Deanship of Graduate Studies
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Seroprevalence of Infections in B-Cell Non-Hodgkin Lymphoma among Palestinians: A Case-Control Study

Bashaar Jamal Ibraheem Dudeen

M.Sc. Thesis

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Prepared By:

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B. Sc. in Medical Laboratory Sciences – Al-Quds University / Palestine

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Thesis submitted in partial fulfillment of the requirement of the degree of Master of Medical Laboratory Sciences – Hematology Track / Faculty of Health Professions / Al-Quds University

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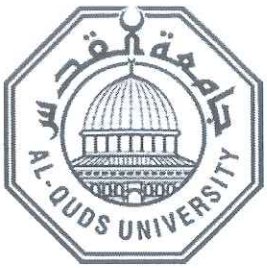

Thesis Approval

Seroprevalence of Infections in B-Cell Non-Hodgkin Lymphoma among Palestinians: A Case-Control Study

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Master thesis submitted and accepted 07/10/2017

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Jerusalem-Palestine

1439 / 2017

Dedication

To my almighty God, who gave me strength and knowledge through my life

To Dr. Rania, the friend, the great teacher and the exceptional human

To the memory of my father who inspired me to be strong despite all the obstacles

To my mother, Mrs. Rassmia Dudeen, for her understanding and overwhelming support

To my brother Jawad and sister Ahlam, for their eternal love

I dedicate this work…

Bashaar Jamal Ibraheem Dudeen

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 .....

Bashaar Jamal Ibraheem Dudeen

Date: 07.10.2017

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I wish to express my sincerest gratitude and appreciation to my supervisor, Dr. Rania Abu Seir, for her continuous support and mentorship throughout this project and for being more than just a teacher, but a friend, an inspirator, and much more.

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I take this opportunity to acknowledge the people who put their time and experience in this project.

Last but not least, I would like to thank my dearest family for their sacrifices and the person they brought me to be, which allowed me to follow my dream. My gratitude and appreciation are beyond any words.

Abstract

Background: The global increase in the burden of non-Hodgkin lymphoma (NHL) has been raising concern worldwide. The etiology of the disease is largely unknown; the factors that have been identified to date include age, gender, immunosuppression, infections and genetic factors. Furthermore, the geographic variability in subtype distribution strongly suggests a role for environmental exposures in NHL lymphomagenesis. Several infections have been linked to NHL. In this study, we aim to investigate the role of infections in NHL risk among Palestinians.

Methodology: In order to investigate the risk factors of B-NHL among Palestinians, we designed a case-control study. The study included 307 histologically confirmed B-NHL cases and 394 cancer-free controls. Cases were ascertained through three hospitals; Al-Watani in the north, Beit-Jala in the South, and Augusta Victoria in Jerusalem. In addition, Palestinians treated at the Israeli Hadassah University Hospital were also recruited. Controls were cancer-free Palestinians, ≥18 years old, recruited through the collaborating hospitals, Al-Makassed Blood Bank in Jerusalem, and thirteen 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. In addition, blood samples were collected form the study participants, then serum was separated and outsourced to the German Cancer Research Center in Heidelberg, Germany, to be screened for infections by multiplex serology assay.

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 seroprevalence of hepatitis C virus (HCV) and hepatitis B virus (HBV) among Palestinians were 1% and 29%, respectively. Additionally, Epstein-Barr virus (EBV) showed a seroprevalence of 96% and human cytomegalovirus (HCMV) was positive among 99% of the controls. Further, 77% of controls tested positive for history of *Helicobacter pylori* infection and 23% tested positive for *Chlamydia trachomatis*. Regarding the association between B-NHL and proxies for infections, the risk of NHL non-significantly decreased with increasing sibship size and birth order. On the other hand,

blood transfusion and exposure to animals both significantly increased the risk of NHL. Furthermore, comparison of levels of antibodies between cases and controls showed significantly lower IgG antibody levels among cases for two EBV antigens (EBNA and VCA), all HCMV three antigens (pp150, pp52 and pp28) and *H. pylori* six antigens (GroEL, UreA, CagA, VacA, HcpC and Omp), in addition to four *C. trachomatis* antigens (MOMP-D, Momp-max, PorB and Tarp-C). Furthermore, seropositivity to EBNA and VCA antigens of EBV were associated with decreased NHL risk, while EA-D showed non-significant increase in the risk of NHL. Moreover, presence of antibodies for all HCMV and *H. pylori* antigens and four *C. trachomatis* antigens (MOMP-D, Momp-max, PorB and Tarp-C) showed significantly decreased risk. Additionally, seropositivity to HCV was associated with non-significantly increased NHL risk (OR=5.00, 95%CI:0.54-46.11). Controversially, seropositivity to *H. pylori* was associated with significantly decreased NHL risk (OR=0.36, 95%CI:0.24-0.53). HBV, EBV and HCMV were non-significantly associated with decrease in NHL risk while *C. trachomatis* was not found to be associated with NHL (OR=0.91, 95%CI:0.55-1.50).

Conclusions: The findings of this work point to a relatively high prevalence of infections among Palestinians. In addition, HCV was highly associated with NHL risk. Further investigation to confirm these findings is required.

Keywords: Non-Hodgkin lymphoma, case–control study, seroprevalence, multiplex serology, antibody level, serostatus.

معدل الانتشار المصلي للعدوى بين مرضى سرطان الغدد الليمفاوية غير الهودجكن–ب في فلسطين: دراسة الحالات والضوابط

إعداد: بشار جمال ابراهيم دودين

إشراف: د. رانية أبو سير

ملخص:

خلفية الدراسة: يعد سرطان الغدد اللمفاوية غير الهودجكن من الأمراض السرطانية التي أثارت قلق العلماء في العالم بسبب الازدياد في معدلات الحدوث. لم تتضح حتى الآن أسباب المرض، ولكنّ الدراسات أكدت على الدور الذي يلعبه كل من الجنس والعمر ونقص المناعة والأمراض المعدية والعوامل الجينية في الإصابة بالمرض. إضافةً إلى ذلك، فإن التباين في التوزيع الجغرافي للأنواع المختلفة من هذا السرطان تشير إلى مساهمة العوامل البيئية في حدوث المرض. من خلال الأبحاث تم التعرف على عدد من الكائنات المعدية التي قد تلعب دوراً في الإصابة بهذا المرض. تهدف هذه الدراسة إلى البحث في العلاقة بين الإصابة بعدد من الكائنات المعدية وخطر الإصابة بسرطان الغدد الليمفاوية غير الهودجكن من النوع ب.

منهجية البحث: تم استخدام دراسة الحالات والضوابط بين الفلسطينيين لمعرفة العوامل التي تؤثر على خطر الإصابة بسرطان الغدد الليمفاوية غير الهودجكن من النوع ب. وقد تم استقطاب 307 حالات مؤكدة التشخيص بالمرض و394 شخصاً سليماً كعينة ضابطة من الفلسطينيين للمشاركة في الدراسة. وقد تم استقطاب الحالات من ثلاثة مستشفيات رئيسية في الضفة الغربية ، المستشفى الوطني في نابلس، ومستشفى بيت جالا في بيت جالا ومستشفى المطلع في القدس، بالإضافة إلى الفلسطينيين

الذين يتلقون العلاج في مستشفى هداسا الإسرائيلي. 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 في القدس 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 صمم سابقاً من قبل الاتحاد الدولي لوبائيات الأورام اللمفاوية ويتناول عدداً من العوامل المسببة للمرض. وقد قام الباحثون بسحب عينة من الدم من المشاركين في الدراسة وتم فصل المصل منها وإرسالها إلى مركز أبحاث السرطان الألماني في هايدلبرغ، ألمانيا لفحصها بتقنية multiplex serology لوجود أجسام مضادة للكائنات المعدية التي تم تحديدها في الدراسة.

النتائج: حسب النتائج التي ظهرت في الدراسة فقد كان العمر الوسيط للإصابة بالمرض 52 عاماً ونسبة الذكور للإناث بين الحالات 1:1. وقد كانت أهم الأنواع الفرعية الموجودة بين المرضى سرطان الخلايا البائية الكبيرة المنتشرة وسرطان الغدد الليمفاوية الجرابية. أما فيما يتعلق بمعدل الانتشار المصلي بين الفلسطينيين فقد تبيّن أن 1% من المجموعة الضابطة لديهم تاريخ إصابة بفيروس الكبد الوبائي C و 29% لديهم تاريخ إصابة بفيروس الكبد الوبائي B . إضافةً إلى ذلك، فإن نتائج فحص الأمصال أتت إيجابية لعدوى فيروس ايبشتاين–بار فيروس (EBV) لدى 96% وعدوى فيروس مضخم الخلايا (HCMV) كانت إيجابية لدى 99% من العينة الضابطة. أما عن معدل انتشار البكتيريا من نوعي *H. pylori* و *C. trachomatis* فقد كانت على التوالي 77% و23%. وبالانتقال للعلاقة بين مؤشرات التعرض للأمراض المعدية وخطر الإصابة بسرطان الغدد الليمفاوية فقد وجدنا في هذه الدراسة أن خطر الإصابة بسرطان الغدد الليمفاوية انخفض بازدياد عدد الإخوة وترتيب الولادة، بينما ارتبط التعرض للحيوانات ونقل الدم بزيادة في خطر الإصابة بالمرض. وبمقارنة

مستوى الأجسام المضادة في عينات المرضى فقد وُجِد أن الوسيط لمستوى الأجسام المضادة كان أكثر انخفاضاً بين مجموعة المرضى لاثنين من مولدات المضاد التي تم فحصها لفيروس EBV وكل مولدات المضاد الخاصة بفيروس HCMV وبكتيريا *H. pylori* وأربع من مولدات المضاد الخاصة بعدوى *C. trachomatis*. وقد كان هذا الانخفاض ذو دلالة إحصائية. إضافة إلى ذلك، فإن العلاقة بين وجود أجسام مضادة لمولدات المضاد من هذه الأنواع وخطر الإصابة بسرطان الغدد الليمفاوية قد أظهرت انخفاضاً في الخطورة ذو دلالة إحصائية. وأخيراً، في هذه الدراسة وجدنا ازدياداً في مستوى خطر الإصابة بالمرض مرتبطاً بالإصابة بفيروس الكبد الوبائي C ولكن العلاقة لم تكن ذات دلالة إحصائية، أما من تبين لديهم تاريخ للإصابة ببكتيريا *H. pylori* فقد ظهر لديهم انخفاض في مستوى خطورة الإصابة بالمرض وقد كانت العلاقة ذات دلالة إحصائية. أما عن تاريخ الإصابة ببقية الكائنات المعدية فقد أظهرت أغلبها انخفاضاً في مستوى الخطورة لكن أي من العلاقات لم تكن ذات دلالة إحصائية.

الاستنتاج والتوصيات: تظهر نتائج هذه الدراسة ارتفاعاً في معدل انتشار الكائنات الدقيقة بين الفلسطينيين. كما أن العلاقة بين الإصابة بفيروس التهاب الكبد الوبائي C قد أظهرت ارتباطاً قوياً بخطر الإصابة بسرطان الغدد الليمفاوية، إلا أن هذه النتائج بحاجة لمزيد من البحث.

الكلمات الدالة: سرطان الغدد الليمفاوية غير الهودجكن، دراسة الحالات والضوابط، معدل الانتشار المصلي، فحص الأمصال المتعدد، مستوى الأجسام المضادة، الحالة المصلية.

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List of abbreviations

Abbreviation	Term
1aNS3	Non-structural protein 3, serotype 1a
AIDS	Acquired immune deficiency syndrome
Ag	Antigen
ASR	Age standardized rate
AVH	Augusta Victoria Hospital
BCR	B-cell receptor
B-NHL	B-cell non-Hodgkin lymphoma
CagA	Cag pathogenicity island protein A
CLL	Chronic lymphocytic leukemia
CI	Confidence interval
C. trachomatis	*Chlamydia trachomatis*
DLBCL	Diffuse large B-cell lymphoma
EA-D	Early antigen-diffuse
EB	Elementary bodies
EBNA	Epstein-Barr nuclear antigen
EBV	Epstein-Barr virus
FDA	Food and Drug Administration
GroEL	Chaperonin GroEL
GST	Glutathione-S-transferase
GWAS	Gene-wide association study
HBc	HBV core antigen
HBe	HBV envelope antigen
HBV	Hepatitis B virus
HBs	HBV surface antigen
HCV	Hepatitis C virus
HCMV	Human cytomegalovirus
HcpC	Helicobacter cysterine-rich protein C
HIV	Human immunodeficiency virus
H. pylori	*Helicobacter pylori*
HTLV-1	Human T-cell leukemia/lymphoma virus

IARC	International Agency for Research on Cancer
IWF	International working formulation
Omp	Outer membrane protein
MALT	Mucosa associated lymphoid tissue
MFI	Median fluorescence intensity
MOH	Ministry of Health
MOMP-A	Major outer membrane, serovar A
MOMP-D	Major outer membrane, serovar D
MZL	Marginal zone lymphoma
NHL	Non- Hodgkin lymphoma
OR	Odds ratio
PorB	Porin B
RB	Reticulate bodies
REAL	Revised European-American classification
SLL	Small lymphocytic lymphoma
SNP	Single nucleotide polymorphism
Tarp-C	Translocated actin recruiting phosphoprotein, C-terminal
Tarp-N	Translocated actin recruiting phosphoprotein, N terminal/ CT456
T-NHL	T-cell non-Hodgkin lymphoma
UreA	Urease alpha subunit
VacA	Vacuolating cytotoxin A
VCA	Viral capsid antigen
WHO	World Health Organization
Zebra	Z-encoded broadly reactive activator

Chapter One

Introduction

The primary goal of this study is investigating the association between infections and non-Hodgkin lymphoma (NHL). This chapter demonstrates the background of this study, the primary research problem. In addition, justification of the study, aims and objectives and the hypotheses are listed here.

1.1 Background

Non-Hodgkin lymphoma is one of the most common malignancies worldwide and the 8th among Palestinians with an incidence rate of 3.5 per 10^5 population (Ekstrom-Smedby, 2006; MOH, 2016). Figure 1.1 shows the incidence rates of the ten most commonly diagnosed types of malignancies in the West Bank during 2015. The increase in NHL incidence and the unknown etiological aspects of the disease require intensive studying. It was estimated that 16% of cancer burden is attributed to infections worldwide and the burden of infection-associated cancer is three-times higher in developing countries (ACS, 2015). Furthermore, infectious diseases still constitute a large problem in developing nations (WHO, 2017).

Increasing evidence is supporting an association between lymphoma and infectious agents. This hypothesis is further supported by the regression of lymphoid malignancies after receiving antimicrobial treatments (e.g. antibiotics in treating *Helicobacter pylori*) (Lehours *et al.*, 2004). This association is investigated in the current study focusing on

six infections that possess oncogenic properties or chronically simulate the immune system.

