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Al-Quds University

Breast Cancer Risk among Patients with Diabetes Attending Beit-Jala Governmental Hospital : A Case Control Study

Imtithal Tawfiq Basim Khateeb

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Breast Cancer Risk among Patients with Diabetes Attending Beit-Jala Governmental Hospital:

A Case Control Study

Prepared By:

Imtithal Tawfiq Basim Khateeb

B. Sc. In Pharmacy – An-Najah National University/ Palestine

Supervisor: Dr. Nuha El-Sharif

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Thesis Approval

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Prepared By: Imtithal Tawfiq Basim Khateeb

Registration No: 21411615

Supervisor: Dr. Nuha El-Sharif

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The names and signatures of the examining committee members are as follows:

1- Head of Committee: Dr. Nuha El-Sharif Signature: ----------

2- Internal Examiner: Dr. Rania Abu Seir Signature: ----------

3- External Examiner: Dr. Hamzeh Al-Zabadi Signature: ----------

Jerusalem – Palestine

1439/2018

Dedication

To:

My parents,

My family,

My friends,

My beloved country, Palestine,

My Grandparents who always prayed for my success, then passed away,

Cancer patients who taught me how to appreciate life, hope, and patience,

Chemotherapy unit staff who were generous humans before being a medical staff,

To all of them, I dedicate this work with love.

Imtithal Tawfiq Basim Khateeb

Declaration:

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

Signed ..Imtithal Al-Khateeb..

Imtithal Tawfiq Basim Khateeb

Date: 19.05.2018

Acknowledgments

As a start, I would like to thank God who gave me strength, patience, motivation to complete this work.

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To All, Thank you

Imtithal Tawfiq Basim Khateeb

Abstract

Background: Diabetes mellitus type 2 (T2DM) and cancer share several common risk factors, such as obesity and the adoption of westernized lifestyle, which is characterized by the sedentary lifestyle and consumption of unhealthy diet. Several studies showed an association between T2DM and the risk for breast cancer (BC). However, the association between T2DM and its medication with BC risk had not been studied in Palestine till to date.

Aim: This study aims to investigate the association between T2DM, its medication/s, and breast cancer among females in the southern region of the West Bank.

Study methodology: In this matched case-control study, data were collected for 474 participants (237 confirmed BC and 237 controls), through the period between June 2016 to October 2017. Study cases were interviewed at the day care unit of Beit-Jala Hospital, while controls were matched by location of residence and age groups. A random sample of those registered at Bethlehem and Hebron governorates who underwent a mammography and confirmed to be free of BC were included in the study. An interview-based questionnaire was used for data collection, structured on the risk factors of BC.

Statistical analysis: All data were entered and analyzed using SPSS v20 (statistical package for social sciences, version 20). Descriptive analysis, Chi-square test, and independent sample T-Test were conducted as needed, to examine the difference between study cases and control group. In the multivariate analysis, an overall model was developed; only factors that showed a significant difference in the previous analysis were included in the last model. Forward conditional logistic regression was used to get adjusted odds ratios.

Ethical considerations: The study was proposed by Al Quds University-SPH research committee, and IRB (International Review Board). In addition, approval from the Ministry of Health as the study was conducted in its setting was assured. A consent form was signed by each participant confirming her willingness to participate.

Results: The mean age of BC diagnosis was 52 years. Among study cases, the most common subtype of BC was ductal carcinoma (58%), and (65%) of the study cases were

diagnosed at the 2nd or 3rd stage of the disease. Furthermore, only (17%) of study cases were found to have BC during a screening program, while 82% were referred after being suspected to have BC. About half of the study cases had full mastectomy.

After conducting multivariate analysis, T2DM itself was not found to increase the risk of BC, but its medication, the long acting Insulin Glargine was found to significantly increase the risk for BC by 14 folds.

Several reproductive factors revealed positive association with BC. Having a menarche after 13 years of age increased the risk by three folds. Using oral contraceptives doubled the risk for BC. Additionally, receiving hormone replacement therapy increased the risk by 4 folds to have BC too. Breastfeeding for a period of 9 years or more decreased the risk to 15% compared to those who didn't breastfeed. Regarding health status history, some chronic illnesses showed a significant association with BC risk. Cardiovascular diseases (adjusted OR= 3.80, 95%CI: 1.87- 8.07), and joint problems (adjusted OR= 2.64, 95%CI: 1.45- 4.82) were shown to triplicate the risk for BC too. Moreover, consanguinity parental marriage; first degree relative, doubled the risk for BC. Family history of BC significantly tripled the risk for BC (adjusted OR= 3.51, 95%CI: 1.47-7.10).

