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Determinants of Lung Cancer among Palestinians in the West Bank: A case control study.

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Jerusalem – Palestine

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DEDICATION

To my dear parents
To my dear husband Khaled
To my dear children: Mira,Masa and Laith
To all my friends

Declaration

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

Signature: …….

Ilaf Bilal Mohammad Abuzarour

Date: ……

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First of all, I am grateful to God (Allah) who enlightened my way in choosing this particular issue for my thesis. Without God‘s guidance and will, I would not be able to do this work and endure all the obstacles and difficulties I encountered throughout my work. Thank you God.

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Abstract

Back ground: In Palestine, lung cancer is the 3rd reported cancer type and is the most common cause of all cancers deaths (MOH, 2016).

Lung cancer research in Palestine is neglected. Several factors play a role in its determination, smoking is known to be one of the main preventable risk factor for lung cancer, which is common among Palestinians. However, its association with LC, including other factors, was not investigated. This study could be a baseline for decisions makers to plan for a national strategy that can help in preventing this cancer.

Aim & Objectives: This study aims to identify the determinants of lung cancer among patients attending the oncology department at two Governmental Hospitals in the West Bank. The objectives were to determine the associations between the various lifestyle habits, socio-demographic, the patients' health status, family history of malignancy, and the environmental and occupational factors with the risk of developing lung cancer.

Study methodology*:* the study was conducted in 2 stages in stage 1, we reviewed all the files of the patients who were diagnosed with lung cancer between 2010- 2017 in AlWatani hospital, and we searched in their files for the risk factors of lung cancer, the pathological typ, and stage. Stage 2 was case-control study in both hospitals. We interviewed 40 lung cancer cases, and 40 non cancer patients (study controls), the cases were attending Alwatani and Bait Jala outpatients' cancer clinic and the oncology department. During the study period study cases were approached with a similar number of controls from the same city attending the hospitals for other reasons.

Statistical Analysis: IBM SPSS 18 was used for data entry and analysis. Continuous variables were compared between the study cases and control group using T-test. Pearson chi-square test or fisher’s exact test was used for comparison of categorical variables

between the cases and controls. Forward logistic regression models were used in the multivariate analysis.

Results: Analysis of the data from the medical records of the patients in first part of the study showed that eighty percent were males with a mean age 61 years (SD±10.96), of whom 30% were general workers and 20% were farmers. However, most female patients were housewives. 78.3% of the patients were smokers 73% of non-smokers were females.

Positive family history of malignancy was found in 15.8 % of patients. Adenocarcinoma was the most common histological type (53.6%) of patients, and about 60 % of patients had metastasis at diagnosis.

In the case-control study, study cases mean age was 54.8 years (SD ±12.3). There was a significant difference between study cases and control group by smoking status (P value <.014), duration of smoking in years (P <.007) and number of cigarettes smoked (P value <.017).Thus these were the main risk factors for lung cancer. Besides living Near a gas emitting factory, using fuel for warming, and the use of "taboon" oven were significant occupational and environmental risk factors. Current low body mass index and positive family history of malignancy were found to be other significant risk factors. Consuming salads and whole grain dark bread were found to be possible significant protective factors for lung cancer.

In the multivariate analysis, smoking and use of "Taboon" oven were the main risk factors for LC with an adjusted odds ratio, AOR 2.98 (CI 95%: 1.154-7.69) and 5.05 (CI 95%: 1.25-20.3) respectively.

Conclusion: The study revealed that modifications of lifestyle factors might play an important role in LC disease prevention. Also, we recommend increasing awareness about lung cancer and establishing a national program for early detection of lung cancer in Palestine.

العوامل المرتبطة بمرض سرطان الرئة في الضفة الغربية: دراسة مسحية ودراسة للحالات و الشواهد.

اعداد: ايلاف ابو زعرور

اشراف: د. نهى الشريف

ملخص:

خلفية الدراسة: في فلسطين، سرطان الرئة هو ثالث أكثر أنواع السرطان، وهو السبب الأكثر شيوعًا لوفيات السرطان (وزارة الصحة الفلسطينية، 2016).

لا يجود أبحاث حول سرطان الرئة في فلسطين، وحيث أنه من المعروف أن التدخين هو عامل الخطورة الرئيسي الذ يمكن الوقاية منه والذي يؤدي للإصابة بسرطان الرئة، وهو شائع بين الفلسطينيين، ولكن لم تبحث أي دراسة محلية علاقة التدخين أو أي عوامل الخطورة الأخرى بسرطان الرئة. إلى جانب عدم وجود برنامج وطني للكشف المبكر عن هذا النوع من السرطان في فلسطين. لذلك، عمدنا في هذه الدراسة لتكون بمثابة أساسا لواضعي السياسات الصحية لوضع خطط إستراتيجية وطنية من شأنها أن تسهم في الوقاية من هذا السرطان.

أهداف الدراسة: تهدف هذه الدراسة إلى تحديد عوامل الخطورة المرتبطة بسرطان الرئة عند مرضى أقسام الأورام في مستشفيان حكوميان في الضفة الغربية. وكانت أهدافها الأساسية هي تحديد العلاقات بين عادات الحياة المختلفة، لا سيما التدخين، والوضع الاجتماعي والاقتصادي والحالة الصحية للمرضى، والتاريخ العائلي للأورام الخبيثة، والعوامل البيئية والمهنية التي قد ترتبط بخطر الإصابة بسرطان الرئة.

منهجية الدراسة: أجريت الدراسة على مرحلتين متتاليتين، ففي المرحلة الأولى قمنا بمراجعة جميع ملفات المرضى الذين تم تشخيصيهم بسرطان الرئة ما بين عام 2010 حتى 2017 وبحثنا في ملفاتهم الطبية عن عوامل الخطورة لسرطان الرئة، ونوع الخلايا والأنسجة المصابة، ومرحلة المرض عند التشخيص. وفي المرحلة الثانية قمنا بدراسة الحالات والشواهد، حيث قابلنا 40 مريض بسرطان الرئة (حالات الدراسة)، و 40 غير مرضى كشواهد للدراسة. وتمت مقابلة جميع حالات سرطان الرئة التي حضرت إلى عيادات الأورام في المستشفى الوطني وبيت جالا أو دخلت الى قسم الأورام خلال فترة الدراسة وتمت مقارنتهم بعدد مماثل من الشواهد من نفس المدينة (وهم من المرضى غير المصابين بالسرطان الذين كانوا يحضرون إلى المستشفيين لأسباب طبية ومرضية أخرى).وقد تم استخدام استبان لجمع معلومات عن الحالة الاجتماعية ونمط الحياة والحالة الصحية العامة والتاريخ العائلي لمرض السرطان المشاركين في هذه الدراسة.

التحليل الإحصائي تم إدخال جميع البيانات وتحليلها باستخدام برنامجSPSS-IBM 18. ففي المرحلة الأولى، تم حساب التكرارات لجميع المتغيرات وقد عرضت البيانات في جداول، وثم تمت مقارنة المتغيرات بين حالات الدراسة ومجموعة الشواهد، وتم استخدام اختبار chi-square لمقارنة المتغيرات الفئوية بين الحالات والشواهد. إضافة إلى استخدام نماذج الانحدار اللوجستي في التحليل متعدد المتغيرات.

النتائج الرئيسية: أظهر تحليل البيانات من السجلات الطبية للمرضى في الجزء الأول من الدراسة أن 80% كانوا من الذكور بمتوسط عمر 61 سنة (SD ± 10.96)، وكان 30٪ منهم عمال و 20 ٪ كانوا مزارعين. وكانت معظم المرضى الإناث ربات البيوت. و 78.3٪ من المرضى كانوا مدخنين وكان 73٪ من غير المدخنين إناث وكان هناك تاريخ عائلي ايجابي لمرض السرطان في 15.8٪ من المرضى، وتبين من خلال التحليل أن ما يقدّر ب 60 ٪ من المرضى تم تشخيصهم في مرحلة متقدمة من المرض.

في الجزء الآخر من الدراسة كان متوسط عمر المرضى 54.8 سنة (SD ± 12.3)، وكان هناك اختلاف واضح بين الحالات والشواهد حسب حالة التدخين (P value <.014)، ومدة التدخين بالسنوات (P <.007) وعدد السجائر المدخنة (P value <.017) وتعد هذه عوامل خطر رئيسية لسرطان الرئة. إلى جانب السكن بالقرب من مصنع يبعث الغازات، وكان نوع وقود التدفئة، واستخدام فرن الطابون عوامل خطورة بيئية مهمة. كذلك فان انخفاض مؤشر كتلة الجسم الحالي، والتاريخ العائلي الإيجابي للأورام الخبيثة هي أيضا من عوامل الخطر الهامة. أما زيادة استهلاك الخضروات والخبز الأسود المصنوع من الحبوب الكاملة من العوامل الوقائية المحتملة لسرطان الرئة.

وفي التحليل متعدد المتغيرات كان التدخين واستخدام فرن الطابون عوامل الخطر الرئيسية حيث أن استعمال السجائر يضاعف خطر الإصابة لثلاثة أضعاف واستخدام فرن الطابون لخمسة أضعاف وكانت AOR 2.980٪ (CI 95 : 1.154-7.69) و 5.047 (CI 95٪ 1.25-20.3 :) على التوالي.

الخاتمة: تبين من خلال نتائج الدراسة أن تعديل نمط الحياة قد يلعب دورا هاما في الوقاية من هذا المرض. وتوصي هذه الدراسة بزيادة الوعي بشأن سرطان الرئة في فلسطين وقد أثبتت أنه ليس مجرد مرض خاص بالمدخنين، إضافة إلى المطالبة بإنشاء برنامج وطني للكشف المبكر عن سرطان الرئة في فلسطين.

List of abbreviations

BJGH	**Biet Jala Governmental Hospital**
BMI	**Body Mass Index**
CI	**Confidence Interval**
Lung cancer	**Lung cancer**
MOH	**Ministry of Health**
OR	**Odds Ratio**
SCLC	**Small cell lung cancer**
SPSS	**Statistic Package for Social Sciences**
SCC	**Squamous cell carcinoma**
OSHA	**Occupational Safety and Health Administration**
DNA	**Deoxyribonucleic acid**
RNA	**Ribonucleic acid**
OCP	**Oral contraceptive pills**
CT	**Computed Tomography**
CVDs	**Cardiovascular Diseases**
ENT	**Ears, nose, and throat**

Table of contents

List of Tables

List of figures:

List of graphs:

Thesis chapters

This thesis is presented in 6 chapters as follows:

Chapter one: contains the background of the study, problem statement and study justification, and study aim and objectives.

Chapter two: includes related data (literature review) of a conducted international, regional and in country studies and researches

Chapter three: includes the study conceptual framework.

Chapter four: includes the study area, study methods, population, sampling, and sample size, ethical consideration will also include data collection, processing and analyzing.

Chapter five: presents the results.

Chapter six: includes discussion and recommendations.

Chapter One: Introduction

Background

Lung cancer (LC) is the most common malignancy that is characterized by its high mortality rates worldwide, it accounts for 1.69 million deaths yearly (WHO, 2015). It is second most common cancer in both men and women after breast cancer in women and prostate cancer in men (CDC, 2016).

The global incidence of lung cancer is increasing. It is the largest contributor to new cancer diagnoses that accounts for 12.4% of total new cancer cases and to death from cancer (17.6% of total cancer deaths). In 2012, about 1.8 million new cases were diagnosed, accounting approximately for 13% of all cancers (Cruz et al., 2011).

It is more common in males. The risk of developing lung cancer is higher among men in all age groups after age 40 years, and predominantly in persons aged 50-70 years. Lung cancer incidence among women is increasing in several parts of the world (Medscape, 2016).

Despite the availability of new diagnostic technologies, improvement in surgical techniques and the development of new biologic treatments, the overall 5-year survival rate for lung cancer in the United States is about15.6%.The situation globally is even worse, with 5-year survival in Europe, China, and developing countries estimated at only 8.9%. (Cruz et al, 2014).

LC is highly preventable disease but still remains among the most common and most lethal cancers globally. Several factors determine the occurrence of LC. On a population level, it is mainly determined by tobacco consumption, the main etiological factor in lung carcinogenesis. However, other contributory factors include genetic susceptibility, poor diet, occupational and environmental exposures such as air pollution, certain metals such as chromium, cadmium and arsenic; some organic chemicals; radiation; coal smoke; as

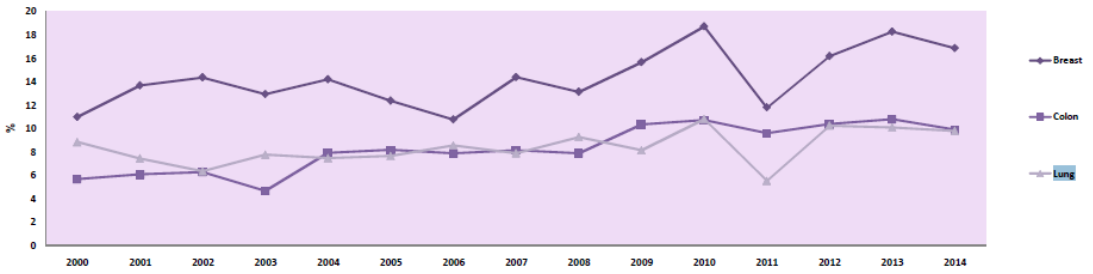
well as indoor emission of fuel burning , in particular among non-smokers (Amphora et al.,2016). In general, trends of lung cancer follow the trends in smoking, thus with increased smoking in developing countries, the incidence of lung cancer is expected to rise in the next coming years (WHO, 2012). Therefore, Lung cancer prevention is possible by avoiding smoking or quitting smoking, making healthy choices, such as physical activity and eating a healthy diet.

Study Problem

In Palestine lung cancer is the fourth reported cancer type and the leading cause of all cancers deaths in the general population (MOH, 2016). However, few local studies have been concerned with the determinants when discussing the epidemiology of lung cancer; which makes it a rich area for research in Palestine. Therefore, it is very important to specify the risk or protective factors in lung cancer locally.

1.3 Justification of the study

In Palestine lung cancer incidence rate was fluctuating between 7 to 10 per 100,000 from 2000 to 2014 as shown in the graph 1. Prevalence is in 2016, it was reported to be 8.3 per 100,000 in the general population (MOH, 2016).



Graph 2 Percentage of Top Reported Cancer from All Cancers, West Bank, Palestine, 2000- 2014.

Source: Palestinian Ministry Of Health, Health Annual Report Palestine. Palestinian Health Information Centre, 2014.

Lung cancer is the most common cancer type among Palestinian men. It constitutes about 13.6% of all cancers, while among women it is ranked as the 7th cause; i.e. about 3.5 % of all cancer types (MOH, 2016). Besides it is the main leading cause of cancer mortality in males which constitutes about 22.8 % of cancer deaths (Abu-Rmeileh et al, 2015).

It's shown in the literature that about one third of cancer cases are caused by preventable risk factors and sedentary lifestyle such as smoking, high body mass index, low fruit and vegetable intake, consuming large amount of saturated fats and calories besides physical inactivity (WHO, 2016).

Smoking is considered the major risk factors for LC. Therefore, its rates are of great importance when studying these risk factors. The Palestinian Central Bureau of statistics data (2015), showed that 24 % of persons aged 18 years and above in Palestine are reported as smokers (;40.9% among males & 5.4% among females) (PCBS 2015).

However, in the past two decades, Nargila smoking is becoming very common among the general population, in particular women. This type of smoking may carry additional risk for lung cancer since several studies showed association between its smoking and lung cancer. A large cohort study showed that active pipe smoking was associated with a relative risk for lung cancer of 5.0 (Henley et al, 2004).

Published national studies showed an increasing prevalence of water-pipe smoking especially among young Palestinian adults. A cross-sectional web-based survey in six Palestinian universities in 2015 found that the prevalence of current water-pipe smoking was 25.9%, with a higher prevalence among men (37.7%) compared to women (14.2%), and a higher prevalence in favor of water-pipe smoking compared to cigarette smoking (19.5%), the prevalence was higher in northern west bank compared to Gaza strip (Tucktuck et al., 2015). Moreover, a cross-sectional study among students at An-Najah National University in 2015 reported a water-pipe prevalence of 22.8%, and this was higher among males (35.5%) versus females (11.5%) (Abu Al-Halaweh et al., 2015).Furthermore, a cross-sectional study in seven universities in the Gaza Strip in 2013, found that 36.0% of the participants were exclusive water-pipe smokers (Abu -Shomar et al., 2013).

In never smokers, second hand smokers or environmental tobacco smoking (ETS) must be of great concern. Although there has been no predominant causal factor that can fully explain lung cancer in never smokers, the risk factors considered important for never smokers include secondhand smoke; radon exposure; environmental exposures, such as indoor air pollution, asbestos, and arsenic; history of lung disease; and genetic factors (Yang et al, 2011).

Since, to date, no published study investigated the determinants of LC in Palestine. This study results will be a baseline for any future research in this field and will help in developing polices and determining priorities in public health programs in the future, whether at the primary of secondary level of prevention and control.

1.4 Aim of the study

To investigate the determinants of lung cancer among Palestinians in two West Bank governmental hospitals.

1.5 Objectives

- To determine the magnitude of association between different lifestyle risk factors including, diet, smoking and the risk of developing lung cancer.
- To determine the association between family history of malignancy and lung cancer.
- To determine the association between socio-demographic factors and lung cancer.
- To investigate the association between medical and reproductive history of the patient, and the risk for lung cancer
- To determine the association between environmental and occupational exposures and lung cancer risk.

1.6 Expected outcome

The study of the determinants of lung cancer may help local decisions makers to specify the risk and protective factors of lung cancer among Palestinians, so they could introduce more public health awareness programs , stronger tobacco control policies and laws, and determine people at risk. Thereafter, preventive and screening programs are made focusing directly on these risk groups.

1.7 Study limitations

The main limitation of this study is the small number of the studied population and this was caused by the fact that most patients are diagnosed at late stage (having metastasis at diagnosis) and thus have bad prognosis and high mortality rate, besides that many lung cancer patients were referred to high qualified centers in cancer treatment such as Israel

and Jordan, thus couldn’t be included in the second part of our study. We could increase the study sample by doubling controls but unfortunately we didn't as the study took place in winter and finding controls not complaining of respiratory symptoms wasn’t feasible.

In the first part of the study we depend on medical files to have information about the patients and their risk factors and this may be not fully reliable data, since there is missed important information in many cases.

And as any case control and descriptive studies there may be some biases which might affect the results like information bias, recall bias, and reporting bias as the participants were patients and were trying either to deny the role of their lifestyle or to blame any other factors except themselves, so some participants answered some questions in a way to achieve their perception.

Limitation of time and finance prevent doing any further tests and imaging especially to exclude masses among controls.

The bad medical condition, depressed mood, respiratory and talking difficulties and the old age of most of the participants, all these factors result in difficulties in filling the questionnaire of patients.

Chapter Two: Literature review

Introduction

In this chapter, literature related to the epidemiology of lung cancer epidemiology will be presented.

2.1 Lung cancer epidemiology worldwide

Lung cancer is a serious public health problem (Jemal et al., 2011). Globally, lung cancer incidence is increasing. In 2012, about 1.8 million new cases were diagnosed, contributing to 13% of all new cancer cases (WHO, 2012). Also, it accounts for the highest mortality rate among all cancers in most countries, in both men and women, with industrialized regions such as North America and Europe have the highest rates. So lung cancer is the leading cause of cancer death and is the most common, and contributing to about 26% of all cancer deaths. (Cruz et al, 2011).