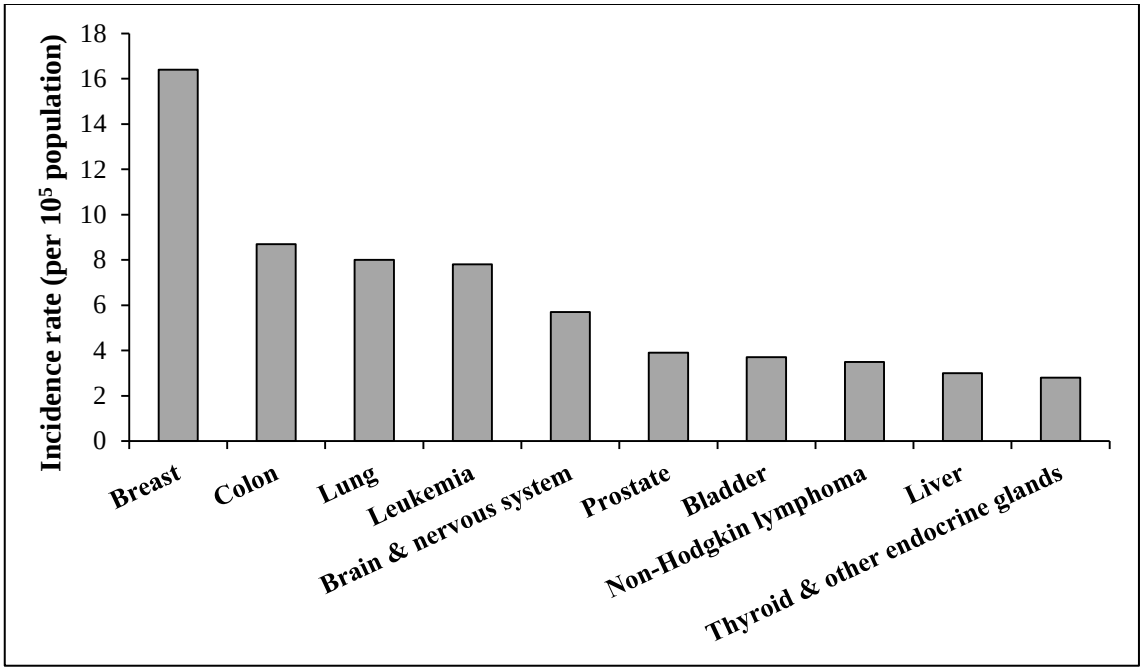

Figure 1.1: Incidence rates of the ten most common types of cancer, 2015, Palestine, West Bank. (Source: (MOH, 2016)).

1.2 Problem Statement

Cancer is the second leading cause of death among Palestinians and a major cause of morbidity. The incidence of NHL has been increasing since 2010 (MOH, 2016). The etiological factors of NHL are yet to be identified and are yet to be studied in Palestine. Exposure to infections has been hypothesized to play a role in lymphomagenesis. This study aims to assess the relationship between history of exposure to infectious agents and the risk of NHL.

1.3 Study Justification

NHL is the 8th most common cancer in Palestine (MOH, 2016). The incidence of NHL have been increasing during the last few years, figure 1.1 shows NHL incidence rates in the West Bank since the establishment of the cancer registry. Although the registry of cancer is still incomplete, an increase of NHL rates can be seen.

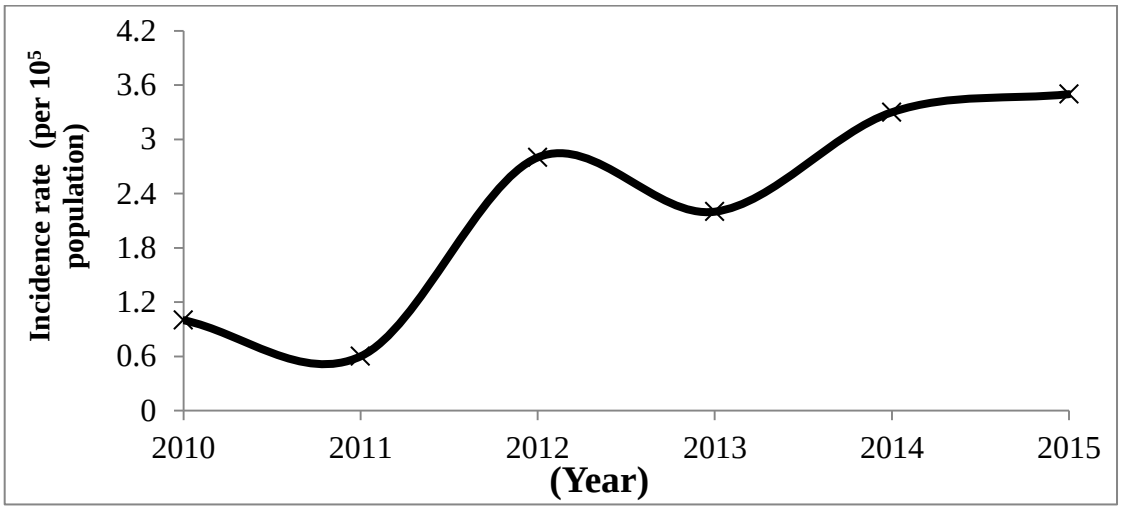

Figure 1.2: NHL incidence rates. (2010-2015). Palestine, West Bank. (Source: Health annual reports (2010-2015)).

Regardless of the huge efforts in identifying NHL's etiological factors, little is known to date. Furthermore, characteristics and risk factors of the disease among Palestinians have not been studied before. Several infectious agents have been found to alter the function of the immune system, resulting in malignant transformations of the immune cells. In this study, we aim to investigate the association between NHL and the history of exposure to six infectious agents.

1.4 Study Hypothesis

In this study, we hypothesized that history of exposure to six infectious agents is associated with increased risk of B-NHL. These infections were: HCV, HBV, EBV, HCMV, *H. pylori* and *C. trachomatis*.

1.5 Study Goal

This study aimed to investigate the possible association between six infectious agents (HCV, HBV, EBV, HCMV, *H. pylori* and *C. trachomatis*) and non-Hodgkin lymphoma of B-cell origin.

1.6 Study Objectives

- To describe the disease demographics and characteristics of B-NHL among Palestinians.
- To estimate the seroprevalence of (HCV, HBV, EBV, HCMV, *H. pylori* and *C. trachomatis*) among the Palestinian population.
- To assess the relationship between proxies for infections and B-NHL risk.
- To assess the relationship between seropositivity to selected antigens and B-NHL risk.
- To assess the relationship between seroprevalence of (HCV, HBV, EBV, HCMV, *H. pylori* and *C. trachomatis*) and B-NHL risk.

1.7 Summary of Thesis Chapters

The first chapter of this study describes the research problem we investigated and the necessity of it. In chapter two a review of the available literature on this topic is provided and in chapter three study framework and variables of the study are described. Further, chapters four and five demonstrate the methodology and the findings of the study. The results started by describing the disease and demographic characteristics and then moved to the association between infections and NHL which is the focus of this study. Finally, the major findings of the study are discussed along with the conclusions and limitations in chapter six and the chapter ends by establishing the recommendations based on our findings.

Chapter Two

Literature Review

This chapter provides an overview of on the epidemiology and etiology of NHL. The main focus of this overview is the association between infections and NHL.

2.1 Epidemiology of Non-Hodgkin Lymphoma

Lymphomas are hematological malignancies arising from lymphoid cells at different developmental stages. There are two types of lymphoma, Hodgkin and non-Hodgkin. Hodgkin lymphoma is characterized by the presence of Reed-Sternberg cells and constitutes 10-15% of lymphomas. Non-Hodgkin lymphoma is a group of heterogeneous malignancies characterized by clonal expansion of malignant immune cells. The heterogeneity of NHLs is caused by the stage of differentiation of malignant cells, cellular origin, clinical behavior, morphologic appearance, and immunologic and molecular phenotypes (CancerResearchUK, 2016; Kusec, 2002; Lenz & Staudt, 2010).

Non-Hodgkin lymphoma is the eighth most common type of cancer among males worldwide and the tenth among females with age standardized rates (ASRs) of 6 and 4.1 per 10^5 population, respectively (Globocan, 2012). Further, NHL is the ninth common cause of cancer mortality with 386,000 new case and 200,000 deaths during 2012 (Globocan, 2012). The incidence of NHL has been rising since 1950s with a rate of 2-4% each year. During the early 1990s, NHL rates stabilized for few years and since the late 90s have been substantially increasing. Since then, the rate of increase in NHL rates is 1-2% (Ekstrom-Smedby, 2006).

NHL is more commonly diagnosed among males; in fact, cancer is overall more common among males. Furthermore, the risk of developing NHL triples after the age of 65 (Rodriguez-Abreu *et al.*, 2007). In addition, there is geographic variation in NHL distribution with developed countries showing higher rates than developing ones. The highest rates of NHL were reported in USA, Australia, New Zealand and Europe, while the lowest rates were in East and South West of Asia (Ekstrom-Smedby, 2006). In Palestine, NHL is the eighth most commonly diagnosed malignancy with an incidence rate of 3.5 per 10^5 population. During 2015, ninety new cases were diagnosed with NHL in the West Bank and thirteen died as a result of it, 15.6% of the newly diagnosed cases were children (MOH, 2016). Unfortunately, the cancer registry in Palestine is still incomplete and there are no statistics regarding the prevalence of the disease in Palestine, but the WHO estimates for the incidence are double this number (Globocan, 2012).

Classification of NHL evolved over the years. The most recent classification was developed by the World Health Organization. Prior to that, two classification systems have been used in diagnosing NHL and for research. The first was the International Working Formulation (IWF), which utilized morphology and clinical behavior in grouping lymphomas. The second was the Revised European-American (REAL) classification. This system classified lymphomas on the basis of immune-phenotypic and genetic characteristics. The currently used WHO classification groups lymphomas on the basis of morphology, immunology, genetics and clinical behavior. Further, the classification recognizes the variability in etiological factors between subtypes and considers each as a distinct entity in the courses of treatment and research. NHL is therefore classified into 36 subtypes, 21 of which are of B-cell origin (Ekstrom-Smedby, 2006; FDA, 2015; Jaffe, 2009; Patel & Hernandez-Ilizaliturri, 2015; Vardiman, 2010).

Among NHL subtypes, diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma are the two most common. DLBCL is an aggressive lymphoma while follicular lymphoma is indolent. Indolent lymphomas can develop to aggressive types with disease development. Moreover, the distribution of NHL subtypes varies geographically; for example, T-cell lymphomas are very rare in developed countries, but in eastern and south central regions of Asia, they constitute 10% of NHL cases. In

addition, indolent lymphomas are more common in developed countries; follicular lymphoma represents about 20-25% of NHLs in USA while it constitute only ~15 in developing countries. On the other hand, and though DLBCL is the most common of subtypes worldwide, the proportion of DLBCL among NHL cases is much higher in developing countries (Ekstrom-Smedby, 2006; Naresh *et al.*, 2004). Moreover, mucosa-associated lymphoid tissue (MALT) lymphoma is a subtype that accounts for 7-8% of NHL cases. It is an extra-nodal lymphoma and is characterized by marginal zone reactive B-cell follicles infiltrated by heterogeneous small B-cells (Luminari *et al.*, 2010). Additionally, Burkitt lymphoma is another aggressive NHL subtype that constitutes 1-5% of cases (Chihara *et al.*, 2015). Other subtypes of NHL include marginal zone lymphoma, mantle cell lymphoma, and chronic lymphocytic lymphoma.

2.2 Etiology of NHL

The process of pathogenesis in NHL is complex and still not well understood. Cancer development in general is a multistep process that requires accumulation of genetic aberrations, and in the case of NHL, these results in clonal expansion of malignant cells forming tumors of leukemic nature. Pathways in which tumorigenic transformations of lymphoma occurs include both direct and indirect mechanisms. Factors that can activate or suppress immune system can lead to lymphoma, such as immunodeficiency, chronic stimulation and autoimmunity. Furthermore, both B and T-cells are intrinsically prone to genetic instability and neoplastic transformations. The process of lymphocyte development is complex. Checkpoints and regulatory mechanisms ensure that immune cells effectively protect the host against pathogens, while at the same time keeping the number of lymphocytes, cell growth and cell death under control. Activation of B-lymphocytes requires successfully recognizing and binding antigens by the variable region of B-cell receptors (BCR). The resulting signal transduction is key to the survival of B-cells and initiation of adaptive immune responses. Moreover, cells that don't bind to antigens strongly enough undergo apoptosis (Dias *et al.*, 2012; Glass *et al.*, 2016; Kusec, 2002; Schuetz *et al.*, 2013; Suarez *et al.*, 2006).

The etiological factors of NHL are largely unknown. Several hypotheses emerged, but there was much inconsistency throughout the studies. This is mainly attributed to the variability in study design and inclusion criteria for the subjects and the limited number

of participants. Furthermore, the variability among NHL subtypes in regard to their etiology and the inability to study each subtype separately with descent numbers shifts the association towards the null. The largest NHL study to date is the InterLymph project undertook by the International Lymphoma Epidemiology Consortium to investigate etiological factors of NHL in a subtype-specific manner. Data for the study were pooled from 20 case-control studies and included 17,471 NHL cases and 23,096 controls from North America, Europe, and Australia (Morton *et al.*, 2014a).

2.2.1 Immunodysregulation

The immune system is responsible to fighting against diseases including cancer; therefore, it is reasonable to deduce that immune dysfunction is of great etiologic importance in lymphomagenesis (Morton *et al.*, 2014b). Malignancies are the second most common cause of death among immunosuppressed individuals. Furthermore, increased risk of several types of cancer among immunocompromised individuals, particularly cancers with known or suspected infectious etiology, was suggested in several studies (Clifford *et al.*, 2009; Engels *et al.*, 2010b; Vajdic *et al.*, 2009; van Leeuwen *et al.*, 2009). Immunosuppression, whether congenital or acquired is an established risk factor of NHL. Moreover, NHL is considered a defining illness of AIDS accounting for 23-30% of AIDS-related mortality (Biggar, 2001; Nolen *et al.*, 2014). In fact, the increase in NHL incidence in the 1970s-1980s has been partially linked to the AIDS epidemic with 100-150% increase in the risk of NHL among AIDS patients (Aboulafia, 1998). Further, AIDS related cancers were related to immunosuppression rather than HIV infection (Hooper *et al.*, 2001). Additionally, 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 EBV infection in the immunologically disordered individuals (Aboulafia, 1998; Grulich *et al.*, 2007).

Further, autoimmune diseases are a result of loss of tolerance to self-antigens and are sometimes treated with immunosuppressive drugs. In addition, these conditions results in chronic immune stimulation and share genetic and environmental factors with NHL (Fallah *et al.*, 2014; Mellemkjaer *et al.*, 2008). Increase in the risk of NHL among individuals with autoimmune diseases have been reported in epidemiological studies

(Ekstrom Smedby *et al.*, 2008; Fallah *et al.*, 2014; Grulich *et al.*, 2007; Mellemkjaer *et al.*, 2008; Morton *et al.*, 2014b).

