 agents have been identified as probably carcinogenic to humans (Group 2A), 292 are considered possibly carcinogenic to humans (Group 2B), and 505 agents are in Group C. At least 45 of Group 1 carcinogens are workplace chemicals (WHO, 2016). The contribution of occupational factors to cancer morbidity was estimated to be 4% (range: 2-8%), but given the number of possible carcinogens (Group 2B) this might be an underestimation for occupational cancer (Purdue et al., 2015). Further investigations on occupation and specific types of cancer estimated that occupational exposures were related to 6.3-13% of lung cancer, 3-19% of bladder cancer and 0.8-2.8% of leukemia cases (Steenland et al., 2003).

Identifying the causal agents that are associated with the disease is the main objective in occupational studies. Exposure assessment is the process of estimation of exposure. Exposure assessment is problematic in epidemiologic studies, and methods of exposure assessment vary. In retrospective case-control studies the issue of exposure assessment for past exposures is even more problematic. Work history is a useful source for exposure data through listing all the jobs that were performed using job titles to describe the job. But with job titles being general and not specific to tasks, using job titles as a proxy of exposure can lead to misclassification. Another issue in occupational studies is the large number of jobs out there and the small number of subjects in each class. To overcome this issue in research, grouping of jobs/exposures based on similarities is a common approach, but it masks the heterogeneity of exposure between subjects which shifts the association towards the null. To overcome this issue, utilizing more detailed description of each job in terms of duties and processes may improve the coding of jobs. Moreover, using a standardized classification better predicts the exposure (Nieuwenhuijsen, 2015).

### 2.4.1 Occupational Health in Palestine

Most knowledge about the Palestinian work force is achieved through censuses held by the Palestinian Central Bureau of Statistics (PCBS). Last report on labor force reported that among the Palestinian population aged 15 years and above, 45.8% were enrolled in the workforce, and that males had higher rates of participation than females (71.9% compared to 19.1%, respectively (PCBS, 2016b).

By economic activity, 20.6% of employed persons were employed in commerce, hotels and restaurants sector, 15.5% in construction, 13% in mining, quarrying and manufacturing economic branches and only 8.7% are in the agriculture, hunting and fishing branches. The majority of the Palestinian workforce (36.4%) are employed in the branches of services that include health and education among other (PCBS, 2016b).

In agriculture, hunting and fishing, and economic activities, a higher participation rates were seen among females and the same applies for the services activities. On the other hand, activities of transportation, storage and communication, construction, and commerce, hotels and restaurants had higher participation rates among males (PCBS, 2016b).

To our knowledge, very few studies on occupational morbidity and mortality were done in Palestine (Al-Khatib et al., 2006; Al-Sari & Al-Khatib, 2012; Al Zabadi & Nazzal, 2014; Khlaif & Qumsiyeh, 2017; Milhem, 2004; Nemer et al., 2015; Nemer et al., 2013). Most of them focused on single exposure or single occupation, but they were limited by sample size and geographic area, and used indirect exposure assessment techniques (Al Zabadi & Nazzal, 2014; Milhem, 2004; Nemer et al., 2015; Nemer et al., 2013). In addition, there were some studies that focused on the knowledge, perception and application of safety practices in certain settings rather than health outcomes of occupational exposures (Al-Sa' ed et al., 2011; Al-zain & Mosalami, 2014; Issa et al., 2010; Milhem, 2004; Yassin et al., 2002; Zyoud et al., 2010).

The PCBS adopted the International Standardized Classification of Occupation-08 and modified it to be suitable to the Palestinian population. The use of international classifications enables comparability between studies but it requires clear job description *and responsibilities. Among Palestinian workforce there's a lack in clear job

description, which limits the ability to proper classification of jobs in epidemiologic studies (PCBS, 2014).

Occupational health and safety remains a neglected area in developing countries on the level of research and regulation due to the social, economic and political challenges (Nuwayhid, 2004; Sweileh et al., 2015). Furthermore, it was estimated that only 5-10% of workers in developing countries have proper access to occupational health services (Elgstrand, 1985; Nuwayhid, 2004). Furthermore, among Palestinians, it was reported that in 2013 the mortality rate from occupational carcinogens was 1 per 100,000, an increase by 11% since 1990 (HealthGrove, 2013).

### 2.5 Summary

In this chapter NHL etiological factors and epidemiology are reviewed focusing on the basis of the association between occupation and cancer, specifically NHL. Further, the chapter gives an overview on NHL, workforce and occupational health in Palestine, providing clarity for the study hypothesis and framework.

# Chapter Three: Study Framework

This chapter shows the conceptual framework for our study and the dependent and independent variables included and their definitions.

## 3.1 Conceptual Framework

Occupational exposures can be either chemical, Physical, or biological. Occupational exposures are among several risk factors that have been proposed to be associated with the increased risk of B-NHL; these exposures have been hypothesized to alter the immune system's function by immune suppression, chronic stimulation, and oncogenic alterations in B-lymphocytes, all of which are mechanisms contributing to lymphomagenesis (Alexander et al., 2007).

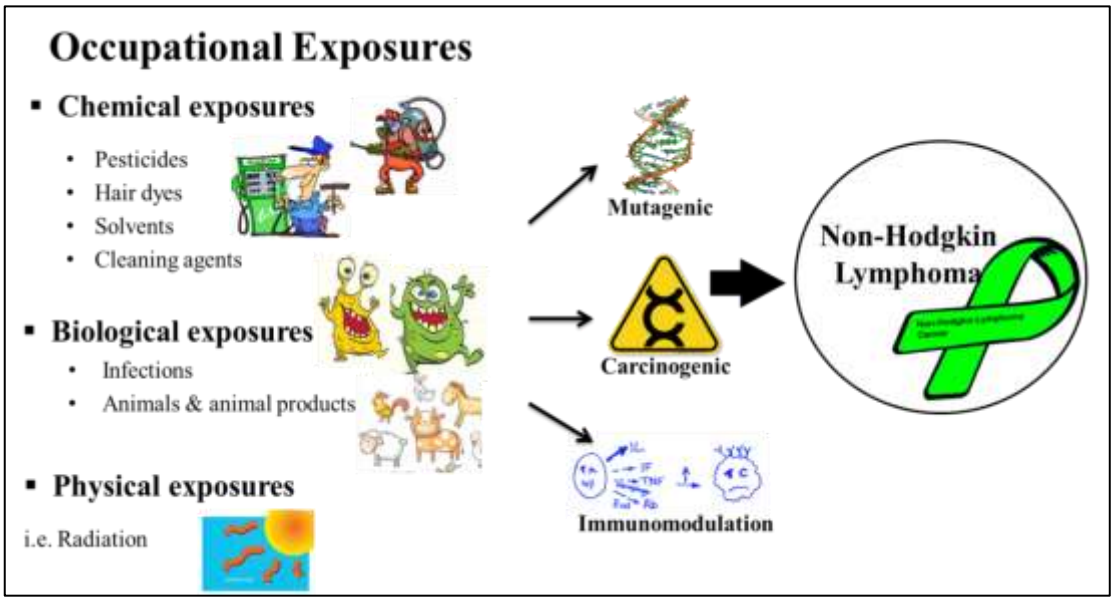


Figure 3.1: Postulated mechanisms of occupational risk factors in NHL lymphomagenesis.

### 3.2 Study Variables

Table 3.1 below shows the variables of this study. The outcome variable was B-NHL. In addition, independent variables included demographic variables, family history, lifestyle and occupational history.

Table 3.1a: Study variables and operational definitions.

| Study variable | Definition | Source | Scale/ Category |
|---|---|---|---|
| **Dependent variable** | | | |
| B-cell non-Hodgkin lymphoma | Any man or woman aged 18 years or older with pathological conformation of first diagnosis of B-NHL | Medical charts/pathology reports | Nominal: Case/Control |
| **Independent variables** | | | |
| Gender | Gender of the participants | Q3 | Nominal: Male / Female |
| Age at recruitment | Number of years between birthdate and interview date | Computed from Date of interview and date of birth reported by participant (Q4) | Continuous |
| Age at diagnosis | Number of years between birthdate and date of diagnosis | Computed from date of birth and date of diagnosis from pathology report | Continuous |
| Years of schooling | Number of years completed in school | Q13 | Ordinal: 0 / 1-6 / 7-9 / 10-12 / >12 |
| Region | Region where the participant was living in at time of recruitment | Q20 | Nominal: North: Nablus, Jenin, Tubas, Qalqilya, Tulkarem, Salfit. Middle: Ramallah, Jericho and Jerusalem. South: Bethlehem, Hebron. |
| Marital status | The social status of the participant at time of recruitment | Q5 | Nominal: Single / First marriage / Other (divorced/widowed) |
| Employment status | Lifetime relationship of participant to workforce | Q20 and Q21 | Nominal: Never / Ever |

Table 3.1b: Study variables and operational definitions.

| Study variable | Definition | Source | Scale/ Category |
|---|---|---|---|
| Family history of cancer | Having first-degree relative (parent, sibling, or child) or second degree relative (grandparent, uncle, aunt, cousin, or nephew/niece) with any type of cancer | Q100 and 101 | Dichotomous :<br>Yes / No |
| Gardening as a hobby | Reporting practicing agriculture as a recreational activity | Q55 | Nominal:<br>Yes / No |
| Type of gardening | Type of gardening activity in relation to place of practicing | Q55 and Q56 | Nominal:<br>Never / Indoor / Outdoor / Indoor and Outdoor |
| Frequency of gardening | Number of weekly hours spent on gardening | Q55 and Q58 | Ordinal:<br>Never / ≤ 20 hours per week / > 20 hours per week |
| Gardening use of pesticides | Application of pesticide on the cultivated plants during gardening | Q 59 | Nominal<br>Yes / No |
| Indoor use of pesticides | Frequency of application of pesticides inside or in the surroundings of the household | Q55 and 56 | Ordinal:<br>Never / Few times per year / ≥ 1 per month - < 1 per week / ≥1 per week |
| Occupational exposures | Chemical, physical, biological or other exposures of interest that a person had been touching, breathing, ingesting or in near vicinity of while at a particular occupation | Part II- Q22 - column exposures | Nominal<br>A list of 22 type of hazard |
| Employment in industry | **Ever employed:** are participants who reported working in an occupation related to the industry.<br>**Never employed :**cases and controls not employed in the particular industry being evaluated but have been ever enrolled in the work force | Part II- Q22- Column job title | Dichotomous:<br>Never / Ever |

# Chapter Four: Methodology

This study is part of a large case-control study that was conducted between 2009 and 2014 to investigate the genetic, lifestyle, environmental and medical risk factors associated with the risk of B-NHL among Palestinians. The methodology of the study was previously published elsewhere in details (Kleinstern et al., 2017; Kleinstern et al., 2016). In summary, this case-control study included 307 B-NHL cases and 394 cancer-free controls. A questionnaire was used for the data collection. In addition, blood samples were collected for the purposes of genetic testing and serology study. Furthermore, a workplace walkthrough was held for exposure assessment. This chapter provides more details regarding the occupational part of the study.

## 4.1 Study Design

A multicenter case-control study of pathologically-confirmed incident B-NHL cases and cancer-free controls was conducted between 2009 and 2014 to investigate which occupations and which occupational exposures were associated with risk of B-NHL.

## 4.2 Study Sample and Power

The study subjects were recruited through the study centers; those who met the inclusion criteria and consented on participation were approached and recruited. A sample size of 307 cases and 394 controls provided the study with at least 80% power to detect an OR of 2.5 based on rates of exposure in controls of ≥5% and a two sided α-level of 0.05.

### 4.3 Study Population

Cases: 389 cases were recruited initially to participate in the study, 82 of which were excluded for not meeting one or more of the inclusion criteria.

Inclusion criteria:

- Pathological confirmation of B-NHL diagnosis.
- Palestinian adults (≥18years old).
- Incident cases (< 24 months of diagnosis).
- Consent on participation.

Controls: A total of 394 hospital and clinic based controls were recruited for this study. For each case at least one control who met the eligibility criteria of controls was recruited from the participating centers. The controls were frequency-matched to cases by gender, age (±5years) and region.

Inclusion criteria:

- Cancer-free at time of recruitment as reported by the controls themselves.
- Palestinian adults (≥18years old).
- Consent on participation.
- Not related by blood to cases or other controls.

### 4.4 Study Centers

Cases were identified through medical records and the Palestinian Cancer Registry. Participating hospitals included: Al-Hussain Hospital in Beit-Jala, Augusta Victoria Hospital (AVH) in Jerusalem and Al-Watani Hospital in Nablus. In addition, Palestinian cases referred for treatment in Hematology day care centers and clinics in Hadassah–Hebrew University Medical Center both in Mount Scopus and Ein-Kerem were also recruited.