Despite that leukemia is the leading cause of cancer death for those men aged 20 to 39 years, lung cancer ranks first among men aged 40 years or older. While Breast cancer is the leading cause of cancer death in women aged 20 to 59 years, it is replaced by lung cancer in women aged 60 years or older (medscape, 2016).

There is a great variation in the prevalence of lung cancer in different geographical areas. However about 70% of all the new cases of lung cancer in the world arise in the developed countries. Central-Eastern and Southern Europe, and Northern America have the highest incidence (>50 per 10^5population) followed by moderate incidence countries which include: China, Korea, Japan, Western Europe, Turkey and Australia with a (35-50 per 10^5 population), and low incidence (<35 per 10^5 population) in countries including Latin America, most Asian countries, Scandinavia, and Middle and Western Africa (Abid et al., 2011).

The probability of developing lung cancer remains equal in both sexes until age 39 years. It then starts to increase among men compared with women, particularly African American men (Meza et al, 2015). Also the risk of developing lung cancer increases with *age.* Lung cancer occurs more commonly in older people that most of the patients diagnosed with lung cancer are 40 or older predominantly in persons aged 50-70 years. Lung cancer incidence among women is increasing in several parts of the world (American Cancer Society, 2016) (Medscape, 2016).

Despite the availability of new diagnostic technologies, improvement in surgical techniques and the development of new biologic treatments, the overall 5-year survival rate for lung cancer in the United States is about 15.6%. The situation globally is even worse, with 5-year survival in Europe, China, and developing countries is estimated at only 8.9%. (Cruz et al, 2014).

Apart from its high incidence, the seriousness of this type of cancer is being in its high mortality. Prognosis for lung cancer has hardly changed during the last year which is due to its symptoms and signs that are highly non-specific.

2.2 Lung cancer epidemiology in the Arab world.

Cancer burden in the Arab world indicates that the cancer incidence is increasing due to multiple factors such as westernized life style, aging and population growth (Salem et al, 2011).

Although Arab world is categorized among the low incidence countries (less than 35 per 10^5 population), still lung cancer prevalence is increasing. It is the most common cancer among males in Palestine, Bahrain, Qatar, United Arab Emirates (UAE), Jordan, Lebanon, and Syria, Arab Maghreb countries, including Algeria, Morocco, and Tunisia. It ranks as the 2nd in Kuwait, the 3rd in Oman; the 4th in Saudi Arabia, Mauritania and Sudan. Lung cancer was 3 times more common in Tunisian, Bahraini and Lebanese than Egyptian, Saudi or Emirati males, and nearly 5 times more common among the Bahraini and Lebanese females than the Omani, Qatari or Sudanese females (Abid L et al., 2011).

In general the median age of diagnosis of LC in the Arab countries is 60 years of age, for example, it is 60 years old in Egypt, 60.8 years in Qatar, 61.2years in Oman, 63.2 years in

Jordan, 63.4 years in U.A. Emirates, 65.8years in Saudi Arabia, 69.5years in Bahrain, 67.0 in Algeria and finally 70.0 years old in Kuwait (Salem et al, 2011).

Among Arab males the age standardized *rates* (ASR) is the highest in Tunisia with incidence of 33.4 per 100,000, followed by Bahrain 28.1 per 100,000, and Lebanon 27.3 per 100,000, while the lowest incidence rates were in Somalia, Djibouti and Sudan, which equal to 2.9, 2.9, 2.4 per 100,000, respectively. While Bahraini females had the highest incidence rate among all the Arab countries (10.5 per 100,000 females) followed by Lebanese females with ASR equal to 9.7 per 100,000 (Habib et al., 2016).

There is no regular national screening program for lung cancer in any Arabic country. However, most of Arab countries have anti tobacco public health program, but still more efforts should be done to minimize the burden of lung cancer and smoking in the Arab communities.

2.3 Lung cancer epidemiology in Palestine

Accurate epidemiological data on lung cancer in Palestine is not available since the national population-based cancer registry is lacking detailed and important data. However, official statistics of the Palestinian Ministry Of Health as well as institution and Hospital - based studies showed that it is the most common cancer in men and most common leading cause of cancer death (MOH., 2016).

Lung cancer ranked the first among reported cancer cases among males. It accounts for 13.6% of all reported cancer cases among Palestinian males in the West Bank.

The incidence rate among males was 11 per 100,000 populations, whereas in female it was 3.2 per 100,000**.** In cancer causing deaths among males, lung cancer was the main leading cause of death followed by colon cancer (MOH., 2016).

Incidence rate of lung cancer in Palestine is considered among the low incidence countries worldwide, but it is considered moderate when compared to other Arab countries (Salim et al., 2011).

2.4 Risk factors for LC

Multiple risk factors for lung cancer were investigated and some of them have greater importance than others. These risk factors can be grouped into two broad categories,

intrinsic factors and extrinsic or environmental factors. Intrinsic factors are inherent to the individual such as sex, age, genetic susceptibility, family history of cancer, and previous respiratory diseases, while extrinsic factors are extraneous to the individual and includes lifestyle factor (tobacco use, diet, obesity and physical activity), occupation and environmental pollution. Smoking in the main risk factor for developing lung cancer, and in general the trends of lung cancer follow the trends of smoking, thus with the increasing prevalence of smoking in developing countries, the incidence of lung cancer is expected to rise in the next coming years (WHO, 2012).

2.4.1 Lifestyle factors and LC

2.4.1.1 Tobacco smoking and Lung cancer risk

In table 2.1, we reviewed studies that were concerned with smoking that might be associated with lung cancer among different populations worldwide.

Tobacco was discovered in the New World by Christopher Columbus in 1492, then it became popular after the Industrial Revolution and continued to be popular until scientific studies in the mid-20th century demonstrated the negative health effects of tobacco smoking, including lung cancer. (Jung et al, 2016).

Medical evidence of the harm caused by smoking in relation to lung cancer was established since 200 years but it was generally ignored until five case-control studies relating cigarettes smoking to the development of lung cancer were published in 1950, one in the United Kingdom and four in the United States. The association was first reported by (Wynder & Graham 1950, Doll & Hill 1952), and a dose-response relationship has been studied by Doll and Peto who correlated the smoking habits of over 34,000 British physicians with mortality from LC over a period of 20 years and found a significant decline in tobacco consumption and mortality in this group in contrast to the general male population, in which neither mortality rates from lung cancer, nor tobacco consumption decreased (Doll et al., 1976). In 1983, Enstrom studied over 10,000 Californian physicians, and British female doctors (Doll et al. 1980) study found similar conclusions.

Now it's well established that cigarette smoking is responsible for over 80 percent of all lung cancer cases (IASLC. 2015), in addition to that lung cancer death risk is around 15 times higher in current smokers compared with never-smokers (Doll et al., 2005).

2.4.1.2 Water-pipe smoking and Lung cancer risk:

In table 2.2, we reviewed the studies that were interested in finding relationship between water-pipe smoking and lung cancer.

Despite the fact that water-pipe contains a wide range of human carcinogens, the contribution of water-pipe smoking to carcinogenesis is not well established. However many studies confirmed that water-pipe smoking increases lung cancer risk, exactly like cigarettes smoking (up to 9 folds) (Boffetta et al.,1998, Gupta et al, 2001), in other studies the risk of lung cancer was increased by water-pipe smoking for up to 6 folds , less than risk from tobacco smoking ,(OR 6.0 (1.78–20.26) (OR 5.83, (95% CI 3.95-8.60, $p < 0.0001$) (Auon et al, 2013) (Koul et al., 2011) respectively.

Lubin and his colleagues (1992) found that water-pipe smoking is less deleterious than cigarettes smoking (Lubin et al., 1992). The odds ratio for tobacco among smokers was 2.6 (95% CI 1.1-6.2), while for water-pipe was 1.8 (95% CI 0.8-4.2).

2.4.1.3 Second-hand smoking and Lung cancer risk

In table 2.3, we reviewed studies that were concerned with smoking that might be associated with lung cancer among different populations worldwide.

Secondhand smoking which is the exposure to environmental tobacco smoke (ETS) also increases the risk for lung cancer. The increased risk was noted in1981 in a study of non-smoking wives of heavy smokers in Japan (Hirayama, 1981). Numerous case- control studies (Chan-Yeung et al., 2003, Asomaning et al., 2008 , Kim CH et al., 2014) and cohorts (Jee et al., 1999 ,Kurahshi et al., 2008 , Wang et al 2015) have consistently concluded a small but real risk for lung cancer. Also, according to those studies, there is a dose-response relationship between a non-smoker's risk of lung cancer and the number of cigarettes and years of exposure to smoke, which gives more evidence that the association between environmental smoking exposure and lung cancer is causal (Hackshaw *et al.* 1997).

2.4.1.4 Diet and the risk of Lung cancer

In table 2.4 we reviewed the studies that examined the relationship between dietary habits and lung cancer risk among different populations worldwide.

The suspicion that diet could also have an effect on lung cancer risk was raised in the 1970s when it was noted that after allowing for smoking, increased lung cancer risk was associated with a low dietary intake of vitamin A (Bjelke, 1975). Following that study many case controls studies have found that lung cancer patients usually consume less fruits, vegetables and related nutrients than controls (Huakang et al., 2016, Gorlova et al., 2008).

Tarabeia J and colleagues (2013) in their study in Israel concluded that traditional cooked vegetables, typical of a Mediterranean Arabian diet had a strong protective effect against LC.

In vitro assessment of cytotoxic and antioxidant activities of grape leaves in Palestine suggests effective cytotoxic activity of Shami grape leaves against lung cancer cells (Harb et al., 2015).

The possible effect of fruits and vegetables consumption on lung cancer risk is still controversial. This apparent relationship could be due to confounding by smoking; because smokers generally consume less fruits and vegetables than non-smokers, but there may be some protective effect of these foods (Wang., 2015).

Heavy consumption of nuts was shown to be associated with a lower overall risk for developing lung cancer regardless of cigarette smoking status and other known risk factors, according to Lee JT and colleagues (2017) study from two large population-based cohort studies.

A case control study found that the increased intake of major sources of Magnisum intake such as bread, banana and nuts were found to have a significant inverse trend with lung cancer risk (Mahabir S et al., 2008).

Association between the consumption of dairy products and poultry and lung cancer risk was studied in many cohort and case control studies, but no enough evidence and relationship was found.Heavy alcohol consumption was found to be a risk factor for Lung Cancer in many studies (Fernández et al., 2017, Kiyohara et al., 2010), while other studies found that it has protective effect. For example, Bae J and colleagues (2002) estimated the relative risk for cancer to be 0.80 (95% CI = 0.48 - 1.33). Other studies relating lung cancer risk to alcohol consumption are summarized in table 2.5.

2.4.1.5 Obesity and physical activity and lung cancer

Despite the fact that obesity is a risk factor for many cancer types, the association between obesity and the incidence of lung cancer remains unclear and inconclusive.

The results of a meta-analysis indicated that obesity and overweight are protective factors against lung cancer, especially in current and former smokers. Besides, the stratified analyses showed that excess body weight was inversely associated with squamous cell carcinoma and adenocarcinoma. (Yang et al, 2013).

El-Zein and her colleagues in their case control study observed an inverse association between BMI 2 years before the index date and lung cancer and that appeared to be largely independent from smoking patterns. Its interpretation may be caused by the preclinical weight loss or to the presence of a true relationship between BMI and lung cancer. (El-Zein et al., 2013). In a large population based cohort in UK low BMI was associated with higher lung cancer risk but this risk was driven by current smokers and previous smokers, and was attenuated or disappeared in never smokers (Bhaskaran K et al., 2014).

In a pooled analysis of nested case-control study, a reduced risk of lung cancer was observed for those who were overweight and obese. Also, there was a decreased risk for lung cancer among current, former and never smokers. For underweight current smokers, former smokers or never smoker no statistical association was found with lung cancer (Sanikini et al. 2018).

Physical inactivity is not recognized as a well-established risk or prognostic factor for lung cancer. A population based case control study has found that increasing recreational physical activity was associated with a lower risk of lung cancer in both males and females, on the other hand increasing occupational physical activity was associated with higher risk among males but not females (Ho V et al., 2017). However, a recently published study case-control found that lifetime physical inactivity is an independent risk and prognostic factor for lung cancer. This association was found to remain significant among never smokers and non-smokers. Moreover, they found a significant positive association between lifetime physical inactivity and lung cancer mortality but was significant in non-smokers (Cannioto et al., 2018).

The reviewed studies about the association between lung cancer risk and obesity and physical activity are summarized in table 2.6.

2.4.2. Family history and the risk of lung cancer:

In table 2.7 we reviewed the studies that explored the relationship between family history and lung cancer risk among different populations worldwide. As shown in the table, a study shows an increased for lung cancer prevalence among the close relatives of lung cancer patients, even after adjustment for smoking habits whereas family history of overall cancer was not associated with an increased risk of lung cancer (Nitadori., et al 2004). Also, lung cancer was estimated to be 4 folds higher among the non-smoking relatives of lung cancer patients diagnosed before the age of 60 years compared with non-smokers without a family history of lung cancer, odds ratio (OR) 4.89; 95% (CI): 1.47–16.25) (Cassidy et al, 2006).

However the contribution of familial effects appears to decrease by age and smoking is the main cause of lung cancer (Hjelmborg, et al. 2016)

2.4.3 Occupational exposures and the risk of lung cancer

In table 2.8, we reviewed studies that were concerned with association between lung cancer risk and occupational exposures among different populations worldwide.

It is estimated that 21% of men with lung cancer and 5% of women are caused by occupational exposures. The commonest is in occupations linked to asbestos exposure, besides the well known risk for pleural malignant mesothelioma, typically builders, plumbers, gas fitters, carpenters, electricians, workers in metal plate and construction ,and fitters constitute the largest high-risk groups., with an estimated 6-8% of all lung cancer in the being associated with asbestos exposure (Brown et al., 2012).

Environmental exposure to asbestos does not increase the risk of lung cancer (Camus *et al.* 1998). According to Selikoff and colleagues *(*1968), there was a five-fold increase in the incidence of lung cancer in non-smokers, and a 61-fold increase in those who are being exposed to both asbestos and cigarettes smoking. The synergistic effect can be explained by the inhibitory influence of cigarette smoke upon the clearance of asbestos (Churg et al. 1987).

Radon decay products contribute to the risk of lung cancer by forming deposits when inhaled and then damaging the respiratory system. It is a naturally-occurring odorless radioactive gas which emanates from uranium in the soil. The elevation of lung cancer risk has been noted among uranium miners in Colorado and iron ore miners in Sweden (Archer *et al.* 1974, Radford et al 1984). Radon exposure may increase lung cancer risk among smokers up to threefold (Samet, 1989).

Exposure to radiations in mines of radium, uranium increases the incidence of LC by 10-30 times, also other industrial pollutants such as beryllim, chrome, nickel, and arsenic are involved in LC etiology. Atmospheric pollution in the cities by aromatic hydrocarbons resulting from incomplete combustion of fuel has carcinogenic properties (Gherasim, 2002, Tirmarche et al., 2011).

A hospital based Case control study in Lebanon found that indoor pollution factors were potential risk factors of lung cancer (Auon et al., 2013).

Studies in Asia have shown a relation between lung cancer and coal used as fuel for cooking in poorly ventilated spaces (Lan et al., 2008). Using coal for indoor cooking throughout life resulted in an elevated lung cancer risk (OR: 7.5; 95% CI 2.2-25.9) among non-smokers in a study in Indian (Sapkota et al, 2008). It is estimated that about half of the global population uses solid fuels for cooking, usually in poorly

ventilated spaces (Rehfuess, 2006).

2.4.4 Socioeconomic status and LC risk

In table 2.9 we reviewed the studies that explored the relationship between lung cancer risk and socioeconomic factors among different populations worldwide.

Socioeconomic factors such as education and income level and social class have a significant effect on an individual's general health. Socio-economic status and education level also play important role in causing lung cancer.

Mitra and colleagues (2016) found that significant inverse association between the indicators of socioeconomic status and lung cancer risk, that there was a stepped gradient by educational attainment, with the highest incidence among men and women with lowest level of education (RR 2.52 CI 95% :2.38-2.68) and lowest income (RR=1.82,CI95%:

1.76-1.90).Similar results were found by Hruba and colleagues (2009) lower education causes a 1.35 increase in LC risk (95% :1.03–1.77) also (Mukti et al,2013 , Hashibe , 2010) had similar association in their studies.

Risk for lung cancer was increased in large families, most likely because of an association with low socioeconomic status (Altieri, 2007).

Furthermore, according to Aldrich in his study (2013), socioeconomic factors may play a greater role than genetic predisposition to lung cancer among African Americans.

2.4.5 Medical history and the risk of lung cancer

In table 2.10, we reviewed studies that were concerned with association between lung cancer risk and the medical history and status of the patient.

Lung cancer risk is elevated in survivors of several cancers. Specially previous breast cancer (Maddams et al 2007, Lorigan et al., 2010) and Hodgkin's lymphoma. This risk is related to previous thoracic radiotherapy (Ibrahim et al., 2013). Lung cancer is twice more common in patients with chronic bronchitis or bronchiectasis (Schottenfeld., 2010). A study in Bangladish by Mukti and her colleagues (2013) found that chronic lung disease is a strong risk factor for lung cancer (OR=1.7778, P = 0.1090).

2.4.6. Reproductive hormones and the risk of lung cancer

In table 2.11, we reviewed studies that were concerned with association between lung cancer risk and hormonal factors among different populations worldwide.

In a therapeutic clinical trial in USA and Canada , it was confirmed that women with lung cancer to be postmenopausal at diagnosis, to have a history of oral contraceptive pills (OCP) use, to have their first birth at a younger age, and to have never breastfed (Cheng et al, 2017).

Premenopausal endogenous hormones appear to have a protective role in developing lung cancer specifically, with later age at menopause (Pesatori et al., 2013).

Baik and his colleagues (2010) in their study found that lung cancer risk increases with longer duration of OCP use. While another study stated that women with previous use of estrogen plus progestin were at reduced risk for LC (HR=0.84; 95% CI 0.71-0.99) (Schwartz et al., 2012).

Table 2.1: Studies on cigarettes smoking and the risk of lung cancer.

Authors	Location and date	Study design	Sample size	Conclusion
(Hjelmborg J, et al.)	Europe ,2016	Population-based cohorts	115,407	The contribution of familial effects appears to decrease by age and smoking is the main cause of lung cancer.
(Chulasiri P et al)	Sri Lankan ,2016	A hospital based case-control study	62 : 248	Cigarettes smoking is a strong risk factor for Lung cancer
(Rennert., et al.)	Israel and the USA ,2015	A population-based case–control study	5731 : 5231	Smoking is a very strong risk factor for lung cancer
(Wang et al., et al)	USA ,2015	a prospective cohort study	93 676	Lung Cancer incidence was much higher in current smokers and former smokers in a dose-dependent manner
(Papadopoulos A., et al)	UK, 2014	A population-based case–control study	2926 : 3555	Heavy smoking might confer to women a higher risk of lung cancer as compared with men.
(Sifaki-Pistolla.,et al.)	Greece ,1992–2013	A Population based – prospective cohort	590,000	There is constantly increasing trends of lung cancer incidences among smokers
(Fukumoto K., et al)	Japan 2014	A Population based -Case control	653 : 1281	Inhalation of cigarette smoke is a significant risk for LC independent from pack-years
(Seki T., et al)	Japan , 2013	A hospital based case-control study	1670 :5855	Ever-smoking was significantly associated with a higher risk of squamous cell and small cell carcinoma.
(Bracci et al.)	USA ,2012	A population-based case-control study	6039 : 2073	Risk of LC was significantly increased with increasing in pack-years of smoking and decreased with increased years since quitting
(Pavlovska I., et al)	Macedonia, 2012	A hospital based Case-control	185 : 185	Smokers had five fold risk to have LC in relation to the non-smokers..
(Kukulj S., et al)	Croatia ,2012	A retrospective cohort study	212	Smoking is the main cause of lung cancer
(Pesch B.,et al)	2012	A pooled analysis of case control studies	29179	Smoking exerted a steeper risk gradient on SqCC and SCLC than on Adenocarcinoma.
(Powell HA., et al)	UK ,2000-2009.	A population-based case control study	12,121: 48,216	Moderate and heavy smoking carry an increased risk of LC in Women more than in men
(Freedman.,et al.)	USA ,2008	A prospective cohort study	463,837	Smoking was associated with increased lung carcinoma risk in both men and women.
(Osaki Y., et al)	Japan ,2007	A Retrospective Cohort	16,383	Confirmed the risk estimates of smoking for LC incidence

		Study		
(Bae J M.,et al)	Korea ,2007	prospective cohort study	14,272	The cigarette smoking is the major risk factor that increases the risk of LC up to four folds compared to non-smokers.
(Jee et al., 1999)	Korea,1999	A prospective Cohort study	157 436	Risk of LC increased with increasing duration and amount of cigarettes smoked.