2.2.2 Lifestyle factors

The geographic variability in the distribution of NHL strongly suggests a role for both environmental and lifestyle factors. Both dietary intake and obesity represent an antigenic challenge to the immune system. Furthermore, smoking and exposure to dietary carcinogens can alter responses of the immune system and therefore contribute to the risk of NHL (Ali *et al.*, 2013; Skibola, 2007).

Several studies reported non-significant associations between tobacco smoking and risk of NHL (Bracci & Holly, 2005; Fernberg *et al.*, 2006; Herrinton & Friedman, 1998; Lu *et al.*, 2011; Morton *et al.*, 2014b; Schollkopf *et al.*, 2005; Wong *et al.*, 2010), while few reported significantly increased risk (ORs range from 1.3 to 2.4) (Besson *et al.*, 2003; Diver *et al.*, 2012; Talamini *et al.*, 2005). Furthermore, moderate consumption of alcohol has been considered beneficial, especially those containing antioxidants which are considered protectors against immune cell damage (Diaz *et al.*, 2002). Lower NHL risk was found among drinkers compared to non-drinkers in a pooled analysis of 9 studies on alcohol consumption and risk of NHL (OR=0·83, 95% CI: 0·76–0·89) (Morton *et al.*, 2005).

In regard to dietary intake, the association with NHL has been inconsistent throughout research. Both protein and fat intake are hypothesized to increase NHL risk while intake of fruits and vegetables are expected to lower the risk (Blinder *et al.*, 2008). Furthermore, obesity is linked to chronic, low-grade inflammation and influences pro-inflammatory responses through releasing leptin (obesity associated hormone), which hypothetically can increase NHL risk (Bassig *et al.*, 2012; Fernberg *et al.*, 2006). Significantly increased risk among people with high BMI was previously reported (Pan *et al.*, 2005; Troy *et al.*, 2010), controversially, other studies did not report any association (Fernberg *et al.*, 2006; Wong *et al.*, 2010).

2.2.3 Genetic risk factors

Translocations and mutations occurring during the development of lymphocytes can disrupt homeostasis leading to proliferation, blocked differentiation and

immortalization. In addition, initially non-lethal genomic lesions may lead to NHL progression through environmental, epigenetic, or genetic factors (Skibola *et al.*, 2007). Furthermore, functioning of adaptive and innate immune responses is a process that involves more than 1,600 genes (Simon *et al.*, 2015). Genetic susceptibility is an established risk factor of NHL. Two-folds increased risk of NHL has been found among individuals who have first-degree relatives with NHL (Wang & Nieters, 2010), though, shared environmental exposures might explain these familial clusters (Ekstrom-Smedby, 2006). Current studies have been focusing on identifying shared gene variants that are related to lymphoma and determining susceptibility to environmentally induced NHL (Kelada *et al.*, 2003).

Candidate gene studies identified several genetic variations in different genes and pathways that are associated with lymphoma predisposition, including, DNA integrity and methylation, B cell survival (proinflammatory and regulatory cytokine genes), innate immunity, as well as oxidative stress, energy regulation, hormone production, vitamin C, matrix metalloproteinase, MAP kinase, lymphocyte traffic and migration and xenobiotic metabolism (Cerhan *et al.*, 2009; Lan *et al.*, 2007; Morton *et al.*, 2009; Skibola *et al.*, 2008a; Skibola *et al.*, 2007; Skibola *et al.*, 2008b).

The immune response pathway has naturally been the focus of much research in relation to NHL causation. Considerable evidence pointed to the role of polymorphisms in *TNF* and *IL-10*- especially in aggressive forms of NHL (Cunningham *et al.*, 2003; Liang *et al.*, 2009; Skibola *et al.*, 2007). Furthermore, associations between variants in NF-κB, IL1 and other related transcription factors with NHL have been reported (Cerhan *et al.*, 2008b; Wang *et al.*, 2009). A number of genetic variations in *TLR1, TLR2, TLR4, TLR6* and *TLR10* genes were reported to be associated with NHL in general or to certain NHL subtypes (Pothlichet & Quintana-Murci, 2013). In addition, a genetic variant in the *CD14* gene was implicated in the development of gastric MALT lymphoma (Ture-Ozdemir *et al.*, 2008).

Several studies of gene-environment interactions involving NHL risk have been conducted. These studies suggested that polymorphisms in different pathways might modify NHL risk. Further, several genetic variations have been reported to contribute in susceptibility to multiple infectious diseases. Two polymorphisms in two key anti-

inflammatory cytokines, IL-10 and TGF-beta, were associated with decreased susceptibility to EBV-associated post-transplant lymphoproliferative disorder (Babel *et al.*, 2007). Furthermore, genetic variations in *TNF* and *IL10R* genes were suggested to modify the association between blood transfusion and NHL risk (Bi *et al.*, 2012). Toll-like receptor-4, as part of the innate immune response, is the main receptor for lipopolysaccharide on marginal zone-B cells. It was found that the rare allele of *TLR4* Asp299Gly attenuates receptor signaling and diminishes the inflammatory response. This rare allele appears to modify the genetic susceptibility to gastric lymphoma in *H. pylori* infected patients (Hellmig, 2009).

2.2.4 Environmental risk factors

Exposure to environmental agents was proposed to account for the unexplained increase in NHL morbidity and mortality, and the variation in the patterns of the disease. Snice then, several agents have been found to be associated with NHL through environmental and occupational studies, although there is much inconsistency through the literature (Zheng *et al.*, 2002). Many infectious agents and chemicals have been found to increase the risk of NHL. In the next parts, more details and examples of important environmental etiological factors of NHL are discussed.

2.2.4.1 Exposure to chemical agents

Chemicals might possess carcinogenic, immunotoxic and mutagenic properties that lead to malignant transformations. Studying NHL etiology, many chemical exposures have been found to be associated with the development of the disease. Growing evidence from occupational and non-occupational studies supports the association between exposure to pesticides (Dreiher & Kordysh, 2006; Jones *et al.*, 2014), polychlorinated biphenyls (Kramer *et al.*, 2012) organic solvents (Orsi *et al.*, 2010; Vineis *et al.*, 2007) and hair dyes (Zahm *et al.*, 1992) and NHL risk. Several other chemicals were also hypothesized to be associated with the risk of lymphoma but findings were contradicting. The biggest challenges in these studies are estimating previous exposures and the limited number of exposed individuals (Wang & Nieters, 2010).

2.2.4.2 Exposure to physical agents

Exposure to radiation is linked to cancer. Furthermore, increased exposure to sunlight results in DNA damage, which triggers immunosuppression, linking exposure to

sunlight with lymphoma (Blinder *et al.*, 2008). The available evidence did not support this hypothesis, but rather, a 25-40% reduction in the risk of NHL have been reported (Armstrong & Kricker, 2007; Bassig *et al.*, 2012; Hakansson *et al.*, 2001).

2.2.4.3 Exposure to infectious agents

Several infections have been known to cause cancer. Furthermore, 16% of incident cancer cases are attributed to infections worldwide. The attributable fraction of infection-related cancer ranges between 3-7% in developed countries and the proportion is three times higher in the developing countries (ACS, 2015).

Infections are established risk factors of NHL (Engels, 2007). Several infectious agents have been associated with NHL and others are yet to be investigated. There are three proposed mechanisms in which infections can cause lymphoma. First, HIV indirectly causes lymphoma through suppressing the immune system, resulting in activation of oncogenic viral infections or the inability of the immune system to detect malignant transformations. Second, oncogenic viruses such as EBV and HTLV-1 directly transform lymphocytes by changing their genetic material. Finally, some infections activate the immune system chronically, leading ultimately to monoclonal expansion of lymphocytes (Engels, 2007).

2.2.4.3.1 Proxies for infections

Immune functioning in adulthood is influenced by childhood social environment and exposure to foreign challenges. Increasing birth order, sibship size, crowding, attendance at day cares, contact with pets and large animals and antibiotic use have been frequently regarded as proxies for infections. These variables provide a useful framework to examine how childhood infectious exposures may be associated with risk of immunologic diseases in adulthood and with B-NHL (Cozen *et al.*, 2007; Romagnani, 2004). Number of siblings could be used as an indicator of age at exposure to common childhood infections, since siblings (especially older siblings) often acquire infections at school and introduce them to the family at home. Family size and birth order were reported to be positively associated with NHL risk (Cozen *et al.*, 2007).

Day care attendance exposes children to infections at an earlier age of life. Higher risk for otitis media (Collet *et al.*, 1994; Louhiala *et al.*, 1995; Marx *et al.*, 1995), recurrent

nasal catarrh, doctor-diagnosed sinusitis, and doctor-diagnosed lower respiratory tract infections have been found to be associated with attending day care, diarrhea, hepatitis A, respiratory tract infections and hemophilic influenza were encountered among day care attendants (Celedon *et al.*, 1999; Mink & Yeh, 2009; Osterholm, 1994; Wald *et al.*, 1988). Therefore, given the wide range of infectious exposures associated with attending day care it is pertinent to explore its relation to NHL risk (Gutensohn & Cole, 1981).

Furthermore, some evidence has indicated that contact with animals may contribute to NHL risk by being a potential route for the transmission of infectious agents including viruses, bacteria or parasites (Boffetta & de Vocht, 2007; Fritschi *et al.*, 2002; Nanni *et al.*, 1996). In addition, blood transfusion has been indicated as a risk factor for NHL, possibly because it can expose the recipients to viruses or other immunomodulating antigens, but the results from epidemiologic studies have been inconsistent (Bi *et al.*, 2012; Cerhan *et al.*, 2001). Viruses transmitted by infected donors' blood particularly hepatitis C may be responsible for the risk associated with transfusions (Alexander *et al.*, 2007; Gitnick, 1998).

Moreover, season of birth was reported to be positively associated to NHL risk (Crump *et al.*, 2014). Additionally, high antibiotics use was indicated in several studies to be associated with an increased risk of NHL. A large Danish cohort reported a modest increase in the risk of different NHL subtypes (Rasmussen *et al.*, 2012). Frequent antibiotic use could be a marker for underlying infections, chronic colonization of certain types of bacteria or relatively impaired immune functions (Bernstein & Ross, 1992; Gonzales *et al.*, 2001). Further, antibiotics themselves may be carcinogenic (Kato *et al.*, 2003).

2.2.4.3.2 Hepatitis C virus

Hepatitis C virus (HCV) is a bloodborne infection that constitutes a major global public health problem. The virus is a small, enveloped with positive- single-stranded RNA (~9600 nucleotide). The virus belongs to the Flaviridae family classified into a unique genus called Hepacivirus. The virus lacks reverse transcriptase and has a single open reading frame that codes a large protein. This protein is cleaved by host cell's proteases to ten proteins that are either structural (Core, E1, E2, and p7) or non-structural proteins

(NS2, NS3, NS4A, NS4B, NS5A, and NS5B). HCV RNA polymerase lacks the capability of proof-reading; therefore it generates genetic variability within the same host "quasi-species" and from host to host. This diversity enables the virus to interact with its host. There are six genotypes of the virus differing from each other by up to 30% of nucleotide sequence with several subtypes for each. The genotype of the virus does not affect the outcome of the infection but controls response to therapy. The most variable regions of HCV's genetic sequence are the E1 and E2 regions, while the 5'UTR and the terminal 3'UTR segment are highly conserved (Gupta *et al.*, 2014; Thomson & Finch, 2005; Viswanatha & Dogan, 2007). Non-structural protein 3 (NS3) is one of the non-structural HCV proteins encoded by the virus's genetic material. NS3 has a dual function, as a protease and as a helicase. The protease is responsible for processing of the non-structural region of the polyprotein, while the activity of the helicase is not yet known. NS3 has been studied as a target for antiviral therapy (Raney *et al.*, 2010).

HCV is endemic in many parts of the world with considerable temporal and geographical variations in the incidence and prevalence. Infection's prevalence was estimated to be 130-170 million people worldwide with geographic variability ranging from <1-2% in developed countries to 5-10% in other countries such as Japan, Italy and Egypt (Alexander *et al.*, 2007; de Sanjose *et al.*, 2008; Gisbert *et al.*, 2003; Hajarizadeh *et al.*, 2013; Thomson & Finch, 2005).

Liver is the main target of HCV. It causes both acute and chronic infections. It is known to cause non-A, non-B viral hepatitis, liver cirrhosis and other hepatic and extra-hepatic disease manifestations. Infected people can remain asymptomatic, and up to 30% of infected people develop cirrhosis, which can lead to liver failure and hepatocellular carcinoma. In addition, HCV has been linked to more than 30 extra-hepatic manifestations including mixed cryoglobulinaemia, porphyria cutanea tarda, membranoproliferative glomerulonephritis, Sjögren's syndrome, thyroiditis, a high prevalence of autoantibodies, and central and peripheral nervous system demyelinating disorders (Fiorino *et al.*, 2015; Thomson & Finch, 2005; Viswanatha & Dogan, 2007).

A clear role of HCV in most illnesses hasn't been established yet, but it is hypothesized that host's immune response to the virus causes the disease manifestations and not the

virus itself. Furthermore, HCV infects cells other than liver cells; sequences of HCV have been detected in peripheral blood cells, kidney, skin, oral mucosa, salivary glands and pancreatic tissues, therefore, recent evidence suggests a role for the virus in the development of several malignancies such as biliary duct carcinoma, bladder cancer, renal cancer, pancreatic cancer, thyroid cancer, breast cancer and prostate-cancer and non-Hodgkin lymphoma (Fiorino *et al.*, 2015).

The persistence of the viral RNA in the mononuclear cells stimulates B-lymphocytes and lead to clonal expansion, suggesting a role for the virus in lymphomagenesis. Epidemiologic evidence has been inconsistent and the mechanism of malignant transformations caused by HCV is unknown. Furthermore, the interaction between E2, which is HCV envelope protein with CD81 receptor in B-lymphocytes with specific anti-HCV surface immunoglobulins lowers the threshold for activation and proliferation of B-lymphocytes. This leads to polyclonal expansion of B-cells that might progress to autonomous proliferation, immune dysregulation and B-cell lymphoma (Mele *et al.*, 2003; Viswanatha & Dogan, 2007). Another hypothesis regarding the mechanism of which HCV causes malignant transformation is the direct role played by HCV in induction of point mutations in immunoglobulin and non-immunoglobulin genes (Viswanatha & Dogan, 2007).

2.2.4.3.3 Hepatitis B virus

Hepatitis B virus (HBV), like HCV, is a major public health problem globally. Unlike HCV, HBV is a small DNA virus of the Hepadnaviridae family. The infectious HBV virion (known as Dane particle) is a double shelled sphere with a diameter of 42 nm and consists of lipids. This sphere surrounds an inner nucleocapsid, which is a complex of virally encoded polymerase, hepatitis core antigen and the viral genomic material. The genome of HBV is a partially double stranded circular DNA and encodes four overlapping ORFs (Marcucci *et al.*, 2012).