Controls were recruited from the previous participating hospitals. In addition, controls were also recruited from Al-Makassed Blood Bank and thirteen Ministry of Health primary health-care centers distributed all over the West Bank as the following: Southern Hebron, Hebron, Bethlehem, Jericho, Ramallah, Northern Ramallah, Jenin, Qalqilya, Jerusalem, Nablus, the Old City of Nablus, Salfit and Tulkarim.

### 4.5 Sample Recruitment

B-NHL cases were identified through medical and the Palestinian Cancer Registry records. After identification, the study was introduced to cases by either the treating doctor or a field worker. If the patient showed interest, the study was explained by a trained field worker. After consenting, participants were administered a face-to-face interview-based questionnaire.

Regarding controls, potential participants were approached by trained interviewers. The participants were asked if they have been diagnosed with cancer prior to the interview, and if they answered yes the interviewer did not proceed with the interview. After the eligible controls consented they were administered the same interview-based questionnaire as cases.

### 4.6 Study Tools

**1. Pathology report:** Confirmation of pathological diagnosis for B-NHL cases was achieved through acquiring pathology report that was filled by the patients' oncologists (appendix 4.1).

**2. Questionnaire:** An extensive interview-based questionnaire (appendix 4.2 and 4.3) was used to collect data from study subjects. The questionnaire was originally developed and validated by the International Lymphoma Epidemiology Consortium (InterLymph) (Besson et al., 2006). The questionnaire was translated from English into Arabic by forward and back translation and a pilot study (n=30) was conducted to test the questionnaire for local use in Palestine. Amendments on the questionnaire were made, accordingly, then interviewers were trained on the interview prior to data collection to ensure the quality of the data.

The 19-pages questionnaire was composed of six sections enquiring data regarding demographic characteristics and other possible risk factors, such as lifestyle factors, medical history, family history of cancer, residential history, in addition to occupational history.

The demographic characteristics part included data regarding: gender, date of birth, marital status, place of residence, and years of schooling. Furthermore, the occupational history, included questions regarding current and previous relationship to workforce, in addition to a list of jobs held by the respondent for at least 6 months. The period of 6 months was determined so that it takes into consideration a minimum duration for exposure accumulation and the instability in jobs among Palestinians. For each job, information on job title, start date, end date, breaks and self-reported exposures were collected. Moreover, the questionnaire included questions regarding family history of cancer, practicing gardening as a hobby, subsistence farming, and housewife role and the risk of B-NHL as semi-occupational exposures.

**3. Workplace walkthrough survey:** A workplace walk-through was conducted for the purpose of confirming that the self-reported exposures were in line with those expected in each of the pre-identified priori risk occupations. Exposure data were collected through an explicit structured interview. Data regarding the participant's job title, job description, tasks description and the use of machines and materials were collected.

Subjects were Palestinians ≥18 years old that were at the time of interview employed for at least 1 year in the industry of interest. The exposures in the workplace might be associated with certain tasks that might not be regularly performed. Also, some jobs have seasonal variability in the tasks, such as in construction, thus a minimum of 1 year was estimated to be necessary to ensure the exposure data in each job was comprehensive.

Occupations of interest were selected to cover the major industries held by study subjects. Jobs were classified by industry to be grouped. Industries of major focus were those related to agriculture, construction, leather and textile, health, education, wood industry, cleaning services, personal services such as hairdressers and beauticians, mechanics, metal and metal fabricating industry, and electrical and electronic repairing.

Moreover, subjects were asked if they had any agricultural activities beside their current occupation. They were asked to describe: 1) their practice by the type of crops, 2) having farm animals, 3) whether the products were consumed for the household or sold, 4) in addition to related exposures such as the use of pesticides and exposure to sunlight.

After listing the exposures in each workplace, they were grouped. Exposure status (exposed vs. unexposed) to the exposure groups predetermined in the questionnaire in each job was confirmed. Exposure groups of interest in this study included: pesticides, organic solvents, radiation (ionizing or non-ionizing), cleaning agents, animals and animal products, infectious agents, medicines, flour and wood dust. Some exposure sub-groups were also examined independently such as gasoline, paints, glues, meat products and sunlight.

Self-reported exposures were one by one compared to the walkthrough exposures in each industry to confirm their agreement. Unrelated exposures were excluded from the analysis.

### 4.7 Ethical Considerations

The participants' signed a consent form (appendix 4.3) that confirm upon the confidentiality of the obtained data and every participant was assured the freedom to accept or refuse participation in the study without intimidations. The project was ethically approved by the institutional review board (IRB) committee of Al-Quds University. In addition, the questionnaires and the databases were securely stored on a safe drive.

### 4.8 Statistical Analysis

Data was coded, entered and analyzed using IBM SPSS statistics (V20.0.0). Data cleaning and checking was required prior to analysis which necessitated re-entry of data for many participants and recoding certain variables.

Descriptive statistics for cases and controls were presented as frequencies and percentages for categorical variables and medians and standard deviations for continuous variables. Descriptive statistics were computed using cross-tabulation and chi-square test was used to compare cases and controls regarding demographic variables, family history of cancer, residential exposures and gardening. P-values $<0.05$ were considered statistically significant.

Job titles were coded based on the International Standardized Classification of Occupations 08 (ISCO-08) (ILO, 2008). The occupational codes were recoded and grouped into industrial groups that were constructed based on the International Standard Industrial

Classification of All Economic Activities (ISIC), revision 4 (UN, 2008). New composite dichotomous variables were created for ever being employed or exposed. Industries were selected for analysis if at least 2% of controls reported being ever employed in that industry for at least 6 months or for industries showing excess risk.

Binary logistic regression was used to examine the association between the risk of B-NHL and ever employment in industry or ever exposure. Subjects who have never been employed in the industry of focus in each analysis were used as the reference category. Crude and adjusted odds ratios (ORs) and 95% confidence intervals (95%CI) were computed. The final multivariate model was adjusted for gender, age, region, years of schooling and family history of cancer. Other potential confounders as marital status and ever employment did not substantially affect risk estimates, therefore, were not included in the final model.

Among study subjects, 19 did not disclose their occupational history and thus were treated as missing data (9 controls and 10 cases). Furthermore, a total of 629 job titles were reported, which were coded to 156 ISCO-08 codes. In addition, 71 subjects reported working in subsistence agriculture either as subsistence crop farmers or subsistence mixed crop and livestock farmers.

For the walkthrough data, we first coded the job titles according to ISCO-08 classification. We further grouped the exposures reported in each job according to list of exposures of interest. The final outcome was a list of "possible" exposures in each industrial group.

Comparison between self-reported exposures and walkthrough obtained exposures was made. Exposures reported in each job for study subjects were one by one reviewed and compared to its parallel industry. If the subject reported an exposure that wasn't included in the list of exposures, the literature was well searched to identify the possible sources for these exposures. Completely irrelevant exposures were excluded prior to the analysis.

# Chapter Five: Results

Here, we provide an overview of characteristics of study subjects and demonstrate our findings regarding occupational risk factors of B-NHL in addition to other related exposures.

## 5.1 Characteristics of Study Population and Family History

In this study, the median age at diagnosis for B-NHL cases was 52 years with a male-to-female ratio of 1:1 (Table 5.1). Regarding histological subtype the most common subtype was DLBCL with approximately 70% of the cases. In addition, FL comprised about 14% of cases and was the second most common subtype among cases (Figure 5.1).

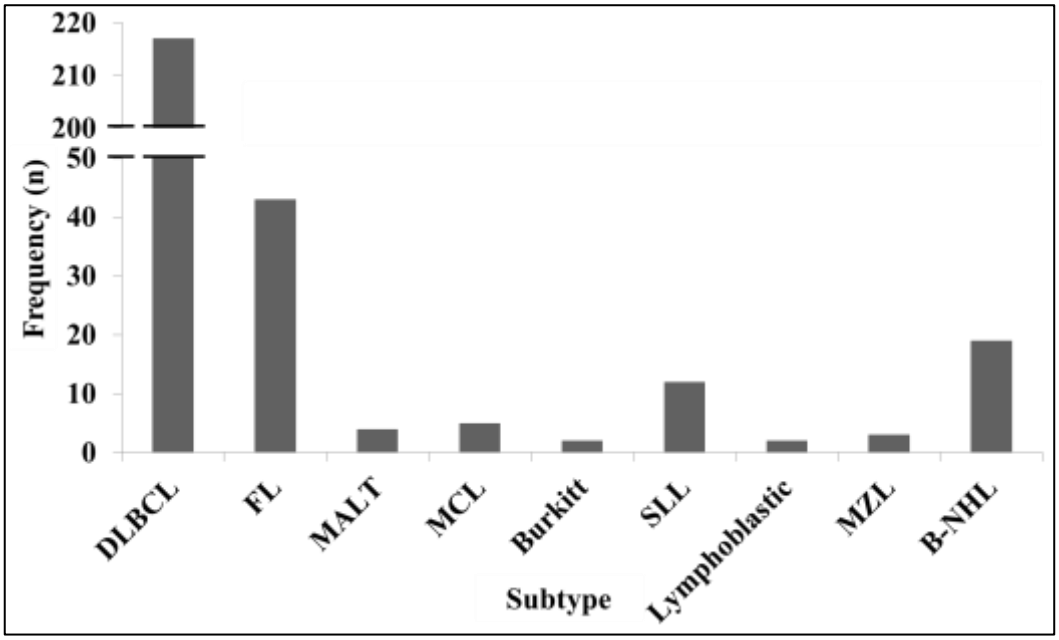


Figure 5.1: Distribution of B-NHL cases by histologic subtype.

By examining the distribution of cases and controls by recruitment center it was found that the majority of cases (31.3%) were recruited from AVH, 22.5% from Hadassah University Hospital, 12.4% from Al-Hussain Hospital, 16.6% from Al-Watani Hospital and 17.8% were recruited through MOH clinics. Regarding controls, approximately 82% were recruited through 13 MOH primary health care centers distributed all over the West Bank, the rest were recruited through AVH, Al-Watani Hospital and Al-Makassed Blood Bank (Table 5.1).

Table 5.1: Demographic characteristics of study subjects.

| **Variable** | **Category** | **Controls (n=394)** | **Cases (n=307)** |
|---|---|---|---|
| | | **n (%)** | **n (%)** |
| Recruitment center | AVH | 32 (8.1) | 96 (31.3) |
| | Hadassah | 0 (0) | 69 (22.5) |
| | Al-Hussain | 0 (0) | 38 (12.4) |
| | Al-Watani | 13 (3.3) | 51 (16.6) |
| | MOH clinics | 322 (81.7) | 53 (17.8) |
| | Makassed | 27 (6.9) | 0 (0) |
| Age at diagnosis (median ± SD) | | 52±16.6 | - |
| Age at recruitment (median±SD) | | 51±15.14 | 53±16.52 |
| Gender | Male | 168 (42.6) | 152 (49.5) |
| | Female | 226 (57.4) | 155 (50.5) |
| Age (Years) | 18-34 | 53 (13.5) | 53 (17.3) |
| | 35-54 | 176 (44.7) | 107 (34.9) |
| | 55-74 | 136 (34.5) | 114 (37.1) |
| | 75+ | 29 (7.4) | 33 (10.7) |
| Years of schooling | 0 | 55 (14.3) | 43 (14.4) |
| | 1 to 6 | 66 (17.2) | 82 (27.5) |
| | 7 to 9 | 83 (21.6) | 54 (18.1) |
| | 10 to 12 | 119 (31) | 75 (25.2) |
| | 12+ | 61 (15.9) | 44 (14.8) |
| Region | North | 78 (19.9) | 75 (24.7) |
| | Middle | 129 (32.9) | 120 (39.5) |
| | South | 176 (44.9) | 97 (31.9) |
| | Other | 9 (2.3) | 12 (3.9) |
| Marital status | Single | 34 (8.6) | 41 (13.4) |
| | Married | 333 (84.5) | 232 (76.1) |
| | Other | 27 (6.9) | 32 (10.5) |
| Employment Status | Never | 155 (40.3) | 105 (35.4) |
| | Ever | 230 (59.7) | 192 (64.6) |
| Employment Status (males) | Never | 5 (3.1) | 4 (2.7) |
| | Ever | 157 (96.9) | 143 (97.3) |
| Employment Status (females) | Never | 150 (67.3) | 101 (67.3) |
| | Ever | 73 (32.7) | 49 (32.7) |

Considering the sociodemographic characteristics of study subject, the median age at recruitment of cases was 53 years and that of controls was 51 years. In addition, approximately 42% of controls were at least 55 years old and only 13.5% were younger than 35 years old. Regarding cases, approximately 48% were 55 years or older and 17.3% were younger than 35. Furthermore, about 42% of the cases had less than 7 years of education, whereas among controls approximately 47% had 10 years or more of schooling. Moreover, 44.9% of the controls were from the south and 32.9% were from the middle. Among cases, 31.9% were from the south, 39.5% were from the middle and 24.7% were from the north. The majority of both study groups were married with higher proportion among controls. As for employment history, 60% of controls reported being ever enrolled in the workforce; 97% among males and 33% among females. Relatively higher overall employment rates were seen among cases (Table 5.1). Additionally, more cases reported history of cancer in their families, family history of cancer was associated with 70% increased risk of B-NHL (Table 5.2).