Continue Table 2.1….

Table 2.2: Studies on water-pipe smoking and the risk of lung cancer.

Authors	Location and date	Study design	Sample size	Conclusion
(Auon J., et al)	Lebanon ,2013	A hospital based Case control study	50 : 100	Waterpipe smoking was significantly correlated with LC risk.
(Koul P A., et al)	India ,2011	A hospital based Case control study	251 :500	Hookah smoking is associated with a significantly increased risk for LC (up to six folds compared to non smokers).
(Gupta D.,et al)	India 2001	A hospital based Case control study	265 : 525	Smoking of WP increases lung cancer risk in similar rates of that of cigarettes
(Henley SJ., et al)	USA,1982-2000	A Prospective cohort study	138 307	Relative risks of LC were statistically significant higher with increased number of pipes smoked per day, years of smoking, and depth of inhalation and decreases with years after quitting.
(Boffetta P.,et al)	Europe ,1998	Case–control studies	5621 : 7255	Smoking of pipe tobacco might exert a carcinogenic effect on the lung comparable to that of cigarettes.
(Lubin JH., et al)	China, 1992	A population-based case-control study	427 : 1,011	Water pipe smoking is less deleterious than cigarettes smoking

Table 2.3: Studies on secondhand smoking and the risk of lung cancer.

Authors	Location and date	Study design	Sample size	Conclusion
(Wang., et al)	USA ,2015	a prospective cohort study	93 676	Risk of LC tended to be increased in nonsmokers with adult home passive smoking exposure ≥30 years, compared with nonsmokers without adult home exposure.
(Kim CH., et al.)	USA ,2014	18 Case control studies	12,688: 14,452	The risk of LC among those ever exposed to secondhand smoke with is higher than those who never exposed.
(Peres J)	USA ,2013	Prospective cohort study	76,000	No Clear association between passive smoking and Lung cancer risk.
(Asomaning.,et al.)	USA,2008	A hospital based Case control study	1669 :1263	Individuals exposed to SHS have an increased risk of LC , also who first exposed before age 25 have a higher LC risk compared to those who are exposed after 25 years old.
(Kurahshi,.et al.)	Japan 2008	A population-based prospective cohort study	28,414	Women who live with smoking husbands have higher risk for LC than whose husbands were not , that association was clearly identified for adenocarcinoma.
(Chan-Yeung ,.et al)	China, 2003	A hospital based Case–control study,	331 :331	Among women, exposure to SHS at home and or at work was a risk factor for lung cancer.
(Jee.,et al)	Korea,1999	A prospective Cohort study	157 436	Relative risk for the wives of current smokers is higher than relative risk for the wives of former smokers.

Table 2.4: Studies on dietary factors and the risk of lung cancer

Authors	Location and date	Study design	Sample size	Conclusion
(Huakang Tu1.,et al)	USA , 2016	A hospital based case-control study	2139 :2163	The fruits and vegetables and "American/Western" patterns of food reduce lung cancer risk.
(Lee JT., et al)	USA ,2017	Two large population-based cohort studies, EAGLE and AARP	2,098 18,533	Nut consumption was inversely associated with LC , this association is independent of cigarette smoking and other known risk factors.
(Hosseini M.,et al)	Iran ,2014	A hospital based case-control study	242 : 484	Vegetables, fruits, and sunflower oil were found to be possible protective factors and bread, rice, beef, liver, dairy products, could be risk factors for the development of lung cancer.
(Tarabeia J., et al)	Israel, 2013	A nested case-control study	149 :284	Traditional cooked vegetables, typical of a Mediterranean Arabian diet had a strong protective effect against LC.
(Gnagnarella P.,et al)	Italy 2004–2010	A prospective Cohort study	4336	High vegetable intake and adherence to the "vitamin and fiber" nutrients was associated with reduced LC incidence.
(Mahabir., S et al)	USA, 2008	A population based case–control study,	1139 : 1210	A significant inverse trend with increased intake of dark bread, banana and nuts with lung cancer risk was found
(Gorlova O.F., et al)	USA, 1995–2008	A hospital based Case-control study	299 :317	Healthy eating patterns are associated with a significant reduction of LC risk among never smoker.
(Anic G.M.,et al)	USA ,1995–2006	A prospective Cohort study	460 770	Diet may have a modest role in decreasing LC risk, especially among former smokers.
(Feskanich D.,et al)	USA 1986 -1990.	A prosepective Cohort study	125,061	Fruits & vegetable consumption was associated with a lower risk of lung cancer among the women but not among the men.

Table 2.5: Studies on alcohol and the risk of lung cancer.

Authors	Location and date	Study design	Sample size	Conclusion
(Fernández-S A., et al)	Spain, 2017	A hospital-based case-control study	402 :383	High consumption of alcohol might increase the risk of LC.
(Kiyohara Ch.,et al)	Japan, 2010	A hospital based case-control study	462 : 379	Excessive alcohol intake cause a significantly higher risk than drinkers with appropriate intake.
(Bagnardi V.,et al)	Italy , 2009.	A population-based case-control study	2,100 :2,120	Heavy alcohol consumption was a risk factor for LC among smokers.
(Tse L A.,et al)	China 2004–2006	A nested Case control study	1208 1069	A possible synergistic effect between alcohol consumption and familial susceptibility for LC might be exist.
(Bae J., et al)	Korea. 1993 to 2002,	A prospective cohort study	13,150	Alcohol consumption showed no statistically significant association with the risk of LC.

Table 2.6: Studies on BMI & Physical activity and the risk of LC.

Authors	Location and date	Study design	Sample size	Conclusion
(Cannioto R., et al)	USA 2018	hospital based case control study.	660: 1335	A significant positive relationship was found between lifetime physical inactivity and lung cancer risk: [Odds ratio (OR)=2.23, (CI): 1.77-2.81]; the association remained significant among never smokers (OR=3.00, 95% CI:1.33-6.78) and non-smokers (OR=2.33, 95% CI: 1.79-3.02).
(Ho V., et al)	Canada 2017	a population-based case-control study	727: 1,351	Increasing recreational PA was associated with a lower lung cancer risk for both sexes(OR_{MEN} = 0.66, (CI: 0.47-0.92); OR_{WOMEN} = 0.55, (CI :0.34-0.88). While increasing occupational PA was associated with higher risk among men (OR_{MEN} = 1.96, (CI: 1.27-3.01).
(Bhaskaran K., et al)	UK 2014	a population-based cohort study	5·24 million	BMI is inversely associated to lung cancer risk in smokers , but no association was found in never smokers.
(El-Zein M.,et al)	Canada 2013	A population-based case-control study	1,076: 1,439	Among those who were underweight at age 20, there was a decreased risk of lung cancer (OR = 0.69, 95% CI: 0.50-0.95).on the contrary, lung cancer risk was higher among those who were underweight 2 years before enrollment (OR = 2.30, 95% CI: 1.30-4.10).

Table 2.7: Studies on family history and the risk of lung cancer.

Authors	Location and date	Study design	Sample size	Conclusion
(Chen L.S. et al)	USA , 2011	A cross sectional study	5,586	Family history of lung cancer increases LC risk among never smokers
Coté et al.	USA ,2012	A case control study.	24,380 :23,305	Positive family history of lung cancer is an independent risk factor for LC.
(Cassidy A et al)	UK ,2006	A population based case–control data	579 :1157	A history of LC in first-degree relatives was associated with a significantly elevated risk of LC among those diagnosed before the age of 60 years.
(Nitadori J., et al)	Japan. 1990-2003	A Population-Based Cohort Study	102,255	A family history of lung cancer in a first-degree relative was associated with a significantly higher risk of lung cancer, whereas family history of overall cancer was not associated with an increased risk of lung cancer.
(Filho V W., et al)	Brazil , 2002	A Hospital-based case-control study	334 :578	A mildly increased risk of LC among persons with a positive history of lung cancer

Table 2.8: Studies on occupational factors and the risk of lung cancer.

Authors	Location and date	Study design	Sample size	Conclusion
(Tual.,et al.)	USA, 2016	A prospective cohort study	51,113	There was an increased risk of LC among daily drivers of diesel tractors farmers.
(Lacourt.,et al.)	Canada,2015	A population based case-control study.	1593 : 1427	Mildly elevated LC risk of lung cancer for individuals who worked in the construction industry.
(Villeneuve PJ., el al)	Canada , 2012	A population-based case-control study	1,681 :2,053	Asbestos exposure in Canadian workplaces increased the risk for LC.
(Wild P., et al)	France, 2012	A population-based case–control study among	246 : 531	Occupational factors are important risk factors and should be considered when defining high-risk lung cancer populations.
(Olsson, A C.et al)	Europe and Canada ,2010	11 case–control studies	13,304: 16,282	Occupational exposure to diesel motor exhaust increase the risk of LC.

Table 2.9: Studies on socioeconomic factors and the risk of lung cancer.

Authors	Location and date	Study design	Sample size	Conclusion
(Mitra D., et al)	Canada,2015	A prospective cohort study	2,734,835	Socioeconomic status (SES) is inversely associated with LC risk
(Aldrich.,et al)	USA,2013	A hospital based case–control study	368 :579	Socioeconomic factors may have a greater effect than genetic predisposition to LC
(Mukti R F., et al)	Bangladesh ,2013	A hospital based case–control study	65: 85	Socio-economic status and education level play important role in causing LC.
(Hrubá1 F., et al)	Central Europe countries, 2009	A population based case–control study	3,403 :3,670	Significant inverse association was found between the indicators of socioeconomic status and the risk of LC.
(Hashibe M., et al)	Nepal, 2010	A hospital-based case-control study	209 : 313	Individuals who had lower education had higher risk of LC.
(Grubb M D., et al.)	USA, 2000-2009	A cross sectional study	222,500	Poverty was positively and significantly associated with lung cancer.

Table 2.10: Studies on medical status and the risk of lung cancer.

Authors	Location and date	Study design	Sample size	Conclusion
(Streb G,. et al)	USA, 2016	Cross sectional study	730	Patients with DM were more likely to have poorly differentiated LC tumors at time of diagnosis
(Liu., et al.)	Sweden ,2015	A retrospective cohort study	439 ,455	Patients with asthma had an elevated risk of cancer. Also cancer patients with previous asthma had a worse prognosis compared with those without asthma.
(Tseng CH.,et al)	Taiwan ,2014	A Prospective cohort study	996,950	Diabetes was significantly associated with a higher risk of LC.
(Powell., et al)	UK ,2013	A nested case-control study	11,888 :37,605	COPD diagnosis is strongly associated with a diagnosis of LC, but this association is largely explained by smoking habit, so it seems unlikely, therefore, that COPD is an independent risk factor for LC.
(Mukti R F., et al)	Bangladesh ,2013	A hospital based case–control study	65: 85	Chronic lung disease is a strong risk factor for lung cancer.
(Yu.,et al.)	Taiwan ,2011	2 Prospective cohort studies.	4480 TB 712,392 no TB	The incidence of LC was approximately 11-fold higher in the cohort of patients with tuberculosis than nontuberculosis individuals..
(HALL G C., et al)	U.K, 2005	A Prospective cohort study	334,120	No increased risk of LC in diabetes was found
(Boffetta P., ET AL)	Sweden , 1965–1994	A prospective cohort study	92,986	Asthma patients were at increased risk of lung cancer, but there was no heterogeneity in risk between the sexes.

Table 2.11: Studies on reproductive hormones and the risk of lung cancer.

Authors	Location and date	Study design	Sample size	Conclusion
(Cheng TY D., et al.)	United States and Canada, 2017	Therapeutic clinical trial.	813	Smoker women with LC were more likely than never smokers to be postmenopausal at diagnosis, to have a history of OC use, to have their first birth at a younger age, and to have never breastfed
(Schwartz A.,et al.)	USA ,1998 - 2012	A prospective cohort study	160,855	Women with previous use of estrogen plus progestin were at reduced risk for LC.
(Pesatori et al.)	Italy ,2013	A Population case-control study	448 :500	Premenopausal endogenous hormones appear to have a protective role in LC development. Specifically, with later age at menopause
(Baik., et al)	USA , 2010	A Prospective cohort study.	107,171	Longer duration of OCP use and younger age at menopause were associated with increased risk of LC.

Chapter Three: Conceptual Framework

In this chapter the study major definitions, concepts, factors, and the study conceptual framework will be presented.

3.1 . Lung cancer definition

Lung cancer is also called as lung carcinoma or bronchogenic carcinoma, and is defined as malignancies which originate in the cells lining the bronchi, bronchioles, and alveoli. Most lung cancers are classified as either small cell lung cancer (SCLC) or non-small cell lung cancer (NSCLC) which accounts for approximately 85% of all lung cancers. It can be further classified into three major subtypes as adeno-, squamous cell, and large cell carcinomas (*Molina, et al*.2008). This classification is required for staging, treatment, and prognosis (Up to date, 2016).

3.2. Pathophysiology of lung cancer:

Primary lung cancer was first recognized as a distinct disease in 1761, long before the advent of cigarette smoking **(**Maorgagni G,1761). The pathophysiology of lung cancer is complex and not completely understood. The genes involved in the pathogenesis produce proteins that influence in cell growth, cell cycle processes, differentiation, apoptosis, tumor progression, and immune regulation (Mazzone et al, 2014). The beginning of lung cancer pathogenesis is with carcinogen-induced events and with long period of promotion and progression in a complex multistep process. For example, cigarette smoke initiates carcinogenesis. Continued smoke exposure thus provides a large population of initiated cells and increasing the chance of transformation, and additional mutations accumulate and cause chronic irritation by promoters like nicotine, phenol, and formaldehyde. The time between starting smoking and cancer occurrence is typically long, taking about 20-25

years for cancer development. Cancer risk declines after smoking cessation, but existing mutated cells may progress if another carcinogen carries on the process (Wu et al., 2011).

The symptoms produced by the tumor depend on its location (central versus peripheral tumor). Central tumors generally cause cough, dyspnea, atelectasis, pneumonia, wheezing, and hemoptysis; in addition to causing cough and dyspnea, peripheral tumors may cause pleural effusion and pain as due to infiltration of parietal pleura and the chest wall. (Wu et al., 2011).

Cough is the most common symptom is produced by irritations of the cough receptors in the airway, it is more common in squamous cell carcinoma and SCLC (generally found in the central airways).Weight loss is the second most common symptom; it happens because cancer induce break down and adipose tissue and muscles. Other presenting symptoms are hemoptysis, dyspnea and chest pain. (Wu et al, 2011).

As the tumor grows, some of the cells break off and spread to other parts of the body through the lymph or the blood, a process known as metastasis. Lung tumors metastasize to adjacent or distant organs, when cancer cells infiltrate in the Mediastinum, they may cause Superior vena cava syndrome (obstruction), pericardial effusion , pleural effusion, and dysphagia, while distant metastatic sites include brain, bone, liver and adrenal glands. (Wu et al., 2011).

Paraneoplastic syndromes are symptoms that occur in cancer patients but not caused by tumor compression or invasion include:

- Ectopic Cushing syndrome that cause gaining weight, hypertension, hypokalemia, and muscle weakness.
- Syndrome of inappropriate antidiuretic hormone production (SIADH) which occur due to ectopic secretion of antidiuretic hormone that increase retaining free water in collecting ducts and thus cause hyponatremia and concentrated urine.
- Hypercalcemia is caused by overproduction of PTHrP that act like parathyroid hormone to increase bone desorption and calcium re-absorption by kidneys and thus increasing calcium concentration in blood.

- Hypertrophic osteoarthropathy and digital clubbing; presented as painful symmetrical arthritis of the ankles, knees, wrists and elbows, besides digital clubbing. Its caused by secretion of various factors such as prostaglandin E2 and others that result in periosteal proliferation of the tubular bones. (Wu K et al, 2011).

3.3. Lung cancer determinants risk factors models:

In this study, we adapted the Mayo clinic risk factors of lung cancer as our study model. They defined the LC risk factors into endogenous or exogenous (Mayo clinic, 2018). In figure 3.1, the study factors are presented. In the following sections, these factors are explained further:

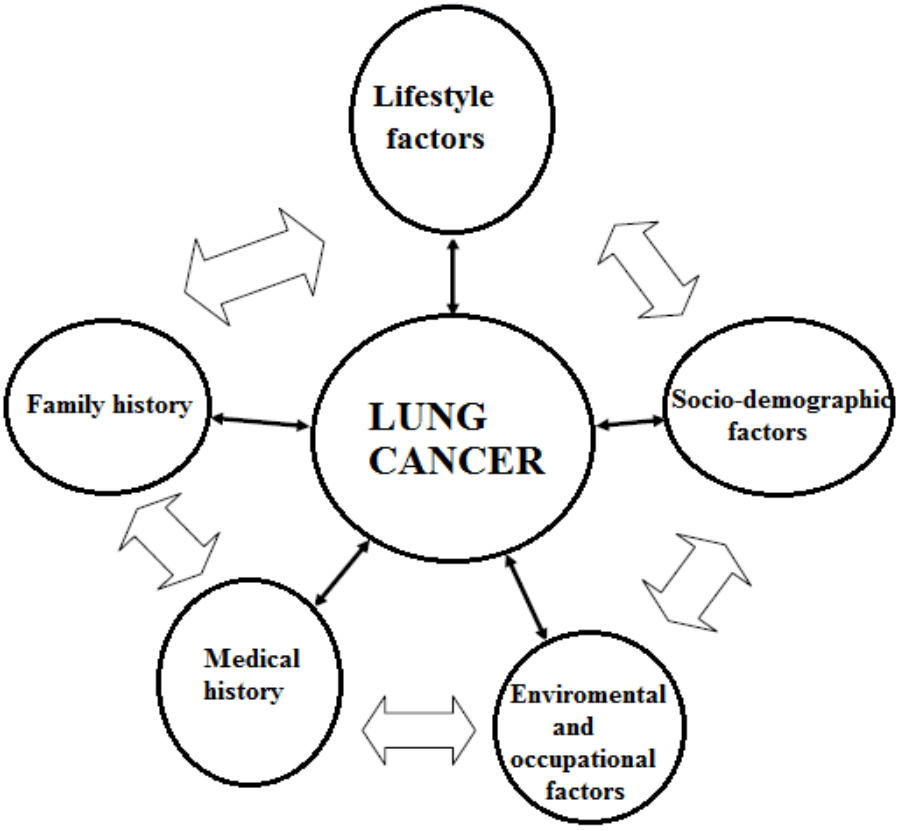


Figure 3.1: The Study conceptual framework (lung cancer determinants and risk factors)

Endogenous factors such as personal and family history of malignancy, also the risk of developing lung cancer is higher among men in all age groups after age 40 years, and predominantly in persons aged 50-70 years. However Lung cancer incidence among women, is increasing in several parts of the world (Medscape, 2016).