HBV is classified into eight genotypes (A to H). It infects hepatocytes and other cells such as spleen, gonads, thyroid gland, pancreas, kidney and adrenal glands. In addition, HBV infects hematopoietic cells and their progenitors and mononuclear cells (Marcucci *et al.*, 2012). Furthermore, HBV is a causal agent for both acute and chronic hepatitis infection; the chronic liver infection can later develop into cirrhosis of the liver or liver

cancer. According to the WHO, more than 686,000 people die every year due to complications of hepatitis B, including cirrhosis and liver cancer, and around 240 million people are chronically infected with hepatitis B virus worldwide (WHO, 2016).

HBV is transmitted through contact with the blood and other body fluids of an infected person. Healthcare workers have a higher risk of acquiring the infection than the general population. Furthermore, the highest prevalence of HBV infection exists in Sub-Saharan Africa and East Asia, where 5–10% of the adult population is chronically infected; this is followed by the Middle East and the Indian subcontinent (2–5%). On the other hand, less than 1% of the population of Western Europe and North America is chronically infected (WHO, 2016).

Age at infection occurrence influences the likelihood of developing a lifelong infection; in children, infection during the first year of life results in 80–90% chance of developing chronic infection, while infection before the age of 6 years has only 30–50% chance. On the other hand, among adults, less than 5% will develop chronic infection and only 20–30% of adults who are chronically infected develop cirrhosis and/or liver cancer (WHO, 2016). HBV prevention is better achieved through vaccination. HBV vaccine has effectivity in preventing chronic HBV of 90-95%. Further, this vaccine is the first cancer prevention vaccine with effectivity of ~70% in preventing hepatocellular carcinoma (Chang & Chen, 2015).

The mechanism of HBV carcinogenesis is unclear, but it is hypothesized that the insertion of viral DNA into hepatocytes' DNA results in the activation of host oncogenes, but the importance of the effect of this insertion in oncogenes' activation and viral protein expression in carcinogenesis is yet to be investigated (Seeger & Mason, 2015).

Laboratory diagnosis of hepatitis B infection focuses on the detection of the hepatitis B surface antigen HBsAg. Acute HBV infection is characterized by the presence of HBsAg and IgM antibodies to the core antigen (HBcAg), while chronic infection is characterized by the persistence of HBsAg for at least 6 months (with or without concurrent HBeAg) (WHO, 2016).

Although the possibility of association between NHL and HBV emerged before HCV (Heimann *et al.*, 1977), HBV have not been investigated as extensively and the association is rather weak. The first case-control that investigated this association came out only in 2002 (Kim *et al.*, 2002). The mechanism of action and the role of HBV in lymphomagenesis are still unknown but hypothesis suggests mechanism similar to those of HCV including chronic antigenic stimulation and direct oncogenic effects.

2.2.4.3.4 Epstein–Barr virus

Epstein–Barr virus (EBV) is a lifelong viral infection caused by human ubiquitous, double stranded DNA, γ-herpesvirus with two distinct types that infects almost 90% of the world population as children and targets B lymphocytes (Alexander *et al.*, 2007; De Roos *et al.*, 2013; Jenson, 2011; Kaneda *et al.*, 2012). The range of illness caused by EBV infection may range from asymptomatic infection, to the acute-self-limited infectious mononucleosis, to other more advanced illnesses in immunocompromised individuals such as lymphoproliferations and malignancies of B-cell and epithelial lineages (Jenson, 2011). Typically, the virus enters a latent phase after the primary infection and remains persistent systemically as an episome in memory B-cells and locally in oropharyngeal epithelial cells. During latency, expression of viral genes stops to avoid detection by the immune system. Factors such as stress, chronic stimulation of B-lymphocytes and some hormonal changes can lead to reactivation of the infection (De Roos *et al.*, 2013; de Sanjose *et al.*, 2007; Heslop, 2005; Jenson, 2011).

EBV was the first identified tumor virus (Heslop, 2005; Thompson & Kurzrock, 2004). Many of the viral products were found to play roles in promoting infection, immortalization and transformation. These products include EBNA-1, EBNA-2, EBNA-3A,B & C, EBNA-LP, LMP1, LMP2A and B, EBER1 and 2, and CSTs. This infection has been linked to a wide range of cancers including nasopharyngeal carcinoma, Burkitt lymphoma, Hodgkin lymphoma, gastric cancers, peripheral natural killer/T-cell lymphoma and smooth muscle tumors (Kaneda *et al.*, 2012; Thompson & Kurzrock, 2004). The mechanism of carcinogenesis in EBV infection in immunocompromised individuals is well established; immunosuppression facilitates reactivation of persistent EBV infection. On the other hand, the process of lymphomagenesis in other EBV associated lymphomas is not as clear (Heslop, 2005; Jenson, 2011; Teras *et al.*, 2015). The suggested mechanisms include DNA methylation, regulation of gene expression

and signal pathways in host cells by viral proteins, targeting host genes by small viral RNAs, altering expression of host cells' miRNAs, and epigenetic alterations such as chromatin conformation and histone modification (Kaneda *et al.*, 2012). Moreover, most EBV associated NHLs are aggressive. They are of rapid growth and necrosis nature (Heslop, 2005). Several studies have reported increased risk among individuals with history of infectious mononucleosis (Becker *et al.*, 2009).

Besides the role of EBV in the development of NHL, the status of EBV infection has been found to have a prognostic value for the clinical course of lymphoma. The overall survival of lymphoma patients was found to be worse in patients who tested positive for EBV-encoded small nuclear RNAs and LMP-1 staining. Patients have poor response to chemotherapy and higher relapse rate. Yet, the presence of the viral genome in tumor cells raises other approaches towards other treatment options that target the virus (Heslop, 2005; Wang BJ, 2016).

2.1.2.4.3.5 Human cytomegalovirus

Human cytomegalovirus (HCMV) is a double stranded DNA virus of the Cytomegalovirus genus of viruses, which in turn is a member of the Herpesviridae viral family. HCMV is also known as human herpesvirus-5 (HHV-5) (Ryan, 2010). The viral capsid is surrounded by protein-rich tegument enveloped in a membrane. The viral DNA encodes 230-250 proteins (Tselis, 2013).

HCMV primary infection is usually asymptomatic and the infection occurs through epithelial cells. The virus starts replicating in the host cells infecting fibroblasts, epithelial cells, endothelial cells, and smooth muscle cells and sheds through body fluids. This phase is called the viremic phase and the body develops immune response towards the viral infection involving adaptive responses. As a consequence to the infection some people develops infectious mononucleosis syndrome during this phase. The virus enters a lifelong latency state after several weeks. During latency the virus load is either absent or low and the viral DNA is maintained as episomes in myeloid precursor cells $CD14^+$ monocytes to $CD34^+$ pluripotent stem cells. The virus can be reactivated to lytic infection through cellular differentiation, inflammation or immunosuppression. Reactivation of the virus occurs periodically but it is usually suppressed by the development of T-cell immunity. Furthermore, reinfection with new

strain of the virus is possible (Griffiths *et al.*, 2015; Manicklal *et al.*, 2013; Tselis, 2013).

HCMV can affect all parts of the nervous system. Furthermore, HCMV is a leading cause of congenital infections; it is the commonest cause of non-genetic hearing loss and it can cause neurodevelopmental delay. In addition, HCMV causes both morbidity and mortality in immunocompromised individuals such as transplant patients and AIDS patients. The seroprevalence of HCMV rises with age and it is associated with socioeconomic status. Both prevalence and infection rate are much higher in developing countries and poor-resourced communities, where the infection is acquired usually very early in life. In developed countries, the infection rate is 60-70% among adults, but it is estimated to be 100% in developing countries (Bai *et al.*, 2016; Ibrahim *et al.*, 2016b; Tselis, 2013).

The possible association between cancer and HCMV infection has been investigated for decades and seroepidemiologic evidence supports such an association. Today, HCMV is not regarded to be an oncogenic virus, but it may favor tumor progression and the term "oncomodulation" was introduced to better explain the role of HCMV in cancer. Oncomodulation means that the virus infects tumor cells and increases their malignant properties without directly transforming them, which may result from the activity of virus regulatory proteins and noncoding RNA, which influence properties of tumor cells including cell proliferation, survival, invasion, production of angiogenic factors, immunogenicity and chromosome stability (Mehravaran *et al.*, 2017; Michaelis *et al.*, 2009). In addition, HCMV may enhance oncogenic activity through chronic inflammation. HCMV DNA and antigens were detected in several cancer types including breast, prostate, brain, colon and salivary glands (Herbein & Kumar, 2014). Furthermore, chronic inflammation is one of the proposed mechanisms of lymphomagenesis. The association between HCMV and lymphoma is inconsistent and few studies examined this association (Kadry *et al.*, 2016; Mehravaran *et al.*, 2017).

2.2.4.3.6 *Helicobacter pylori*

Helicobacter pylori (H. pylori), is a gram-negative, spiral, microaerophilic bacterium found usually in the stomach and a member of superfamily VI of gram-negative bacilli, now called Epsilonproteobacteria. It has been identified in 1982 by Australian scientists

Barry Marshall and Robin Warren, who isolated it from a person with chronic gastritis and gastric ulcers, conditions not previously believed to have a microbial cause. Further, *H. pylori* was also linked to the development of duodenal ulcers and stomach cancer. However, over 80% of individuals infected with the bacterium are asymptomatic and only1-2% of infected individuals develops cancer. Interestingly, it is hypothesized that the bacterium may play an important role in the natural stomach ecology (Blaser, 2006; Ferreri *et al.*, 2009).

Actual infection rates vary from nation to nation; the developing world has much higher infection rates than the West (Western Europe, North America, Australasia), where rates are estimated to be around 25% (Pounder & Ng, 1995). *H. pylori* is highly heterogeneous; strains are divided on the basis of geographical associations into seven population types: hpEurope, hpEastAsia, hpAfrica1, hpAfrica2, hpAsia2, hpNEAfrica and hpSahul (Shiota & Yamaoka, 2014). Host-related factors such as the age at which this bacterium is acquired, host's genetics and inflammatory responses, and environmental factors seem to influence the possible pathologic outcome of the infection (Brown, 2000; Yamaoka, 2010). Infections are usually acquired in early childhood in all countries (Kusters *et al.*, 2006), however, the infection rate of children in developing countries is higher than in industrialized countries probably due to poor sanitary conditions, perhaps combined with lower antibiotics usage for unrelated pathologies. In developed nations, it is currently uncommon to find infected children, but the percentage of infected people increases with age with about 50% infected for those over the age of 60 compared to around 10% between 18 and 30 years, the higher prevalence among the elderly reflects higher infection rates in the past when the individuals were children rather than more recent infection at a later age of the individual (Kusters *et al.*, 2006). In the United States, prevalence appears to be higher in African-American and Hispanic populations, most likely due to socioeconomic factors (Everhart *et al.*, 2000; Smoak *et al.*, 1994). The lower rate of infection in the West is largely attributed to higher hygiene standards and widespread use of antibiotics. Despite high rates of infection in certain areas of the world, the overall frequency of *H. pylori* infection is declining (Everhart *et al.*, 2000), yet, antibiotic resistance is appearing in *H. pylori*; many metronidazole- and clarithromycin-resistant strains are found in most parts of the world (Megraud, 2004).

H. pylori is currently classified as type I carcinogen by the International Agency of Research against Cancer (IARC). Two related mechanisms by which *H. pylori* could promote cancer are under investigation. One mechanism involves the enhanced production of free radicals near *H. pylori* and an increased rate of host cell mutation. The other proposed mechanism has been called a "perigenetic pathway" (Tsuji *et al.*, 2003), and involves enhancement of the transformed host cell phenotype by means of alterations in cell proteins, such as adhesion proteins. *H. pylori* has been proposed to induce inflammation and locally high levels of TNF-α and/or interleukin 6 (IL-6). According to the proposed perigenetic mechanism, inflammation-associated signaling molecules, such as TNF-α, can alter gastric epithelial cell adhesion and lead to the dispersion and migration of mutated epithelial cells without the need for additional mutations in tumor suppressor genes, such as genes that code for cell adhesion proteins (Suganuma *et al.*, 2008).

Little is known about the role of virulence properties of the bacterial strain in influencing infection outcome. Among the reported virulent factors of *H. pylori* are cytotoxin-associated antigen-A (CagA), CagE, IceA, BabA, HopQ, vacuolating cytotoxin (VacA), the chaperonin GroEL (GroEL), urease subunit A (UreA), γ-glutamyl transpeptidase (gGT), *Helicobacter* cysteine-rich protein (HcpC), outer inflammatory protein (OipA), and outer membrane protein (Omp) (Ferreri *et al.*, 2009; Shiota & Yamaoka, 2014; Yamaoka, 2010). CagA is *H. pylori*'s best studied virulent factor. It is carried by 70% of the strains with geographic variation in the distribution. CagA has been associated with severe outcomes including peptic and duodenal ulcers and gastric adenocarcinoma (Ferreri *et al.*, 2009; Shiota & Yamaoka, 2014). Furthermore, in a study conducted in Germany CagA, VacA and HcpC and GroEL were reported to be associated significantly with chronic atrophic gastritis (Gao *et al.*, 2009b). In addition, CagA and GroEL were significantly associated with gastric cancer (Gao *et al.*, 2009a). Moreover, VacA is another extensively studied virulent factor that induces several cellular activities such as membrane-channel formation, cytochrome *c* release from mitochondria leading to apoptosis, and binding to cell-membrane receptors followed by initiation of a proinflammatory response. Further, outer membrane proteins that might function as adhesive protein might trigger proinflammatory response (Yamaoka, 2010).

H. pylori is the first identified bacterium to be linked to malignancies. It has been linked to gastric carcinoma and MALT lymphoma. Among some individuals with chronic gastritis or untreated gastritis, the resulting antigenic stimulation induces lymphoid follicles in the gastric mucosa and provides the background for MALT lymphoma development. Further, causality between this infection and MALT lymphoma is demonstrated through studies using treatments for *H. pylori* eradication in treating MALT patients in about 80% of the cases. CagA have been linked to MALT lymphoma among other outcomes of the infection, but evidence is still contradictive (Lehours *et al.*, 2004).

2.2.4.3.7 *Chlamydia trachomatis*

Chlamydia trachomatis (C. trachomatis), is a species of the genus Chlamydiae; a gram negative, non-motile, ovoid in shape, non-spore forming, obligate intracellular parasitic bacteria. The life cycle of *Chlamydia* has two stages; an extracellular infectious stage called elementary bodies (EB) and intracellular non-infectious stage called reticulate bodies (RB). Moreover, the infection may persist in infected humans for years (Becker, 1996; Darougar *et al.*, 1972).