Table 5.2: Family history of cancer and association with B-NHL risk.

| Variable | Category | Controls | Cases | OR (95%CI) |
|---|---|---|---|---|
| | | n (%) | n (%) | |
| Family history of cancer | No | 212 (61.6) | 143 (48.4) | 1 (-) |
| | Yes | 132 (38.4) | 150 (51.2) | 1.7 (1.2-2.3) |

Table 5.3: Association between B-NHL risk and residential exposures.

| Residential exposure | Category | Controls | Cases | OR (95%CI) | OR* (95%CI) |
|---|---|---|---|---|---|
| | | n (%) | n (%) | | |
| Pesticide use indoors | Never | 137 (43.5) | 79 (31.9) | 1 (-) | 1 (-) |
| | Few Times/ year | 109 (34.6) | 88 (35.5) | 1.4 (0.9-2.1) | 1.4 (0.9-2.2) |
| | ≥ 1/month - < 1/week | 26 (8.3) | 28 (11.3) | 1.9 (1-3.4) | 1.9 (1-3.5) |
| | ≥1/week | 43 (13.7) | 53 (21.4) | 2.1 (1.3-3.5) | 2.1 (1.2-3.6) |
| Contact with animals | No | 265 (68.7) | 165 (54.1) | 1 (-) | 1 (-) |
| | Yes | 121 (31.3) | 140 (45.9) | 1.9 (1.4-2.5) | 1.7 (1.2-2.4) |
| Housewives € | Never | 41 (18.4) | 26 (17.3) | 1 (-) | 1 (-) |
| | Ever | 182 (81.6) | 124 (82.7) | 1.1 (0.6-1.8) | 0.8 (0.4-1.5) |

* OR adjusted for gender, age (5 years intervals), years of schooling (categorical), region and family history of cancer.
€ Analysis excluded women employed in agriculture.

### 5.2 Residential Exposures and Risk of B-NHL

Our result showed that indoor use of pesticides was associated with an increase in the risk of B-NHL. In addition, a positive dose-response relationship was found between frequency

of pesticide application and B-NHL risk. Furthermore, contact with domestic animals was significantly associated with 1.7-folds increase in the risk of B-NHL. In addition, In addition, 306 females out of 381 reported ever being housewives. Housewives were not at risk of B-NHL (Table 5.3).

### 5.3 Occupational Risk Factors of B-NHL

This part of the study focused on the occupational risk factors of B-NHL. First, a description of occupational history of subjects was demonstrated, then, we examined the association between B-NHL risk and occupational exposures and ever held occupations. A total of 629 job titles were reported by 230 controls and 192 cases who have ever participated in the workforce. In addition, 71 study subjects reported practicing subsistence farming.

Table 5.4 describes the distribution of the reported job titles among major occupational groups. Approximately 27% of cases reported being ever employed in elementary occupations, and another 26% were employed in occupations related to crafts. On the other hand, controls reported being more commonly employed in groups 2,3 and 4; these groups include occupations in education, health, engineering, business and finance services, legal professionals, in addition to clerical support occupations like secretaries.

Table 5.4: Distribution of ever held occupations by case and control status in major group according to ISCO-08.

| Group code | Group Name | Controls | Cases |
|---|---|---|---|
| | | n (%) | n (%) |
| Group1 | Managers | 18(5.1) | 4(1.4) |
| Group2,3,4 | Professionals, Technicians and Associate Professionals, Clerical Support Workers | 135(38.5) | 66(23.8) |
| Group5 | Services and Sales Workers | 26(7.4) | 33(11.9) |
| Group6 | Skilled Agricultural, Forestry and Fishery Workers | 4(1.1) | 4(1.4) |
| Group7 | Craft and Related Trades Workers | 73(20.8) | 72(25.9) |
| Group8 | Plant and Machine Operators and Assemblers | 34(9.7) | 19(6.8) |
| Group9 | Elementary Occupations | 59(16.8) | 74(26.6) |
| Group0 | Armed Forces Occupations | 2(0.6) | 6(2.2) |

Occupations were then grouped and recoded into industries. Industries that had at least 2% of the controls were selected for the analysis.

### 5.3.1 Workplace walkthrough

A total of 133 workplace walkthrough data were collected. In addition, 23 participants practiced subsistence farming and their exposure data were also collected (Table 5.5). We compared self-reported exposures reported from the case-control study to the list of exposures found in each industrial group confirmed by the walkthrough.

Table 5.5: Distribution of walkthroughs by industry and identified exposures of priori high risk.

| Industry | n | Exposures |
|---|---|---|
| Crop farmers | 9 | Pesticide, sunlight, gasoline, organic solvents |
| Mixed and livestock farmers | 6 | Pesticide, sunlight, gasoline, organic solvents, animals and animal products, infectious agents |
| Textile | 4 | Infectious agents, organic solvents |
| Wood | 5 | Wood dust, paints, organic solvents, glues, sunlight, gasoline |
| Metal production | 3 | Radiation, electromagnetic field |
| Mechanics | 4 | Organic solvents, sunlight, gasoline |
| Construction | 33 | Wood dust, organic solvents (paints), inorganic solvents, sunlight |
| Painter | 1 | Paints, glues, organic solvents |
| Trade | 16 | Infectious agents, EMF |
| Education | 6 | Infectious agents, organic solvents |
| Health and social work | 5 | Cleaning agents, infectious agents, organic solvents, radiation ( radioactive radiation, EMF), medicine |
| Protection services | 4 | Varied by workplace |
| Office based occupations | 10 | Infections |
| Cleaners | 8 | Infectious agents, cleaning agents, inorganic solvents, sunlight |
| Transportation | 10 | Gasoline, sunlight, infectious agents |
| Food production | 6 | Meat products, flour, infectious agents |
| Gas station attendant | 1 | Gasoline, organic solvents, sunlight |
| Electrical and electronic repair | 2 | Asbestos, electromagnetic fields, radiation |
| Subsistence farmers | 23 | Pesticides, sunlight, animals, infections, gasoline |

### 5.3.2 Occupational self-reported exposures and risk of B-NHL

We started the investigation of occupational risk factors by examining the association between occupational exposures and the risk of B-NHL and several exposures showed positive association with B-NHL risk. Exposures to pesticides and infections were both associated significantly with increased risk of B-NHL with an odds ratio of 2.7. In

addition, exposure to radiation showed significantly increased odds of B-NHL risk, types of radiation included exposure to sunlight, electromagnetic fields and ultraviolet light. The association between specific exposure to sunlight and the risk of B-NHL was further examined and showed a significant positive association with an adjusted odds ratio of 2.1 (Table 5.6). Moreover, exposure to organic solvents was found to be non-significantly associated with slightly increased risk of B-NHL (adjusted OR=1.4, 95%CI: 0.8-2.4). Additionally, exposure to glues was associated with significantly increased risk (adjusted OR=3.5, 95%CI: 1.1-11), but neither did paints nor benzene show any association (Table 5.6).

Table 5.6: Association between B-NHL risk and self-reported exposure to certain agents.

| **Occupational exposure** | **Exposure status** | **Controls (n=385)** | **Cases (n=297)** | **OR (95%CI)** | **OR* (95%CI)** |
|---|---|---|---|---|---|
| | | **n (%)** | **n (%)** | | |
| Pesticides | Unexposed | 362 (94) | 253 (85.2) | 1 (-) | 1 (-) |
| | Exposed | 23 (6) | 44 (14.8) | 2.7 (1.6-4.6) | 2.7 (1.5-4.9) |
| Infections | Unexposed | 362 (94) | 253 (85.2) | 1 (-) | 1 (-) |
| | Exposed | 23 (6) | 44 (14.8) | 2.7 (1.6-4.6) | 2.7 (1.5-4.9) |
| Animals and animal products | Unexposed | 363 (94.3) | 280 (94.3) | (-) | 1 (-) |
| | Exposed | 22 (5.7) | 17 (5.7) | 1 (0.5-1.9) | 0.6 (0.4-0.9) |
| Hair dyes | Unexposed | 378 (98.2) | 292 (98.3) | 1 (-) | 1 (-) |
| | Exposed | 7 (1.8) | 5 (1.7) | 0.9 (0.3-2.9) | 2.7 (0.6-11.8) |
| Flour | Unexposed | 362 (94) | 287 (96.6) | (-) | 1 (-) |
| | Exposed | 23 (6) | 10 (3.4) | 0.5 (0.3-1.2) | 0.8 (0.3-1.8) |
| Cleaning agents | Unexposed | 293 (76.1) | 223 (75.1) | (-) | 1 (-) |
| | Exposed | 92 (23.9) | 74 (24.9) | 1.1 (0.7-1.5) | 1.2 (0.8-1.9) |
| Wood dust | Unexposed | 373 (96.9) | 283 (95.3) | (-) | 1 (-) |
| | Exposed | 12 (3.1) | 14 (4.7) | 1.5 (0.7-3.4) | 1.2 (0.5-2.9) |
| Medicine | Unexposed | 373 (96.9) | 295 (99.3) | (-) | 1 (-) |
| | Exposed | 12 (3.1) | 2 (0.7) | 0.2 (0.05-1) | 0.2 (0.05-1.1) |
| Radiation | Unexposed | 341 (88.6) | 231 (77.8) | (-) | 1 (-) |
| | Exposed | 44 (11.4) | 66 (22.2) | 2.2 (1.5-3.4) | 2.1 (1.3-3.3) |
| Sunlight | Unexposed | 343 (89.1) | 235 (79.1) | 1 (-) | 1 (-) |
| | Exposed | 42 (10.9) | 62 (20.9) | 2.2 (1.4-3.3) | 2.1 (1.3-3.4) |
| Organic Solvents | Unexposed | 345 (89.6) | 254 (85.5) | (-) | 1 (-) |
| | Exposed | 40 (10.4) | 43 (14.5) | 1.5 (0.9-2.3) | 1.4 (0.8-2.3) |
| Glues | Unexposed | 381 (99) | 284 (95.6) | 1 (-) | 1 (-) |
| | Exposed | 4 (1) | 13 (4.4) | 4.4 (1.4-13.5) | 3.5 (1.1-11) |
| Paints | Unexposed | 364 (94.5) | 278 (93.6) | 1 (-) | 1 (-) |
| | Exposed | 21 (5.5) | 19 (6.4) | 1.2 (0.6-2.2) | 1.2 (0.6-2.4) |
| Gasoline | Unexposed | 365 (94.8) | 284 (95.6) | 1 (-) | 1 (-) |
| | Exposed | 20 (5.2) | 13 (4.4) | 0.8 (0.4-1.7) | 0.7 (0.3-1.5) |

* OR adjusted for gender, age (5 years intervals), years of schooling (categorical), region and family history of cancer.

Regarding exposure to medicine, a non-significant negative association was found with B-NHL risk (adjusted OR=0.2, 95%CI: 0.05-1.1). Further, occupational exposure to animals was not associated significantly with the risk of B-NHL, but exposure to meat products and animal skin both non-significantly reduced the risk of NHL (Table 5.6). As for other exposures considered in this analysis, neither exposure to wood dust, nor exposure to flour or cleaning agents were associated with risk of B-NHL. Controversially, exposure to hair dyes was non-significantly associated with increased B-NHL risk (Table 5.6).

### 5.3.3Agricultural activities and the risk of B-NHL

**Gardening as a hobby**

Practicing gardening as a hobby was found to be associated with significant increase in the risk of B-NHL (adjusted OR=1.6). Moreover, outdoor gardening increased the risk of B-NHL by 2 folds and there was a significantly increased dose response relationship between number of weekly hours spent gardening and the risk of B-NHL, but neither the type of crops nor the use of pesticide showed significant associations (Table 5.7).