Furthermore, body mass index (BMI) showed a positive dose-response association with BC; i.e. the higher the BMI the greater the risk for BC was found. The use of electric blanket significantly tripled the risk too. As for dietary habits, some kinds of food showed a significant association with increased risk of BC. Soft drinks and butter either doubled or triplicate the risk for BC. In contrast, chicken intake showed a negative "protective" significant association with BC risk (adjusted OR= 0.43, 95% CI: 0.22- 0.86).

Conclusions: This is the first study of its type in Palestine and had consistent results with the published research that investigated the association between T2DM, its medication and BC risk. Most studies were conducted on datasets that were collected from patients' medical records. Our study used the classical matched case-control, which made it unique in its results.

Our results showed a significant association between BC risk and use of the long acting diabetes medication "Insulin Glargine". Furthermore, we were also able to show that consanguinity is a strong risk factor for BC. In addition, reproductive factors, health status

factors, family history of BC and lifestyle factors were also confirmed to be important risk factors for BC.

The relationship between T2DM and BC is still a hot field in research which needs further investigation in the Northern area of Palestine. Furthermore, T2DM association to other cancer types needs to be investigated.

خطر الإصابة بسرطان الثدي بين المريضات بالسكري في مستشفى بيت جالا الحكومي: دراسة الحالات والضوابط

إعداد: امتثال توفيق باسم الخطيب

إشراف: د. نهى الشريف

الملخص

خلفية الدراسة: يشترك مرض السكري من النوع الثاني (T2DM) مع السرطان في العديد من عوامل الخطر، مثل السمنة واعتماد أسلوب الحياة الغربية الذي يتميز بقلة النشاط البدني واستهلاك النظام الغذائي غير الصحي. وأسلوب الحياة هذا مرتبطاً بأمراض مثل السكري والسرطان وكلاهما آخذ في الارتفاع. هذا و قد أظهرت العديد من الدراسات وجود ارتباط بين السكري من النوع 2 وخطر احتمال الإصابة بسرطان الثدي. وبالرغم من ذلك، لم تتم دراسة مرض السكري وأدويته المرتبطة بمرض سرطان الثدي من قبل ذلك في فلسطين.

هدف الدراسة: تهدف هذه الدراسة إلى التحقق من العلاقة بين النوع 2 من مرض السكري وأدويته، وخطر الإصابة بسرطان الثدي عند الإناث في الضفة الغربية.

منهجية الدراسة: استُخدمت دراسة الحالات والضوابط لدراسة العوامل المسببة لسرطان الثدي، تم جمع البيانات ل 474 امرأة مشاركة (237 حالة مؤكدة التشخيص بالمرض و 237 امرأة كعينة ضابطة). تم استقطاب الحالات ومقابلتها في وحدة الرعاية النهارية في مستشفى بيت جالا، أما المجموعة الضابطة فقد تم مطابقتها من ناحية موقع الإقامة والفئات العمرية مع الحالات، وقد تم اختيار المجموعة الضابطة عشوائيا في محافظتي بيت لحم والخليل ممن تأكد خضوعهن لتصوير الثدي، وعدم إصابتهم بالسرطان. وجُمعت البيانات باستخدام استبيان أجابت من خلاله المشاركات عن أسئلة الباحث عن طريق مقابلة.

التحليل الإحصائي: تم إدخال وتحليل البيانات باستخدام برنامج SPSS (الحزم الإحصائية للعلوم الاجتماعية). استخدم التحليل أحادي المتغير، اختبار (Chi square)، لفحص مدى الارتباط بين

الحالات والضوابط، واستخدم اختبار (T-test) عند الحاجة. في التحليل متعدد المتغيرات، تم تطوير نموذج، تضمن جميع عوامل الخطر ذات الدلالة الإحصائية الناتجة من التحليل أحادي المتغير فقط.