Exogenous factors are factors that are found to be associated with lung cancer such as lifestyle factors including smoking, exposure to second-hand smoke, exposure to radon gas, exposure to asbestos and other carcinogens.

3.3 Lung cancer determinants and risk factors:

1. Lifestyle factors: cigarettes smoking is the number one cause of lung cancer (accounts for about 90% of cases), other forms of smoking such as pipes may also increase the risk for lung cancer.

2. Environmental and occupational exposures ; such as silica , asbestos, arsenic beryllium, cadmium, chromium, nickel and diesel fumes, besides radon gas which is the second cause of lung cancer.

3. Socio-demographic factors; male and adults have higher risk.

4. Family history of lung cancer; may be explained by similar exposures.

5. Medical history; patients with chronic interstitial lung disease or HIV are more exposed to get lung cancer.

3.3.1 Smoking:

Smoking as an identified risk factor for lung cancer including: active cigarette smoking, passive smoking (exposure to secondhand cigarette smoke) (Furrukh, 2013), third hand smoking "nicotine and other residual chemicals left on surfaces by tobacco smoke (Mayo clinic, 2016)" and pipe and cigar smoking (Alberg et al., 2008).

Tobacco came from the leaves of plants Nicotiana. It is used as a drug, in bioengineering, and as ornamental plant. Rustica and Nicotiana tabacum are the main commercial species, with alkaloid nicotine is the addictive constituent of tobacco responsible for its addiction and tolerance. Tobacco proceeded and cured for many days (oxidation, degradation, and stripping), so the cured tobacco became more inhalable and carcinogenic.

Cigarettes contain high levels of acrolein, that is toxic to the cells lining the lungs, besides nitrogen oxides, acetaldehyde, phenols, and formaldehyde, which could be carcinogenic, as well as free radical which induce oxidative damage. (Furrukh, 2013).

To make them extractable tobacco carcinogens are metabolized by *cytochrome P-450* enzymes. And infrequently others (e.g. *Lipoxygenase, cyclooxygenase, myeloperoxidases, and monoamine oxidases*). The oxygenated metabolites undergo further transformations; detoxification and secretion by *glutathiones, sufatases,or uridine-5'-diphosphate-glucuronosyltransferases*.Few of the metabolites generated during these processes react with the DNA to synthesize DNA adducts in a process called metabolic activation. Carcinogens *including polcyclic aromatic hydrocarbons and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone* have to go into metabolic activation to express their carcinogenic effects. The damage could be repaired, or apoptosis may be induced, but miscoding may produce permanent mutations, like *K-Ras, p53, p16, fragile histidine triad protein,* or others.And that cause the suppression of tumor suppressor genes or the activation of Onco-genes. So the susceptibility of developing lung cancer depends on the balance between the metabolic activation and detoxification of potential carcinogens in smokers. About 20 potential carcinogens in 3,500 chemicals have been found in a burning cigarette. (Furrukh. M ,2013).

3.3.2. Dietary factors and alcohol consumption

It is believed that behavioral modifications such as reduced carbohydrate intake, caloric restriction, structured exercise, and/or pharmacologic interventions such as the use of metformin, in obese populations may help to reduce their cancer risk (Hopkins et al., 2016).

Although many studies analyzed the association between different dietary habits and lung cancer, most results are controversial or unclear. Of the well established inverse relationship was that high fruit and vegetable consumption is associated with a lower risk of lung cancer; Fruits and vegetables containing carotenoids and other antioxidants have been hypothesized to decrease lung cancer risk, but many case control and cohort studies failed to confirm this relationship and concluded that it may be confounding by smoking (Vieira.et al., 2015)

The risk for lung cancer is increased by a frequent intake of fried foods; that association may be a result of inappropriate methods used in food preparation and cooking practices. (Lei et al. ,1996). No association was found between coffee consumption and lung cancer risk, or tea consumption and lung cancer risk. (Abigail, 2014).

Regarding alcohol consumption and the risk of developing LC; a pooled analysis using standardized exposure and covariate data from 7 prospective studies found that slightly greater risk for the consumption of > or = 30 g alcohol per day when compared to non alcoholic (Freudenheim, 2005).

3.3.3 Obesity and physical activity

Most of the evidence that links obesity to cancer risk comes from large cohort studies. There are several potential theories to explain the relationship between obesity and cancer. The chronic low-level inflammation, that might cause DNA damage which leads to cancer (Gregor et al., 2011). The fat tissue (adipose tissue) is expected to produce excess amounts of estrogen, high levels of which have been associated with increased risks of breast, uterine, liver, kidney, colon, esophagus, gastric, pancreatic, gallbladder, and leukemia, and might also lead to poorer treatment (Tahergorabi et al., 2016). Moreover, fat cells may also have direct and indirect effects on other cell growth regulators, including mammalian target of rapamycin (mTOR) and AMP-activated protein kinase. This association is well established for breast cancer, colon cancer, stomach cancer and others but not for lung cancer which is believed to be protective (Roberts et al., 2010) and (Bhaskaran K et al.,2014). Recently, there is convincing evidence that decreasing the magnitude of the systemic hormonal and inflammatory changes has significant clinical benefits to reduce cancer risk among obese people (Hopkins et al., 2016).

The suggested mechanism to explain this relationship is that leanness may be involved in the carcinogenic progress of smoking ; some studies found that BMI was inversely correlated with the level of 8-hydroxydeoxyguanosine in urine , which is an indicator of oxidative DNA damage in smokers, thus BMI may be an independent factor for person susceptibility to smoking related cancers (Loft S et al., 1992).

Another genetic mechanism was found by a study which reported that one allele of the fat mass and obesity - associated (FTO) gene, has been linked to increased BMI, was associated with a lower risk of lung cancer (Brennan et al,. 2009).

Emerging evidence shows that physical activity (PA) plays a significant role in lung cancer risk reduction. The majority of studies support the fact that total and recreational physical activity reduces lung cancer risk by 20-30% for women and 20-50% for men, and there is evidence of a dose-response effect. Several plausible biological factors and mechanisms have been hypothesized linking physical activity to reduced lung cancer risk including: improved pulmonary function, reduced concentrations of carcinogenic agents in the lungs, enhanced immune function, reduced inflammation, enhanced DNA repair capacity, changes in growth factor levels and possible gene-physical activity interactions (Emaus and Thune, 2011).

Recreational PA is thought to decrease lung cancer risk in both men and women. While occupational PA was associated with higher lung cancer risk in men but not in women (Ho et al., 2017).

Other studies stated that being physically active and having a healthy body weight are crucial for prevention of various chronic diseases, even several types of cancer, Patel and his colleagues found that that physical activity, BMI, and waist circumference are

not associated with lung cancer risk, regardless of smoking status (Patel., 2017).

3.3.4. Environmental and occupational risk factors:

Environmental and occupational factors play a major role in many types of cancers, that many carcinogens are found in the air we breathe, in the water we drink, and in the food we eat, that complex unavoidable exposure to carcinogens makes studying cancer etiology extremely complicated and challenging.

Radon is a colorless, odorless, natural radioactive gas formed in the decay series of uranium-238, is responsible for about half of the human annual radiation exposure globally. Radon is found indoors and outdoors. It is present at very low levels in outdoor air and in drinking water and it can be found at high levels in the air in houses and buildings, and in the water from underground sources, as well water (Robertson et al, 2013).

Continued exposure to radon and its degradation products is estimated to be the second cause of lung cancer after smoking. The ionizing radiation emitted during the decay of radon may induce a variety of cytogenetic effects that can be carcinogenic. The resulted

effects of alpha particle exposure from radon include generation of reactive oxygen species, mutations, chromosomal aberrations, changes in the cell cycle, deregulation of cytokines and the production of proteins responsible for cell-cycle regulation and carcinogenesis. The cellular and molecular carcinogenic effects of radon are numerous and complex. (Robertson et al., 2013).

Asbestos fibers are found in the rocks and soils and consist of six distinct types, that are rod like. In the past, exposure to asbestos fibers in unregulated workplaces has given rise to pleural and lung fibrosis asbestosis, lung cancer, and pleural and peritoneal malignant mesothelioma. (Heintz et al.,2010). Asbestos affects the cell signaling pathways. Either through direct interactions with the epidermal growth factor receptor activating the Ras-Raf-extracellular signal regulated kinase (ERK) pathway, that controls expression and transcriptional activity of the Fos family members of the activator protein-1 transcription factor(AP-1). Also it activates ERK5. AP-1, ERK1/2 and ERK5 activation outcomes; include cell proliferation, migration, and aspects of neoplastic transformation. (Heintz et al., 2010)

Another pathway by which asbestos regulate gene expression and cell fate; is by the genesis of reactive oxygen species. Crocidolite and amosite, are the most potent types of asbestos that are associated with the causation of malignant mesothelioma by producing oxidants. Besides the high iron content of these asbestos types leads to the generation of reactive oxygen species such as the highly DNA-damaging hydroxyl radical (OH),H2O2, the superoxide radical (O22), and reactive nitrogren species are released from many types of asbestos fibers in the alveolar or peritoneal macrophages, after phagocytosis of the inhaled asbestos fibers. The reactive species may initiate cell events both externally and within cells in a dose response reaction to induce cell proliferation and injury. (Heintz et al.,2010)Crystalline silica was classified as a human carcinogen by the International Agency for Research on Cancer.(International Agency for Research on Cancer.2012).

According to OSHA, exposures to silica occur when workers cut, grind, crush, or drill silica-containing materials such as concrete, masonry, tile, and rock**.**

A cohort study in China from 1960 to 2003 of 34,018 workers without exposure to carcinogenic confounders were investigated. Cumulative silica exposure was estimated. During a mean 34.5-year follow-up, 546 lung cancer deaths were identified. The joint

effect of smoking and silica was more than an additive and close to be multiplicative. The findings of this study confirm that silica is a human carcinogen, and indicate that smoking cessation may help reduce lung cancer risk for silica exposed workers.(Liu et al.,2013). When particles of crystalline silica deposited in the lungs, the macrophages which ingest the particles will initiate an inflammatory process by releasing cytokines such as tumor necrosis factors, interleukin 1, leukotriene B4 and others. These stimulate fibroblasts to proliferate and produce collagen around the silica particle, causing fibrosis and the formation of the nodules with characteristic concentric onion-skinned arrangement of collagen fibers, central hyalinization, and a cellular peripheral zone (Cassel et al., 2008).

Arsenic is considered to be a human carcinogen. Millions of people worldwide are chronically exposed through drinking water. The contamination of drinking water with arsenic is a serious public health problem. Although measures have been taken, the natural origin of that contamination requires strategies to monitor it's concentrations in drinking water and to examine markers associated with early health effects. Arsenic exposure exhibits its deleterious health effects through the initiation of oxidative stress, changes in DNA methylation, histone modification, and mitochondrial RNA expression (Martinez et al., 2011).

Beryllium is light, non magnetic, and a good conductor of heat and electricity that is found in soil, rocks, coal, and oil. It is a widely used metal in the manufacturing of cars, computers, golf clubs, and electrical equipment. The exact mechanism of how beryllium cause lung cancer is not fully understood but one study suggests a potential role for *overmethylation* of p16, a tumor suppressor gene, but is not proven (Benson et al., 2010).

Nickel is a natural element, that is found in soils, water resources, air, sediments, plants and animals. It's released into the environment from natural phenomena as volcanic eruptions or from industrial activities like nickel mining, nickel production and use. Exposure to nickel happens via inhalation of dust particles, ingestion of contaminated water and food, and dermal contact with nickel containing materials. The most common adverse health effect in humans to nickel exposure is allergy, but also it has been associated with lung cancer, especially in workers of nickel refineries and processing plants. (Cameron et al., 2011).

The proposed mechanism of nickel induced carcinogenicity ,that nickel compounds enter the cell, activate the receptor CaSR, inducing intracellular Ca^{2+} mobilization and triggering of the calcium and hypoxia inducible factor pathways. When nickel is in the nucleus, it binds to DNA and reacts with H_2O_2 to generate reactive nickel -oxygen complexes, causing the oxidation of thymine and cytosine residues accompanied by 8-OH-dG formation. This oxidative stress damages DNA and inhibits DNA repair pathways. Nickel compounds also initiate indirect damage through inflammation by stimulating polymorphonuclear leukocytes to produce ROS. Nickel also damages heterochromatin, thus suppressing the expression of genes located near heterochromatin, therefore induce an epigenetic loss of histone H4 and H3 acetylation and DNA hypermethylation; that suppression make the cell more susceptible to neoplastic transformation. In addition, nickel down-regulates the tumor suppressor gene p53, activates the proto-oncogene c-Myc and triggers the AP-1 transcription factor, causing cellular proliferation and cancer development.(Cameron et al., 2011).

Cadmium is a heavy metal that has been classified as a human carcinogen by the International Agency for Research on Cancer (IARC). The mechanism of carcinogenesis following exposure to cadmium has been studied using *in vitro* cell culture and animal models. Exposure of cells to cadmium results in their transformation. The administration of cadmium in animals results in tumors of multiple organs including lung cancer. It has been demonstrated that Cadmium induces cancer by changing gene expression, inhibition of DNA damage repair, stimulating oxidative stress, and inhibition of apoptosis (Joseph, 2009).

3.3.5. Socio- demographic factors and lung cancer risk

As mentioned earlier most lung cancer cases can be explained by external environmental, and occupational exposure to carcinogens. The effect of each of these factors usually vary with socio-demographic determinants such as gender, age, ethnicity, country and region within a single country (Hosseini et al, 2009).

3.4. Gender:

Generally, the risk that a man will have lung cancer in his lifetime is nearly 1 in 14; while for a woman it's about 1 in 17. These numbers include both smokers and non-smokers (American Cancer Society, 2016). So lung cancer occurs more commonly in men than in

women. The age adjusted incidence rate of lung cancer is much higher in men than women (35.5 per 100,000 versus 12.1) however this difference is decreasing due to a continued decline in the male incidence of lung cancer (Alberg. et al., 2008). In the United States, the risk of developing lung cancer is equal in both sexes until the age of 39 years. It then starts to increase among men compared with women (Medscape, 2016).

The most common cause of lung cancer which is smoking is much more common among men (23.1%) than women (18.3%); however, the difference is narrowing. (Cruz et al., 2011). On the other hand, for never smokers (who have smoked less than 100 cigarettes in their life, and nonsmokers) the age adjusted incidence rate of lung cancer is higher for women than men based on several prospective cohort studies (Cruz et al., 2011).

However, whether women are less or more susceptible than men to the carcinogenic effects of cigarette smoke remains controversial; that the gender differences in susceptibility could be related to differences in the metabolism of nicotine and metabolic activation or detoxification of the lung carcinogens. (Cruz et al., 2011).

3.4.1. Age

The risk of developing lung cancer increases with *age.* Lung cancer occurs more commonly in older people. That two third of the patients diagnosed with lung cancer are 65 or older, less than 2% are younger than 45 years (American Cancer Society, 2016). The available data from 2004 to 2008 reported that the median age at diagnosis of lung cancer is 71 years, no reported cases in persons younger than 20 years. whereas about 0.2% of cases were diagnosed in patients aged 20 to 34 years old ; 1.5% of cases were 35 to 44 years; 8.8% between 45 and 54 years; 20.9% of the cases age were between 55 and 64 years; 31.1% between 65 and 74 years; 29% between 75 and 84 years; and 8.3% at 85 years and older. (Cruz et al., 2011).

3.4.2. Ethnicity and Race

Race usually has a strong socioeconomic association. Menck found that lung cancer incidence is higher among blacks African Americans ,Native Hawaiians and other Polynesians than among whites in the United States (Menck et al. 1982).

Its estimated that black males have about 20% more risk to develop lung cancer than white men. But both black and white women have lower rates (American Cancer Society, 2016).

Possible explanation is that African American smokers may be more susceptible to lung carcinogens from cigarette smoke than European American smokers. (Cruz et al., 2011).

However Palestinians and Arabs in general are Caucasians.

3.4.3. Socioeconomic status (SES)

Socioeconomic status is inversely related to lung cancer risk; that people of lower SES are at higher risk for developing lung cancer. (Alberg et al, 2008).

This can be explained by the fact that lung cancer risk factors are more concentrated among people of lower SES. Much of the excess risk among low SES populations may be attributable to cigarette smoking; since low SES is associated with higher smoking prevalence, high-tar cigarettes, not using cigarettes filter and lower quit rates. Besides that people of lower SES are more exposed to other risk factors. For example, eating less healthful diets and more exposure to occupational and environmental carcinogens (Gadgeel et al., 2003)

3.5. Family history and genetic predisposition

About 8% of lung cancer is due to inherited factors. (Yang et al ,2013). Family history is a rare risk factor in developing LC; that the risk of have lung cancer is 1% with >3 affected relatives. (Furrukh , 2013) .A positive family history of overall cancer is not associated with a higher risk of lung cancer. (Nitadori et al, 2006).

In general smokers with a history of early onset lung cancer in a first degree relative have a higher risk for lung cancer with increasing age than smokers without such a family history. (Cruz et al., 2011). So inherited factors affect the individuals variation in the susceptibility to lung cancer caused by smoking. (Alberg et al .2008).

The family history association with lung cancer is stronger in young patients and females. (Schwartz et al, 1996). Family history found to be more strongly associated with the risk of squamous cell carcinoma than with other histological types of lung cancer (Nitadori et al, 2006).

The inherited susceptibility to lung cancer was studied by many researchers. Wilson et al found that a locus on chromosome 6q23-25 was associated with a major susceptibility to lung cancer (Bailey-Wilson et al, 2004). Common genetic polymorphisms on

chromosomes 5, 6 and 15 which are involved in pathways that affecting the ability of carcinogens in cigarette smoke to bind to and damage the DNA. These genes are involved in carcinogen metabolism detoxification, and DNA repair genes (Alberg et al. 2008).

3.6. Personal medical history:

Chronic Obstructive Pulmonary Diseases including emphysema and chronic bronchitis are progressive and fatal deterioration of lung function over time. The damage to the lungs in COPD is caused by oxidative stress (exogenous from smoking and endogenous), inflammatory cytokinerelease, protease activity and autoantibody activation cause airway destruction, air trapping and lung hyperinflation (Brusselle et al, 2015). Thus the chronic inflammation in COPD causes lung damage resulting in increased rate of cell division to restore cellular stasis, the cell division paired with increased DNA damage due to smoking increase the genetic mutations and thereby the chance of carcinogenesis (Caramori et al, 2011).

Chapter four: Methodology

4.1 Introduction

In this chapter, study setting, study designs, sampling method and sample size, selection of the study population with its inclusion and exclusion criteria, study tools (questionnaire and chest X ray), field work and data collection are presented. In addition, study statistical analysis method, as well as study ethical considerations are presented.

4.2 Study settings

The study was done in the two major hospitals that provides cancer care in the west Bank, i.e. Alwatani and Biet Jala (BJGH) governmental hospitals.

AlWatani Govermental hospital is a general hospital that presents medical health care for Palestinian residents in secondary and tertiary levels. Many medical specializations are found in it such as nephrology, neurology, cardiovascular hematology, rheumatology and oncology, patients are admitted to the inpatient wards, other patients are examined and followed up and treated in the outpatient clinics. Its oncology department is one of the four main oncology departments across the West Bank (AlWatani, BJGH, Augusta Victoria Hospital (AVH), and An-Najah educational hospitals). Cancer patient's services including diagnosis, treatment, hospitalization, and follow-up are delivered at the oncology department and through the outpatient clinic for patients derived from northern of the West Bank. All patients' records are kept in the paper filling archives presented within the hospital.