Table 5.7: Association between B-NHL and practicing gardening as a hobby.

| | | Controls | Cases | OR | OR* |
|---|---|---|---|---|---|
| | | n (%) | n (%) | (95%CI) | (95%CI) |
| Gardening as a hobby | No | 226 (58.4) | 138 (45.5) | 1 (-) | 1 (-) |
| | Yes | 161 (41.6) | 165 (54.5) | 1.7 (1.2-2.3) | 1.6 (1.1-2.2) |
| Type of gardening | Never | 226 (58.9) | 138 (45.7) | 1 (-) | 1 (-) |
| | Indoor | 50 (13) | 29 (9.6) | 1.0 (0.6-1.6) | 0.7 (0.4-1.3) |
| | Outdoor | 101 (26.3) | 127 (42.1) | 2.1 (1.5-2.9) | 2.1 (1.4-3) |
| | Both | 7 (1.8) | 8 (2.6) | 1.9 (0.7-5.3) | 1.8 (0.3-5.8) |
| Frequency (hours/week) | Never | 226 (60.6) | 138 (46.3) | 1 (-) | 1 (-) |
| | ≤20 | 130 (34.9) | 130 (43.6) | 1.6 (1.2-2.3) | 1.6 (1.1-2.2) |
| | >20 | 17 (4.6) | 30 (10.1) | 2.9 (1.5-5.4) | 2.7 (1.4-5.3) |
| Grow fruit & vegetable | Other | 35 (22.7) | 44 (27.2) | 1 (-) | 1 (-) |
| | Crops | 119 (77.3) | 118 (72.8) | 0.8 (0.5-1.3) | 0.8 (0.5-1.4) |
| Pesticide use in gardening | No | 73 (47.4) | 73 (48.3) | 1 (-) | 1 (-) |
| | Yes | 81 (52.6) | 78 (51.7) | 1.0 (0.6-1.5) | 0.9 (0.5-1.5) |

* OR adjusted for gender, age (5 years intervals), years of schooling (categorical), region and family history of cancer.

**Subsistence farming**

Table 5.8 shows the association between B-NHL risk and practicing subsistence farming and some of the related exposure to this practice. There was a non-significant association for practicing subsistence agriculture among Palestinians, but reporting exposure to

pesticides and animals elevated the risk almost 3 times for pesticides and 4.5 times for animals, although non-significantly. In addition, exposure to sunlight was significantly associated with elevated risk of B-NHL (adjusted OR=14.3, %95CI: 2.8-71.7).

Table 5.8: Association between B-NHL and subsistence farming.

| | | **Controls** | **Cases** | **OR (95%CI)** | **OR* (95%CI)** |
|---|---|---|---|---|---|
| | | **n (%)** | **n (%)** | | |
| Subsistence agriculture** | Ever | 335 (89.8) | 243 (88) | 1 (-) | 1 (-) |
| | Never | 38 (10.2) | 33 (12) | 1.2 (0.7-2) | 1.2 (0.7-2.2) |
| Pesticide | Unexposed | 27 (71.1) | 16 (48.5) | 1 (-) | 1 (-) |
| | Exposed | 11 (28.9) | 17 (51.5) | 2.6 (1-6.4) | 2.8 (0.8-10.2) |
| Animal | Unexposed | 33 (86.8) | 26 (78.8) | 1 (-) | 1 (-) |
| | Exposed | 5 (13.2) | 7 (21.2) | 1.8 (0.5-6.2) | 4.5 (0.8-26) |
| Sunlight | Unexposed | 32 (84.2) | 16 (48.5) | 1 (-) | 1 (-) |
| | Exposed | 6 (15.8) | 17 (51.5) | 5.7 (1.9-17.2) | 14.3 (2.8-71.7) |

* OR adjusted for gender, age (5 years intervals), years of schooling (categorical), region and family history of cancer.
**analysis excluded agricultural workers.

Table 5.9: Risk of B-NHL among housewives.

| | **Category** | **Controls** | **Cases** | **OR (95%CI)** | **OR* (95%CI)** |
|---|---|---|---|---|---|
| | | **n (%)** | **n (%)** | | |
| Subsistence farming | Unexposed** | 167 (91.8) | 112 (90.3) | 1 (-) | 1 (-) |
| | Exposed | 15 (8.2) | 12 (9.7) | 1.2 (0.5-2.6) | 1.6 (0.6-4.1) |
| Cleaning agents | Unexposed | 114 (62.6) | 67 (54) | 1 (-) | 1 (-) |
| | exposed | 68 (37.4) | 57 (46) | 1.4 (0.9-2.3) | 1.6 (0.9-2.6) |
| Meat Products | Unexposed | 177 (97.3) | 123 (99.2) | 1 (-) | 1 (-) |
| | exposed | 5 (2.7) | 1 (0.8) | 0.3 (0.03-2.5) | 2 (0.1-34.9) |
| Flour | Unexposed | 168 (92.3) | 117 (94.4) | 1 (-) | 1 (-) |
| | exposed | 14 (7.7) | 7 (5.6%) | 0.7 (0.3-1.8) | 1.6 (0.5-4.7) |
| Farming and sunlight | Unexposed | 166 (91.2) | 113 (91.1) | 1 (-) | 1 (-) |
| | exposed | 16 (8.8) | 11 (8.9) | 1 (0.5-2.3) | 1.3 (0.5-3.1) |
| Farming and pesticides | Unexposed | 213 (95.5) | 129 (86) | 1 (-) | 1 (-) |
| | exposed | 10 (4.5) | 21 (14) | 3.5 (1.6-7.6) | 3.3 (1.3-8.2) |
| Farming and animals | Unexposed | 172 (94.5) | 119 (96) | 1 (-) | 1 (-) |
| | exposed | 10 (5.5) | 5 (4) | 0.7 (0.2-2.2) | 0.9 (0.2-3.2) |

* OR adjusted for age (5 years intervals), years of schooling (categorical), region and family history of cancer.
** Unexposed group include housewives who never practiced agriculture.

**Housewives**

Although Palestinian housewives were not found to be at risk of B-NHL, those who reported being involved in subsistence farming duties had a 60% increase in the risk of B-NHL. In addition, exposure to cleaning agents, meat products and flour among housewives

non-significantly increased the risk of B-NHL, and exposure to sunlight and animals along with being a housewife and practicing subsistence agriculture wasn't associated with risk of B-NHL. Additionally, exposure to pesticides along with being a housewife practicing subsistence agriculture significantly increased the risk of B-NHL to 3.3 (Table 5.9).

Table 5.10: Association between B-NHL and ever employment in different industries.

| Industry | Category | Controls n (%) | Cases n (%) | OR (95%CI) | OR* (95%CI) |
|---|---|---|---|---|---|
| Agriculture | Never | 218 (94.8) | 171 (89.1) | 1 (-) | 1 (-) |
| | Ever | 12 (5.2) | 21 (10.9) | 2.2 (1.1-4.7) | 1.7 (0.8-3.9) |
| Crop farming | Never | 222 (96.5) | 175 (91.1) | 1 (-) | 1 (-) |
| | Ever | 8 (3.5) | 17 (8.9) | 2.7 (1.1-6.4) | 2.4 (0.9-6.2) |
| Livestock or mixed farming | Never | 225 (97.8) | 187 (97.4) | 1 (-) | 1 (-) |
| | Ever | 5 (2.2) | 5 (2.6) | 1.2 (0.3-4.2) | 0.5 (0.1-2.2) |
| Textile | Never | 212 (92.2) | 169 (88) | 1 (-) | 1 (-) |
| | Ever | 18 (7.8) | 23 (12) | 1.6 (0.8-3.1) | 1.9 (0.9-4.1) |
| Wood | Never | 219 (95.2) | 182 (94.8) | 1 (-) | 1 (-) |
| | Ever | 11 (4.8) | 10 (5.2) | 1.1 (0.5-2.6) | 0.8 (0.3-2.2) |
| Metal production | Never | 219 (95.2) | 184 (95.8) | 1 (-) | 1 (-) |
| | Ever | 11 (4.8) | 8 (4.2) | 0.9 (0.3-2.2) | 0.9 (0.3-2.2) |
| Electrical & electronic repair | Never | 221 (96.1) | 185 (96.4) | 1 (-) | 1 (-) |
| | Ever | 9 (3.9) | 7 (3.6) | 0.9 (0.3-2.5) | 1.1 (0.4-3.3) |
| Mechanics | Never | 222 (96.5) | 185 (96.4) | 1 (-) | 1 (-) |
| | Ever | 8 (3.5) | 7 (3.6) | 1.1 (0.4-3) | 0.8 (0.3-2.4) |
| Construction | Never | 173 (75.2) | 142 (74) | 1 (-) | 1 (-) |
| | Ever | 57 (24.8) | 50 (26) | 1.1 (0.7-1.7) | 0.8 (0.5-1.4) |
| Painters | Never | 221 (96.1) | 187 (97.4) | 1 (-) | 1 (-) |
| | Ever | 9 (3.9) | 5 (2.6) | 0.7 (0.2-2) | 0.8 (0.2-2.6) |
| Trade | Never | 212 (92.2) | 175 (91.1) | 1 (-) | 1 (-) |
| | Ever | 18 (7.8) | 17 (8.9) | 1.1 (0.6-2.3) | 1.3 (0.6-2.6) |
| Education | Never | 197 (85.7) | 169 (88) | 1 (-) | 1 (-) |
| | Ever | 33 (14.3) | 23 (12) | 0.8 (0.5-1.4) | 1.1 (0.6-2.2) |
| Health and social work | Never | 192 (83.5) | 183 (95.3) | 1 (-) | 1 (-) |
| | Ever | 38 (16.5) | 9 (4.7) | 0.2 (0.1-0.5) | 0.2 (0.1-0.6) |
| Protection services | Never | 225 (97.8) | 180 (93.8) | 1 (-) | 1 (-) |
| | Ever | 5 (2.2) | 12 (6.2) | 3 (1.-8.7) | 2.7 (0.8-9.1) |
| Office based occupations | Never | 195 (84.8) | 177 (92.2) | 1 (-) | 1 (-) |
| | Ever | 35 (15.2) | 15 (7.8) | 0.5 (0.2-0.9) | 0.05 (0.2-1) |
| Cleaners | Never | 212 (92.2) | 178 (92.7) | 1 (-) | 1 (-) |
| | Ever | 18 (7.8) | 14 (7.3) | 0.9 (0.4-1.9) | 0.9 (0.4-2) |
| Transportation | Never | 206 (89.6) | 181 (94.3) | 1 (-) | 1 (-) |
| | Ever | 24 (10.4) | 11 (5.7) | 0.5 (0.2-1.1) | 0.5 (0.2-1.3) |
| Food production | Never | 215 (93.5) | 182 (94.8) | 1 (-) | 1 (-) |
| | Ever | 15 (6.5) | 10 (5.2) | 0.8 (0.3-1.8) | 0.7 (0.3-1.6) |
| Personal services | Never | 225 (97.8) | 187 (97.4) | (-) | (-) |
| | Ever | 5 (2.2) | 5 (2.6) | 1.2 (0.3-4.2) | 2.5 (0.6-10.2) |
| Hairdressers and beauticians | Never | 227 (98.7) | 187 (97.4) | 1 (-) | 1 (-) |
| | Ever | 3 (1.3) | 5 (2.6) | 2 (0.5-8.6) | 5.3 (0.9-30.6) |

* OR adjusted for gender, age (5 years intervals), years of schooling (categorical), region and family history of cancer.

### 5.5.4 Occupational history and risk of B-NHL

Table 5.10 shows the distribution of study subjects in the various industries and the association with B-NHL. Employment in agriculture was associated with non-significantly increased risk of B-NHL. The risk of B-NHL was even higher for crop farmers. In contrast, livestock farmers were found to have decreased risk.

Several other industries showed positive association with B-NHL risk, but most were insignificant. Those include employment in the textile industry, personal services and protection services. Interestingly, hairdressers and beauticians had 5-folds increased risk for B-NHL, although the numbers were very small.

On the contrary, employment in the health sector was found to be associated with significantly decreased risk of B-NHL and employment in office based (white collar) jobs showed decreased risk with borderline-significance. The risk of B-NHL was also found to be lower among those employed in transportation sector, although the association was not statistically significant.

# Chapter Six: Discussion, Conclusions, Limitations and Recommendations

This case-control study of 307 cases and 394 controls was designed and conducted to study the occupational risk factors and other risk factors of B-NHL for the first time in Palestine. The results of this study shed light on the urgent needs for occupational health programs for assessment and identification for areas for intervention and prevention. This chapter highlights and discusses the major findings and the conclusions derived based on the study, in addition to the limitations of the study and our recommendations.

## 6.1 Discussion

### 6.1.1 Characteristics of study subjects and family history

The study included 307 cases from the major Palestinian hospitals providing services to cancer patients. Palestinian NHL cases were found to have a median age at diagnosis almost 10 years younger than in developed countries (CancerResearchUK, 2016; Smith et al., 2015).These finding have been consistent with reports from Asian countries (Mozaheb, 2012), India (Nair et al., 2016), Egypt (Abdel-Fattah & Yassine, 2007), Jordan (Almasri et al., 2004), Saudi Arabia (Rauf et al., 2015), Iraq (Yaqo et al., 2011), Kuwait (Ameen et al., 2010) and other developing countries (Perry et al., 2016b).