C. trachomatis strains are divided into three biovars and each biovar contains multiple serovars. About 12 different serotypes of *C. trachomatis* have been identified and different antigenic components have been recognized. Infection with *C. trachomatis* causes ocular and genital infections. Ocular infections cause trachoma and inclusion conjunctivitis, severe repeated infections might lead to blindness. Genital infections lead to non-gonococcal urethritis in men and acute salpingitis and cervicitis in women. In addition, lymphogranuloma venereum can be caused by certain strains of the bacterium. (Becker, 1996; Darougar *et al.*, 1972). Serovars A-C cause non-congenital blindness, while serovars D-K are the most prevalent in STIs (Elwell *et al.*, 2016). More than 500 million people have trachoma in Africa and Asia and sporadic cases occur all over the world. Furthermore, genital tract infections of *Chlamydia* are among the most common sexually transmitted infections worldwide (Becker, 1996).

The link between cancer and *Chlamydia* was made plausible based on its ability to cause persistent infections, and as a result, chronic antigenic stimulation, which have been linked to development of cancer and lymphomas. *C. trachomatis* is a strong

immunogen that activates innate and adaptive immune responses. Moreover, genetic damage and neoplastic changes can be induced as a result of inflammation, in addition to the fact that *C. trachomatis* can inhibit host cell apoptosis. Therefore, it was suggested that this infection may play a role in cervical carcinogenesis and rectal carcinoma (Anttila *et al.*, 1998; Becker, 1996; Chanudet *et al.*, 2007; Malhotra *et al.*, 2013; Paavonen, 2001; Wotherspoon *et al.*, 1991). Further, different Chlamydial species have been linked with various lymphomas of MALT type (Chanudet *et al.*, 2007; Stefanovic & Lossos, 2009)

2.2.4.3.8 Other infectious agents

Several other infectious agents have also been studied as NHL etiological factors. These include viral infections such as human herpes virus-8 (HHV8), which causes Kaposi sarcoma and HIV-associated primary effusion lymphoma (Gantt & Casper, 2011). In addition, human T-cell lymphotropic virus- type I (HTLV-I) is an established cause of adult T-cell leukemia/lymphoma. Moreover, exposure to zoonotic oncogenic viruses has also been under investigation for its association with NHL risk since abattoir workers, meat cutters and veterinarians have been found to be at increased risk of NHL (Briggs *et al.*, 2003; Svec *et al.*, 2005; Tatham *et al.*, 1997).

Other protozoan and bacterial infections have been suggested to be involved in the etiology of NHL, including *Borrelia afzelii*, *Campylobacter jejuni*, *Chlamydia pssitaci* and *Coxiella burnetii* (the infectious agent associated with Q fever) (Engels, 2007; Flowers & Skibola, 2016). Additionally, among African children malaria (*Plasmodium falciparum*) has been found to play a role in the etiology of Burkitt lymphoma (Vineis *et al.*, 2000).

Chapter Three

Study Framework

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

3.1 Conceptual Framework

Both viral and bacterial infections have been linked to the development of NHL. They are hypothesized to directly or indirectly alter the function of the immune system through immunosuppression, chronic antigenic stimulation and oncogenic alterations in B-lymphocytes, leading to malignant transformations (Engels, 2007).

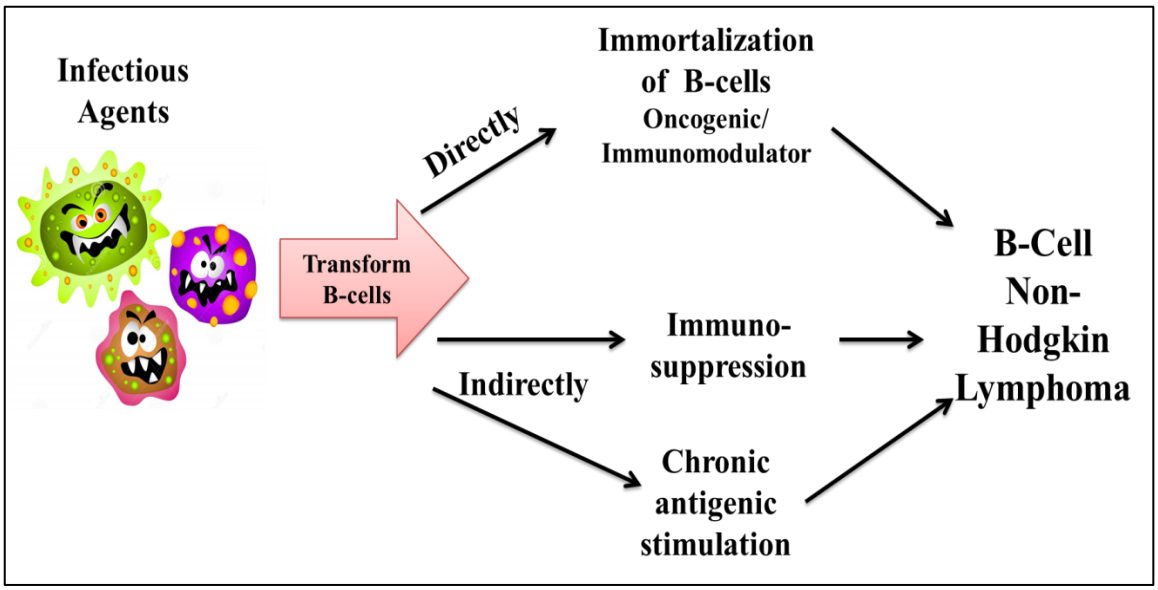

Figure 3.1: Postulated mechanisms of infectious risk factors in NHL lymphomagenesis.

3.2 Study Variables

In this study, the outcome variable was B-NHL. In addition, independent variables included the demographic characteristics, disease characteristics and infectious risk factors. The demographic variables included gender, age, region, educational level, marital status and recruitment center. Moreover, the disease characteristic variables consisted of age at diagnosis, histological subtype, disease stage and spread and presence of B-symptoms. Furthermore, for the infections antibody levels were reported as continuous median florescence intensity (MFI), from these MFIs categorical scores were created for each of the detected antibodies and serostatus for each infection was determined based on the number of antibodies above the cut-off point.

Chapter Four

Methodology

A large case-control project was established in the West Bank and Jerusalem to investigate the risk factors of non-Hodgkin lymphoma. During the study period, 307 B-NHL cases and 394 cancer-free controls were recruited. The project aimed to explore environmental, lifestyle, medical and genetic risk factors of NHL. A questionnaire was used to collect epidemiological data and blood samples were withdrawn from study subjects for serological and genetic analysis. In this part, the focus is on investigating the infectious risk factors of NHL through serological testing. This chapter provides more details regarding this part of the study.

4.1 Study Design and Power

This sero-epidemiological study is a frequency-matched case-control study conducted among Palestinians during the period between 2009 and 2014. Subjects were recruited throughout the West Bank. Eligible cases were confirmed incident B-NHL cases that were at least 18 years old by the time of the study. On the other hand, the control group included cancer-free adult Palestinians that frequency matched the cases by age, gender and region. 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.

4.2 Study Setting

Cases were recruited through three major Palestinian hospitals that provide cancer care in the West Bank and Jerusalem; Al-Watani Hospital in the North, Augusta-Victoria Hospital (AVH) in the middle and Beit-Jala Hospital in the South. Cases were introduced to the study either by their treating physicians or trained field workers. If the subject showed interest, the field worker obtained a written consent, withdrew a blood sample and conducted the interview. Furthermore, Palestinians from all over the West Bank referred to receive cancer treatment in Hadassah Hospital in Israel were recruited in the study.

Moreover, control subjects were recruited through the participating hospitals in addition to Al-Makassed Blood Bank in Jerusalem and thirteen primary health care centers supervised by the Palestinian Ministry of Health.

4.3 Study Population

This study included 307 incident B-NHL cases and 394 cancer-free controls. Eligible cases were:

- Adults (≥18 years old).
- Incident cases (diagnosis ≤18 months).
- Pathologically confirmed B-NHL.
- Consented to participate in the study.

Further, individuals who did not meet the inclusion criteria were excluded from the study. Exclusions consisted of cases that did not have pathological conformation for B-NHL or were diagnosed more than 18 months prior to recruitment.

On the other hand, controls were frequency-matched to cases by gender, age (± 5 years) and region. The eligibility criteria for inclusion of controls were:

- Adults (≥18 years old).
- Cancer-free as determined by the subject.
- Consent upon participation.

Individuals were excluded from the study if they had cancer or if they were related by blood to any of the study participants. In addition, those who did not consent upon participation were also excluded from the study.

4.4 Study Tools

For the purposes of the study, data were collected utilizing a face-to-face interview-based questionnaire and a pathology questionnaire. Participants who consented to participate in the study were administered the questionnaire and the physicians were asked to fill out the pathology report. In addition, two blood samples from each participant were obtained for serological and genetic analysis. Details regarding samples and analysis of the genetic part of the study are not related to this part, therefore, they will not be discussed here. Moreover, this section describes the tools of the epidemiological part of the study.

4.4.1 Questionnaire

The questionnaire used for the epidemiological study (appendix 4.1) was adapted from a questionnaire originally developed and validated by the InterLymph (Besson *et al.*, 2006). The questionnaire was translated for local use (appendix 4.2) to collect data regarding several risk factors of NHL. In addition, the Arabic questionnaire was validated by forward and backward translation and a pilot study was conducted to test its suitability. Amendments were done correspondingly. The questionnaire consists of six parts including demographic characteristics, occupational history, residential history, lifestyle, medical history and family history. After confirming eligibility and obtaining written consent, the questionnaire was administered face-to-face by trained field workers during a 20-30 minutes interview. The field workers were trained on the interview prior to the start of the process of data collection by the study supervisors.

4.4.2 Pathology questionnaire

In order to describe the clinical characteristics of B-NHL among Palestinians, the treating physicians of the patients were asked to fill a pathology questionnaire (appendix 4.3). This form enquired after the date of diagnosis, specific NHL subtype,

immunohistochemical characteristics, presence of B-symptoms, and stage and spread of the disease.

4.5 Blood Samples

From each participant, 10 ml plain blood samples were drawn to test for infections. Blood samples were centrifuged and aliquoted to serum within 24 hours of sample collection. The samples were stored at −80°C until shipment on dry ice to the German Cancer Research Center, Heidelberg for analysis.

4.6 Multiplex Serology and Antibodies

Serologic testing was performed for 261 B-NHL cases (85% of cases) and 346 controls (88% of controls). IgG antibodies to several antigens were measured by fluorescent bead-based multiplex serology. The selection of infectious agents for the analysis was based on the literature and the availability of multiplex serology test. Furthermore, selection of individuals for the analysis was based on a set of requirements set by the German Cancer Research Center in Heidelberg, Germany.

Serological analyses to measure antibodies to the chosen microbial proteins were conducted at the German Cancer Research Center in Heidelberg, Germany. Frozen serum samples were shipped on dry ice. The antibody detection method was based on glutathione-*S*-transferase (GST) capture ELISA as described by Sehr *et al*. (Sehr *et al.*, 2002; Sehr *et al.*, 2001) in combination with fluorescent bead technology (Kjaerheim *et al.*, 2007; Waterboer *et al.*, 2005).

Briefly, full-length viral proteins were expressed in bacteria in fusion with an N-terminal GST domain. Glutathione cross-linked to casein was coupled to fluorescence-labeled polystyrene beads (MultiAnalyte, Luminex, Austin, TX) and GST fusion proteins were affinity-purified on the beads directly in a one-step procedure. Bead types of different color and each carrying a different antigen were mixed and incubated with human sera at 1:100 dilution. Antibody bound to the beads *via* the viral antigens was stained by biotinylated anti-human-Ig and streptavidin-*R*-phycoerythrin. Beads were examined in a Luminex 100 analyzer (Luminex) that identifies the bead color—and thus the antigen carried by the bead—and quantifies the antibody bound to antigen *via* the

median R-phycoerythrin fluorescence intensity (MFI) of at least 100 beads of the same internal color.

Background MFI (reactivity with GST alone, usually below 100 MFI) was subtracted from the MFI values obtained with specific proteins to obtain net MFI. Negative values were set to zero. Positive and negative standard sera were included in all analyses.

Serostatus of each of the pathogens was determined as positive or negative based on a cut-off value for each agent defined by minimal number of antibodies above the MFI cut-off level as previously described (Karachaliou *et al.,* 2016). Table 4.1 shows the pathogens included in this study, their corresponding antigens and the cut-off number of positive antibodies required to determine seropositivity. In addition, the table provides a description of these antigens and the MFI cut-off value for each one.

Table 4.1a: Infections and their corresponding antigens selected for multiplex serology.

Agent	**Agent cut off (# of antibodies)**	**Antigen**	**Full name**	**Indicator for**	**Antibody cut off (MFI)**
HCV	≥ 1	1aNS3	Non-structural protein 3, serotype 1a	Chronic infection	200
HBV	≥ 2	HBc	HBV core antigen	Chronic infection	150
		HBe	HBV envelope antigen	Chronic infection	150
EBV	≥ 2	Zebra	Z-encoded broadly reactive activator	Reactivated persistent infection	100
		EBNA	Epstein-Barr nuclear antigen	Chronic infection	250
		EA-D	Early antigen-diffuse	Reactivated persistent infection	100
		VCA	Viral capsid antigen	Chronic infection	250
HCMV	≥ 2	pp150	Tegument protein- also called UL32	Viral activity	150
		pp 52	DNA polymerase processivity subunit UL44-also known as ICP36	Viral activity	150
		pp 28	Tegument protein- also called UL99	Viral activity	150
H. pylori	≥ 3	GroEL	Chaperonin GroEL - virulent factor	History of *H.pylori* infection positive for GroEL	100
		UreA	Urease alpha subunit - virulent factor	History of *H.pylori* infection positive for UreA	150

Table 4.1b: Infections and their corresponding antigens selected for multiplex serology

Agent	Agent cut off (# of antibodies)	Antigen	Full name	Indicator for	Antibody cut off (MFI)
		CagA	Cag pathogenicity island protein A, N-terminal -virulent factor	History of H.pylori infection positive for this virulent factor	600
		VacA	Vacuolating cytotoxin A, C-terminal -virulent factor	History of *H.pylori* infection positive for this virulent factor	80
		HcpC	Catalase, Helicobacter cysterine-rich protein C - virulent factor	History of *H.pylori* infection positive for this virulent factor	110
		Omp	Outer membrane protein -virulent factor	History of *H.pylori* infection positive for this virulent factor	170
C. trachomatis	≥ 2 or pgb3 alone>500	MOMP-A	Major outer membrane, serovar A	Surface antigen (in EBs &RBs)	80
		MOMP-D	Major outer membrane, serovar D	Surface antigen (in EBs &RBs)	80
		Momp-max			100
		PorB	Porin B	Surface antigen (in EBs &RBs)	70
		Tarp-N	Translocated actin recruiting phosphoprotein, N terminal/ CT456	Surface antigen	110
		Tarp-C	Translocated actin recruiting phosphoprotein, C-terminal	Surface antigen	90
		Pgb3	Polypeptide encoded by open reading frame 3 of the plasmid	Virulent factor	100

4.7 Ethical Considerations

The project was ethically approved by the institutional review board (IRB) committee of Al-Quds University and all the appropriate institutions including MOH, Hadassah Hospital, AVH and Al-Makassed. In addition, the questionnaires and the databases were securely stored on a safe drive. Furthermore, the consent of the participants was obtained prior to conducting the interview through a written consent that confirms the confidentiality of data (appendix 4.4). Individuals were assured the freedom to participate in the study without intimidations.