BJGH is a central hospital in the southern part of the West Bank. It has many vital medical specialties such as orthopedic, CVDs, ENT, surgery and oncology departments. Each medical specialty has an in-patient ward and out-patient clinic. The patients' medical records are computerized. The oncology department provides primary, secondary, and

tertiary health care for cancer patients in the south of the West Bank. Diagnostic and therapeutic procedures are also presented at BJGH. These procedures include medical imaging and laboratory testing for diagnosis and follow-up, surgery and chemotherapy for curative and palliative entities. Patients could be admitted to the oncology ward to be under observation. Also cancer patients are followed up in the outpatient clinics by medical oncologists.

4.3 Study Design

The study is divided into two stages. Stage 1 is a medical record based retrospective study. Data was retrieved from records of lung cancer patients attending the oncology clinic from 2010 till 2017.

The second stage is a case-control study. The participants of this study were survived patients attending AlWatani and BJGH at the study period. The ratio of study cases to control group was 1:1.

4.4 Study population

In stage 1: all patients' medical records who were diagnosed with lung cancer between 2010- 2017 in AlWatani hospital were revised and explored. All data related to the study objectives and is reported in these records risk factors of lung cancer, the pathological type, and stage and prognosis of LC were retrieved in special form prepared and filled by the study researcher (Annex 1).

In stage 2: Study cases were patients attending Alwatani and BJGH oncology clinics and/or admitted in the oncology wards and diagnosed as having lung cancer of any grade during the time of the study data collection period, i.e. October 2017 to December 2017.

Study control group was patients attending Alwatani and BJGH clinics except oncology and respiratory clinics, and/or admitted in any ward except oncology or respiratory wards during the time of data collection for this study ,because when the patient has respiratory symptoms ,especially if extended for more than two weeks without apparent diagnosis, we can't rule out lung cancer except by a chest CT scan and that was not feasible.

4.4.1 Study cases inclusion and exclusion criteria

Inclusion criteria:

- The cases who were included in the study were all the survived patients diagnosed as having primary lung cancer which is confirmed by a pathology report and CT scan, and registered in the oncology clinics of Alwatni and Bet Jala hospitals.
- Visiting the oncology out-patient clinics and/or admitted in the oncology wards as a case of lung cancer.
- Participants' consent to participate in the study was required.

Exclusion criteria

- Any patient diagnosed as lung cancer but his medical file is not presented in the hospital archives.
- Any patient diagnosed as lung cancer case in the hospital archives but this diagnosis is not confirmed by lung biopsy.
- Any patient has lung cancer due to metastasis (not primary).

4.4.2 Control group inclusion and exclusion criteria

Inclusion criteria

- Any patient admitted to Alwatani and BJGH for receiving health care.
- Any patient reported not to have lung cancer or any type of malignancy and this approved by his medical record and his routine chest x ray.
- Participants' consent for the participation in the study was required too.

Exclusion criteria

- Any patient reported to have any recent or previous diagnosis of any type of cancer.
- Any patient admitted to the hospitals for respiratory disease or complains of any respiratory symptoms.

- Any patient had abnormal chest x ray.

4.5 Study period

The study was carried out in October 2017 till December 2017. The questionnaire, the consent form, Ministry of Health approval and permission, and the logistic preparation were ready by the end of September 2017. Data collection and study population interviews started in October 2017. After three months, the number of eligible participants that were included in the study was 40 cancer cases and 40 controls.

4.6 Sampling and sample size

In stage one, when reviewing patients files of the years 2010 till 2017; 189 files were explored.

Sample size calculation we calculated the sample size from Epitools open source calculator—SSCC, and it was 38 cases.

About 50 patients have to attend the clinic for follow up and chemotherapy sessions at least once monthly. Therefore, we expected to see at least 80% of these study cases during the study period. Therefore, all lung cancer patients who attended the oncology clinics during the study period were included in the study sample. Total number of study cases was 40 participants from both Alwatani and Bet jala.

For these cases we took 40 controls from the same hospitals , thus the ratio of cases to controls was 1:1, increasing the number of controls could strengthen the study and increase it power, but unfortunately we couldn't because the study period was short and it was in winter; when the respiratory diseases and complains increase.

4.7. Data source and study tools

4.7.1 Participant's medical record

In stage 1 the patients files were explored to ascertain diagnosis, stage, pathological type, treatment, prognosis, and for risk factors such as age, gender, marital status smoking, family history, and occupation. Every file was explored in details to collect more accurate data of what we can find in the national cancer registry, where forms are not fully filled and lacks precise information about the patients and the disease.

4.7.2 Structured interview questionnaire

A face-to-face interview questionnaire was developed using several previously validated questionnaires. The questionnaire was divided into sections to cover the study objectives. The full questionnaire, in Arabic is presented in the Annex 2. The following sections cover the questionnaire and source of questionnaire parts.

- The socio-demographic section included questions about participant's gender, date of birth, marital status, number of siblings, profession, education, residence type, residence area, and monthly income
- The lifestyle section included questions about smoking habits, alcohol drinking, diet.
- The health status part contains questions about the participant's chronic diseases including history of diabetes mellitus type I and type II, Asthma, COPD,TB ,Asbestosis. Also the questionnaire asked about the usage of some medications that contains aspirin, in addition to analgesics.
- Hormonal history for married females , such as menarche ,OCP use, hormones and breast feeding.
- The last part of the questionnaire contained questions regarding the history of malignancy and the family history of malignancy especially lung cancer.

4.7.3 Chest x ray:

To exclude the probability of undiagnosed lung cancer in controls, the chest x ray on their admission was reviewed by the attending doctor and that was reported to the researcher by the data collectors to make sure that there is no lung masses or abnormalities before filling a questionnaire for them. Chest radiography has the advantage of low cost, low radiation dose, and easy accessibility. While Computed tomography (CT) has a much higher sensitivity for the detection of small intrapulmonary lesions than does chest radiography. A nested case control study in Japan to evaluate the sensitivity and specificity of annual lung cancer screening using low-dose CT and chest x ray from a local Cancer Registry found that lung cancer screening using low-dose CT has a higher sensitivity and a lower specificity than usual lung cancer screening by chest X-ray and sputum cytology,

sensitivity and specificity were 88.9 and 92.6% for low-dose CT and 78.3 and 97.0% for chest X-ray, respectively (Toyoda et al, 2008).

Since all the admitted cases to the hospitals have routine chest x ray, we took controls from inpatients who met the inclusion exclusion criteria, and have normal CXR.

4.8 Field work

The cases medical files on Avicenna (The Palestinian ministry of health electronic system) were revised to confirm that Lung cancer was primary, and to check the pathology and CT scan reports.

There was 2 data collectors in the second stage of the study, one in each hospital, in AlWatani the data collector was a medical doctor, working as general practitioner in the hospital , and in BJGH the data collector was a registered nurse, and she worked as data collector with many master students. Data collectors were offered a detailed presentation of the study objectives, inclusion and the exclusion criteria, and study tools, the questionnaire was explained, and the meaning of every question was clarified for them, and they were trained to interview participants in precisely the same way. There was regular, close contact with data collectors during the study period.

Study cases were interviewed during their waiting time for clinic visit in the out-patients clinics or during their stay in the ward if they were inpatients. While controls were inpatients and were interviewed during their stay in the hospitals.

Before filling the study questionnaire, study aim and objectives were clarified for the participants. After the participant accepts to participate, he /she signed the consent form (Annex 4).

Height and weight of each participant were measured using the scales found at the clinics of the hospitals (Seca model 700, Seca GmbH, Hamburg, Germany). Same interviewer was performing the interviews with the cases and the controls in the same hospital.

4.9 Statistical analysis

IBM SPSS 18 was used to enter, clean and analyze the collected data.

For descriptive analysis, frequencies were calculated for all study variables and were presented in tables and figures.

To examine the binary associations, univariate analysis was done using the cross tabulation and the significance of Pearson and Fisher exact chi square-as needed- at *P*-value 0.05 was calculated for both parts of the study.

Multivariate analysis was done after the univariate analysis, all the variables that showed significant differences between study cases and control group were introduced in the multivariate analysis. Logistic regression model was used. The logistic regression was used to compare odds ratio with confidence interval of 95%. *p*-value < 0.05 were used.

4.10 Ethical approval

Before starting the study, we got the approval from Al Quds University-School of Public Health research committee. Also, we obtained the approval to conduct the study at the 2 hospitals from the MOH (Annex 3) Also all participants were informed about the study aim and objectives and signed a consent form before participating (Annex 4).

4.11 Variables operational definitions

Age variable: composed of three categories (≤59, 60-69, and ≥70 years).

Marital status variable: composed of four categories (single, married, divorced, and widow).

Number of children variable: composed of three categories (≤ 4, 5-8, and ≥9).

Area in west bank: composed of three categories (north, middle, south).

Place of residence variable: is the place in which the participant lives (refuges camp, urban, and rural).

Years of education variable: composed of six categories (0-6, 7-10, 11-12, diploma, bachelor, postgraduate).

Job variable: composed of two main categories (office job and field job). Office job includes; teacher, engineer, journalist, office job, accountant, clerk. Field job includes: construction worker, driver, painter, carpenter, mechanics.

Participant's monthly income: composed of five categories (≤1000 NIS, 2000-3000, 3001-4000, 4001-5000, and >5001 NIS).

House type: composed of two categories (house ,apartment).

Tobacco smoking variable: composed of two categories (smoking, not smoking).

Age starting smoking: composed of four categories (≤19 ,20-29 ,30-39 , ≥40).

Number of cigarettes per day: composed of four categories (≤ 19, 20-29 ,30-39 ,≥40).

Age of menopause: composed of three categories (≤ 40, 41-50 ,51-60).

Family Member with malignancy: composed of three categories (First degree relative, Second degree relative, More than one relative).

Body mass index (BMI): is a measure of body fat based on height and weight that applies to adult men and women. Composed of three categories (underweight: under 18.5 kg/m2, normal weight: 18.5 to 25, overweight: 25 to 30, obese: over 30)

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Chapter Five: The Results

5.1 Introduction

In this chapter, study results for both study parts will be presented. Part 1 presents the data collected from patients' medical records for the period 2010-2017; and part 2 presents the interview questionnaire's data. In the first part, we will present the descriptive patients' medical records data. In the second part, the case control study descriptive and multivariate analysis will be shown.

Part 1: Medical records data, 2010-2017

5.1 Patients' Socio-demographic Variables of the patients' medical records

We revised 189 lung cancer patients' medical records at Al Watani oncology department. Eighty percent were males with a mean age 61 years (SD±10.96). Almost 95% of them were married and 60% had more than 3 children. Of males, 30% were general workers and 20% were farmers. However, most female patients were housewives. About half of the patients were from cities (table 5.1).

Table 5.1 Patients'' socio-demographic characteristics, medical records at Al-Watani hospital 2010 -2017

Variable		Frequency n=189	Percentage
Age	< 59 years	81	42.9%
	60-69 years	60	31.7%
	≥ 70 years	48	25.4%
Gender	Female	37	19.6%
	Male	152	80.4%
Area in West Bank	North area	173	91.5%
	Middle area	16	8.5%
Residency	City	85	45.0%
	Village	85	45.0%
	Camp	19	10.1%
Marital Status	Single	6	3.2%
	Married	178	94.2%
	Widow/divorced	5	2.6%
Number of Children	≤4	59	32.4%
	5-8	91	50.0%
	≥9	32	17.6%
Occupation	Do Not working/ housewife	41	22.4%
	Employee*	21	11.5%
	General worker **	59	32.3%
	Seller	14	7.7%
	Soldier	8	4.4%
	Farmer	30	16.4%
	Medical staff	3	1.6%
	others	21	11.5%

* Teacher, Engineer, journalist, Office job, Accountant, clerk, seller.

** construction worker, driver, painter, carpenter.

5.3 Smoking and family history of malignancy:

Smoking, occupation and family history of malignancy were the only risk factors that were found in the patients' medical records. Of these patients, 78.3% were smokers and. 66.2% of them were smoking one pack per day (table 5.2). Positive family history of malignancy was found in 15.8 % of those patients. Of them, 69% had a first degree relative with a malignancy (Table 5.2).

Table 5.2 Smoking and family history among LC patients

Risk factor		Count	percentage
Smoking	Nonsmoker	41	21.7%
	Smoker	148	78.3%
Cigarettes Packs per day	One pack	98	66.2%
	Two packs	25	16.9%
	Three packs	2	1.4%
	four packs	1	0.7%
	Past Smokers	22	14.9%
Family History of Cancer	No Family History	155	84.2%
	Positive Family History	29	15.8%
Family Member with malignancy N=29	First degree relative*	20	69.0%
	Second degree relative	4	13.8%
	More than one relative	5	17.2%

* father, mother, sister, brother

5.4 Lung Cancer histopathology and staging

In table 5.3, we found that the main complains for patients at presentation were respiratory symptoms (~70%):i.e. cough, dypnea, chest pain, hemoptysis, and 20% had weight loss at presentation.

IN the record, adenocarcinoma was the most common histological type among patients (53.6 %), followed by Squamous cell carcinoma (20.9 %). About 60 % of them were diagnosed with stage 4 (distant metastasis), on the other side only 6.4% of the patients were diagnosed in stage 1-lung cancer.

In the period between 2010-2017, 61.4% of the patients were died, 30.7 % had unknown fate after referral or since the last contact, only 7.9% of the patients were following up at the study time in the oncology clinic. The average period of follow up was about 1 year.

Table 5-3 Medical history, histopathology, staging, and prognosis of the patients

		Count	Percentage
Presenting Complain of the patient	No complain	2	1.2%
	Respiratory symptoms *	118	69.4%
	Weight loss	33	19.4%
	Metastasis symptoms * *	5	2.9%
	General fatigue	6	3.5%
	SVC obstruction	6	3.5%
Histopathology type	Adenocarcinoma	82	53.6%
	Squamous cell	32	20.9%
	Large cell	5	3.3%
	Small cell carcinoma	16	10.5%
	poorly differentiated carcinoma	8	5.2%
	NSCLC	10	6.5%
Affected Lung	Right	91	52.0%
	Left	72	41.1%
	BOTH	12	6.9%
Stage of cancer	Stage 1	12	6.4%
	Stage 2	28	15.0%
	Stage 3	36	19.3%
	Stage 4	111	59.4%

*Cough, dypnea, chest pain, hemoptysis.

**Bone pain, sever back pain, headache, paralysis, liver metastasis.

5.5 Differences between males and females by socio-demographic, smoking and family history of cancer, and clinical features

In patients' medical records, there are fewer females than males (1:4). The average males and females patients' age at presentation was 59 years old. Table 5-4 shows no significant differences between males and females by age and place of residence. However, females reported to have significantly smaller family size compared to males ($p<0.05$). Only 5 out of 37 females were having a job, also few (n=2) females were current smokers. 68% of males were smoking at least one cigarette pack a day. No significant difference in number of family members with cancer between males and females.

Table 5-4 socio-demographic and risk factor variables differences by gender

		Females N=37		Males N=152		P value
		N	%	N	%	
Age	≤ 59 years	17	45.9%	64	42.1%	0.538
	60-69 years	9	24.3%	51	33.6%	
	≥70 years	11	29.7%	37	24.3%	
Area in the West Bank	North	35	94.6%	138	90.8%	0.455
	Middle	2	5.4%	14	9.2%	
Place of residency	City	16	43.2%	69	45.4%	0.842
	Village	18	48.6%	67	44.1%	
	Refugee camp	3	8.1%	16	10.5%	
Marital status	Single	5	13.5%	1	0.7%	.--
	Married	27	73.0%	151	99.3%	
	Widow/divorced	5	13.5%	0	.0%	
Number of Children	≤ 4 individuals	16	51.6%	43	28.5%	0.022
	5-8 individuals	9	29.0%	82	54.3%	
	≥ 9 individuals	6	19.4%	26	17.2%	
Occupation	Not working/housewife	32	86.5%	9	6.2%	--
	Employee*	4	10.8%	17	11.6%	
	General Worker**	0	.0%	45	30.8%	
	Seller	0	.0%	14	9.6%	
	soldier	0	.0%	8	5.5%	
	Farmer	1	2.7%	29	19.9%	
	others	0	.0%	21	14.4%	
	medical	0	.0%	3	2.1%	
Smoking Status	Nonsmoker	30	81.1%	11	7.2%	.000
	Smoker	7	18.9%	141	92.8%	
Cigarettes Packs per day	0ne pack	2	28.6%	96	68.1%	--
	two packs	0	.0%	25	17.7%	
	Three packs	0	.0%	2	1.4%	
	four packs	0	.0%	1	.7%	
	Past smokers	5	71.4%	17	12.1%	
Family History of malignancy	No Family History	32	88.9%	123	83.1%	.393
	Positive Family History	4	11.1%	25	16.9%	
Family Member with malignancy	First degree relative***	3	75.0%	17	68.0%	--
	Second degree relative	0	.0%	4	16.0%	
	More than one relative	1	25.0%	4	16.0%	

* Teacher, Engineer, journalist, Office job, Accountant, clerk.

** construction worker, driver, painter, carpenter.

*** father, mother, sister, brother

In table 5-5, males we reported to complain less from of respiratory symptoms, but reported more weight loss. The most histological type of LC type as documented in patients' medical records was Adenocarcinoma, which was identified for 63% of female patients. The tumor was more often found in the right lung in both genders. Interestingly,

we found that males' life expectancy after prognosis is lower than female patients, although, no significant difference was found in the stage of diagnosis; in the 3rd and 4th stage.

Table 5-5 Clinical data differences by Gender

		Females N=37		Males N=152		P value
		N	%	N	%	
Presenting Complain	No symptoms	0	.0%	2	1.4%	--
	Respiratory *	27	84.4%	91	65.9%	
	Weight loss	3	9.4%	30	21.7%	
	Metastasis **	1	3.1%	4	2.9%	
	General fatigue	1	3.1%	5	3.6%	
	SVC obstruction	0	.0%	6	4.3%	
Histopathology type	Adenocarcinoma	20	62.5%	62	51.2%	--
	Squamous cell	4	12.5%	28	23.1%	
	Large cell carcinoma	0	.0%	5	4.1%	
	Small cell carcinoma	3	9.4%	13	10.7%	
	Poorly differentiated carcinoma	3	9.4%	5	4.1%	
	NSCLC	2	6.3%	8	6.6%	
Affected Lung	Right	21	63.6%	70	49.3%	.323
	Left	10	30.3%	62	43.7%	
	Both lungs	2	6.1%	10	7.0%	
Stage of cancer	Stage 1	2	5.4%	10	6.7%	.940
	Stage 2	6	16.2%	22	14.7%	
	Stage 3	6	16.2%	30	20.0%	
	Stage 4	23	62.2%	88	58.7%	
Prognosis of the patient	Alive	1	2.7%	14	9.2%	.022
	Died	18	48.6%	98	64.5%	
	Unknown fate	18	48.6%	40	26.3%	

*Cough, dypnea, chest pain, hemoptysis.

**Bone pain, sever back pain, headache, paralysis, liver metastasis.

5.6 Smoking status by the socio-demographic, family history of cancer, and clinical features

It was found in the medical records that about 80% of those with LC were smokers. About half of them aged ≥ 59 years old.

73% of non-smokers were females, but no significant differences were found in smoking status by patients' prognosis. or stage of diagnosis. However, there was a significant difference between the histopathological types according to smoking status. It's clear that

Adenocarcinoma is more prominent among nonsmokers (73%) than smokers (47.4%), and about one forth of smokers had Squamous cell carcinoma.

Table 5-6 Socio-demographic characteristics stratified by Smoking status.