الاعتبارات الأخلاقية: تم تقديم مقترح الدراسة إلى لجنة أبحاث جامعة القدس للعلوم الاجتماعية. تم الحصول على الموافقة الإدارية من وزارة الصحة لأن الدراسة أجريت في مستشفياتها وعياداتها. تم تسليم نموذج موافقة لكل مشتركة في الدراسة ليتم الموافقة عليه وتوقيعه قبل المشاركة.

النتائج: كان متوسط عمر التشخيص لسرطان الثدي 52 سنة. في النساء المصابات كان نوع السرطان الأكثر الأكثر شيوعا هو سرطان الأقنية (58 ٪)، هذا وقد شُخصت ما نسبته 65 ٪ من الحالات في المرحلة الثانية أو الثالثة من المرض. علاوة على ذلك ، تبين أن 17٪ فقط من الحالات تم تشخيصها من خلال برامج المسح الوقائي ، بينما تم تشخيص 82٪ منها بعد الاشتباه في إصابتها. و قد خضعت حوالي نصف النساء المصابات لاستئصال كامل للثدي.

بعد ضبط عدة عوامل ، لم يثبت أن السكري نفسه يزيد من خطر الإصابة بسرطان الثدي، إلا أن دواء السكري الأنسولين طويل المفعول (جلارجين) ضاعف خطر الإصابة بسرطان الثدي بمقدار 14 مرة.

وقد لوحظ من نتائج الدراسة أن العديد من العوامل الإنجابية ارتبطت ارتباطًا إيجابيًا مع خطر الإصابة بسرطان الثدي ؛ فقد تبين أن البلوغ بعد سن 13 ضاعف خطر الإصابة 3 مرات، وكذلك تناول الحبوب المانعة الحمل ضاعفت الخطر 3 مرات أيضا، و العلاج بالهرمونات البديلة زادت الخطر بنسبة 4 أضعاف. على العكس من ذلك، وجد أنه مع الرضاعة الطبيعية وفترة الرضاعة الطبيعية فوق 9 سنوات انخفضت المخاطر إلى 15 ٪ إذا ما قورنت بعدم الرضاعة بتاتا. أما فيما يتعلق بتاريخ الحالة الصحية المرضي، أظهرت بعض الأمراض المزمنة ارتباطًا كبيرًا بخطر الإصابة بسرطان الثدي مثل أمراض القلب والأوعية الدموية (AOR 3.88) ومشاكل المفاصل (AOR 2.64).

إضافة إلى ذلك، ضاعف زواج الوالدين الأقارب من الدرجة الأولى من خطر الإصابة. وكذلك التاريخ العائلي لسرطان الثدي زاد بشكل كبير من خطر الإصابة بسرطان الثدي (AOR 3.51).

علاوة على ذلك، أظهر مؤشر كتلة الجسم (BMI) وجود علاقة إيجابية مع سرطان الثدي. بمعنى أنه كلما زاد مؤشر كتلة الجسم ، لوحظ وجود خطر متزايد. ولوحظ أن استخدام البطانيات الكهربائية قد ضاعف من خطر الإصابة بالسرطان ثلاث مرات. نظرا لنوع الغذاء، أظهرت العديد من الأطعمة ارتباطًا كبيرًا مع زيادة خطر الإصابة بسرطان الثدي، فالاستهلاك المتكرر للمشروبات الغازية

والزبدة ضاعف الخطر بالإصابة مرتين أو ثلاثة. في المقابل، قلل تناول الدجاج من خطر الإصابة بسرطان الثدي (AOR 0.43).

الخلاصة: هذه الدراسة هي الأولى من نوعها في فلسطين، وكانت نتائجها متوافقة مع الأبحاث المنشورة التي بحثت العلاقة بين مرض السكري وأدويته وخطر الإصابة بسرطان الثدي. أجريت معظم الدراسات على مجموعات البيانات التي يتم جمعها من السجلات الطبية للمرضى. استخدمت دراستنا دراسة الحالات مع المجموعة الضابطة، مما جعلها فريدة في نتائجها.

أظهرت النتائج التي توصلنا إليها وجود ارتباط كبير بين خطر الإصابة بسرطان الثدي ودواء السكري انسولين جلارجين (طويل المفعول)، هذا وقد تمكنا من إظهار أن زواج الأقارب هو عامل خطر قوي لسرطان الثدي. وأيضاً العوامل الإنجابية، و الحالة الصحية، والتاريخ العائلي للسرطان، واستهلاك أنواع معينة من الطعام أظهرت ارتباطاً بخطر الإصابة.