Furthermore, although DLBCL is the most common NHL subtype worldwide, the higher rates of DLBCL in the developing countries along with lower rates of FL compared to developed countries suggests involvement of genetic factors, or progression of less aggressive lymphomas such as FL and MZL to more aggressive forms of the disease (Mozaheb, 2012; Perry et al., 2016a).

Gender and age are established risk factors for NHL worldwide. Males are at greater risk of NHL, and the risk after the age of 60 is almost three times higher (Alexander et al., 2007; Boffetta, 2011). In our analysis the male-to-female ratio was 1:1. Previous reports reported 50% higher risk among men in USA (Fisher & Fisher, 2004), approximately 1.2:1 in the UK (CancerResearchUK, 2016). In addition, in Oman the male to female ratio was 1.7 (Nooyi & Al-Lawati, 2011), and similar ratios were also reported in Kuwait, Qatar, Saudi Arabia and United Arab Emirates (Al Hamdan et al., 2009).

As an indicator for socioeconomic status we considered years of schooling. Cases had significantly lower education level compared to controls. National surveys showed that about 9% of Palestinians never attended school by the end of 2016, whereas 13.5% had between 1 to 6 years of schooling in the primary education level, 38% had between 7-9 years, 21% had between 10-12 and 18% had at least 13 years of schooling (PCBS, 2016c).

Family history of cancer is a strong indicator for genetic predisposition and genetic susceptibility to NHL; family history resembles the interaction between genetic susceptibility and shared behaviors and environmental exposures (Wang et al., 2007). In this study having a family history of cancer among first or second degree relative significantly increased the risk of NHL. The Scandinavian Lymphoma Etiology (SCALE) study reported an association between risk of NHL and having a father or sibling with history of cancer but not a mother, in addition, family history of hematopoietic malignancy was associated with risk of NHL with an OR of 1.8, the odds of the disease increased 2-folds when that family member was a sibling. Among parental history, having a father with hematopoietic malignancy was a better predictor for NHL risk (Chang, Smedby, Hjalgrim, et al., 2005). Furthermore, an Italian study reported a significant increase in the risk of NHL by 3-folds among people with first degree relative history of hematopoietic malignancy, and a history of any cancer among first degree relatives was associated with increased NHL risk, a dose response relationship with the number of relatives affected was observed (Negri et al., 2006). Another study of NHL risk and family history did not find any association between family history of any site of cancer and the risk of NHL (Chatterjee et al., 2004).

Furthermore, only half of the study subjects reported ever being enrolled in the workforce and males had higher employment rates. Last workforce reports among Palestinians

reported 46% participation rate during 2014 and 2015, among males the participation rate was approximately 72% while among females the rates did not reach 20% (PCBS, 2016b). The higher employment rates among the control group in both males and females might be due to the fact that in the study we examined both job history and current employment therefore it reflects prevalence.

### 6.1.2 Residential exposures

We examined the association between indoor use of pesticide and the risk of B-NHL and found that application of pesticides for at least once per month significantly increased the risk of B-NHL. In addition, as the frequency of use increased, the risk increased significantly. In a case-control study done in Iowa, Los Angeles County, and the Detroit - and Seattle metropolitan areas home and garden use of pesticide was examined and a positive association between house treatment for termites and the risk of NHL was found, but not for all or other insect treatments (Colt et al., 2006). Furthermore, Buckley and his colleagues found that using pesticides at home with increased frequency increased the risk of NHL by 7-folds (Buckley et al., 2000).

Moreover, contact with pets or large domestic animals was found to be significantly associated with increased risk. Similar findings for contact with domestic animals during childhood were observed in a study held in Denmark and Sweden, the reported OR was 1.1 (95%CI: 1-1.2) (Smedby et al., 2007). Moreover, a Canadian study found a positive association between raising farm animals including pigs, bison, elks and ostriches and the risk of NHL (McDuffie et al., 2002). In contrast, exposure to household pets was not found to be associated with NHL risk in a study in Sweden (Dryver et al., 2004). Contact with animals is a proxy for infections. Infections that occur early in life are crucial in the development of immune system. Increased susceptibility to infections has shown contradicted results (Goldin et al., 2011; Grulich et al., 2005).

### 6.1.3 Occupational risk factors of B-NHL

Identification of the specific agents in each occupation is the main goal in occupational studies, but it is hard to obtain accurate exposure data by self-reporting, especially for past exposures since they are prone to recall bias or might be never even known. Therefore, two aspects of exposures that complete each other were considered in this study. The first was to look into classes of exposures that might influence the risk of the disease. The second

was to classify exposures by industry, which makes identifying specific etiologic factors more difficult to identify but overcome the disadvantages of recall bias (Scherr et al., 1992) . In addition, differential misclassification as a result of reliance on self-reporting is hard to be estimated; cases generally tend to recall their past exposures better than controls.

ISCO-08 classification depends in its structure on skill level and skill specialization, which are connected to the level of knowledge and education required in the occupation (ILO, 2008). Regarding occupational characteristics of subject, cases in our analysis were found to be more likely employed in elementary occupations, services and sales, and trades and related occupations, but less likely to be employed in occupations that require higher skill levels (major groups 1-4). This distribution is consistent with the previous finding of low educational level among cases.

Furthermore, odd exposures that were not in line with those expected after conducting the walkthrough were excluded. It is noteworthy to point to the possibility of under-reporting for some exposure classes that are not well known among the general population such as inorganic solvents, EMF, and ionizing radiation. Therefore, exposures with low counts were either grouped to a relevant major exposure category, or not included in this analysis.

#### 6.1.3.1 Pesticides, radiation, animals, flour and the risk of B-NHL

The association between pesticide exposure and NHL has been long studied. Our findings supported the presence of an association between exposure to pesticides and NHL risk on more than one level. First, a significantly increased association between occupational exposure to pesticide and B-NHL risk was found (Table 5.6). Second, employment in agriculture increased the risk of B-NHL, especially among those who reported employment in agriculture as vegetable and crop farmers (Table 5.9). The risk of NHL among farmers was continuously reported to be increased ('t Mannetje et al., 2008; La Vecchia et al., 1989; Zheng et al., 2002). In addition, a study in Canada reported increased risk among farmers that have worked for more than 10 years (Karunanayake et al., 2008) and another study conducted among men and women in northern Germany reported an increased risk between being an agricultural worker and risk of both high and low grade NHL (Richardson et al., 2008). Furthermore, several previous investigations of pesticide exposure and NHL risk observed a positive association (Mao et al., 2000; Pahwa et al., 2012; Salem et al., 2014). Genotoxic and non-genotoxic mechanisms of pesticide-induced

lymphomagenesis have been proposed. Demonstrated causes of the association included contamination with byproducts such as polychlorinated biphenyls (PCBs), dioxins, and furans. In addition, the role of pesticides themselves as carcinogens and their role in hepatotoxicity, immunotoxicity and endocrine disruption were reported (Dreiher & Kordysh, 2006). Contrary to our findings, other studies found no association between working in agriculture and the risk of NHL (Chia et al., 2012; Dryver et al., 2004; Mester et al., 2006; Schenk et al., 2009; Zheng et al., 2002), or exposure to pesticide and the risk of NHL (Dryver et al., 2004; McDuffie et al., 2001).

The Palestinian society is known to be an agricultural society rather than an industrial one. The household farming survey of 2015 that looked into the availability of garden in Palestinian households and its use in agricultural activities and keeping domestic breeding stock reported that 33% of households in the West Bank have gardens, and that approximately 94.1% utilized them for agricultural activities. They also reported that the most cultivated crops were horticultural trees including olive trees and citrus trees, and temporary (vegetables and field) crops. In addition, 10% of households in Palestine reared domestic livestock such as sheep, goats, poultry and bee hives. Furthermore, 98% of those using gardens in agricultural activities consumed the products for household (PCBS, 2016a). Another report by the PCBS indicated that 58.1% of holders' main occupation was not agriculture and that one third of the employees were permanent unpaid family members, whereas, approximately 40% were temporary unpaid family members. As for waged employees, they comprised 27% of laborers of which only 2.4% were permanent (PCBS, 2012). Moreover, only 8.7% of the Palestinian labor force are employed in the agriculture industry (PCBS, 2016b). Domestic farming and utilizing unpaid family members in farm work were considered in our analysis; we examined the association between subsistence farming generally and among housewives, and the risk of B-NHL. In addition, we further studied the risk of exposures encountered among these groups. No significant increase in the risk of B-NHL was found among subsistence farmers, but housewives involved in farming were found to have 60% increase in the risk of B-NHL compared to ordinary housewives. Furthermore, no significant association between B-NHL risk and pesticide use in gardening was found (Table 5.7), but pesticide exposure among subsistence farmers increased B-NHL risk by 2.8-folds (Table 5.8) and among housewives who reported exposure to pesticides and having farming duties as part of their domestic tasks the risk increased by 3.3-folds (Table 5.9). In a population-based case-control study

conducted in eastern Nebraska among women no increased risk was associated with ever living or working in a farm, but among women who reported personally mixing or applying pesticides a small increase in the risk was found. In addition, handling organophosphate insecticides increased the risk of lymphoma by 4.5-folds, and use of chlorinated hydrocarbon insecticides on dairy cattle increased the risk by 3-folds (Zahm et al., 1993). Similarly, a positive association with a significant dose-response relationship among women who were exposed to pesticides was observed by a Canadian study (Mao et al., 2000).

Moreover, in a recent study on farming practices in the West Bank, it was found that two-thirds of crop farmers reported using herbicides and fungicides to sterilize the soil, and a common use of chemically treated seeds with fungicides. The study also reported irrational use of pesticides among Palestinian farmers (Harb et al., 2016). Other studies in Palestine reported overuse of pesticides, not considering the appropriate pre-harvest interval after pesticide application, and poor knowledge and use of personal protective equipment. Furthermore, pesticide misuse is reported as a major health problem in most developing countries (Al-Sa' ed et al., 2011; Al-zain & Mosalami, 2014; Harb et al., 2016; Issa et al., 2010; Yassin et al., 2002; Zyoud et al., 2010).

Farmers are subject to a wide range of exposures that may also be related to NHL risk. In addition, to pesticides; exposure to sunlight, fertilizers, organic and inorganic dusts, engine fuels, animals and zoonotic infections are common among farmers. Harb and his colleagues reported, in addition to pesticide use among Palestinian farmers, that in 68% of farms chemical fertilizers such as (25% $P_2O_5$) and 21% $NH_4$ were added, and 80% used organic fertilizers. The misuse of these materials was also reported. Moreover, it was common to use hormones to get better harvest (Harb et al., 2016). Furthermore, among Palestinians, the Household Survey reported that 10% of households in Palestine reared domestic livestock such as sheep, goats, poultry and bee hives (PCBS, 2016a).

Occupational exposure to radiation and electromagnetic fields, whether ionizing or non-ionizing, has been hypothesized to cause cancer, therefore, its role in etiology of NHL has been suggested and investigated, but results were inconsistent and not strong enough to support such evidence (Band et al., 2004; Freedman et al., 1997; Pearce & Bethwaite, 1992). On the other hand, Exposure to ionizing radiation was found to be insignificantly

associated with NHL risk in a previous case-control study in Sweden and exposure to low frequency magnetic fields was associated with an increased risk with borderline significance (Dryver et al., 2004). In this study exposure to radiation was associated with 2-folds increased risk. Radiation exposure pooled several radiation types including UV, ionizing radiation, electromagnetic fields and exposure to sunlight, the latest was the most reported therefore we looked into it separately from the other types of radiation. Sunlight exposure was significantly associated with increased risk of B-NHL, and among subsistence farmers who reported exposure to sunlight the risk was 14 times higher, but not among housewives with agricultural duties. The association between sunlight exposure and NHL risk was supported by a previously held population based case-control study (Hakansson et al., 2001; Zhang et al., 2007), but the current evidence does not support these findings. The increased risk for NHL among those with history of melanoma and skin cancers and the immunosuppressive effect of sunlight exposure led researchers to hypothesize that sun exposure increase the risk of NHL but recent studies contradicted this hypothesis and reported 25-40% reduction in the risk of NHL for sun exposure. (Armstrong & Kricker, 2007; Bassig et al., 2012; Hakansson et al., 2001).