		Nonsmoker N=41		Smoker N=148		P value
		N	%	N	%	
Age	≤ 59	19	46.3%	62	41.9%	.874
	60-69 years	12	29.3%	48	32.4%	
	≥70	10	24.4%	38	25.7%	
Gender	Female	30	73.2%	7	4.7%	.000
	Male	11	26.8%	141	95.3%	
Area in West Bank	North	38	92.7%	135	91.2%	.765
	Middle	3	7.3%	13	8.8%	
Place of Residency	City	17	41.5%	68	45.9%	.610
	Village	21	51.2%	64	43.2%	
	Camp	3	7.3%	16	10.8%	
Marital status	Single	4	9.8%	2	1.4%	.004
	Married	34	82.9%	144	97.3%	
	Widow	2	4.9%	2	1.4%	
	Divorced	1	2.4%	0	.0%	
Number of Children	≤ 4	14	38.9%	45	30.8%	.327
	5-8	14	38.9%	77	52.7%	
	≥ 9	8	22.2%	24	16.4%	
Occupation	Do not working/ Housewife	25	62.5%	16	11.2%	.000
	Employee*	6	15.0%	15	10.5%	
	Worker**	2	5.0%	43	30.1%	
	Seller	0	.0%	14	9.8%	
	soldier	1	2.5%	7	4.9%	
	Farmer	4	10.0%	26	18.2%	
	others	2	5.0%	19	13.3%	
	medical	0	.0%	3	2.1%	
Family History of malignancy	No family history	34	87.2%	121	83.4%	.570
	Positive family history	5	12.8%	24	16.6%	

* Teacher, Engineer, journalist, Office job, Accountant, clerk.

** construction worker, driver, painter, carpenter.

5.7 Stage of diagnosis by the socio-demographic characteristics and clinical features of the patients

The results in table 5-7 did not show significant difference of stages by the various patients' socio-demographic characteristics. However, in table 5-8, the stage of disease at presentation differed significantly according to histological type, Adenocarinoma is found in most patients with stage 2 ,3 and 4 (61.2% of patients in stage 4 have adeno-carcinoma)

and about one third of patients in stage one had Poorly differentiated cells in their histopathology reports. Also prognosis and survival of lung cancer patients is markedly affected by stage of disease. There was a steady increase in death rates with advanced stages and this increase was significant (P value=.001), although numbers were small for an absolute clear association.

Table 5-7 relationship of socioeconomic characteristics and risk factors and stage

		Stage 1		**Stage 2**		**Stage 3**		**Stage 4**		
		N	%	N	%	N	%	N	%	
Age	≤ 59	5	41.7%	12	42.9%	17	47.2%	47	42.3%	.980
	60-69 years	3	25.0%	8	28.6%	11	30.6%	37	33.3%	
	≥70	4	33.3%	8	28.6%	8	22.2%	27	24.3%	
Gender	Female	2	16.7%	6	21.4%	6	16.7%	23	20.7%	.940
	Male	10	83.3%	22	78.6%	30	83.3%	88	79.3%	
Area in the West Bank	North	10	83.3%	26	92.9%	35	97.2%	100	90.1%	.411
	Middle	2	16.7%	2	7.1%	1	2.8%	11	9.9%	
Residency	City	3	25.0%	14	50.0%	14	38.9%	53	47.7%	.726
	Village	8	66.7%	12	42.9%	18	50.0%	47	42.3%	
	Camp	1	8.3%	2	7.1%	4	11.1%	11	9.9%	
Marital status	Single	--	--	1	3.6%	2	5.6%	3	2.7%	--
	Married	12	100%	25	89.3%	33	91.7%	106	95.5%	
	Widow/divorce	--	--	2	7.2%	1	2.8%	2	1.8%	
Number of Children	≤ 4	4	33.3%	8	29.6%	12	35.3%	35	32.7%	.947
	5-8	6	50.0%	16	59.3%	15	44.1%	53	49.5%	
	≥ 9	2	16.7%	3	11.1%	7	20.6%	19	17.8%	
Smoking	Nonsmoker	2	16.7%	8	28.6%	6	16.7%	25	22.5%	.677
	Smoker	10	83.3%	20	71.4%	30	83.3%	86	77.5%	
Cigarettes Packs per day	One pack	9	90.0%	11	55.0%	20	66.7%	57	66.3%	--
	≥two packs	--	--	5	25.0%	7	23.3%	16	17.6%	
	Past smokers	1	10.0%	4	20.0%	3	10.0%	13	15.1%	
Occupation	Do not working	3	27.3 %	4	14.8 %	8	22.2 %	26	24.3 %	
	Employee *	--	--	3	11.1%	4	11.1%	14	13.1%	
	General worker**	1	9.1%	8	29.6%	10	27.8%	26	24.3%	
	Seller	1	9.1%	2	7.4%	3	8.3%	8	7.5%	
	soldier	1	9.1%	1	3.7%	2	5.6%	4	3.7%	
	Farmer	3	27.3%	6	22.2%	5	13.9%	16	15.0%	
	others	2	18.2%	2	7.4%	2	5.6%	13	12.1%	
	medical	--	--	1	3.7%	2	5.6%	--	--	

* Teacher, Engineer, journalist, Office job, Accountant, clerk.

** construction worker, driver, painter, carpenter.

Table 5-8 Relationship between LC stage by LC patients' clinical features

		Stage 1		Stage 2		Stage 3		Stage 4		P value
		N	%	N	%	N	%	N	%	
Family History of malignancy	No Family history	12	100%	23	82.1%	30	83.3%	90	84.9%	--
	Positive family history	--	--	5	17.9%	6	16.7%	16	15.1%	
Presenting complain of the patient	No symptoms	1	9.1%	--	--	--	--	1	1.0%	--
	Respiratory symptoms ***	5	45.5%	19	76.0%	23	69.7%	70	70.7%	
	Weight loss	5	45.5%	4	16.0%	7	21.2%	16	16.2%	
	Metastasis****	--	--	1	4.0%	0	.0%	4	4.0%	
	General fatigue	--	--	--	--	1	3.0%	5	5.1%	
	SVC obstruction	--	--	1	4.0%	2	6.1%	3	3.0%	
Affected Lung	Right	5	41.7%	18	66.7%	16	44.4%	52	53.1%	--
	Left	7	58.3%	9	33.3%	17	47.2%	37	37.8%	
	Both lungs					3	8.3%	9	9.2%	
Histopathology type	Adenocarcinoma	2	20.0%	13	52.0%	15	48.4%	52	61.2%	.009
	Squamous cell	1	10.0%	6	24.0%	9	29.0%	15	17.6%	
	Large cell	2	20.0%	1	4.0%	1	3.2%	1	1.2%	
	Small cell carcinoma	1	10.0%	1	4.0%	3	9.7%	10	11.8%	
	Poorly differentiated carcinoma	3	30.0%	1	4.0%	2	6.5%	2	2.4%	
	NSCLC	1	10.0%	3	12.0%	1	3.2%	5	5.9%	
Prognosis of the patient	Alive	3	25.0%	5	17.9%	2	5.6%	5	4.5%	.001
	Died	3	25.0%	13	46.4%	18	50.0%	81	73.0%	
	Unknown fate	6	50.0%	10	35.7%	16	44.4%	25	22.5%	

***Cough, dypnea, chest pain, hemoptysis.

****Bone pain, sever back pain, headache, paralysis, liver metastasis.

Part 2: The case-control study

There was a very low refusal rate of participation (<5%) among those whom we invited to participate and other candidates were approached. The study sample consisted of 80 participants of whom 40 were lung cancer patients and a similar number of control group without. This part of study is totally independent of the first study results since the survival rate among patients from AlWatani hospital was low. We only could have 22 patients alive at the interview time. Therefore, we included 18 lung cancer patients from Beit Jala hospital in Bethlehem.

5.8 Association between the study socioeconomic variables and LC

There was no significant difference in the group average ages (study controls mean 48.6 years, SD ±13.06) and cases group 54.8 years, SD ± 12.3) (T-test p value >0.05). Socio-demographic characteristics for study cases and control group are shown in table 5.9. No significant difference was found between study cases and control group for most of the socio-demographic variables except for family size.

Table 5-9: Association between study cases and control group by their socioeconomic characteristics

Socioeconomic characteristics		**Study Cases N=40**	**Control Group N=40**	***P value***
		N (%)	**N (%)**	
Gender	Female	4 (10.0)	8 (20.0)	.210
	Male	36 (90.0)	32 (80.0)	
Age years	≤ 59	21 (52.5)	27(67.5)	.563
	60-69	12 (30.0)	9 (22.5)	
	≥ 70	4 (10.0)	2 (5.0)	
	Missing	3 (7.5)	2 (5.0)	
Residency location	North WB	22(55)	22 (55)	1.0
	Middle WB	2 (5.0)	2 (5.0)	
	South WB	16 (40)	16 (40)	
Residency place	City	11(27.5)	16(40.0)	.410
	Village	25(62.5)	22(55.0)	
	Camp	4 (10.0)	2 (5.0)	
Marital status	Single	2 (5.0)	2 (5.0)	--
	Married	34 (85.0)	36 (90.0)	
	Divorced	--	1(2.5)	
	Widow	4 (10.0)	1(2.5)	
Family size	≤ 4 people	5 (12.8)	13(32.5)	.011
	5-8 people	22 (56.4)	24(60.0)	
	≥9 people	12(30.8)	3 (7.5)	
Parents Consanguinity	Not related	24 (60.0)	26 (65.0)	.293
	First Degree relatives	14 (35.0)	9 (22.5)	
	from the same family	2 (5.0)	5 (12.5)	
House type	House	32 (80)	26 (65.0)	.133
	Apartment	8 (20)	14 (35.0)	
Level of education	Primary	18(45.0)	7 (17.5)	.100
	Secondary	10(25.0)	16 (40.0)	
	High School	3 (7.5)	6 (15.0)	
	Diploma	3 (7.5)	2 (5.0)	
	Bachelor	5 (12.5)	5 (12.5)	
Working status	No	1 (2.5)	---	---
	Yes	17 (42.5)	28 (70.0)	
	Worked in the past	22 (55.0)	12 (30.0)	
Monthly income Shekels	<1000	10 (25)	6 (15.0)	.140
	1000 - 2000	19 (47.5)	13 (32.5)	
	2001 - 3000	5 (12.5)	9 (22.5)	
	3001 - 5000	5 (12.5)	6 (15.0)	
	> 5000	1 (2.5)	6 (15.0)	

5.9 Smoking habits variables

Most patients were smokers (62.5%),while most control group were not (65%), and this difference was not significant (P value <.014), also 84% of study cases start to smoke before the age of 19, whereas (57.1%) of control group start smoking before 19 years old. 57.1% of control group smoke for less than 19 years, on the other hand about 70% of study cases smoke for more than 20 years and the difference between the 2 groups was significant (P value <.007). About 70% of control group individuals consume less than 30 cigarettes per day while 70% of study cases smoke more than 30 cigarettes per day, this difference is significant (P value <.017).

Having a smoking parent/s or being a secondhand smokers or past smoker doesn't differ significantly between study cases and control group. Water- pipe smoking is not significantly different between study cases and control group (p value= 0.07).

Table 5-10: Association between study cases and control group by smoking habits:

		Study Cases N=40	**Control group N=40**	***P* Value**
		N (%)	N (%)	
Smoking	No	15 (37.5)	26 (65.0)	.014
	Yes	25 (62.5)	14 (35.0)	
Age of Starting smoking	≤19	21 (84.0)	8 (57.1)	.065
	20 ≤	4 (16.0)	6(42.9)	
Smoking Duration in years	≤19	3 (12.0)	8 (57.1)	.007
	20-29	7 (28.0)	2 (14.3)	
	30 - 39	3 (12.0)	3 (21.4)	
	40	12 (48.0)	1 (7.1)	
Number of cigarettes per Day	19 and less	1 (4.0)	3 (21.4)	.017
	20-29	6 (24.0)	7 (50.0)	
	30-39	4(16.0)	3 (21.4)	
	≥40	14(56.0)	1 (7.1)	
Smoking Parent/s	No	13 (32.5)	14 (35.0)	.813
	Yes	27(67.5)	26 (65.0)	
Second Hand Smoking	No	13 (32.5)	18 (45.0)	.251
	Yes	27 (67.5)	22 (55.0)	
Past Smoker	No	35 (87.5)	34 (85.0)	.745
	Yes	5 (12.5)	6(15.0)	
Water-pipe smoking	No	33 (82.5)	38(95)	.07*
	Yes	7 (17.5)	2 (5)	

*significance is calculated using Fisher exact test.

5.10 Food and nutritional variables

Most eating patterns and food were similar between study cases and control group, the only most significant difference was in eating vegetables, more than 60% of control group eat vetgetables on daily base, while most study cases do not (P value < 0.05). No difference was found between study cases and control group in alcohol consumption (P value >0.05).

Controls consume more black bread than cases, this difference is significant (P value < 0.05).

Table 5-11: Association between study cases and control group by some food and drinks consuming.

		Study Cases N=40	**Controls group N=40**	***P*-Value**
Milk	zero or less than three / month	27 (67.5)	21 (52.5)	.153
	1-4 / week	11 (27.5)	10 (25.0)	
	5-6 / week	1 (2.5)	5 (12.5)	
	once or more / day	1 (2.5)	4 (10.0)	
Pastries	zero or less than three / month	27 (67.5)	16 (40.0)	.099
	1-4 / week	11 (27.5)	21 (52.5)	
	5-6 / week	1 (2.5)	1 (2.5)	
	once or more / day	1 (2.5)	2 (5.0)	
Biscuits	zero or less than three / month	18 (45.0)	12 (30.0)	.127
	1-4 / week	20 (50.0)	20 (50.0)	
	5-6 / week	1 (2.5)	1 (2.5)	
	once or more / day	1 (2.5)	7 (17.5)	
Nuts	zero or less than three / month	18 (45.0)	22 (55.0)	.729
	1-4 / week	15 (37.5)	14 (35.0)	
	5-6 / week	3 (7.5)	2 (5.0)	
	once or more / day	4 (10.0)	2 (5.0)	
Fish	zero or less than three / month	28 (70.0)	26 (65.0)	.633
	1-4 / week	12 (30.0)	14 (35)	
Chicken	zero or less than three / month	2 (5.0)	1 (2.5)	.918
	1-4 / week	32 (80.0)	34 (85.0)	
	5-6 / week	5 (12.5)	4 (10.0)	
	once or more / day	1 (2.5)	1 (2.5)	
Fruits	zero or less than three / month	6 (15.0)	1 (2.5)	.150
	1-4 / week	15 (37.5)	13 (32.5)	

	5-6 / week	1 (2.5)	3 (7.5)	
	once or more / day	18 (45.0)	23 (57.5)	
Salads	zero or less than three / month	6 (15.0)	1 (2.5)	.030
	1-4 / week	20 (50.0)	14 (35.0)	
	5-6 / week	2 (5)	1 (2.5)	
	once or more / day	12 (30.0)	24 (60.0)	
Grapes-leaves	zero or less than three / month	24 (60.0)	30 (75.0)	.152
	1-4 / week	16 (40.0)	10 (25.0)	
Egg	zero or less than three / month	11(27.5)	10 (25.0)	.304
	1-4 / week	21 (52.5)	20 (50.0)	
	5-6 / week	3 (7.5)	8 (20.0)	
	once or more / day	5 (12.5)	2 (5.0)	
Cheese	zero or less than three / month	11 (27.5)	6 (15.0)	.290
	1-4 / week	18 (45.0)	17 (42.5)	
	5-6 / week	5 (12.5)	11 (27.5)	
	once or more / day	6 (15.0)	6 (15.0)	
White-bread	zero or less than three / month	5 (12.5)	9 (22.5)	.049
	1-4 / week	11 (27.5)	3 (7.5)	
	once or more / day	24 (60.0)	28 (70.0)	
Black- bread	zero or less than three / month	25 (62.5)	17 (42.5)	.015
	1-4 / week	11 (27.5)	8 (20.0)	
	once or more / day	4 (10.0)	15 (37.5)	
Alcohol consumption	No	38 (95.0)	76 (95.0)	1.00*
	Yes	2 (5.0)	4 (5.0)	

*significance is calculated using Fisher exact test.

5.11 Indoor and outdoor pollution variables

Living near a gas emitting factory was a significant risk factor in study cases compared to control group (P value <.014). Also heating fuel type is significantly different between study cases and control group, that about half of control group use electricity, while 70% of patients were using gas, wood and others fuel type (P value <.041). Using traditional Tabbon has a significant association to lung cancer risk (P value <.010). While type of job (office or field) doesn't differ very much between study cases and control group, exposure to different gases in work increases the risk for lung cancer; about 53% of study cases were exposed to gases in their work, while 75 % of control group were not but this difference is not significant.

Table 5-12: Association between study cases and control group by exposure to indoor and outdoor pollutants

		Study Cases N=40	Controls group N=40	*P* Value
		N (%)	N (%)	
Living Near Crowd road	No	23 (59.0)	25 (62.5)	.748
	Yes	16 (41.0)	15 (37.5)	
Was Living Near Crowd road	No	23 (57.5)	22 (55.0)	.822
	Yes	17 (42.5)	18 (45.0)	
Living Near electric generator	No	34 (87.2)	32 (80.0)	.390
	Yes	5 (12.8)	8 (20.0)	
Live Near a gas emitting factory	No	27 (67.5)	36 (90.0)	.014
	Yes	13 (32.5)	4 (10.0)	
Warming fuel Type	Electricity	12 (30)	21 (52.5)	.041
	Fuel *	28 (70)	19 (47.5)	
Use of Taboon oven	No	28 (70.0)	37 (92.5)	.010
	Yes	12 (30.0)	3 (7.5)	
Current Job	Field job	12 (70.6)	16 (57.1)	.483
	Office job	4 (23.5)	7 (25.0)	
	Housewife	1 (5.9)	5 (17.9)	
Exposure To gases in job	No	8 (47.1)	21 (75.0)	.058
	Yes	9 (52.9)	7 (25.0)	
Old Job	Field job	20 (76.9)	10 (76.9)	.638
	Office job	4 (15.4)	1 (7.7)	
	Housewife	2 (7.7)	2 (15.4)	
Exposure to Gases in the old job	No	10 (38.5)	8 (57.1)	.257
	Yes	16 (61.5)	5 (42.9)	

*Gas, Kerosene, wood

5.12 Health status and medical history variables

In table 5-13, the study shows that the pre-existing chronic pulmonary disease (COPD) and emphysema could be associated with having lung cancer risk since 30% of LC patients had COPD and 7.5% had emphysema. Also, there was only one study case with Tuberculosis. Other diseases did not show any significant difference (table 5-13). Additionally, study cases had significantly lower current BMI compared than controls.

Table 5-13: Association between study cases and control group by health status.