ولا تزال العلاقة بين مرض السكري وسرطان الثدي مجالا غنياً للبحث، وتحتاج إلى مزيد من التحقق والدراسة في منطقة شمال فلسطين، ودراسة مستفيضة لفهم علاقة السكري بسرطانات أخرى غير سرطان الثدي.

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List of abbreviations

Abbreviation	Definition
T2DM	Type 2 Diabetes Mellitus
BC	Breast Cancer
MECC	Middle East Cancer Consortium
SEER	Surveillance, Epidemiology, and End Results program
CVD	Cardio-Vascular Diseases
OCP	Oral Contraceptive
HRT	Hormone replacement therapy
OR	Odds ratio
HR	Hazard ratio
RR	Relative risk
AOR	Adjusted odds ratio
CI	95% Confidence interval
SES	Socio-economic status
SD	Standard deviation
SE	Standard error
BI-RADS	Breast Imaging-Reporting and Data System
BMI	Body mass index
TZD	Thiozolidendions
PCBS	Palestinian Central Bureau of Statistics
MoH	Ministry of Health
SPSS	Statistical Package for Social Science
WHO	World Health Organization
ICD10	International coding of diseases 10
FBS	Fasting blood sugar
BRCA	Breast cancer susceptibility gene
IGF	Insulin-like growth factor

Chapter One

Background and Significance

1.1. Background

Diabetes mellitus Type 2 (T2DM) is a major health problem which showed a step acceleration in prevalence worldwide in the past two decades (CDC, 2012). The world prevalence of diabetes in adults was 6.4% in 2010 and might increase to 7.7% by 2030 (J. E. Shaw, Sicree, & Zimmet, 2010). Between 2010 and 2030, there will be a 69% increase in number of adults with diabetes in developing countries and a 20% increase in developed countries. Arab world will have the second highest increase in percentage of people with T2DM in 2030 (J. E. Shaw et al., 2010).

The association between T2DM and cancer was firstly observed 60 years ago (Rawson, 1956). Studies found that there is an increased risk among diabetics for specific cancers; i.e. liver, pancreas, endometrial, breast among women, non-Hodgkin lymphoma, stomach, colon, and kidney cancers. But, prostate cancer incidence was shown to be lower among diabetic patients type 2, and no consistent association was found for lung and ovarian cancers (Johnson et al., 2012). The relative risk (RR) for developing cancer in diabetic patients ranges from RR= 2.0-2.5 for liver, pancreatic and endometrial cancers, and 1.2-1.5 for breast, colon and bladder cancers (Xu, 2014). It was shown that strength and direction of this association depends on the type of diabetes, its duration, type and duration of medication, and the type of specific cancer (Tabak et al., 2009). T2DM does not only increase the risk of BC, but also increases mortality rate of females, with a crude mortality rate of 45.7 per 100,000 person-years (Tseng, Chong, & Tai, 2009). Although this increase might be minimal, but the consequence would be significant at the population level

(Hardefeldt, Edirimanne, & Eslick, 2012). Among Palestinians, a recent retrospective cohort study among Israeli Arabs showed that T2DM rate was lower among cancer cases than among cancer-free adult Arabs, but this difference was not statistically significant (Idilbi, Barchana, Milman, & Carel, 2013).

The modifiable risk factors for cancer among diabetic patients were mostly related to lifestyle factors; i.e. obesity, poor diet, physical activity and smoking. Also, socioeconomic status was shown to affect both the occurrence of T2DM and cancer. Several studies support the hypothesis that metabolic syndrome and its components might play an important role in the etiology and progression of certain cancer types and a worse prognosis for some cancers (Xue F et al, 2007). More specifically, obesity and T2DM have been shown to be associated with breast, endometrial, colorectal, pancreatic, hepatic and renal cancer (Brauna, Bitton-Worms, & le Roith, 2011). On the other hand, an inverse association was found between Mediterranean diet and cancer, (OR=0.4, 95% CI: 0.26-0.61). It was also concluded that greater adherence to Mediterranean diet is associated with lower odds not only for cancer, but for T2DM, as it seems to moderate the prevalence of obesity and risks of chronic diseases, in general (Idilbi et al., 2013).