4.8 Statistical Analysis

Data was coded and entered using IBM SPSS statistics (V20.0.0). Descriptive statistics of study population were calculated as frequencies and percentages for nominal variables, and medians and interquartile ranges (IQRs) for continuous variables utilizing cross-tabulation. In addition, chi-square test was used to calculate p-values. Statistical significance level was established at 0.05 and all tests were two-sided.

Antibody levels were reported as continuous variables (MFI) which were not normally distributed, therefore, the Kruskal-Wallis non-parametric test was used to compare median levels of antibodies among the study groups to evaluate whether NHL risk differed by quantified value of activity.

Logistic regression was used to calculate the association between B-NHL and antigen seroprevalence (odds ratios (OR) and confidence intervals (CI)) comparing higher to lower quartiles. Quartile distribution among the controls was used to determine cut-off values and score antigen MFIs among NHL patients.

Furthermore, pathogens were assigned a dichotomous serostatus for each (positive versus negative) based on a cut-off number of positive antibodies. The association between the dichotomous serostatus and the risk of B-NHL for each of the infections was calculated using logistic regression. Potential confounding was evaluated by the change in the effect estimate for a specific antibody measure when including the covariate in the model compared with the model without the covariate. The final model was adjusted by gender, region, age, years of education and family history of cancer.

Chapter Five

Results

Characteristics of study subjects and disease characteristics are described in this chapter. In addition, the findings regarding infectious risk factors of B-NHL are demonstrated.

5.1 Demographic and Clinical Characteristics of Study Subjects

In this study, 307 pathologically B-NHL cases and 394 cancer-free controls were recruited. The male to female ratio among controls was 0.7: 1 while among cases it was 1:1. Furthermore, the median age at recruitment was slightly lower among controls and an imbalance in the distribution of subjects among age groups was seen. Most of the subjects were married, and they were recruited from all over the West Bank with the majority being from the middle governorates (Table 5.1).

Moreover, we used the educational level (measured as years of schooling), as an indicator for socioeconomic status. Cases had lower educational level compared to controls; about 40% of the cases had less than six years of schooling while more than 45% of controls had at least ten years of schooling. Additionally, the majority of cases were recruited through AVH and Hadassah, while 80% of the controls were recruited through MOH clinics (Table 5.1).

Table 5.1: Demographic characteristics of study subjects.

Variable	Category	Controls n (%)	Cases n (%)
Gender	Male	168 (42.64)	152 (49.51)
	Female	226 (57.36)	155 (50.49)
Age at recruitment (years)	Median (IQR)	51 (40-62)	53 (41-65)
Age	18-24	14 (3.55)	14 (4.56)
	25-34	39 (9.9)	39 (12.70)
	35-44	85 (21.57)	42 (13.68)
	45-54	91 (23.1)	65 (21.17)
	55-64	85 (21.74)	66 (21.50)
	65-74	51 (12.94)	48 (15.64)
	75-84	24 (6.09)	29 (9.45)
	≥85	5 (1.27)	4 (1.30)
Schooling (years)	0	57 (14.58)	44 (14.57)
	1-<6	68 (17.39)	81 (26.82)
	6-<10	84 (21.48)	55 (18.21)
	10_12	75 (19.18)	62 (20.53)
	>12	107 (27.37)	60 (19.87)
Region	North	34 (8.63)	41 (13.44)
	Middle	333 (84.52)	232 (76.07)
	South	27 (6.85)	32 (10.49)
Marital Status	Single	34 (8.63)	41 (13.44)
	Married	333 (84.52)	232 (76.07)
	Divorced/ Widowed	27 (6.85)	32 (10.49)
Recruitment center	AVH	32 (8.12)	96 (31.27)
	Beit-Jala	0 (0)	38 (12.38)
	Al-Watani	13 (3.30)	51 (16.61)
	MOH Clinics	322 (81.73)	53 (17.79)
	Al-Makassed	27 (6.85)	0 (0)
	Hadassah	0 (0)	69 (22.48)

Regarding characteristics of NHL, cases had a median age at diagnosis of 52 years with more than 40% of cases diagnosed between 45 and 64 years old. The major histological subtype was DLBCL, constituting 70% of the cases. In addition, the second most common NHL subtype was follicular lymphoma. Further, characteristics of disease shows that about 60% of study subjects where diagnosed at late stages (III or IV), and

146 cases spread extranodally. Moreover, B-symptoms were reported in 158/307 cases (Table 5.2).

Table 5.2: B-NHL characteristics.

Variable	Category	n (%)
Age at diagnosis (years)	Median (IQR)	52 (38-63)
Age at diagnosis	18-24	17 (5.57)
	25-34	50 (16.39)
	35-44	40 (13.11)
	45-54	65 (21.31)
	55-64	64 (20.98)
	65-74	45 (14.75)
	75-84	22 (7.21)
	≥85	2 (0.66)
Histological diagnosis	DLBCL	217 (70.68)
	Follicular	43 (14.0)
	MALT	4 (1.30)
	Mantle cell	5 (1.63)
	Burkitt	2 (0.65)
	SLL & prolymphocytic	12 (3.91)
	Lymphoblastic	2 (0.65)
	Low grade lymphoma	13 (4.23)
	Marginal zone	3 (0.98)
	Other B-cell NHL	6 (1.95)
Spread	Extranodal	146 (47.56)
	Undefined	161 (52.44)
Stage	I	43 (15.30)
	II	71 (25.27)
	III	51 (18.15)
	IV	116 (41.28)
B-symptoms	Yes	158 (55.83)
	No	69 (24.38)
	Unknown	56 (19.79)

5.2 Prevalence of Infectious Agents among Palestinians

This study gives an insight on the seroprevalence among the Palestinian population for the examined viral and bacterial agents. As determined by the control group, 99% of the population tested positive for history of infection with HCMV and 97% tested positive

for EBV, in addition, antibodies for *H. pylori* showed a positive result for history of infection among 77% of the controls. Furthermore, indicators for infection history with HBV and HCV showed positive history among 29% and 1% of the controls, respectively. As for *C. trachomatis* 23% showed history of infection with this bacterium (Table 5.3).

Table 5.3: Seroprevalence of infectious agents among Palestinians.

Agent	**Seroprevalence (% among controls)**
HCV	1
HBV	29
EBV	97
HCMV	99
H. pylori	77
C. trachomatis	23

5.3 Infectious Risk Factors of B-NHL

To study the infectious risk factors of NHL, we started by examining proxies to infections and their association with B-NHL. Next, multiplex serology was used to screen 346 controls (87.8%) and 261 B-NHL cases (85%) for infections. Levels of antibody titers were measured as MFI. These levels were used to compare levels of antibodies among cases and controls. In addition, seropositivity to infectious agents was determined based on a cut-off number of positive antibodies to assess the relationship between serostatus and B-NHL.

5.3.1 B-NHL risk and proxies for infections

Table 5.4 shows the results regarding proxies for infections. Decreased odds of NHL with increasing sibship size and birth order were found, indicating inverse relationship with NHL risk. On the other hand, day care attendance was not found to be associated with risk of B-NHL. Controversially, examination of contact with pets and large animals and history of blood transfusion before the current illness revealed significantly increased risk of B-NHL, the corresponding ORs and CIs were (OR=1.7, 95% CI: 1.2-2.4) for the first and (OR=2, 95%CI: 1.3-3.2) for the second. Moreover, slightly increased risk has been reported among those that have been hospitalized during their first year of life.

Table 5.4: Odd ratios (OR) and 95% confidence intervals (CI) for B-NHL association with selected proxies for infections.

Variable	Category	Controls n (%)	Cases n (%)	OR (CI)	Adjusted OR (CI)
Number of siblings	0-2	19 (4.87)	21 (6.89)	Reference (-)	Reference (-)
	3-5	101 (25.9)	81 (26.56)	0.73 (0.37-1.44)	0.61 (0.28-1.33)
	6+	270 (69.23)	203 (66.56)	0.68 (0.36-1.3)	0.53 (0.26-1.11)
Birth order	1	69 (18.06)	71 (23.36)	Reference (-)	Reference (-)
	2-3	118 (30.89)	115 (37.83)	0.95 (0.63-1.44)	0.95 (0.61-1.50)
	4+	195 (51.05)	118 (38.82)	0.59 (0.39-0.88)	0.59 (0.38-0.91)
Day care attendance	Home care	356 (96.74)	285 (96.94)	Reference (-)	Reference (-)
	Day care	12 (3.26)	9 (3.06)	0.94 (0.39-2.25)	1.03 (0.39-2.74)
Contact with animals	Never	265 (68.65)	165 (54.1)	Reference (-)	Reference (-)
	Ever	121 (31.35)	140 (45.90)	1.86 (1.36-2.54)	1.69 (1.21-2.38)
Blood transfusion	Never	314 (86.98)	223 (74.83)	Reference (-)	Reference (-)
	Ever	47 (13.02)	75 (25.17)	2.25 (1.5-3.36)	2.01 (1.29-3.16)
Hospitalization during infancy	Never	130 (94.20)	131 (89.73)	Reference (-)	Reference (-)
	Ever	8 (5.8)	15 (10.27)	1.86 (0.76-4.54)	1.26 (0.42-3.79)

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

5.3.2 B-NHL risk and antibody levels

Comparison of MFIs between study groups showed significantly higher levels of titers among controls for two EBV antibodies, EBNA and VCA, three HCMV antibodies (pp150, pp52 and pp28), six *H. pylori* antibodies (GroEL, UreA, CagA, VacA, HcpC and Omp) and four of the *C. trachomatis* antibodies (MOMP-D, momp-max, PorB and Tarp-C). The difference in MFI between cases and controls was significant for these antigens as table 5.5 shows.

Table 5.5: Median antibody titers for (MFIs) to individual antigens by study group.

Agent	Antigen	Controls Median (IQR)	Cases Median (IQR)	P-value
HCV	1aNS3	12 (5-21)	12 (5-19)	0.413
HBV	HBc	16.5 (3-600)	14 (4-243)	0.870
	HBe	14.5 (1-432)	12 (1-174)	0.774
EBV	Zebra	862.5 (153-2084)	709 (130-2223)	0.113
	EBNA	3692.5 (1692-5735)	2687 (728-4779)	**0.001**
	EA-D	335 (50-1549)	372 (53-1629)	0.911
	VCA	6946.5 (4741-9558)	6332 (4050-7994)	**0.000**
HCMV	pp150	2860 (1334-4794)	2145 (833-4005)	**0.001**
	pp 52	6532.5 (4547-8506)	5710 (3596-7307)	**0.000**
	pp 28	2639.5 (1514-4397)	1964 (887-3460)	**0.000**
H. pylori	GroEL	2945.5 (460-5444)	740 (60-2932)	**0.000**
	UreA	133.5 (26-955)	48 (7-388)	**0.000**
	CagA	1767.5 (85-8330)	713 (82-4715)	**0.014**
	VacA	92 (33-284)	35 (12-110)	**0.000**
	HcpC	64 (25-271)	32 (11-99)	**0.000**
	Omp	997 (226-2406)	255 (39-1127)	**0.000**
C. trachomatis	MOMP-A	12 (6-23)	10 (3-22)	0.199
	MOMP-D	10 (4-22)	7 (1-13)	**0.001**
	Momp-max	17 (9-35)	12 (6-29)	**0.003**
	PorB	14 (6-24)	9 (4-17)	**0.000**
	Tarp-N	27 (8-103)	22 (6-71)	0.061
	Tarp-C	21 (8-90)	16 (6-54)	**0.013**
	Pgb3	6 (1-20)	5 (1-59)	0.129

5.3.3 Seropositivity of antibodies and risk of B-NHL

Since levels of antibodies were not normally distributed among study subjects, MFIs were converted to scores. Median MFI among controls was used to determine the cut-off points for scores as described in the statistical analysis part of the methodology. Table 5.6 shows the association between B-NHL risk and each of the antibodies comparing higher to lower quartiles. Antibodies against antigens of HBV, HCV and EBV did not show any association to the risk of B-NHL even after adjustment. In

addition, the antibody level for four of the *C. trachomatis* antigens (MOMP-A, PorB, Tarp-N and Pgb3), one *H. pylori* antigen (CagA) and one HCMV antigen (pp150) showed non-significant negative association to the risk of B-NHL. On the other hand, antibodies for two HCMV antigens (pp52 and pp28), *H. pylori* antigens (GroEL, UreA, VacA, HcpC and Omp), in addition to the *C. trachomatis* antigens MOMP-D, Momp-max, PorB and Tarp-C, all showed significantly protective association to B-NHL risk.

Table 5.6: Odds ratios (OR) and 95% confidence intervals (CI) for seropositivity of antibodies and risk of B-NHL comparing highest to lowest quartiles.

Agent	Antibody	OR (95%CI)	Adjusted OR (95%CI)
HCV	1aNS3	0.82 (0.59-1.13)	0.93 (0.65-1.32)
HBV	HBc	0.88 (0.64 -1.21)	0.88 (0.62-1.25)
	HBe	0.91 (0.66-1.25)	0.93 (0.66-1.33)
EBV	Zebra	0.85 (0.62-1.17)	0.9 (0.63-1.28)
	EBNA	**0.61 (0.44-0.85)**	**0.64 (0.45-0.91)**
	EA-D	1.10 (0.80-1.52)	1.15 (0.81-1.63)
	VCA	**0.64 (0.46-0.89)**	**0.66 (0.47-0.95)**
HCMV	pp150	**0.67 (0.49-0.93)**	**0.67 (0.47-0.95)**
	pp52	**0.55 (0.4-0.77)**	**0.52 (0.36-0.76)**
	pp28	**0.65 (0.47-0.90)**	**0.65 (0.46-0.93)**
H. pylori	GroEL	**0.33 (0.23-0.47)**	**0.32 (0.22-0.47)**
	UreA	**0.61 (0.44-0.85)**	**0.6 (0.42-0.85)**
	CagA	**0.69 (0.5-0.96)**	**0.68 (0.48-0.97)**
	VacA	**0.39 (0.28-0.55)**	**0.37 (0.25-0.53)**
	HcpC	**0.49 (0.35-0.69)**	**0.48 (0.33-0.68)**
	Omp	**0.38 (0.27-0.54)**	**0.35 (0.24-0.51)**
C. trachomatis	MOMP-A	0.94 (0.68-1.3)	0.95 (0.66-1.36)
	MOMP-D	**0.57 (0.41-0.79)**	**0.54 (0.37-0.77)**
	Momp-max	**0.54 (0.38-0.75)**	**0.49 (0.33-0.71)**
	PorB	**0.59 (0.43-0.83)**	**0.66 (0.46-0.95)**
	Tarp-N	0.82 (0.59-1.13)	0.79 (0.55-1.13)
	Tarp-C	**0.68 (0.49-0.94)**	**0.63 (0.44-0.9)**
	Pgb3	0.84 (0.61-1.16)	0.74 (0.51-1.08)

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

5.3.4 Seroprevalence of infections and B-NHL risk

We examined the association between B-NHL and seroprevalence of infectious agents determined as detailed earlier. Controls had higher prevalence of *H. pylori* infection than cases. The association was significantly negative between history of infection with *H. pylori* and B-NHL risk. In addition, seroprevalence for all the other infections (HBV, EBV, HCMV and *C. trachomatis* was either equal or a little higher among controls, but the association was not significant for any of them even after adjustment. On the contrary, infection with HCV showed higher seroprevalence among B-NHL cases, yet the association was not statistically significant (Table 5.7).