Workers in metal manufacturing and fabricating occupations and workers in electrical and electronic repair industry are occupationally exposed to various types of radiation. Our study was not able to detect an association between metal workers and the risk of B-NHL. Previous studies reported increased risk welders and solderers, this association was found to be related to exposure to heavy metals such as arsenic, nickel, cadmium, lead, chromium, and mercury ('t Mannetje et al., 2008; Band et al., 2004; Karunanayake et al., 2008; Zheng et al., 2002). In addition, in a population-based case-control study in Germany, elevated risk among blacksmiths, toolmakers, and machine tool operators for low grade lymphomas was observed (Richardson et al., 2008). Furthermore, employment in metalworking industries was found to be associated with a significantly increased risk of NHL among men in Kansas and Nebraska. Exposure to metals and organic solvents welding fumes, metal fumes and electromagnetic fields were suggested to explain this association ('t Mannetje et al., 2016; Zheng et al., 2002). Controversially, exposure to welding fumes was not found to be associated with risk of NHL in a study in southern Sweden, but employment as a welder was associated with 40% increased NHL risk. Furthermore, exposure to nickel, zinc and cadmium were not found to be associated with

NHL risk and neither did employment in smithwork industry or silver plating (Dryver et al., 2004).

Similarly, ever employment as an electrical and electronic repairer was not found to be associated with B-NHL risk in this study. Previous studies among repair workers were inconsistent, some studies found increased risk among technicians and electricians (Band et al., 2004; Karunanayake et al., 2008). Furthermore, an increased risk among male electrical and electronic equipment repairers who had worked at their job for at least 10 years for all NHL subtypes was also observed previously. Exposure to electromagnetic fields, solvents and polychlorinated biphynels were reported as possible causal agents in this association ('t Mannetje et al., 2016; Mester et al., 2006; Neasham et al., 2011; Zheng et al., 2002).

Exposure to animals and animal products was suggested to increase farmer's risk to lymphoproliferative malignancies. Explanations for this association included exposure to zoonotic infectious agents (Svec et al., 2005). Furthermore, contact with animals and meat products leads to prolonged antigenic stimulation which in combination with other factors may act to induce cancer of lymphoid tissue ('t Mannetje et al., 2008; Boffetta & de Vocht, 2007). In our investigation, no association between exposure to animals and B-NHL risk was found, and among livestock and mixed crop and livestock farmers, a 50% reduction in NHL risk was found (Table 5.9). Additionally, animal exposure among housewives who reported subsistence farming activities was not associated to NHL risk (Table 5.8). On the other hand, contact with domestic animals increased the risk of B-NHL by 1.9-folds (Table 5.3) and animal exposure among subsistence farmers increased the risk by 4.5-folds (Table 5.8). Exposure to farm animals was reported to be associated with 25% reduction in the risk of NHL in southern Sweden (Dryver et al., 2004). In contrast, several studies reported increased risk among livestock farmers, animal breeders and veterinarians ('t Mannetje et al., 2008; Boffetta & de Vocht, 2007; Svec et al., 2005).

Upon considering agricultural exposures, it is important to keep in mind that exposure to these agents is not restricted to farmers, but workers in other industries experience these exposures too. Exposure to meat products is common among butchers, cooks and other food preparation occupations, in addition to housewives. Exposure to meat products was associated with non-significant 60% reduction in NHL risk in our analysis and workers in

food manufacturing and preparation industries experienced marginal reduction in B-NHL. Controversy, a 2-folds increase in the risk was found among exposed housewives, although this finding was based only on one exposed case. Theories suggest that zoonotic viruses such as bovine leukemia virus might explain the possible association between NHL and meat exposure. Other theories related it to chronic antigenic stimulation caused by animal proteins (Neasham et al., 2011; Svec et al., 2005). Furthermore, both housewives and workers in food production industry are susceptible to exposure to flour too, which was not associated with risk of B-NHL in this analysis. Further, individual analysis of housewives revealed 60% increase in B-NHL risk among housewives who reported exposure to flour. Employment in food industry was previously reported to be associated with slightly decreased risk of NHL mortality (Svec et al., 2005). On the other hand, a multicenter prospective cohort study of 348,555 European subjects, in addition to several other studies, found a statistically significant increased OR among butchers ('t Mannetje et al., 2016; Boffetta & de Vocht, 2007; McLean et al., 2004; Neasham et al., 2011; Zheng et al., 2002).

#### 6.1.3.2 Infections, cleaning agents, medicine, hair dyes and B-NHL risk

Triggers of immune responses, possibly stimulate lymphocyte proliferation, leading consequently and as a result of recurrent exposure, to increased risk of NHL (Svec et al., 2005). Several infectious agents have been linked to NHL risk and occupations that increase the susceptibility to infections through contact with public, animals, and body fluids have also been investigated (Svec et al., 2005). Exposure to infections was significantly associated with risk of B-NHL in our study (adjusted OR=2.7, 95%CI: 1.5-4.9) (Table 5.6). Furthermore, previously published analysis on the association between infection with HBV and risk of B-NHL among Palestinians supports the current finding (Kleinstern et al., 2016).

In this analysis, ever employment as a teacher or in the trade sector was not found to contribute to the risk of NHL. Moreover, the risk among hairdressers was elevated, and a negative association between B-NHL risk and ever employment in office-based occupations with borderline significance was found, and employment in health and social work services was significantly associated to decreased risk (Table 5.10). Previous studies have reported increased risk among teachers (Boffetta & de Vocht, 2007; Miligi et al., 1999; Zheng et al., 2002), especially teachers of primary levels ('t Mannetje et al., 2008). In addition, health and social workers (Band et al., 2004), salesmen and secretaries (Linet

et al., 1993), hairdressers and cosmetologists (Lamba et al., 2001; Svec et al., 2005) were found at increased risk.

Among healthcare workers it was hypothesized that the increased risk is associated to exposure to solvents, antineoplastic drugs, night shifts, ionizing and nonionizing radiation, sterilizing agents in addition to infectious agents ('t Mannetje et al., 2016; Ji & Hemminki, 2006; Mester et al., 2006). In our study a significant decrease among healthcare workers in the risk of B-NHL was found (Table 5.10) and exposure to medicine reduced the risk non-significantly to 0.2 (Table 5.6). Furthermore, occupational exposure to infected blood is one of the strongest risk factors of hepatitis infections (Alter, 2007). Possible association between HCV infection and NHL considering its association to lympho-proliferative diseases and the virus's role in B-cell regulation has been studied extensively (Gisbert et al., 2003; Matsuo et al., 2004). Prevalence of both HCV and HBV are higher in the developing countries and experiencing steady increase (Alter, 2007).

Hair dyes were proven by animal studies to contain possible mutagenic or carcinogenic aromatic amines (de Sanjose et al., 2006; Takkouche et al., 2005). Previous studies showed positive relationship between hair dyes and bladder cancer (Gago-Dominguez et al., 2001). As for NHL, results have been inconsistent, and have been reported to vary by type of product, period, duration, and intensity of use, in addition to variations of association with different NHL subtypes. Moreover, hairdressers are prone to exposure to infectious agents as a result of contact with the public, and exposure to hair permanent solutions, various solvents and ammonia all of which are hypothesized as etiologic factors of NHL ('t Mannetje et al., 2016; Karunanayake et al., 2008; Miligi et al., 1999). Exposure to hair dyes was found to increase B-NHL risk by 2.7 folds (Table 5.6) and hairdressers and beauticians had 500% increase in the risk of B-NHL according to our findings (Table 5.10). These findings are consistent with previously published findings on the association between personal use of black hair dyes and overall risk of B-NHL among Palestinians (Kleinstern et al., 2017). Furthermore, contrary to our findings, several previous studies did not find association for exposure with hair dyes (Dryver et al., 2004; Mao et al., 2000). Among Palestinian hairdressers a cross-sectional study found that in Hebron city hairdressers had adverse respiratory symptoms, and through checking the workplace conditions they reported that most salons lacked proper ventilation to reduce

exposure to hazardous materials, and that very few salons provided proper protective equipment (Nemer et al., 2013).

Exposure to cleaning agents wasn't associated with significant increase of B-NHL risk, neither was employment in cleaning and building services. On the contrary, among housewives, 60% increase in B-NHL risk was found for exposed housewives. Several epidemiological studies have reported increased risk among launderers and dry-cleaners that may come in contact with aliphatic chlorinated solvents and aromatic organic solvents with potentially carcinogenic effects such as trichloroethylene, tetrachloroethylene, chloroform, carbon tetrachloride, and methylene chloride ('t Mannetje et al., 2016; 't Mannetje et al., 2008; Lynge et al., 2006; Schenk et al., 2009; Zheng et al., 2002).

#### 6.1.3.3 Wood dust, organic solvents and risk of B-NHL

Exposure to wood dust and ever employment in wood industry were not found to be associated to NHL risk (Tables 5.6 and 5.10). On the contrary, an Australian study observed significant association between exposure to wood dust and NHL risk (Fritschi et al., 2005). Furthermore a pooled analysis of 10 international case-control studies and other previous studies did not support an evidence for association between employment in wood industry and NHL risk (Boffetta & de Vocht, 2007). Among wood workers, exposure to arsenic compounds was reported to be a predictor of NHL risk (Richardson et al., 2008). Arsenic insecticides are basically used to protect farm fencing materials in addition to use in vineyards and sheep-dips, and has been established as a human carcinogen (Pearce & McLean, 2005). Risk of NHL among wood workers has also been attributed to exposure to solvents including benzene and formaldehyde and to treatments used during processing or preservation such as fungicides, coal-tar derivatives, arsenic pesticides, wood proofing, and lacquers and varnishes ('t Mannetje et al., 2016; Band et al., 2004; Boffetta & de Vocht, 2007; Dryver et al., 2004; Mao et al., 2000). Furthermore, exposure to wood dust was also reported among workers in pulp and paper industries, lumber and sawmill industry, furniture industry, carpenters, fencing workers, forestry workers and some construction workers but with lower levels (Mao et al., 2000). Contamination of wood dust should be considered in assessment of association between wood dust and NHL risk.

Construction workers are prone to a wide range of exposures and exposure status might change between tasks and sites. Exposure to sunlight, paints, paint thinners and strippers,

dusts, asbestos are plausible agents in the association. In our analysis no association between employment in construction and NHL risk was found (Table 5.10). Results of previous studies were not consistent. Increased risk of NHL was reported previously among workers in construction and engineering ('t Mannetje et al., 2008; Richardson et al., 2008).

Several studies have reported causative relationship between NHL and exposure to organic solvents (Mao et al., 2000; Tatham, Tolbert, & Kjeldsberg, 1997). The suggested mechanism of action includes immunotoxicity (Vineis et al., 2007). Exposure to organic solvents in our study was not found to be associated with B-NHL risk. A French study that investigated the association between lymphoid neoplasms and occupational exposure to organic solvents in men observed a marginal association for exposure with NHL risk (OR=1.4, 95%CI: 1.0 to 2.0), but neither intensity nor frequency of exposure showed trends with risk (Orsi et al., 2010). Furthermore, a large population-based case-control study of 1,591 cases and 2,515 controls in San-Francisco Bay Area observed no association to support a role for solvent exposure as an etiologic factor for NHL (Bassig et al., 2012). Moreover, a review of epidemiologic literature reported supportive evidence for the association between NHL risk and exposure to organic solvents, the review included 45 studies and found significant associations in 55.5% of them (Rego, 1998). Among commonly used organic solvents we examined the association between exposure to paints and glues. We did not find an evidence for an association between paint exposure or ever employment as a painter, but exposure to glues was significantly associated with an OR of 3.3. Similarly, Increased risk among painters and decorators has been previously reported ('t Mannetje et al., 2008; Band et al., 2004; Dryver et al., 2004).

Furthermore, gasoline is a petroleum product used mainly as a fuel. Benzene is a component of gasoline and an established leukemogenic agent; IARC has classified it as group 1 carcinogen in 1982. In addition, in its recent updates, IARC considered reassessment of benzene's association with ALL, CLL, NHL and multiple myeloma (Lan et al., 2004; Smith et al., 2007; Vlaanderen et al., 2011). In this study gasoline exposure was more common among controls and a non-significant decrease in the risk of NHL was observed, but scientific evidence supports a relationship between exposure to benzene and the risk of lymphoma given its ability to cause chromosomal and genetic changes that are linked to lymphomagenesis in addition to damaging the bone marrow. Benzene is also used

commonly in shoe manufacturing, petroleum refining, rubber manufacturing as an industrial solvent (Smith et al., 2007). A systematic review of 43 case-controls studies of lymphomas and 26 cohort studies of petroleum refinery workers reported supportive evidence for a positive association between NHL and exposure to benzene; some elevation was observed in 93% of the case-control studies and 53% reported statistically significant associations. Furthermore, 88% of the cohorts reviewed reported higher morbidity and mortality rates of lymphoma among petroleum workers (Smith et al., 2007). Another review of 44 cohorts found a meta-relative risk (mRR) of 1 for association between NHL and benzene exposure (Vlaanderen et al., 2011). Moreover, a case control study in Southern Sweden reported an increased risk among workers who were exposed to gasoline (Dryver et al., 2004). Additionally, a previous cross-sectional study of 250 workers exposed to benzene and 140 controls to study the impact of exposure to low levels of benzene found significantly low white blood cell and platelet counts and two genetic variants were found to influence the susceptibility to benzene hematotoxicity providing an evidence for gene environment interaction (Lan et al., 2004).