Menopausal status, along with obesity were found to interfere in the association between T2DM and BC; Postmenopasal diabetic women, with estrogen receptor positive BC added, had about a 20-27 percent increased risk of BC; (HR=1.22, 95%CI: 1.01-1.47) (Michels et al., 2003). This association is explained by the mechanism of the T2DM-cancer link which has been hypothesized to be mainly related to hormonal (insulin & insulin-like growth factor (IGF)-1), inflammatory or metabolic hyperglycemia characteristics of the T2DM (DeCensi et al., 2010; Muti et al., 2002), and even to certain T2DM treatments (Currie et al., 2012; Currie, Poole, & Gale, 2009). Moreover, obesity was suggested to be a mediator in this mechanism; the associations of glucose, insulin, and IGF-1 pattern were associated with BC risk in women with greater BMI (body mass index > 26) (Muti et al., 2002).

T2DM medications were also shown to affect the risk of BC. Diabetes insulin therapy and BC risk is still an active area of investigation. Insulin replacement therapy showed mixed results which indicated there is a little effect on BC incidence (Owens, 2012). However, the long term (>6 yrs) use of insulin replacement therapies, and incidence of BC is still under research. Furthermore, sulfonyureas, like Glipizide, have been used for more than 50 years; A slightly elevated risk of developing BC has been observed (Currie et al., 2009).

However, Metformin (Glucophage) which is the most commonly prescribed oral medication for T2DM was found to lower the incidence of BC compared to Sulfonylureas (Goodwin, Thompson, & Stambolic, 2012). Whether a non-diabetic BC-diagnosed female would benefit from taking Metformin is not known yet. Studies suggest that BC may affect how a cell uses glucose and that treating with Metformin may correct this change. Many clinical trials are trying to determine if Metformin benefits BC patients independent from T2DM (Currie et al., 2009).

1.2. Problem Statement

T2DM and BC risk association remains unclear, particularly because the two diseases share several risk factors, including obesity, a sedentary lifestyle, and possibly intake of saturated fat and refined carbohydrates, that may confound this association.

Since the Palestinian population is adopting many of the lifestyle characteristics of more affluent societies, this adoption might be associated with diseases such as diabetes and cancer. However, the association between T2DM, its medications, and risk of cancer, to our knowledge, is not yet studied in Palestine. Our study results will help in developing effective intervention programs to deal diabetes and BC in Palestine.

1.3. Study Justification

T2DM is a hot subject in the Palestinian research, and so is cancer, due to their high and accelerating prevalence. BC, which is the most prevalent type of cancer among female cancer cases in Palestine, is the cancer type that will be studied in our research (MOH, 2016).

Among Palestinian population, it was the year 2000 when the first baseline data on diabetes mellitus and impaired glucose tolerance was published. Among Palestinians aged 25 years or more, the prevalence of diabetes was 9.6% and 10.0% in females and males, respectively. The prevalence of impaired glucose tolerance was 8.6%; 10.3% in females, 6.2% in males. The prevalence of total glucose intolerance (diabetes mellitus + impaired glucose tolerance) was 18.4% (Husseini et al., 2009a). During the period between 2005 to 2014, T2DM jumped surprisingly in the rank from being the 11th cause of death in Palestine to the fourth one (Institue for Health Metrics and Evolution, 2018), with a percentage of 8.9% of all deaths, following cardiovascular diseases which accounted for 29.5% of all deaths, cancer deaths 14.2% then came cerebrovascular

diseases 11.3% (MOH, 2014). In the MoH report of 2015, T2DM was categorized alone, due to its increasing prevalence.