Table 5.7: Odds ratios (OR) and 95% confidence intervals (CI) for dichotomous determination of seropositivity to selected infectious agents and risk of B-NHL.

Agent	**Sero-status**	**Controls n (%)**	**Cases n (%)**	**OR (CI)**	**Adjusted OR (CI)**
HCV	Negative	343 (99)	257 (98)	Reference (-)	Reference (-)
	Positive	3 (1)	4 (2)	1.78 (0.39-8.02)	5.00 (0.54-46.11)
HBV	Negative	245 (71)	195 (75)	Reference (-)	Reference (-)
	Positive	101 (29)	66 (25)	0.82 (0.57-1.18)	0.84 (0.56-1.25)
EBV	Negative	9 (3)	10 (4)	Reference (-)	Reference (-)
	Positive	337 (97)	251 (96)	0.67 (0.27-1.67)	0.58 (0.20-1.62)
HCMV	Negative	5 (1)	8 (3)	Reference (-)	Reference (-)
	Positive	341 (99)	253 (97)	0.46 (0.15-1.43)	0.85 (0.25-2.93)
H. pylori	Negative	78 (23)	114 (44)	Reference (-)	Reference (-)
	Positive	268 (77)	147 (56)	**0.38 (0.26-0.53)**	**0.36 (0.24-0.53)**
C. trachomatis	Negative	267 (77)	201 (77)	Reference (-)	Reference (-)
	Positive	79 (23)	60 (23)	1.01 (0.69-1.48)	0.91 (0.55-1.50)

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

Chapter Six

Discussion, Conclusions, Limitations and Recommendations

This sero-epidemiological study was conducted to investigate the association between history of infections and the risk of B-NHL among Palestinians. The findings of this study provide an estimate for the prevalence of several of the infectious agents that have not been previously estimated. Furthermore, the study shed light on the role of these infections in lymphomagenesis. This chapter highlights the major findings, recommendations and limitations of the study.

6.1 Discussion

6.1.1 Demographic and clinical characteristics of study subjects

A total of 307 B-NHL cases participated in this study from all over the West Bank. Age and gender are both established risk factors of NHL. The median age at diagnosis for NHL was 52, which is 10 years younger than that reported in industrial countries (Smith *et al.*, 2015). The young age structure of the Palestinian population might in part explain this difference, but it also can reflect higher levels of exposure to etiological factors (Mozaheb, 2012). Several other developing countries in the area reported similar results (Abdel-Fattah & Yassine, 2007; Almasri *et al.*, 2004; Ameen *et al.*, 2010; Rauf *et al.*, 2015; Yaqo *et al.*, 2011). Further, male-to-female ratio in our study was found to be 1:1. NHL is reported to be more common among males, a 20-70% increase in the risk have been previously reported among males (CancerResearchUK, 2016; Fisher & Fisher, 2004; Nooyi & Al-Lawati, 2011).

Level of education was measured as years of schooling in this study, and it was found that cases had lower educational level than controls. Furthermore, education was used as an indicator for socioeconomic status. Thus, to adjust for the slight imbalance between cases and controls in terms of age, gender, geographic distribution and educational level the multivariate model was adjusted for these factors. Furthermore, previous analysis of the other risk factors of NHL indicated a strong association between NHL and family history of cancer (Kleinstern *et al.*, 2017), therefore, it was included in the adjusted model.

Regarding histological subtypes of NHL among Palestinians, DLBCL is worldwide reported as the most common subtype of NHL, yet, in this study the proportion among cases was 2-folds higher than that reported worldwide. Furthermore, follicular lymphoma constitutes 20-30% of NHL worldwide (Alexander *et al.*, 2007), but in developed countries the proportion is higher (Mozaheb, 2012). Among our cases, 14% were found to be of follicular subtype. Reports from Jordan, a country with both geographic and cultural proximity to Palestine, were consistent with our findings (Almasri *et al.*, 2004). The difference in the geographic distribution of subtypes suggests a role for genetic factors in the etiology of the disease (Mozaheb, 2012).

Late diagnosis of cancer in third world countries constitutes a large problem in cancer care. In addition, B-symptoms are a group of systemic symptoms that can help in determining the prognosis of the disease. The presence of B-symptoms is associated with higher levels of inflammatory proteins, a marker for low response to chemotherapy and worse survival rates (Sharma *et al.*, 2009). In this study, nearly 60% of NHL cases were reported to be diagnosed with at least stage III disease and B-symptoms were reported among 56%. Furthermore, 48% had extra-nodal involvement. Similarly, more than 60% of cancer cases were reported to be diagnosed at late stages of the disease among Palestinians (Kharroubi & Abu Seir, 2016). Furthermore, in Egypt, a study found that 70% of NHL cases were diagnosed in stages III and IV (Abdel-Fattah & Yassine, 2007), and among Bedouins in south Israel, 40% were diagnosed at stage IV (Levi *et al.*, 2013). Another Egyptian study reported extra-nodal involvement among 21% of lymphoma cases (Kadry *et al.*, 2016). Comparatively, in Switzerland, it was reported that of 180 NHL cases, 21.7% experienced B-symptoms and 63.9% were

diagnosed at stages III or IV of the disease of which 24.4% had more than 2 extra-nodal sites (Zucca *et al.*, 2000).

6.1.2 Prevalence of infectious agents among Palestinians

In this study, multiplex serology was used to screen study subjects for a group of infectious agents. Multiplex serology is a relatively new technology. Compared to ELISA, it allows for simultaneous analysis of hundreds of samples, examining antibodies against multiple viral antigens instead of one per well (Waterboer *et al.*, 2005).

Based on the positivity of HCV among the control group, the seroprevalence was found to be 1%. Previous estimations of HCV's prevalence in Palestine were limited by population and size. The most recent estimate of seroprevalence of HCV among hemodialysis patients in the West Bank found a seroprevalence of 7.4% (Al Zabadi *et al.*, 2016). This is much higher than what is found in our study, and this could be explained by the high-risk population of the study. Furthermore, another study attempted to investigate HCV's seroprevalence in Gaza and it was estimated to be 4% among blood donors (Novack *et al.*, 2007). Furthermore, the prevalence of HCV among Palestinian blood donors in MOH hospitals blood banks and the National Blood Bank was reported to be 0.1% (MOH, 2016). Estimates from surrounding countries are also available; in Jordan the prevalence among the general population was reported to be 0.42% (Hamoudi *et al.*, 2013).

HBV prevalence among controls was found to be 29%, which is high compared to other estimates. The selection of antigens affects the estimation of prevalence. In this study, HBc and HBe were used as markers for history of HBV infection. Most studies utilized HBsAg or anti-HBs for testing HBV serologically. Anti-HBs is elicited either by natural response to viral exposure or by vaccination (Kleinstern *et al.*, 2016). A study that estimated HBV prevalence among four Palestinian high risk groups utilized HBsAg, HBeAg and anti-HBc to test for HBV. The study reported a prevalence range for anti-HBs between 10% and 30% for the four groups (Adwan *et al.*, 2005).

EBV infects most individuals during their lifetime (de Sanjose *et al.*, 2007). In developing countries, the majority of the population becomes infected before

adolescence. Poor socioeconomic conditions were found to be associated with early primary infection with EBV and HCMV (Hjalgrim *et al.*, 2007; Straus *et al.*, 1993; Tselis, 2013). The seroprevalence of EBV among the controls was found to be 97%. Comparatively, an Iranian investigation of seroprevalence of EBV among adults found that 85% of the study subjects tested positive for IgG antibodies to EBV antigens (Pourahamad *et al.*, 2014). Furthermore, a nationwide sero-epidemiologic study in Taiwan reported a seroprevalence of 88.5% among the Taiwanese population (Chen *et al.*, 2015). In addition, in USA, the overall EBV seroprevalence among children 6-19 years old was found to be 66.5%; the seroprevalence was highest among those 18-19 years old and reached 82.9% (Dowd *et al.*, 2013).

The seroprevalence of HCMV is, like EBV, highest in developing countries, but reliable estimates are not available (Manicklal *et al.*, 2013). Among the control group of our study, 99% tested positive for HCMV antibodies. Previous reports on this virus among Palestinians showed that among pregnant women, 96.6% were positive for CMV-IgG antibodies (Neirukh *et al.*, 2013). Other reports from Sudan showed a seroprevalence measures ranging from 72.2% among pregnant women in Western Sudan (Hamdan *et al.*, 2011) to 98.9% among pregnant women in Khartoum (Altayeb *et al.*, 2016). Further, a third study in Khartoum State investigated the seroprevalence of HCMV among blood donors and it was found to be 97.3% (Ibrahim *et al.*, 2016a). In Pakistan, the seroprevalence of HCMV IgG antibodies as measured in a population-based survey was found to be 93.2% (Ibrahim *et al.*, 2016b). Altogether, the estimation of HCMV's seroprevalence reported here was reliable.

Testing *H. pylori* using serological testing is very common in sero-epidemiologic studies, although it's been found to underestimate the prevalence by 30% (Goh *et al.*, 2011). Studies regarding the prevalence of *H. pylori* infection showed higher rates in developing countries compared to developed ones (Goh *et al.*, 2011; Khedmat *et al.*, 2013). As the findings of this study showed, the seroprevalence of *H. pylori* was 77%. The data available on the prevalence of *H. pylori* in Palestine are not comparable to our findings since mostly they screen for current infection rather than history of infection. In addition, most studies differed by the target population and the method of testing, therefore, estimates varied from study to another and between countries. For example, in the general Iranian population, seroprevalence estimates ranged between 60 and 80%,

while among symptomatic patients, the total prevalence was estimated to be 87%. In addition, reports from Turkey estimated *H. pylori* prevalence to be about 60% in the general population and 80% in symptomatic patients. Among Egyptians, the seroprevalence was 91.7% in the rural population (El Dine *et al.*, 2008), while estimates from Saudi Arabia's major cities reported the seroprevalence to be 51% in Makkah (Khan & Ghazi, 2007) and 28% in Al-Madinah (Hanafi & Mohamed, 2013). Furthermore, a study in Gaza estimated the seroprevalence in the Strip to be 48.3%, and among Arabs in Israel it was reported to be 42.1% (Khedmat *et al.*, 2013). Further, a study conducted among symptomatic patients in Ramallah, Palestine to identify virulence genes in *H. pylori* found that 65.9% were positive for CagA and 40.9% were positive for VacA (Essawi *et al.*, 2013).

C. trachomatis is the most common sexually transmitted infection worldwide. Although serological testing of *C. trachomatis* active infection is of debate, detection of IgG antibodies is sufficient to detect previous infections. The prevalence of *C. trachomatis* infection was found to be 23%. The prevalence of *C. trachomatis* among women attending gynecology and infertility clinics in Gaza was estimated to be 20% (El Qouqa *et al.*, 2009). Comparable estimates of the prevalence of the infection was not found since the reported estimates selected high risk groups and the used tests were indicators for active infections rather than previous ones. On the contrary, the assay used in this study is an indicator for past exposure and the sample differs, affecting comparability of findings.

6.1.3 Infectious risk factors of B-NHL

The core objective of this study was to investigate the association between infections and NHL. To achieve this goal, we started by examining the relationship between exposure to infections as a child, estimated using proxies for infections, and then by screening for past infections utilizing serological testing. In the next part, the major findings regarding this association are highlighted.

6.1.3.1 Proxies for infections and B-NHL risk

Multiple proxies for infections were investigated in this study, and it was found that birth order of four or higher reduced NHL risk by 50% compared to first born, however, the association was not significant. In addition, the risk of NHL was found to decrease

upon increasing sibship size, although non-significantly. Previous studies of birth order and sibship size yielded inconsistent associations with NHL risk. Grulich *et al.* reported a protective effect of early birth order (Grulich *et al.*, 2005). Furthermore, a population-based case-control study in the United States found that risk of NHL increased with increasing sibship size in women and heterosexual men (Holly *et al.*, 1999). Smedby *et al.* also reported a positive association between sibship size, higher order of birth and NHL risk (Smedby *et al.*, 2007). Controversially, Rudant et al. supported the findings reported here regarding the association between sibshp size, birth order and NHL risk (Rudant *et al.*, 2011). Moreover, attending day care was not found to be associated to NHL risk in this study, and neither Rudant *et al.* did report an association (Rudant *et al.*, 2011). On the contrary, Smedby *et al.* reported increased risk among children attending day care during the first two years of their lives but not after (Smedby *et al.*, 2007). Children of higher birth order can more likely be exposed to infections at earlier age. The age at which exposure to common infections is of great importance for the proper development and maturation of T-helper cells (Rudant *et al.*, 2011).

Exposure to pets and large animals was associated with significantly increased risk of B-NHL in this study. Animals of different types, large and small, as a source of infectious agents, have long been recognized as a risk factor for NHL (Grulich & Vajdic, 2005; McDuffie *et al.*, 2002). Increased risk of lymphoma has been reported in individuals with contact to animals as children (Smedby *et al.*, 2007) and residing in a farm or raising farm animals increased the risk of NHL (McDuffie *et al.*, 2002; Smedby *et al.*, 2007), but not household pets (Dryver *et al.*, 2004; Rudant *et al.*, 2011; Smedby *et al.*, 2007). On the contrary, contact with farm animals before one year old was found protective against NHL (Rudant *et al.*, 2011). It could be argued that household pets are usually immunized and clean, thus they are less likely to be a source of infection compared to farm animals. In this study, the lifetime history of exposure to animals was investigated rather than early life exposure, this might explain the contradiction in the previous findings supporting protective role for exposure to infections early in life.

Moreover, self-reported blood transfusion before the development of B-NHL was found to be significantly associated with increased risk with the disease. This finding is consistent with previous reports from cohort studies that described an increased risk of NHL, particularly of low grade lymphomas, associated with a previous history of blood

transfusion (Cerhan *et al.*, 1997; Erber *et al.*, 2009). A large population-based case-control study reported an OR of 1.26 (95% CI: 0.91–1.73), in which the risk was significantly higher for cases with a longer duration since the first transfusion especially for transfusions for reasons other than surgery or trauma (Cerhan *et al.*, 2008a). Although blood banks are required to test blood donations for viral markers, blood transfusions are suspected to cause about 6% of all Hepatitis C infections. It is worth noting here that screening for HCV is performed in Palestinian blood banks since 1992. Hepatitis C infection appears to be mainly associated with B-cell NHL, which might explain the positive association between blood transfusion and B-NHL in this study (Imai *et al.*, 2002; Ohsawa *et al.*, 1999). Accordingly, the hypothesis was further supported by the association between HCV and risk of B-NHL, which though it was found non-significant, it was elevated (OR=5, 95%CI: 0.54-46.11).