Moreover, ever employment as a mechanic was not found to be associated with NHL. Previous studies among repair workers were inconsistent, some studies found increased risk among mechanists (Band et al., 2004; Karunanayake et al., 2008). In addition, car repair workers were found to have 50% increase in the risk of NHL in a cohort study in Europe (Neasham et al., 2011). Another case-control study in Southern Sweden reported increased risk among workers in automobile repair who were exposed to gasoline and aromatic hydrocarbons. In addition, exposure to heavy metals and exhaust fumes among mechanic was reported to increase the odds of the disease ('t Mannetje et al., 2016; Dryver et al., 2004; Neasham et al., 2011; Zheng et al., 2002).

Drivers are exposed to automobile emissions and fuels which are hypothesized to increase their risk of NHL ('t Mannetje et al., 2016; 't Mannetje et al., 2008; Cano & Pollan, 2001; Richardson et al., 2008; Smith et al., 2007). Yet, employment in transport industry was not associated with NHL risk in our study (Table 5.10).

Textile workers were found to be at increased risk of B-NHL in our study although the association wasn't statistically significant. Multiple specific occupations are classified in this industry including both garment makers and fabric makers. Textile workers might be

exposed to solvents, dyes, electromagnetic fields, formaldehyde and infectious agents as a result of exposure to public ('t Mannetje et al., 2016; Svec et al., 2005).

Furthermore, our findings pointed to an association between employment in protective services and the risk of NHL (Table 5.10). Upon examining the exposures entailed by workers it was found that exposures varied from person to another by the workplace, therefore we were not able to relate this association to a common exposure.

In this study we were able to identify several exposures that were associated with NHL risk including pesticides, infections and hair dyes. In addition, we identified several industries that were associated with NHL risk. Farming activities and employment in agriculture industry apparently entails high risk to NHL. Furthermore, ever employment as a hairdresser or in protection services was associated with higher NHL risk.

### 6.2 Conclusions

Farming practices and the uncontrolled use of pesticides are evidently a threat to the health of Palestinians. Furthermore, the lack of proper occupational health and safety programs and regulations put workers at the line of danger from suffering of both acute and chronic health problems; therefore, urgent calls must be made to prevent further harm.

### 6.3 Limitations

This study is the first to investigate occupational risk factors of B-NHL in Palestine. In addition, to our knowledge it is the first occupational study that covers the West Bank and the Palestinian labor force at various industries with different patterns of exposures. Furthermore, we used two approaches to investigate the association between occupation and B-NHL. First, we looked directly into specific occupational exposures for association with NHL, and then we indirectly looked for etiologic factors through looking into the association between industry and the risk of NHL.

Despite all the efforts provided to strengthen the design and outcomes of this study, there remain some limitations that may affect the outcomes and the generalizability of this study. Recall bias in retrospective case-control studies is a universal problem. Although it is unlikely that recall have significantly affected job history, differential and non-differential misclassification of exposure status might have affected the ability to detect true

associations since it is hard to recall past exposures and that subjects may have been unaware of being ever exposed. In addition, cases may recall their past exposures better than controls. In our design we tried to reduce the possibility of differential bias by using face-to-face interviews rather than self-administered questionnaires.

Moreover, relying on job titles in classification of occupations rather than using task description might have resulted in a non-differential misclassification between industrial classes and shifting the association towards the null. In addition, grouping of jobs into industrial groups masks the heterogeneity of exposure among workers in the same industry limiting the ability to draw significant associations.

Given the relatively small numbers in each group and the large number of comparisons made, caution should be taken in the interpretation of our findings since findings are susceptible to chance. Furthermore, we were unable to stratify the analysis by histologic subtype, which, as a result of their etiologic heterogeneity, some subtype specific associations might have skipped our attention.

### 6.4 Recommendations

**For Public Health Practitioners:** Occupational health and safety is a goal that can only be achieved through the practice of each and every individual. Occupational health and safety promotion programs for workers and employers should be organized. Furthermore, training programs for workers on safe practices and use of personal protective equipment should take place regularly and in a workplace specific manner. In addition, the misuse of pesticides is addressed as a major public health issue among Palestinian farmers; therefore, education programs are necessary to promote rational use of pesticides for the protection of workers in the agricultural industry, consumers and the environment.

**For Researchers:** Further investigations to confirm the current findings with larger numbers and more reliable exposure assessment approaches should be performed. These approaches should be based on real biological and environmental measurements of exposure levels. In addition, further research should examine the total exposure effect and the association with NHL risk.

**For Decision Makers:** Occupational health and safety should be a priority. Regulations should be developed and implemented and workplace specific safety trainings should be compulsory for employers to protect the workforce, which is the productive proportion of the community

**For the Ministry of Health:** The health information system should be further developed to facilitate research. Cancer registry is still underdeveloped and requires more attention. In addition, the most recent recommendations for cancer diagnosis require utilization of state-of-the-art immunostaining, which provide more accurate diagnosis, and as a result better treatment plans. Furthermore, occupational health is a neglected area in Palestine that needs to be prioritized. Specialized practitioners of occupational medicine should be recruited. In addition, occupational hygienists specialized in all industrial sectors should be trained.

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# Appendices

## Appendix 4.1

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## 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.BcellC.unspecified.**

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

**7. Site of biopsy:**

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

**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.Autologus 6.2. Allogenic

**12. LDH at diagnosis:_____**

## Appendix 4.2

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## English Study Questionnaire

# 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 ☐ | 2. Partial Primary (< 6th grade) ☐ | 3. Primary school completed ☐ |
| 4. Partial Secondary ☐ | 5. High school completed ☐ | 6. Diploma ☐ |
| 7. Bachelor degree ☐ | 8. Higher research degrees ☐ | |

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

**Q17)Did you receive technical training? (If no go to 20)**

1. Yes ☐ 2. No ☐

**Q18) How long did you train?_____**

**Q19) What was the profession that you trained for? _____**

**Q20) Where were you, your parents and grandparents born?**

| Relative | Country | City |
|---|---|---|
| Interviewee | | |
| Mother | | |
| Father | | |
| Grandfather (father side) | | |
| Grandmother (father side) | | |
| Grandfather (mother side) | | |
| Grandmother (mother side) | | |

## Part II: Job Information

**I would like to ask you about your previous jobs and about your current ones, what type of exposures did you have in that work? Please report if you switched positions within the same employer. Please report periods of unemployment, military services, maternity leave etc.),**

**Q21) Are you currently employed?**

1. Yes ☐ 2. No ☐

**Q22) Before your illness, did you have a regular job?**

1. Yes ☐ 2. No ☐

| Occupation | Start time | Finish time | Breaks | Place | Exposures |
|---|---|---|---|---|---|
| 1)What is your current occupation: | | | | | |
| 2) What were your former jobs<br>**a.** | | | | | |
| **b.** | | | | | |
| **c.** | | | | | |
| 3) Were you ever occupied in one of the following? | | | | | |
| 1. Agriculture & gardening | | | | | |

**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 (pharmaceticals) **20** flour dust **21** cleaning materials **22**. wood dust **23**.Other

| | | | | | |
|---|---|---|---|---|---|
| 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<br>a. doctors<br>b. nurses<br>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 (pharmaceticals) **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 settle-ment** | **House type** | **Which storey did you live on** | **Water source** | **# of persons residing in the house** | **# of rooms** | **Bath-room** | **From what year to what year?** |
|---|---|---|---|---|---|---|---|---|
| Current Residence | | | | | | | | |
| Previous<br>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 dying, 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?** ☐

**Q34) On average, how many times do you dye your hair?**

**1.** less than once/yr **2.** one-three times/yr **3.** four-six times/yr **4**. more than seven times/yr

**Q35) What color do you use in general?**

**1.** black **2.** brown **3**. blonde **4.** henna color **5**. others

**Q36) Is the dye that you use artificial?**

**1.** Yes ☐ **2.** No ☐

**Q37)Did you ever have a severe sun burn in childhood?**

**1.** Yes ☐ **2.** No ☐

**Q38) How many hours per week do (did) you expose to sunlight outdoor not as part of your work but including your leisure time and your travelling to and from the work?** ☐

**Q39) When you are out of door, is your head covered?**

**1.** always **2**. most of the times **3.** sometimes **4.** Never

**Q40) When you are out of door, do you wear long sleeves?**

**1.** always **2.** most of the times **3**. sometimes **4**. Never

**Q41) Do you use sun screen when you go out in the sun**

**1**. always **2**. most of the times **3.** sometimes **4.** Never

**Q42) Were you breast fed?**

**1.** Yes ☐ **2.** No ‘ ☐ **3**. Don’t know ☐

**Q43) Have you ever been vegetarian? (if no, go to Q45)**

**1.** Yes ☐ **2.** No ☐

**Q44) How many years have you been vegetarian?** ☐

**Q45) Do you eat meat regularly ?**

**1.** Yes ☐ **2.** No ☐

**Q46) How many times a week do you eat met?** ☐

**Q47) How many fruits per day do you eat on average?**

**1**:zero **2**:1-3 **3**: 4-7 **4**: more than 7

**Q48) How many vegetables do you eat per day on average?**

**1**:zero **2**:1-3 **3**: 4-7 4:more than 7

**Q49)What kind of oil do you mainly cook with?**

**1.** olive **2:** soya **3:** canola **4:**sunflower **5:**other _____

| Q50) How often do you usually eat or drink...? *Please tick one box for each line* | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 1) never | 2) <1 /wk | 3) 1 /wk | 4) 2-4X/ week | 5) 5-6X/ week | 6) 1 /day | 7) >1 /day | 8) Number of servings per day |
| **Fruits** | | | | | | | | |
| **Vegetables** | | | | | | | | |
| **Meat or chicken** | | | | | | | | |
| **Fish** | | | | | | | | |
| **Whole milk What about reduced fat milk** | | | | | | | | |
| **Other milk products (like yogurt, cheese, chocolate milk, pudding** | | | | | | | | |
| **drink water** | | | | | | | | **___glasses** |
| **Other non-alcoholic drinks (hot or cold)** | | | | | | | | **___glasses** |
| **Alcoholic drinks** | | | | | | | | **___glasses** |

## Part V: Hobbies

**We would like to ask you about your hobbies that you used to practice, like the physical activities, arts, and others.**

**Q51) During the last 10 years, have you practiced regular physical activity? (if not, go to Q55)**

1. Yes ☐ 2. No ☐

**Q52) What type of activity have you practiced?**

1. Strenuous (like Jogging) ☐
2. Moderate (like walking) ☐
3. Light (like gardening) ☐

**Q53) How often did you perform physical activity ?**

1. Three times a week or more ☐
2. Two times a week ☐
3. Once a week ☐
4. Less than this ☐

| # | 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) | | | | |

**Q54) Did you practice any of the following physical activities, and how often?**

**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 ☐ | | |
| 2. Shigella ☐ | | |
| 3. Campylobacter ☐ | | |
| 4. Yersinia ☐ | | |
| 5. Strongiloidosis ☐ | | |
| 6. Ameba ☐ | | |
| 7. Other parasitic infection ☐ | | |
| 8. E.coli ☐ | | |
| 9. I was told it was a viral infection ☐ | | |
| 10. They did not find the causative agent ☐ | | |
| 11. They didn't check ☐ | | |
| 12.Other ☐ | | |

**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.Rhreumatic 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. Mammorgraphy (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 | Uncle | aunts | Cousin/ nephew | 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

**GF(m):** grandfather on mother's side

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

**GF(f) :** grandfather on father's side

**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 | Uncl e | aunts | cousins/ nephew | Niece |
|---|---|---|---|---|---|---|---|---|
| 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

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## Arabic Study Questionnaire

# الورم الليمفاوي الغير هودجكن
# Non-Hodgkin Lymphoma

**الشخص الذي أجرى المقابلة: _____**

**كود الشخص الذي أجرى المقابلة : _____**

**هل تم؟ توقيع الموافقة عن علم للمشاركة ☐**

**إلصاق رقم الشخص المشارك على الاستبيان ☐**

**إلصاق رقم الشخص المشارك على أنابيب الدم ☐**

**إلصاق رقم الشخص المشارك على الاستبيان الباثولوجي ☐**

**سحب ثلاث أنابيب حمر و انبوبين بنفسجيين ☐**

**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 أخر ☐ _____**

## القسم الأول : المعلومات السكانية

**للمجموعة الضابطة فقط**:

هل أنت مرافق (لمريض لمفوما / لمريض أخر)? _____

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

**س6) 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 ؟**

| رقم الطفل | الجنس | تاريخ الميلاد | | |
|---|---|---|---|---|
| | | يوم | شهر | سنة |
| 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.** أخر ☐