As for cancer in Palestine, the total number of new reported cancer cases in the West Bank in the last annual health report was 2,536, with an increase of 5.7% from the 2,400 new reported cases in 2015. In 2016, the incidence rate of cancer in West Bank was 86.4 new cases per 100,000 people. The number of new reported cases in females was 1,330, which resembled 52.4% of new reported cancer cases, and 1,206 among males with 47.6% of new reported cancer cases. BC ranked the first type of cancer in the West Bank among all type of cancer, with 388 cases, accounting for (15.3%) of total reported cancer cases. In addition, BC was the most prevalent type of cancer among females where it accounted for 28.9% of the total reported cancer cases among Palestinian females. Colorectal cancer ranked the second with 262 cases, which accounted for 10.3% of all reported cancer cases. The geographical distribution of reported cancer cases showed that Bethlehem governorate had the highest incidence rate of cancer cases, it had reached 160.1 per 100,000 population. Jericho and Al Aghwar governorate become second with an incidence rate of 123.2 per 100,000 population, followed by Tulkarm with an incidence rate of 108.5 per 100,000 populations (MOH, 2016). Among cancer types, BC was the third type of cancer that caused death in Palestine with a rate of 11.2%, came after lung (17.5%), and colon cancer (12.4%) (MOH, 2017).

1.4. Study Aim

To determine the relationship between T2DM, its medication/s, and breast cancer among females in the southern region of the West Bank.

1.5. Study Objectives

1. To determine the prevalence of T2DM among females over 40 years in the southern region of Palestine.
2. To study characteristics of breast cancer cases in the southern region of Palestine.
3. To determine the association between socio-demographic factors and breast cancer.
4. To determine the association between reproductive factors and breast cancer.
5. To determine the association between health status of women, and breast cancer.
6. To determine the association between diabetes, its medications, and breast cancer.
7. To determine the association between family history of cancers, and breast cancer.

8. To determine the association between lifestyle factors (physical activity, diet intake), and breast cancer.

1.6. Thesis Structure

This thesis will be presented in 6 chapters as follows:

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

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

Chapter three: includes the study conceptual framework.

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

Chapter five: it presents the results.

Chapter six: includes discussion, study limitations, conclusions and multi-level recommendations.

Chapter Two

Literature Review

2.1. Diabetes

According to studies in the late 20th century, it was thought that diabetes prevalence will increase to 5.5% of the adult population all around the world (King, Aubert, & Herman, 1998). Unfortunately, it is the year 2018, and prevalence of diabetes is already 8.8%, and thought to be increased to 10% by the year 2045 (Statista, 2018). The number of people with diabetes has risen from 108 million in 1980 to 422 million in 2014. In 2015, an estimated 1.6 million deaths were directly caused by diabetes. Another 2.2 million deaths were attributable to high blood glucose in 2012 (WHO, 2017). Prevalence of T2DM is higher in developed than in developing countries currently, but the major part of the increase will occur in the developing countries, with a 42% increase in the developed countries and a 170% increase in the developing countries. Thus, by the year 2025, more that 75% of people with diabetes will be in developing countries. Furthermore, the majority of people with diabetes in the developing countries are 10 years younger (45–64 years) than those in the developed countries, (≥65 years). Regarding gender distribution, there are more women than men with diabetes, especially in developed countries (King et al., 1998).

Among Palestinian population, the prevalence of T2DM in adults was 9.7% in 2000, increased to 15.3% by 2010. Prevalence in men increased from 9.1% to 16.9% and in women from 10.2% to 13.6%. According to an estimation model, the prevalence would be 20.8% for 2020 and 23.4% for 2030 (Abu-Rmeileh, Husseini, Capewell, & O'Flaherty, 2013). The number of T2DM new cases in Palestine reported annually, or incidence rate, has ranged between 150 to 220 per 100,000 population, but reported cases are considered

to represent half of actual cases (Emro, W H O, 2016). In 2016, the new reported T2DM cases in MoH primary health care diabetes clinics in West Bank were 5,148 cases, distributed to 2,370 cases among males with an incidence rate of 174.6 per 100,000 population, and 2,778 among females with an incidence rate of 211.5 per 100,000 population (MOH, 2016).

2.2. Cancer

Cancer constitutes an enormous burden on society in more and less economically developed countries alike. The occurrence of cancer is increasing because of the growth and aging of the population, as well as an increasing prevalence of established risk factors such as smoking, overweight, physical inactivity, and changing reproductive patterns associated with urbanization and economic development (Torre et al., 2015).