Hospitalization for infection during the first year of life was associated with non-significant increase in NHL risk. This was in line with what was reported previously by Paltiel *et al.* (Paltiel *et al.*, 2006) and Goldin *et al*. (Goldin *et al.*, 2011) who reported an increased risk of NHL among individuals who were hospitalized for infections during infancy in Israel and Sweden, respectively. On the other hand, Rudant *et al.* did not find an association between infections during early life or surgical operations for ear, nose or throat infections before the age of three years (Rudant *et al.*, 2011).

6.1.3.2 Infections and B-NHL risk

Regarding the association between NHL and HCV, the used multiplex serology method for testing of HCV using antibodies to NS3 antigen was previously validated and showed 100% sensitivity and 99.6% specificity (Dondog *et al.*, 2015). Comparing between seroprevalence of HCV between B-NHL cases and controls, the association between HCV and B-NHL was found to be non-significantly increased. Further, the odds ratio increased from 1.78 to 5 after adjustment for possible confounders. Though, the number of positive HCV individuals that the analysis was based on is very small and should be taken into consideration when interpreting these findings. On the other hand, comparing MFIs as a continuous measure or as quartiles both did not yield any association to B-NHL risk.

Epidemiologic evidence regarding the association between B-NHL and HCV infection has been favoring an association. Differences in the design, population selection, geographic regions, HCV prevalence and testing methods might explain the inconsistency, but the number of studies that support this association is increasing (Morton *et al.*, 2004; Viswanatha & Dogan, 2007; Xiong *et al.*, 2017). Furthermore, in a cross-sectional study of HCV and NHL risk in Switzerland that included 180 newly diagnosed NHL patients, the reported seroprevalence of HCV among NHL case was estimated to be 10 times higher than that estimated among blood donors (Zucca *et al.*, 2000). In addition, a multi-center case-control study conducted in Italy found a significantly increased association between HCV infection and B-NHL for both indolent and aggressive subtypes. The association was not dependent on the serotype of HCV. The findings of the study estimated that approximately one of each 20 B-NHL cases is attributed to infection with HCV (Mele *et al.*, 2003). Further, the InterLymph conducted a pooled-analysis of 7 studies form Europe, North America and Australia. The analysis included 4,784 NHL cases and 6,269 matched controls. A significantly increased association between NHL risk and HCV infection was reported (OR=1.78, 95%CI: 1.4-2.25). The risk was elevated for MZL, DLBCL and lymphoplasmacytic lymphoma, but not for follicular lymphoma (de Sanjose *et al.*, 2008). Moreover, an Egyptian case-control study reported significantly increased NHL risk among HCV-RNA positives but not among anti-HCV positives (Cowgill *et al.*, 2004). Similarly, the Connecticut women case-control study reported non-significantly increased NHL risk among HCV positive individuals; the association was highest between HCV and both B-NHL and follicular lymphoma (Morton *et al.*, 2004).

Regarding the association between HBV infection and B-NHL risk, the findings reported here didn't support such an association. The first published case-control study of HBV and risk of NHL was conducted between 1997 and 1998 and included 222 newly diagnosed NHL cases, 439 controls who were patients of non-hematological malignancies, and 444 controls with no cancer. The prevalence of HBsAg among study groups was 12.6%, 7.3% and 4.7%, respectively. A significantly increased risk of NHL was found among HBV carriers (Kim *et al.*, 2002). Furthermore, the Korean Cancer Prevention Study is a cohort study conducted among workers in South Korea and their dependents. The study utilized HBsAg as a marker of chronic HBV infection. It was found that the prevalence of HBV among the study population was 8.8% and that 1,038

cases developed NHL during study period. The seroprevalence of HBV among cases was 12.8% and the hazard ratio was estimated to be 1.58 (Engels *et al.*, 2010a). In addition, an Italian case-control study reported higher prevalence of HBV among NHL cases. The association was significantly increased among all NHL cases and specifically B-NHL cases (Taborelli *et al.*, 2016). The high prevalence of HBV infection among controls compared to the reported estimates suggests a selection bias that might result in an underestimation for the investigated association, limiting the generalizability of our findings.

In this study, it was hypothesized that uncontrolled EBV infection can lead to the development of NHL in immunocompetent individuals. To test this hypothesis, serum samples withdrawn from NHL cases and healthy controls were checked for four markers for the infection. Individuals that have IgG antibodies to VCA and EBNA-1 antigens have latent EBV infection, therefore it tests positive in most adults. On the other hand, having IgG antibodies to Zebra and EA-D antigens reflects viral reactivation in the host and uncontrolled infection (De Roos *et al.*, 2013). Evidence regarding the association between NHL and EBV infection was controversial, mainly due to differences in the methods (De Roos *et al.*, 2013). In this study, there was no significant association between risk of B-NHL and EBV-seropositivity, neither there was association between seropositivity to each of the tested EBV antibodies alone except for EBNA that showed association with significantly decreased risk of B-NHL (OR=0.64, 95%CI: 0.45-0.91) and EA-D which showed weak non-significant increase in the risk of B-NHL (OR=1.15, 95%CI: 0.81-1.63). Similarly, a nested case-control study of two cohorts reported no association between NHL risk and EBV serostatus or any of the viral antigens (EBNA-1, EBNA-2 and EA-D) (Bertrand *et al.*, 2010). Furthermore, a recent meta-analysis of the cancer prevention study-II of the association between NHL and EBV used prospectively-controlled plasma EBV antibodies form 225 NHL cases and 2:1 matched controls. In the study, a seroprevalence of 92.7% was found among controls. They used the same four antigens used in our study to test for EBV. Non-significantly increased OR was reported between serostatus of EBV and risk of NHL (OR=1.28, 95%CI:0.67–2.47), in addition, EA-D showed non-significantly increased association with NHL. On the other hand, the analysis of the eight studies reported no significant associations between NHL and serum levels of VCA, EBNA-1 or Zebra antigens (Teras *et al.*, 2015). Moreover, a nested case-control study within the Women's

Health Initiative Observational Study cohort measured IgG antibodies to EBV antigens VCA, EBNA1 and EA-D in addition to EBV DNA load in prediagnostic samples of 491 B-cell NHL cases and 491 controls. No association between EBV infection and NHL risk was found based on seropositivity to VCA, but significantly decreased association was found based on the detection of EBNA1 (OR=0.5, 95%CI: 0.3-0.8) (De Roos *et al.*, 2013) and thus supporting our findings. The high prevalence of EBV poses difficulties in understanding the association between NHL and the infection (de Sanjose *et al.*, 2007).

HCMV is another member of the herpesvirus family that infects young hosts and remains latent in host cells. Reactivation of HCMV might have devastating outcomes especially in immunocompromised individuals (Tselis, 2013). The association between NHL and HCMV is plausible. In this study, a negative association between seropositivity to HCMV antigens was found, though, using HCMV serostatus, and after adjustment for possible confounders, the odds ratio did not show an association between HCMV and B-NHL. Relatively few studies examined this association. An Iranian study examined 25 paraffin-embedded blocks for HCMV infection and 20% of the blocks were found to be HCMV positive (Mehravaran *et al.*, 2017). Furthermore, in Egypt, a study of lymphomas and viral infections showed a significant association between positivity to HCMV-IgM antibodies but not IgG (Kadry *et al.*, 2016).

The association between NHL and *H. pylori* has been studied for over than two decades, specifically MALT lymphoma. In fact, *H. pylori* is considered to be causal in the case of MALT lymphoma (Lehours *et al.*, 2004). In this study, a negative association between risk of B-NHL and seropositivity to both antibody levels and pathogen was found. Controversially, in Switzerland a significantly increased risk for gastric NHL was found among individuals seropositive to *H. pylori* antibodies (Zucca *et al.*, 2000). Furthermore, a French study investigated the association between the risk of MALT lymphoma and seven of *H. pylori*'s virulent factors (CagA, CagE, VacA, IceA, BabA, HopQ and OipA) by comparing isolates from patients with MALT lymphoma to those who have gastritis only. None of the seven factors contributed to the risk of MALT lymphoma individually (Lehours *et al.*, 2004). On the other hand, Anttila *et al.* did not find an association between malignant lymphomas and serological markers of *H. pylori* infection (Anttila *et al.*, 1998). Possibility clearing of the infection among cases due to

advanced stages of NHL and cytotoxic treatments might lead to differential underestimation of the exposure among cases, shifting the association, which can explain our findings (Gao *et al.*, 2009b). Further, the number of MALT lymphoma cases was low, so a separate analysis could not be performed. Therefore, the analysis pooled all B-NHL subtypes together, and the association might be masked due to the heterogeneity in the etiology of NHL subtypes.

In screening for *H. pylori* infection, attention should be paid to *H. pylori* antibody levels since it varies greatly depending on the test kit used, especially in screening for current infections. Both urinary and serological testing of *H. pylori* has been used in epidemiologic studies. Urine-based tests are more convenient and easier to use as a noninvasive method. In addition, it is preferable to use local strains of *H. pylori* as antigen source in developing testing kits in order to obtain the best results (Gao *et al.*, 2009b). The currently used multiplex serology method was previously validated. The original method detected 15 antibodies specific for *H. pylori* antigens (Cad, Cagδ, CagM, CagA, catalase, HcpC, HP0231, HP0305, HpaA, HyuA, GroEL, NapA, Omp, UreA, and VacA). Concordance between results from this method and results of ELISA test was moderate. After the analysis, the six antigens used in our study were identified as independent virulent factors and used for testing for *H. pylori* infection (Gao *et al.*, 2009b).

The association between NHL and *C. trachomatis* was rarely investigated. The seroprevalence of *C. trachomatis* didn't differ by study group, but seropositivity to some of the tested antigens was found to be associated with decreased NHL risk. Those included TarpC, PorB, Momp-max and MOMP-D. Contrary to our findings, a previous study reported higher prevalence of *C. trachomatis* in formalin-fixed paraffin-embedded biopsies of pulmonary MALT lymphoma (Chanudet *et al.*, 2007). Further, serological evidence from a case-control study supported an association between lymphoma and *C. trachomatis* infection (Anttila *et al.*, 1998).

6.2 Strengths and Limitations

This multicenter case-control study investigates the association between NHL and infectious agents in Palestine; our study is the first and largest to date on this topic. Furthermore, selection of the controls allows the estimation of the seroprevalence of the

selected agents among Palestinians for the first time. In addition, this sero-epidemiologic study utilized a newly developed multiplex serology, a method that allows the simultaneous analysis of large numbers of serum samples for antibodies against multiple viral antigens instead of the other serologic methods such as ELISA which allows the analysis of sera for antibodies to only one antigen per well (Waterboer *et al.*, 2005).

Regardless of the efforts to strengthen the study, several limitations rose and were hard to overcome. First, due to the limited sample size, we were not able to stratify the analysis by histologic subtypes. The etiological heterogeneity between subtypes might have limited the ability to find an association.

Population-based epidemiological seroprevalence estimations among Palestinians are scarce; as a result, comparable seroprevalence estimates among the Palestinian population were not available for most of the agents investigated. In addition, controls were conveniently sampled. Therefore, the generalizability of our findings is limited.

Furthermore, it is advised to use prediagnostic specimens in biomarker-based assays to improve the accuracy of the data (Wang & Nieters, 2010). In this study, although cases were incident ones, they were recruited during receiving treatment. Cytotoxic treatments might lead to washing out of the antibodies or keeping them under the detectable limit. In addition, during advanced stages of the disease, the probability of washing out the infection exists. Therefore, differential misclassification bias might lower the seroprevalence among cases but not controls, shifting the association towards the null and even falsely pointing to negative associations.

6.3 Conclusions

Although we were unable to find an evidence for association between B-NHL and infectious agents, epidemiological evidence in general supports the hypothesis. Further, seroprevalence estimates in our study points to high rates of infections among Palestinians.

6.4 Recommendations

Our study highlights the urgent need for additional representative large population-based seroprevalence studies. Further, more studies on the role of infectious agents in the etiology of B-NHL should be performed using prediagnostic samples. Moreover, in addition to serology, pathogen DNA load in the malignant tissue is considered as a strong predictor for causative association, especially in chronic infections.

Additionally, immunohistopathological analysis and screening of NHL cases for infection markers is important in diagnosing and developing treatment plans with better survival outcomes. These tests are available in limited number of facilities in Palestine and needs to be considered in the future.

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Appendices

Appendix 4.1

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 **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 a. doctors b. nurses c. physiotherapist					
11. Photoimager					
12. Veterinary					
13. Air crew					
14. Butcher					
15. Hair dresser					
16.Asbestos worker					
17. Leather worker					
18. Construction Workers					
19 Cleaners					
20. House wives					
21. others:					

Exposures codes:

1. Pesticides **2.** Meat products **3.** Organic solvents **4.** inorganic Solvents **5**. Gasoline **6**. UV radiation **7**.Cosmic radiation **8.** Ionizing radiation **9**. electromagnetic radiation **10**. Infectious agents / microorganisms **11**. Animals **12**. Antibiotics **13.** Paints **14**. Hair dyes **15**. Asbestos **16.** animal skin **17**. Glues **18**. sunlight **19**. medicines (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 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 4.2

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 أ.الأطباء ب.الممرضين 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 النقط 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: الشارع:_____ المدينة (البلدة): _____								
السابق: 1. الشارع:_____ المدينة (البلدة): _____								
2. الشارع:_____ المدينة (البلدة): _____								
3. الشارع:_____ المدينة (البلدة): _____								
4. الشارع:_____ المدينة (البلدة): _____								
5. الشارع:_____ المدينة (البلدة): _____								

***مبنى

- **نوع المنزل:** 1. منزل خاص 2. مبنى سكني (اقل من 10 عائلات) 3. مبنى سكني (أكثر من 10 عائلات) 4. خيمة 5.سكن في مزرعة 6.أخرى
- **الطابق :** 1 طابق أرضي 2. طابق ثاني 3. طابق ثالث 4. طابق أعلى 5.أخرى
- **مصدر الماء:** 1.أنابيب 2. بئر 3. صهاريج 4. مياه معدنية 5. لا أعرف 6. أخرى
- **الحمام :** 1. في الداخل 2. في الخارج 3.أخرى

القسم الرابع : العادات

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

س 24) ما هي قياساتك الجسمية؟

المؤشرات	القياس عند المرض	القياس 6 اشهر قبل المرض
الطول		
الوزن		

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

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

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

س 26) هل أنت مدخن حاليا؟

1.نعم 2. لا

س 27) هل أقلعت عن التدخين؟

1.نعم 2. لا

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 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 4.3

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 4.4

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 : _____