		Study Cases N=40	Controls group N=40	*P value*
		N %	N %	
Aspirin	No	24 (60)	27 (67.5)	0.45
	Yes	16 (40)	13 (32.5)	
Regular use of NSAIDS	No	7 (17.5)	12 (30.0)	.142
	Yes	10 (25.0)	4 (10.0)	
	SOS	23 (57.5)	24 (60.0)	
COPD*	No	28 (70.0)	40 (100.0)	.--
	Yes	12 (30.0)	--	
Emphysema	No	37 (92.5)	40 (100.0)	--
	Yes	3 (7.5)	--	
Asthma	No	33 (82.5)	37 (92.5)	.176
	yes	7 (17.5)	3 (7.5)	
Tuberculosis	No	39 (97.5)	40 (100.0)	---
	Yes	1 (2.5)	-	
Diabetes Mellitus	No	26 (65.0)	28 (70.0)	0.63
	Yes	14 (35)	12 (30)	
BMI	Low weight	10 (25.6)	4 (10)	0.046
	Normal	19 (48.7)	16 (40)	
	Overweight or obese	10 (25.6)	20 (50)	
BMI	Mean (SD)	23.1 (4.39)	26.6 (6.15)	0.05**
BMI 2 years	Mean (SD)	25.5 (5.17)	26.9 (6.0)	0.27**
BMI 10 years	Mean (SD)	26.3 (6.98)	27.5 (6.16)	0.38**

* Chronic Obstructive Pulmonary Disease

**P value is calculated by T-test.

5.13 Reproductive Hormonal effect:

About 67% of female study cases had menopause before the age of 50, whereas all control females had menopause after 51 years old. 75% of married female patients had their 1st pregnancy before the age of 19 years old, 57% on control group were 20 years old or more, but this difference is not significant. There was no marked difference between case and control groups by age of menarche, gravida, breast feeding, OCPS use.

Table 5-14: Association between study cases and control group by hormonal history among women in the study

		Study Cases N=	Controls Group N=	*P value*
		N %	N %	
Menarche Age	≤12	1 (25.0)	1 (14.3)	0.658
	13-15	3 (75.0)	6 (85.7)	
Age of 1st Pregnancy	≤ 19	3 (75.0)	3 (42.9)	0.303
	20-29	1 (25.0)	4 (57.1)	
Breast Feeding	No	1 (25.0)	2 (25.0)	1.00
	Yes	3 (75.0)	6 (75.0)	
Gravida	0	--	1 (12.5)	--
	1-3	1 (25.0)	1 (12.5)	
	4-6	--	2 (25.0)	
	7 ≤	3 (75.0)	4 (50.0)	
Oral Contraceptives Pills (OCPS)Use	No	3 (75.0)	7 (87.5)	0.584
	Yes	1 (25.0)	1 (12.5)	
Duration of OCPS use	≤1 year	1 (100.0)	--	--
	2-3 years	0 (.0)	1 (100.0)	
Menstrual Period	Menopause	4 (100.0)	3 (37.5)	--
	Regular	--	4 (50.0)	
	Irregular	--	1 (12.5)	
Menopause Age	≤ 40	1 (25.0)	--	--
	41-50	3 (75.0)	--	
	51-60	--	2 (100.0)	

5.14 Family history:

There is a significant association between positive family history of malignancy and risk of lung cancer (P value < 0.030); that 42.5% of study cases reported a positive family history of cancer.

17.5 % of study cases had have positive family history of lung cancer, while 95% of control group have not, but this difference is not significant.

Table 5-15: Association between study cases and control group by family history.

		Study Cases N=40	Controls group N=40	P value
		N %	N %	
Family history of lung Cancer	No	33 (82.5)	38 (95.0)	.077*
	Yes	7 (17.5)	2 (5.0)	
Family history of malignancy	No	23 (57.5)	32 (80.0)	.030*
	Yes	17 (42.5)	8 (20.0)	

*significance is calculated using Fisher's exact test.

Multivariate analysis

All variables that were significant (p<0. 05) in univariate analysis were included in a multivariate model, adjusted Odds ratio was calculated using forward logistic regression model.

Table 5-16 shows that only being a smoker increases the risk (adjusted Odds ratio) for lung cancer by 3 folds ,and using Taboon for cooking increased it by 5 folds.

Table 5-16: Multivariate logistic regression model between study cases and control group.

		Sig.	AOR	95% C.I.	
				Lower	Upper
Smoking	Yes	.024	2.980	1.154	7.69
	no		reference		
Use of Taboon oven	Yes	.023	5.047	1.25	20.3
	no		reference		

Variables in the model: age, gender, place of residence, fuel type, house type, BMI, family history of malignancy, parental consanguinity, water pipe use

*AOR (95% CI): adjusted odds ratio (95% confidence interval)

Chapter 6: Discussion

This study revealed a number of associations between probable risk and protective factors for lung cancer among the Palestinian population. We were able to find out that lung cancer is not just a smoker's disease, but smoking is still a major risk factor. In this chapter will be discussing the major finding of the study and compare it to the present literature.

6.1. Socio-demographic study factors:

6.1.1 Gender:

In this study the males to females ratio with lung cancer in both medical records (4:1) and the case-control sample (9:1) was high. This male to female ratio is more apparent compared to other studies ratio in Lebanon (3:2) and Iraq (3:1) (Auon J et al., 2013, Habib et al., 2016). This probably reflects the fact that males are at a higher risk of developing lung cancer compared to females which is expected to be due to lifestyle factors such as smoking (American Cancer Society, 2016). In our study most females were nonsmokers while most male's patients were smokers with significant difference between them. Also, it might be due to differences in the metabolism of nicotine and metabolic activation or detoxification of the lung carcinogens (Cruz et al., 2011). Also, we found that the prognosis of lung cancer was worse in males than females and this difference is significant. Few articles compare survival rates of LC between men and women. Johnson and associates found a statistically significant difference in survival in favor of women (Johnson et al., 1988, Ouellette et al.1998), this can be explained by the fact that most female patients are non smokers and have adeno-carcinoma which have better prognosis then other histological types, besides earlier stage at diagnosis , and are more likely to be diagnosed with localized disease (Barrera-Rodriguez et al., 2012).

6.1.2 Age:

The risk of developing lung cancer is shown to increase with age and this fact was confirmed in this study. The mean age of patients with lung cancer in this study was 59.5 (SD ± 13.9) in females and was 61.6 (SD)±10.13 years old in males. Among the survived patients study, the average age for study cases was 54.8 (SD ± 12.3) years old. This result is almost similar to previously published data in Arab countries such as Iraq (Habib et al.,2012) and Lebanon (Auon et al., 2013), while in the United States (USA), the mean age at which lung cancer is diagnosed is 70 years. In addition, higher lung cancer incidence in elderly people was explained by having more co-morbidities and being less tolerant to toxic factors than their younger counterparts (American Cancer Society, 2016).

Therefore, a potential explanations of our results could be that lung cancer trend is crawling toward young ages where young adults are now exposed to different new exposures such as environmental air pollution and adapting westernized lifestyle where smoking habits has changed, and is not limited to cigarette smoking.

6.1.3 Occupational and environmental factors

In this study 86.5% of female patients were housewives. But, most male patients were working in jobs such as construction workers (30%) and farming (20%).This implies that occupational exposure to gases and toxic substances might be factors that increased the risk of lung cancer among males. This association was confirmed by a Wild and colleagues (2012) study in France in which they found that occupational factors are important risk factors and should be considered when defining high-risk lung cancer patients. Lacourt and colleagues (2015) also found that a mildly elevated LC risk was among individuals who worked in the construction industry. This may be due to the fact that genetic susceptibility combined with exposure to carcinogens such as asbestos, radon (found naturally in the environment and homes) that we don't know exactly if its concentration around us is comparable to global accepted ranges, also solvents, and other people’s tobacco smoke may play a role too.

In this study, individuals who were using fuel for heating in their houses had a higher lung cancer risk than those who did not. Using traditional Taboon oven at homes was noted to increase the risk of developing lung cancer among the survived patients. The risk to LC by this exposure was not investigated before. This result can be justified by the nature of

Taboon cooking which produces a kind of smoke that is considered very toxic to the lungs. Similar results were found among those exposed to wood cooking in a recent study in Mexico (Báez-Saldaña, et al., 2016).

Another type of pollution that we found in our study that is associated with an increased risk for LC was living in polluted neighborhoods. Gas emitting factory was found in our study to increase the risk of having lung cancer than those who never did in the univariate analysis, but not in multivariate. This could be viewed as an indicator of the air pollution near the residence, and lung cancer risk was related to air pollutants in previous studies (Wild et al., 2010).

6.1.4 Socioeconomic factors

Despite that socioeconomic factors such as education level and income level and social class have a significant effect on an individual's general health, in our study no significant association was found with this factors and LC. Our results contradicts other studies which showed a relationship between the various socioeconomic indicators and lung cancer risk, and found a significant inverse association between the indicators of socioeconomic status and lung cancer risk (Mitra et.,2016,Hruba et al.,2009,Mukti et al,2013, Hashibe ,2010).

Our results may be explained by the small number of sample or due to small differences in educational level and income among the study participants.

6.2. Lifestyle risk factors:

6.2.1. Smoking:

Cigarette and water pipe smoking versus second hand smoking were investigated in this study. Our results reported that cigarette smoking is a major risk factors for developing lung cancer among Palestinians. These result were expected since the relationship between cigarette smoking and lung cancer has been established since 1950s (Wynder & Graham 1950), and confirmed in multiple studies in different countries (Hjelmborg Jet al., 2016, Rennert et al., 2015, Aoun et al., 2013). Also, biological evidence showed that cigarette contains is a well known carcinogenic chemicals that promotes cellular changes and promote the growth of tumors (Furrukh, 2013). Cigarette smokers in our study had a threefold excess risk for having lung cancer as compared to nonsmokers. Although this risk was significant, but still was less than expected. This could potentially be explained

by the study small sample size, besides the high prevalence of smoking in general among its males participants.

Additionally, it was found in the study that the prolonged duration of smoking increased the risk of lung cancer. Individuals who smoked for more than 20 years were shown to have higher risk of developing lung cancer compared with those who smoked for less than 19 years. The number of cigarettes smoked was positively associated with lung cancer risk. People who smoked for more than 2 packs per day were at higher risk of LC. This result is very similar to studies that found a dose-response relationship between the duration and amount of cigarettes smoking with the incidence of LC (Wang et al., 2015, Jee et al., 1999). Whereas, a population based case control study in Japan found that inhalation of cigarette smoke was a significant risk for LC regardless of pack-years. (Fukumoto et al., 2014).

The other source of smoking in this study was water pipe smoking "Nirgela". Water pipe smoking is very prevalent nowadays in Palestine. This habit was and is still very popular among men and women in Nablus governorate. In our study we found that lung cancer risk was higher among water-pipe smokers compared with nonsmokers, but this difference was not significant. This is consistent with a recent study in Lebanon that waterpipe smokers had a significant 6 times higher risk compared with non-smokers (OR = 6.0/95% CI: 1.78–20.26). (Auon et al., 2013). In this study there was very small number of water-pipe smokers among controls whose mean age was 48.6 years ±13.06, this can be explained by the fact that in the past decades water-pipe smoking wasn't popular as it is in young adults nowadays. However additional future studies are necessary to clear up this relationship.

Finally, no association between second hand smoking and lung cancer risk was found. This result is similar to what Judy Peres found in a large prospective of more than 76000 women who failed to find any clear association between passive smoking and Lung cancer risk (Peres et al., 2013).

Other studies showed that the risk of lung cancer tended to increase in nonsmokers with adult home passive smoking exposure ≥30 years compared with nonsmokers without adult home exposure (Wang et al., 2015). However passive smoking is a public health problem worldwide and nonsmokers who are exposed to secondhand smoke are inhaling many of

the same carcinogens substances and poisons as smokers, and that increase their risk of developing lung cancer by 20–30%. (CDC, 2014). A possible explanation for our results is that secondhand smoking is difficult to measure. Exposure to smoking occurs in everyday life, at home, work, in public transport, restaurants, especially in absence of any regulations that forbid smoking in public places.

6.2.4. Dietary habits:

Consumption of vegetables is shown in this study to decrease the risk of lung cancer and might have a role is lung cancer prevention. These results are concordance with other study results that showed high fruits & vegetable consumption was associated with a lower risk of lung cancer (Huakanget al., 2016). Tarabieh and colleagues (2013) found that the Mediterranean Arabian diet (cooked vegetables) had a strong protective effect against LC and that explains why the incidence of LC in Arab countries is considered low when compared to other countries. Fruits and vegetables contain carotenoids and other antioxidants which are believed to decrease lung cancer risk (Vieira et al., 2015). On the other hand, the results of this study didn't show any protective role from the consumption of foods prepared from grape leafs which is very popular in Palestine. In vitro assessment of cytotoxic and antioxidant activities of grape leafs suggests an effective cytotoxic activity of Shami grape leafs against lung cancer cells (Harb et al., 2015).

Dark bread that is made of whole grain wheat flour could be a possible protective risk factor for lung cancer. This association may be related to the magnesium (Mg) content in bread that is made from whole-grain. Wheat flour is a better source of Mg than bread made from refined white flour because the Mg-rich germ and bran are removed during the refining process (Fleet et al., 2001). This protective relationship was studied and confirmed earlier in a large case control study in USA, which showed a significant inverse trend with increased intake of dark bread with lung cancer (Mahabir et al., 2008). On the other hand a hospital-based case control study in Iran demonstrated that bread intake showed positive trend with the risk of lung cancer development (Hosseini et al., 2014). Again this difference between dark and white bread role in lung cancer development may be related to protective contents in whole grain dark bread such as magnesium.

6.3. Family history:

In this study, a positive family history of malignancy was found in 15.8 % of patients in the first part of the study, of these 69% had a first degree relative with a malignancy, and about 17% had more than one family member with malignancy. There is a significant association between positive family history of malignancy and risk of lung cancer (P value < 0.030) and 42.5% of study cases reported a positive family history of cancer. 17.5 % of cases had have positive family history of lung cancer, while 95% of controls have not, but this difference was not significant. Previous studies have documented that family history is linked to people's risk of developing lung cancer, irrespective of smoking status especially in young ages and never smokers (Chen et al., 2011). The presence of different types of cancer in the history of the family of an individual increases the risk of lung cancer. Similar results were found in a Turkish study which concluded that the lung and other system cancers (except prostate and gastrointestinal system cancers) were significantly increased at the brothers of patients with lung cancer (Ergu¨n et al., 2009). These findings could have important implications for the integration of family history data into cancer prevention, screening, and control of cancer.

6.4. Medical history and lung cancer risk

In this study, current body mass index (BMI) was significantly lower in study cases than controls. Similar findings was shown in a large population based cohort in UK , where low BMI was associated with higher lung cancer risk but this risk was driven by current smokers and ex-smokers and was attenuated or disappeared in never smokers (Bhaskaran et al.,2014). This finding could be explained by the presence of a real relationship between BMI and lung cancer risk. The potential biological mechanism underline this association is that leanness may be involved in the carcinogenic progress of smoking and the role of some enzymes such as urinary 8-hydroxydeoxyguanosine, which serves as an indicator of oxidative DNA damage in smokers (Loft al.,1992). Also a study reported that one allele of the fat mass and obesity-associated (FTO) gene, which has been linked with increased BMI, was associated with a decreased risk of lung cancer (Brennan et al., 2009). Another interpretation of higher lung cancer risk among lean patients could be the preclinical weight loss as explained by Mariam elzein et al (El-Zein et al., 2013).

Pre-existing chronic pulmonary disease (COPD) was associated with lung cancer risk. But this difference is not significant between study cases and controls group. 30% of LC patients had COPD.In the results literature that COPD diagnosis is strongly associated with a diagnosis of lung cancer. This relationship is largely explained by smoking habits, and it may that COPD is an independent risk factor for LC, besides genetic predisposition could also modify the risk of lung cancer from COPD. (Powell et al., 2013). The association between COPD and lung cancer risk can be explained by molecular changes. The damage to lungs in COPD patients is caused by oxidative stress process (exogenous from smoking and endogenous inflammatory cytokinerelease, protease activity and autoantibody activation) which causes airway destruction, air trapping and lung hyperinflation and thus lung damage and increased rate of cell division to restore cellular stasis, thereby the chance of carcinogenesis is increased. (Brusselle et al, 2015).

6.5. Reproductive hormones and the risk of Lung cancer

In this study, about 67% of female cases had menopause before the age of 50, whereas all control females had menopause after 51 years old. Early menopause (≤50 years old) may increase the risk for lung cancer, but these associations were not significant. In a therapeutic clinical trial in USA and Canada published (2018) confirmed that women with lung cancer were diagnosed in the post-menopause period (Cheng et al, 2017). A possible explanation for these findings might be indicated that premenopausal endogenous hormones appear to have a protective role in developing lung cancer specifically, with later age at menopause, which was previously confirmed by another study (Pesatori et al., 2013).

6.7 Study limitations

In the first part of the study we depend on medical files to have information about the patients and their risk factors and this may be not fully reliable data, since there is missed important information in many cases.

The main limitation in the second part of this study is the small number of the studied population due to bad medical prognosis, high referral rate, and high mortality rate among lung cancer patients. And as any case control and descriptive studies there may be some biases which might affect the results like information bias, recall bias, selection

bias, and reporting bias Limitation of time and finance prevent doing any further tests and imaging especially to exclude masses among controls.

6.8 Conclusions:

This study is the first one in Palestine that aimed to explore the possible protective and risk factors and lung cancer. Most results of this study were expected and comparable to other international studies results, while some others were unexpectedly contradicted the literature. Its results showed that cigarette smoking is the major risk factor for developing lung cancer but not the only factor especially the use of water pipe smoking that is the increased trend nowadays. Using Taboon oven for cooking, using fuel in warming and exposure to industrial gases and other air pollutants increase the risk for several lung diseases such as chronic bronchitis which by itself increased the risk to develop the lethal lung cancer. Besides family history of malignancy may have impact on developing lung cancer. On the other hand vegetables and whole grain dark bread consumption could be considered as protective factors of getting lung cancer. However additional studies are necessary to confirm these results.

6.9. Recommendations

6.9.1 Recommendations for policy makers and health care team:

- More awareness campaigns should be carried out to remind people of the harm caused by tobacco and water-pipe smoking for human health.
- Paying more attention to lung cancer diagnosis among health care providers.
- Increasing awareness of people about indoor and outdoor pollutants.
- Establishing a national screening program for the early detection of lung cancer. Introducing screening methods for early detection of lung cancer , chest CT scan is the best screening method because of its high sensitivity, it can be done for adults aged 55 to 80 years who have a 30 pack-year smoking history and high risk group, an alternative less costive method could be chest x ray accompanied with sputum cytology , this method is used in Japan.
- Improving the quality of the national cancer registry, and modify to include more details related to each cancer type.

6.9.2. Recommendations for the community:

- Stop smoking, and don't initiate it and away from place with smoking. Water pipe is a bad smoking habit.
- Living a healthy lifestyle: Increase the consumption of fruits and vegetables.
- Visit your physician whenever you complain of respiratory symptoms mainly cough lasting for more than 2 weeks.
- Perform a screening for lung cancer.

6.9.3. Recommendations for the future research:

- Conducting more detailed researches with larger sample size and including more hospitals and health care facilities over a more extended period of time.
- Considering the type of lung cancer (histopathology) and relating it to the risk factors.
- Confirming the absence of lung cancer among controls by more advanced and reliable methods such as CT scan.
- Focusing on non smokers female and young patients to exclude confounding by smoking and to explore other risk factors in more details.