The number of new cancer cases is expected to rise by about 70% over the next 2 decades. Cancer is the second leading cause of death globally, and was responsible for 8.8 million deaths in 2015. Globally, nearly 1 in 6 deaths is due to cancer, and approximately 70% of deaths from cancer occur in low- and middle-income countries (WHO, 2018). Based on GLOBOCAN estimates, about 14.1 million new cancer cases occurred in 2012 (Globocan, 2012). Over the years, the burden of cancer, like diabetes, has shifted to less developed countries, which currently accounts for about 57% of cases and 65% of cancer deaths worldwide. Lung cancer is the leading cause of cancer death among males in both more and less developed countries, and has surpassed BC as the leading cause of cancer death among females in more developed countries; BC remains the leading cause of cancer death among females in less developed countries, then come liver and stomach cancer among males and cervical cancer among females. Although incidence rates for all cancers combined are nearly twice as high in more developed than in less developed countries in both males and females, mortality rates are only 8% to 15% higher in more developed countries. This disparity reflects regional differences in the mix of cancers, which is affected by risk factors and detection practices, and/or the availability of treatment. Risk factors associated with the leading causes of cancer death include tobacco use (lung, colorectal, stomach, and liver cancer), overweight/obesity and physical inactivity (breast and colorectal cancer), and infection (liver, stomach, and cervical cancer). A substantial portion of cancer cases and deaths

could be prevented by broadly applying effective prevention measures, such as tobacco control, vaccination, and the use of early detection tests (Torre et al., 2015).

Cancer in Palestine, according to Ministry of Health, was the second leading cause of death in 2016 accounting for 14% of the total deaths, after cardiovascular diseases which accounted for 30.6% of all causes of death. (MOH, 2016).

2.3. Breast Cancer

BC is the most frequently diagnosed cancer and the leading cause of cancer death among females worldwide, with an estimated 1.7 million cases and 521,900 deaths in 2012 (Torre et al., 2015), while its incidence in 2000 was 1 million worldwide annually (Mcpherson, Steel, & Dixon, 2000). BC most recent incidence rate was estimated to be 124 per 100,000 population (Statista, 2017). It accounts for 25% of all cancer cases and 15% of all cancer deaths among females. More developed countries accounted for about one-half of all BC cases and 38% of deaths. Highest rates were reported in Britain (Mcpherson et al., 2000), then North America, Australia/New Zealand, and Northern and Western Europe. Intermediate rates were found in Central and Eastern Europe, Latin America, and the Caribbean. Low rates were found in most of Africa and Asia, but rates were on the rise in most of developing countries (Berry et al., 2005). In 2017, it was estimated that the lifetime probability of a woman to develop BC is 12.4% (Statista, 2017).

BC as many other cancers, is increasing in less developed countries recently (G. a Colditz, Sellers, & Trapido, 2006). Almost 45% of BC incidence cases and more than 55% of related deaths, occur in low and middle income countries (Engla, 2010). The most widely cited reason for this increase is the “Westernization” of the developing world. Westernization accounts for good habits (socioeconomic improvements that increase life expectancy and women reproductive control), and on the other hand, the adoption of some undesirable habits (dietary changes, decreased exercise, delayed childbearing, having fewer children, hormone replacement therapy, reduced breastfeeding), and all increase BC risk and are becoming more prevalent in lower income countries (Engla, 2010). Unfortunately, westernization in developing countries is not accompanied with effective BC screening programs and there is a limited access to treatment (Torre et al., 2015). Another factor accounting for that increase on the other side, is the increase in screening activity, which means increase in diagnosis (Althuis, 2005). Mortality rates of BC in developing countries are also increasing (Jemal, Center, DeSantis, & Ward, 2010).

In Arab countries, like the whole world, BC is the most common cancer among women with a young age of around 50 years at presentation. Locally advanced disease is very common and total mastectomy is the most commonly performed surgery. Population-based screening in those countries with affluent resources and accessible care should be implemented (El Saghir et al., 2007). In the Arab middle east countries, it was recorded that BC affects younger women than their counterparts in industrialized nations, with increasing age-standardized incidence rates from 46.7 per 100,000 in 1998, to 84 per 100,000 in 2007 (Shamseddine, Tfayli, Temraz, & Abou Mrad, 2010). Information about cancer incidence for populations in Cyprus, Egypt, Israel (Jews and Arabs), and Jordan for the period 1996–2001 was presented by the Middle East Cancer Consortium (MECC). Age-standardized incidence rates per 100,000 females were highest among Israeli Jews (93.1), then Cypriot females (57.7), Egyptian females (49.6), Jordanian females (38.0), and Israeli Arab females (36.7) (Barchana, 2006).