**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 ؟**

| | | |
|---|---|---|
| 1.لم أذهب إلى المدرسة ☐ | 2. أساسي جزئي ( < الصف السادس) ☐ | 3.أكملت الدراسة الأساسية ☐ |
| 4.ثانوي جزئي ☐ | 5. أكملت الدراسة الثانوية ☐ | 6. دبلوم ☐ |
| 7. درجة البكالوريوس ☐ | 8. درجات عليا ☐ | 9. درجة أكاديمية جزئية ☐ |

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

**س17) هل تلقيت تدريبا تقنيا ؟ ( إذا كانت الإجابة " لا " ، اذهب إلى س 20 )**

1.نعم 2. لا

**س 18) كم كانت مدة التدريب ؟ _____**

**س 19) ما هي المهنة التي تدربت عليها؟ _____**

## آباؤك و أجدادك

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

| القريب | الدولة | المدينة |
|---|---|---|
| الشخص المقابل | | |
| الأم | | |
| الأب | | |
| الجد ( من جهة الأب ) | | |
| الجدة ( من جهة الأب ) | | |
| الجد ( من جهة الأم ) | | |
| الجدة ( 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 حاليا؟**

**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 نفط | | | | | |
| 9. فنيو المختبر | | | | | |
| 10.مقدم خدمات الرعاية الصحية<br>أ.الأطباء<br>ب.الممرضين<br>1.فنيو العلاج الطبيعي | | | | | |
| 11.فنيو الأشعة | | | | | |
| 12.طبيب بيطري | | | | | |
| 13.الملاحين والاطقم الجوية | | | | | |
| 14.الجزار ( اللحام ) | | | | | |
| 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 النفط ومشتقاته
6. الأشعة فوق البنفسجية
7. الإشعاع الكوني
8. الإشعاع الناتج عن التأيين
9. الموجات المغناطيسية الحيوية
10. الميكروبات / الكائنات الدقيقة
11. الحيوانات
12. المضادات الحيوية
13.الأطلية/الدهان
14.أصباغ الشعر
15. الأسبستوس
16 . جلد الحيوانات
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:**<br>الشارع:_____<br>المدينة (البلدة): _____ | | | | | | | | |
| **السابق:**<br>1. الشارع:_____<br>المدينة (البلدة): _____ | | | | | | | | |
| 2. الشارع:_____<br>المدينة (البلدة): _____ | | | | | | | | |
| 3. الشارع:_____<br>المدينة (البلدة): _____ | | | | | | | | |
| 4. الشارع:_____<br>المدينة (البلدة): _____ | | | | | | | | |
| 5. الشارع:_____<br>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

**س28 ) كم سنة دخنت ؟** ☐

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

| الفترة الزمنية | عدد السجائر |
|---|---|
| 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 " ، اذهب إلى 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 وذهابك 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) 1-3 3) 4-7 4) أكثر من 7

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

1) ولا مرة 2) 1-3 3) 4-7 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:**

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|
| | ولا مرة | < مرة / الأسبوع | مرة / الأسبوع | 2-4 أيام / الأسبوع | 5-6 أيام /الأسبوع | مرة واحدة / يوم | > مرة/ يوم | الكمية / اليوم |
| 1-فواكه | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | _____ |
| 2-خُضراوات | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | _____ |
| 3-لحوم أو دجاج | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | |
| 4-سمك | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | |
| 5-حليب كامل / قليل الدسم | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | |
| 6-منتجات الحليب (مثل اللبن أو الجبن أو الشكولاتة بالحليب) | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | |
| 7-شرب الماء | | | | | | | | ____أكواب |
| 8-مشروبات أخرى غير كحولية (ساخنة وباردة) | | | | | | | | ____أكواب |
| 9-مشروبات كحولية | | | | | | | | ____أكواب |

## 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 " ، اذهب إلى س 55 )**

1.نعم 2. لا

**س 52) ما هو نوع الجهد الذي مارسته؟**

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

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

1. ثلاث مرات في الأسبوع أو أكثر
2. مرتين في الأسبوع
3. مرة واحدة أسبوعيا
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 | ☐ | ☐ | ☐ | ☐ |
| 2 | ألعاب رياضية ( ألعاب قوى ) ، جمباز | ☐ | ☐ | ☐ | ☐ |
| 3 | تمارين لياقة بدنية، اشتراك في نادي لياقة بدنية ، جهاز ركض بيتي | ☐ | ☐ | ☐ | ☐ |
| 4 | المشي السريع والركض | ☐ | ☐ | ☐ | ☐ |
| 5 | الكاراتيه ، جودو ، تايكوندو | ☐ | ☐ | ☐ | ☐ |
| 6 | المصارعة | ☐ | ☐ | ☐ | ☐ |
| 7 | الملاكمة | ☐ | ☐ | ☐ | ☐ |
| 8 | رفع الأثقال | ☐ | ☐ | ☐ | ☐ |
| 9 | الرقص و الدبكة | ☐ | ☐ | ☐ | ☐ |
| 10 | الكشافة | ☐ | ☐ | ☐ | ☐ |
| 11 | السباحة | ☐ | ☐ | ☐ | ☐ |
| 12 | ركوب الدراجات الهوائية | ☐ | ☐ | ☐ | ☐ |
| 13 | تسلق الجبال | ☐ | ☐ | ☐ | ☐ |
| 14 | التزلج والتزحلق | ☐ | ☐ | ☐ | ☐ |
| 15 | المشي الطويل وصيد الأسماك | ☐ | ☐ | ☐ | ☐ |
| 16 | الأنشطة المائية (الإبحار ، ركوب الأمواج ، والتزحلق على الماء) | ☐ | ☐ | ☐ | ☐ |

**س 55) هل تعتني بالحديقة كهواية؟ ( إذا كانت الإجابة " لا " ، اذهب إلى 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 " ، اذهب إلى س64 )**

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. أبد

**س 65) هل تذكر اسم المبيد (المبيدات) الحشرية (التي استخدمتها في البستنة أو في منزلك) ؟ ( إذا كانت الإجابة " لا " ، إذهب 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 أشقاءك الأكبر منك سنا ؟** 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 حاليا)؟**
1. التلوين
2. النحت
3. الفخاريات والسيراميك
4. الزُجَاجِيّات
5. الطباعة والطباعة على الحجر
6. العمل الحديدي
7. فن تشكيلي
8. غيرها _____

**س 70) خلال ممارستك للأشغال اليدوية ، هل تعرضت ( تتعرض ) للمواد الكيماوية التالية:**
1.ألوان زيتية
2. أطلية سائلة ( أكريلية)
3.دهانات أخرى
4. مذيبات ( التربنتين ، 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 الكيميائية 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 أخر عدوى |
|---|---|---|
| 1. Salmonella (السالمونيلا) ☐ | | |
| 2. Shigella (شيغيلّا) ☐ | | |
| 3. Campylobacter (الكامبيلوبكتر) ☐ | | |
| 4. Yersinia (اليَرْسَنِيَّيا) ☐ | | |
| 5. Strongiloidosis (الأسْطونِيَّات) ☐ | | |
| 6.الأميبا ☐ | | |
| 7. عدوى طفيلية أخرى ☐ | | |
| 8. E.coli (اي كولاي) ☐ | | |
| 9.أعلمت بأن المسبب فايروس ☐ | | |
| 10 . لم يجدوا المسبب ☐ | | |
| 11. لم يتم الفحص ☐ | | |
| 12.أخرى ☐ | | |

**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. 21 – 40 سنة | | |
| 3. 11-20 سنة | | |
| 4. 1-10 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 الأتية ؟ إذا كان الجواب نعم، متى؟ (استخدم رمز زمن العدوى الموجود تحت الجدول لتحديد العمر)**

| المرض | نعم | لا | لا أذكر | العمر |
|---|---|---|---|---|
| 1.التهاب الكبد A | | | | |
| 2.التهاب الكبد B | | | | |
| 3.التهاب الكبد C | | | | |
| 4.Herpes (القوباء): الشفتين،الأنف ، الأذن ، أخرى | | | | |
| 5. Infectious Mononucleosis<br>Epstein Bar Virus (حمى ) | | | | |
| 6.Asthma (الربو) | | | | |
| 7.Eczema ( الأكزيما) | | | | |
| 8.Tonsillitis (إلتهاب اللوزتين) | | | | |
| 9.Measles ( الحصبة) | | | | |
| 10.Mumps (النكاف) | | | | |
| 11.Rubella (الحصبة الألمانية) | | | | |
| 12. حمى الرُّوماتزم Rheumatic fever | | | | |
| 13. التهاب المفاصل Rheumatoid arthritis | | | | |
| 14. السل | | | | |
| 15.Brucellosis (الحمى المالطية) | | | | |
| 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. 21 – 40 سنة 3. 11-20 سنة 4. 1-10 سنوات 5. أقل من سنة

**س 86) هل تلقيت التطعيمات ضد الأمراض التالية؟**

| المرض | نعم | لا | لا أذكر | العمر عند التطعيم الأول | العمر عند اخر تطعيم |
|---|---|---|---|---|---|
| 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. 21 – 40 سنة | |
| 3. 11-20 سنة | |
| 4. 1-10 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؟**

| أشعة X | عدد المرات | السنة |
|---|---|---|
| 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 طفلا بصحة جيدة فيما عدا تعرضي لأمراض الطفولة العادية
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 "، اذهب إلى س96 )**

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؟**

| الأدوية | أبدا | أحيانا | بشكل منتظم | |
|---|---|---|---|---|
| | | | سنة البدء | سنة الانتهاء |
| 1. الستيرويدات ( الكورتزون 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 المُضادة 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 تمييع 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 " ، اذهب إلى س100 )**

1.نعم 2. لا

**س 99) ما هو العلاج الذي تلقيته؟**

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

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

1.نعم 2. لا 3.لا أعرف

| نوع السرطان | الأشقاء | الأم | الأب | الطفل 1 | الطفل 2 | الطفل 3 |
|---|---|---|---|---|---|---|
| 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 أقربائك من الدرجة الثانية مصاب بالسرطان ؟ (إذا كانت الإجابة نعم ، فمن هو)**

1.نعم 2. لا 3.لا أعرف

| نوع السرطان | الجدة من جهة (الأم) | الجد من جهة (الأم) | الجدة من جهة (الأب) | الجد من جهة (الأب) | العم أو الخال | العمة أو الخالة | ابن/ة العم أوالخال | ابن/ة الأخ/ت/ الأخ/ت |
|---|---|---|---|---|---|---|---|---|
| 1.أي سرطان (نوعه) | | | | | | | | |
| 2.الأورام الليمفاوية الغير هودجكن Non Hodgkin Lymphoma | | | | | | | | |
| 3.الأورام الليمفاوية الهودجكن Hodgkin 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.إلتهاب المفاصل(الروماتزم) | | | | | | |
| 4. الأمراض المناعية الذاتية (Autoimmune Diseases) | | | | | | |
| 5. الأمراض المناعية الاخرى | | | | | | |

**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 | الجدة من جهة (الأم) | الجد من جهة (الأم) | الجدة من جهة (الأب) | الجدة من جهة (الأب) | العم أو الخال | العمة أو الخالة | ابن/ة العم أوالخال | ابن/ة الأخ/ت/ ت/ الأخ |
|---|---|---|---|---|---|---|---|---|
| 1.العدوى المتكررة | | | | | | | | |
| 2.الحساسية | | | | | | | | |
| 3.إلتهاب المفاصل(الروماتزم) | | | | | | | | |
| 4. الأمراض المناعية الذاتية (Autoimmune Diseases) | | | | | | | | |
| 5. الأمراض المناعية الاخرى | | | | | | | | |

**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

**س106) 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 حدا ما
3. غير معتمد إلى حد ما
4. غير معتمد

## Appendix 4.4

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## Informed Consent Form

## 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 شُخِصَ بهذا المرض) ، أوكمجموعة 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 الشعوربعدم الراحة نتيجة أخذ عينات الدم. ولا يوجد هناك أي آثار جانبية أخرى متوقعة من المشاركة في هذه الدراسة.

الإسم:_____

اوافق على اجراء المقابلة ( التوقيع ) _____

أوافق على إعطاء عينة الدم (التوقيع)_____

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

التاريخ : _____