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Annex 1 : Medical files data form

File # :

DOB :_____ AGE _____

Gender :Male female

Residency _____ place :_____

Marital status : Married single widow divorced

Number of children : _____

Smoking :Nonsmoker smoker years_____

Work : worker employee solider house farmer

Family Hx : NO YES ,who ?_____ type? _____

Presenting symptoms : cough hemoptysis wt loss others_____

Histopathology :_____

Right lung left lung

Stage :_____

Date of diagnosis:_____

Treatment : Surgery chemotherapy radiation conservative

Date of last contact :_____

Note :

Annex 2: The Questionnaire

Control 0 Case 1 تاريخ المقابلة: __ __ / __ __ / __ __ __ __

اولا: المتغيرات الاجتماعية

_____	1. SD	رقم الاستمارة
1☐ذكر 0☐انثى	2. SD	الجنس
__/__/_____	3. SD	تاريخ ميلادك
|___|	4. SD	ما هو تحصيلك العلمي الأعلى؟ 1- اساسي (0- 6) 2- أعدادي (7-10) 3- ثانوي (11-12) 4- كلية 5- جامعي
_____ محافظة _____ منطقة	5. SD	أين تقيم حاليا؟
	6. SD	ما نوع السكن؟ 1-بيت مستقل 2- شقة في عمارة 3- بيت شعر 4- بيت صفيح
1☐نعم 0☐لا	7. SD	هل منزلك قريب (مئة متر أو أقل) من طريق مزدحم بالسيارات ؟
1☐نعم 0☐لا	8. SD	هل عشت يوما في منزل قريب (مئة متر أو أقل) من طريق مزدحم بالسيارات؟
1☐نعم 0☐لا	9. SD	هل عشت يوما في منزل قريب (مئة متر أو أقل) من مولد كهرباء؟
1☐نعم 0☐لا	10.	هل تعيش او عشت يوما قريب (مئة متر أو أقل) من مصنع يبعث غازات ؟
_____	11. SD	كيف تدفئون منزلكم؟ 1-غاز □ 2-حطب □ 3-كاز □ 4-كهرباء □ 5-هواء ساخن □ 6-مركزية □
_____	12. SD	على ماذا تطبخون؟ 1-غاز □ غيره:.....
1☐نعم 0☐لا	13. SD	هل تستخدمون الطابون في المنزل ؟
|___|___|	14. SD	ما عدد أفراد الأسرة المقيمة في منزلك الحالي؟ (بما فيهم انت)
|__|	15. SD	ما دخل الأسرة الشهري ؟ (بالشيكل) 1- أقل من 1000 2- (1000 – 2000) 3- (2001 – 3000) 4- (3001 – 5000) 5- أكثر من 5000
1☐نعم 0☐لا	16. SD	هل تعمل حاليا؟
	17. SD	ما هو عملك الحالي؟
	18. SD	ما هو العمل و ما مدته؟
|__|	19. SD	صلة القرابة بين والدك ووالدتك؟ 0- لا قرابة 1- أقرباء درجة أولى (ابناء عم، ابناء عمة، أبناء خالة) 2- من نفس عائلة الأم أو عائلة الأب
|___|	20. SD	ما هي حالتك الاجتماعية؟ 1- أعزب 2- متزوج 3- مطلق 4- أرمل

	المهنة 1	المهنة 2	المهنة 3
أ. نوع المهنة			
ب. مدة العمل			
ج. التعرض للغازات السامة والدخان			

ثانيا :نمط الحياة

<table>
<tr><td>1☐نعم 0☐لا</td><td>1. LS</td><td>هل تدخن حاليا أي نوع من أنواع التبغ التالية مثل السجائر أو السيجار أو الغليون.....الخ ما عدا الأرجيلة سأسألك لاحقا عليها الإجابة لا، انتقل للسؤال 6</td></tr>
<tr><td>1☐نعم 0☐لا</td><td>2. LS</td><td>هل تدخن أيا من هذه الأنواع السابقة (السجائر أو السيجار او الغليون...) يوميا؟</td></tr>
<tr><td>|___|___|</td><td>3. LS</td><td>كم كان عمرك عندما بدأت التدخين؟</td></tr>
<tr><td>|___| سنة</td><td>4. LS</td><td>كم من الوقت مضى عليك وأنت تدخن؟</td></tr>
<tr><td></td><td>5. LS</td><td>في المتوسط كم من منتجات التبغ التالية تدخن يوميا خلال الثلاثين يوما الماضية ؟

اذا كانت الاجابة انه لا يدخن نوع معين من التالي نكتب كلمة (لا شيء) او صفر كتابة وليس ارقام

<table>
<tr><td></td><td>العدد يوميا</td></tr>
<tr><td>أ- السجائر</td><td></td></tr>
<tr><td>ب- السجائر اللف المصنعة يدويا</td><td></td></tr>
</table>

<table>
<tr><td></td><td colspan="3">عدد المرات</td></tr>
<tr><td></td><td>في اليوم</td><td>في الاسبوع</td><td>في الشهر</td></tr>
<tr><td>ج- غليون</td><td></td><td></td><td></td></tr>
<tr><td>د- سيجار</td><td></td><td></td><td></td></tr>
</table>
</td></tr>
<tr><td>1☐نعم 0☐لا</td><td>6. LS</td><td>هل يدخن أحد والديك (حاليا أو في السابق)</td></tr>
<tr><td>1☐نعم 0☐لا</td><td>7. LS</td><td>هل يدخن أي احد من افراد عائلتك داخل المنزل ؟</td></tr>
<tr><td>1☐نعم 0☐لا</td><td>8. LS</td><td>في الماضي هل سبق لك التدخين يوميا؟ الإجابة لا انتقل للسؤال 9</td></tr>
<tr><td>|___|</td><td>9. LS</td><td>كم كان عمرك عندما توقفت عن التدخين ؟</td></tr>
<tr><td>1☐نعم 0☐لا</td><td>10. LS</td><td>هل تدخن الارجيلة حاليا ؟ الإجابة لا، انتقل للسؤال 13</td></tr>
<tr><td></td><td>11. LS</td><td>كم مرة تدخن الارجيلة ؟ إجابة واحدة فقط
<table>
<tr><td></td><td>اليوم</td><td>الاسبوع</td><td>الشهر</td></tr>
<tr><td>عدد المرات</td><td></td><td></td><td></td></tr>
</table>
</td></tr>
<tr><td>|___|</td><td>12. LS</td><td>كم كان عمرك عندما بدأت تدخن الأرجيلة ؟</td></tr>
<tr><td>|___|</td><td>13. LS</td><td>كم سنة دخنت الأرجيلة؟</td></tr>
<tr><td>1☐نعم 0☐لا</td><td>14. LS</td><td>هل سبق وان تناولت مشروباً كحولياً؟ (مثل البيرة، النبيذ، الويسكي) خلال السنة الماضية ؟
الإجابة (لا)، انتقل للفقرة التالية</td></tr>
<tr><td>|___|</td><td>15. LS</td><td>في المتوسط: كم يوما تشرب المشروبات الكحولية في الأسبوع ؟</td></tr>
<tr><td>|___|</td><td>16. LS</td><td>عندما تشرب الكحول: في المتوسط كم كأسا تشرب في المرة الواحدة؟</td></tr>
<tr><td>|___|___|</td><td>17. LS</td><td>كم كان عمرك عندما تناولت الكحول للمرة الأولى ؟</td></tr>
</table>

	18. LS	هل تتناول أي من التالية :

	لا يتناول أو أقل من مرة في الشهر 1	3-1 في الشهر 2	مرة في الأسبوع 3	4-2 في الأسبوع 4	6-5 في الاسبوع 5	مرة في اليوم 6	3-2 في اليوم 7	5-4 في اليوم 8	6+ في اليوم 9
حليب									
كيك أو معجنات									
بسكويت									
مكسرات									
سمك او تونا									
دجاج									
فواكة									
سلطات									
ورق عنب									
بيض									
جبنة									
خبز ابيض									
خبز اسمر									
	لا يتناول أو أقل من مرة في الشهر	**3-1 في الشهر**	**مرة في الاسبوع**	**4-2 في الاسبوع**	**6-5 في الاسبوع**	**مرة في اليوم**	**3-2 مرات في اليوم**	**5-4 في اليوم**	**6+ في اليوم**

ثالثا التاريخ الطبي:

كغم ____	1. MH	ما هو وزنك الحالي ؟
كغم ____	2. MH	كم كان وزنك منذ 10 سنوات ؟
كغم ____	3. MH	كم كان وزنك منذ عامين ؟
سم ____	4. MH	ما هو طولك؟
	5. MH	اجب عن الاسئلة التالية عن مسكنات الالم التي تناولتها بانتظام خلال ال5 اعوام الماضية ،على الاقل قرص واحد اسبوعيا ولمدة شهرين

هل تناولت أي من التالية بشكل منتظم (على الاقل قرص واحد اسبوعيا ولمدة شهرين)خلال ال 5 اعوام الماضية ؟	كم قرص يوميا او اسبوعيا تناولت بانتظام خلال ال 5 اعوام الماضية ؟	ما هي المدة التي تناولت بها الاقراص بانتظام خلال ال 5 اعوام الماضية؟	هل اخذتها بانتظام خلال العام المنصرم ؟
Aspirinاو مشتقاته 1☐نعم 0☐لا 2☐ لا اعلم	_____ # حبة لكل: ☐ يوم ☐ أسبوع ☐لا أعرف	____ ☐ أسابيع ☐ أشهر ☐ سنوات	0☐لا 1☐ نعم 2☐ لا اعلم

مسكنات الم لا تحتوي اسبرين مثل Acamol or Trufen 1☐نعم 0☐لا 2☐ لا اعلم	_____ # حبة لكل: ☐ يوم ☐ أسبوع ☐لا أعرف	_ _ _ ☐ أسابيع ☐ أشهر ☐ سنوات ☐لا أعرف	☐لا أعرف	0☐لا 1☐ نعم 2☐ لا اعلم

6. MH

هل سبق وأخبرك طبيبك بأنك مصاب بأي من الامراض الرئوية التالية ؟

			كم كان عمرك عندما تم تشخيص المرض ؟
أ-	التهاب الشعب الهوائية المزمن	1☐نعم 0☐لا	___ ___ ___
ب-	انتفاخ الرئة	1☐نعم 0☐لا	___ ___ ___
ت-	الربو ☐الطفولة ☐ الكبار	1☐نعم 0☐لا	___ ___ ___
ث-	السل الرئوي	1☐نعم 0☐لا	___ ___ ___
ج-	الأسبستوس	1☐نعم 0☐لا	___ ___ ___
ح-	أمراض الرئة، غير سرطان (حدد)___ ___ ___ ___	1☐نعم 0☐لا	___ ___ ___
خ-	السكري ☐الطفولة ☐ الكبار	1☐نعم 0☐لا	___ ___ ___

التاريخ الانجابي: <u>إن كان المريض ذكر او امرأة عزباء انتقل للقسم التالي</u>

|__|	1. RH	كم كان عمرك عندما تزوجت أول مرة؟
1☐نعم 0☐لا	2. RH	هل أنت حامل حاليا ؟
|___|___|	3. RH	كم عدد المرات التي حملت بها؟ (شامل الحمل العادي والخداج الإجهاض و فقدان الجنين و الحمل في القنوات و الحمل الحالي إن وجد).
|___|___|	4. RH	كم عدد الأحمال التي أدت إلى إنجاب أطفال أحياء؟
|___|___|	5. RH	كم عدد ما أنجبت من ذكور؟
|___|___|	6. RH	كم عدد ما أنجبت من إناث؟
|___|___|	7. RH	كم كان عمرك في أول حمل ؟ (مهما كانت نتيجته، إجهاض أو حمل كامل أو خداج)
1☐نعم 0☐لا	8. RH	هل أرضعت الأطفال رضاعة طبيعية؟ **الجواب (لا)، انتقل للسؤال** 11
|___|___|	9. RH	كم كان عمرك عندما أرضعت أول طفل؟
|__| سنة	10. RH	لو جمعنا كل فترات الرضاعة لجميع الأطفال، كم فترة إرضاعهم مجموعة ؟ (بالسنوات)
1☐نعم 0☐لا	11. RH	هل استخدمت حبوب مانعة للحمل لمدة شهرين أو أكثر لأي سبب (تنظيم دورة، حب شباب، منع حمل) ؟ **الجواب (لا)، انتقل للسؤال** 16
|___|___|	12. RH	كم كان عمرك في أول استخدام لحبوب منع الحمل؟

1☐نعم 0☐لا	13. RH	هل تستخدمين حبوب منع الحمل حاليا؟ **الإجابة (نعم)، انتقل للسؤال** 15
|__|__|	14. RH	كم كان عمرك عندما توقفت عن استخدام حبوب موانع الحمل؟
|__|__|	15. RH	لو جمعنا الفترة التي استخدمت فيها حبوب منع الحمل، ما طول الفترة؟ **بالسنوات**
|__|__|	16. RH	في أي عمر بدأت عندك الدورة الشهرية؟ سن البلوغ
|___|	17. RH	طبيعة دورتك الشهرية : 1- منتظمة 2- ليست منتظمة 3- أستعمل هرمونات بديلة 4- توقفت الدورة الشهرية نهائيا -- **أنتقل للسؤال 18**
|___|	18. RH	كم كان عمرك عندما توقفت دورتك الشهرية؟
1☐نعم 0☐لا	19. RH	هل تعرضت لعملية إستئصال رحم؟ **الإجابة (لا)، انتقل للسؤال** 21
|___|___|	20. RH	كم كان عمرك عندما تم استئصال الرحم؟
|___|	21. RH	هل تعرضت لعملية استئصال أحد المبايض أو كليهما؟ 0- لم أتعرض -- **انتقل للسؤال 23** 1- نعم، أحد المبايض تم استئصاله 2- نعم، كلاهما
|___|___|	22. RH	كم كان عمرك عندما استئصال المبايض او احدهما؟
1 ☐نعم 0☐لا	23. RH	هل استخدمت هرمونات أنثوية بديلة لمدة شهرين أو أكثر لعلاج هبات انقطاع الدورة أو لتخفيف أعراضها؟ **الإجابة (لا)، انتقل للفقرة التالية**
|___|___|	24. RH	كم كان عمرك عندما بدأت استخدام الهرمونات البديلة؟
|__|__| سنة	25. RH	لو جمعنا الفترة التي استخدمت فيها الهرمونات البديلة ما مجموع الفترة ؟
|___|___|	26. RH	كم كان عمرك عندما توقفت عن استعمال الهرمونات البديلة؟

التاريخ االعائلي :

1☐نعم 0☐لا	1. FH	هل أصيب أحد أقربائك بسرطان الرئة أو هو مصاب به حاليا **الإجابة (لا) انتقل للسؤال 3**
	2. FH	من من اقربائك اصيب بسرطان الرئة؟

	مريض 1	مريض 2	مريض 3	مريض 4
أ. صلة القرابة				
ب. العمر عند التشخيص				

1☐نعم 0☐لا	3. FH	هل عانى أو يعاني أحد أقربائك من نوع آخر من السرطان؟ **الإجابة (لا) انتقل للفقرة التالية**
	4. FH	من من أقربائك عانى او يعاني نوعا آخر من السرطان؟

	مريض 1	**مريض 2**	**مريض 3**	**مريض 4**
أ. صلة القرابة				
ب.نوع السرطان				
ج.العمر عند التشخيص				

Annex 3 :The letter from Public health faculty to MOH.

Al-Quds University
Jerusalem
School of Public Health

جامعة القدس
القدس
كلية الصحة العامة

التاريخ: 26/8/2017

حضرة الدكتورة أمل أبو عوض المحترمة
مدير عام التعليم الصحي/ وزارة الصحة الفلسطينية

الموضوع: مساعدة الطالبة ايلاف بلال محمد أبوزعرور

تحية طيبة وبعد،،

تقوم الطالبة ايلاف بلال محمد أبوزعرور بالتحضير لرسالة ماجستير تحت عنوان:

"محددات/ مسببات الإصابة بمرض سرطان الرئة في شمال الضفة الغربية في فلسطين".

في المرحلة الاولى من الدراسة سيتم مراجعة جميع ملفات المرضى المصابون بسرطان الرئة بين عام 2007-2017 وتحديد العوامل التي ساهمت بإصابتهم بسرطان الرئة ، اضافة الى تحديد نوع سرطان الرئة من حيث نوع الخلايا والمرحلة التي وصل اليها عند اكتشافه ، وكذلك معرفة عدد السنوات التي عاشها المريض بعد التشخيص .

في المرحلة الثانية سيتم توزيع استبيانات على المرضى المصابين بسرطان الرئة والذين يراجعون في المستشفيات المذكورة اعلاه والإطلاع على ملفاتهم الطبية لدراسة وتحديد عوامل الخطورة لديهم والتي ادت الى اصابتهم بسرطان الرئة ، وسيتم اخذ عينة عشوائية من المرضى المراجعين في عيادات خارجية اخرى بنفس المستشفيات بحيث يكونون غير مصابين بسرطان الرئة او أي امراض تنفسية او سرطانات اخرى ليقوموا بتعبئة نفس الاستبيان ومن ثم سيتم دراسة ومقارنة عوامل الخطورة بين الفئتين (المصابين وغير المصابين بسرطان الرئة).

إن هذه الدراسة هي الأولى من نوعها في فلسطين والتي تستهدف دراسة المسببات المحتملة للإصابة من هذا النوع من السرطان، آملين أن تساهم الدراسة في توضيح وضع المرضى المصابين بالإمراض السرطانية الأخرى.

أرجو من حضرتكم الموافقة بإجراء هذه الدراسة في مستشفى الوطني ومستشفى بيت جالا الحكوميين، والإيعاز للمسؤولين بتسهيل مهمة الطالبة. علماً بان الدراسة ستكون لأغراض البحث العلمي فقط.

مع فائق الشكر والاحترام،،

عميد كلية الصحة العامة

مرفق ملف البحث والاستمارة التي سيتم استخدامها

نسخة: الملف

Annex 4: Consent form

موافقة على المشاركة في بحث علمي

تحية طيبة وبعد،

نطلب منك أن تأخذاي وقتك لقراءة النموذج وأن تطرحاي أي أسئلة قد تكون لديك قبل الموافقة على المشاركة في الدراسة.

أنتاي مدعواة للمشاركة ببحث علمي سريري سيجرى في مستشفيات وزارة الصحة الفلسطينية بعنوان " عوامل الخطورة المرتبطة بالإصابة بسرطان الرئة عند الفلسطينيين في الضفة الغربية " وهو بحث يجرى من قبل الطالبة في كلية الصحة العامة الطبيبة ايلاف بلال ابوزعرور.

ويهدف هذا البحث لدراسة عوامل الخطورة التي قد تسهم في الإصابة بسرطان الرئة ، وتكمن أهمية هذا البحث في كونه يسلط الضوء على أهم العوامل التي قد تزيد من فرصة الإصابة بسرطان الرئة وبالتالي توعية المجتمع واتخاذ الإجراءات الوقائية و سن التشريعات للحد من هذا المرض.

المشاركة في هذا البحث اختيارية. ولن يخسر أي فرد أي منافع في حال تقرر عدم المشاركة أو التوقف عن المشاركة في أي وقت. وبمجرد الإمضاء على هذه الموافقة، تقراي بأنك توافقاي اختيارياً على المشاركة في هذا البحث، وأن المعلومات المدونة أعلاه قد شُرحت شفهيا.

في حال وافقت على المشاركة في هذه الدراسة، سيبقى أسمك طي الكتمان. و لن يكون لأي شخص حق الإطلاع على ملفك الطبي باستثناء الطبيب المسؤول عن الدراسة ومعاونيه، ولجان الأخلاق المهنية المستقلة.

لقد قرأت استمارة القبول هذه وفهمت مضمونها. تمت الإجابة على أسئلتي جميعها. وبناء عليه فأنني حراة مختاراة أوافق على الاشتراك في هذا البحث، وإني أعلم أن الباحثة ايلاف ابوزعرور ستكون مستعدة للإجابة على أسئلتي، وأنه باستطاعتي التواصل معها عبر البريد الالكتروني. كما أعرف بأنني حرة في الانسحاب من هذا البحث متى شئت حتى بعد التوقيع على الموافقة. وسأحصل على نسخة أصلية من هذا النموذج.

التاريخ ---------- اسم المشارك اة---------- إمضاء المشاركاة----------

للمزيد من الاستفسارات :dr_elaf@yahoo.com توقيع الباحثة : ----------

شكراً على الاهتمام والاستعداد للمشاركة في هذه الدراسة البحثية