The Palestinian community is one of the developing communities, and has the low income characteristics pattern. Recently, this community adopted the western lifestyle pattern, and is expected to contribute to the increasing number of western diseases (Haidar & Zureik, 1987). It was revealed that 32% of the cases of BC occurred in Hebron governorate during 2016, the highest percentage among the other governorates, while the lowest percentage was in Jenin governorate at 2% (MOH, 2016). Studies from the Israel Cancer Registry and Jerusalem area were reviewed. BC accounted for 30% of all new cases of cancer, and 23% of all cancer deaths (Nissan et al., 2004). The incidence of BC is increasing in the Arab women, more than the increase in the Jewish females. In a study that was conducted in Jerusalem area by Israeli Ministry of Health, it was found that crude incidence for BC in Israel in 1995 was 13.6 per 100,000 in Arab women and 102.2 per 100,000 among Jewish women. Incidence of BC has increased by 93.7% from 1970 up to 1995 in Arab women, while in the Jewish women the increase was only 31.7%. This increase might be real, but it might reflect the increase of number by Palestinian women who come to have therapy in Jerusalem. It was found that 11% of the Palestinian group were less than 35 years as compared to only 5% of the Jewish group. Cases that were diagnosed in screening mammography were 39% of Jews, and only 9% in the Palestinian group. Tumors in Palestinian women were larger at diagnoses, and generally were detected by physical examination and not by screening mammography. Late diagnosis was the major factor related to the higher mortality in the Palestinian group (Nissan et al., 2004). During the

period 1979–2002, age-adjusted incidence rates among Arab women increased by 202.1% (14.1 per 100 000 in 1979–1981 compared with 42.6% in 2000–2002). The age-adjusted incidence of BC in the Arab population was doubled from 1980 to 2002. The mortality rate ratio between Jewish and Arab women also declined during the years, particularly owing to an increase in mortality rates among Arab women with no change in mortality among Jewish women (Tarabeia, 2016).

2.4. Breast Cancer Risk Factors

2.4.1. Age

The incidence of BC increases with age, doubling about every 10 years until the menopause, when the rate of increase slows dramatically (Mcpherson et al., 2000). Table 2.1 is derived from breast cancer risk factors summary magazine,

Table 0.1: Incidence of breast cancer by age among females.

Female age	**Chances of developing breast cancer in the next 10 years**
20	1 in 1674
30	1 in 225
40	1 in 69
50	1 in 44
60	1 in 29
70	1 in 26
Lifetime risk (0-85)	1 in 8

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According to international data, in the Middle East, BC diagnosis age is younger than the world in the age group 25-34 years; Highest rates were reported in Egypt and the lowest were reported in Jordanian and Israeli Arab populations. While between 57% and 68% of all BC in the Arab populations of Egypt, Jordan, and Israel were diagnosed before the age of 55 years, only 44% of BC cases in Cypriots and 37% among Israeli Jews were diagnosed in the same age group (Barchana, 2006). Among Palestinians, the mean age of BC diagnosis was 51.5 years, which was 4 years younger than Jews in the same region (Nissan et al., 2004).

2.4.2. Marital status

Being single not only increases the risk of BC (OR=1.18, 95%CI: 1.15-1.20), but also single women are diagnosed in a later stage of cancer (Hinyard L et al, 2017).

2.4.3. Consanguinity

In the Arab world, marriage among relatives is so often. Marrying a relative is practiced in many parts of the world and only recently the rate has declined in Western countries to below 1% of all marriages (Denic & Bener, 2001). Therefore, very few studies took this issue into account. In a study that was done in 2001 in the United Arab Emirates, consanguinity, which is marriage from relative, had increased the risk of breast cancer among daughters. Of 1445 analyzed subjects, 40% (579) had unrelated and 60% (866) had related parents. Among the subjects' in-laws, 41% (594) were consanguineous with RR=0.66, with no difference at the age at diagnosis (P = 0.29) (Denic & Bener, 2001).

2.4.4. Socio-demographic factors

High socio-demographic and economic factors are thought to be a risk all over the world, by 20% increase in the risk in higher socioeconomic groups, and among higher income (Hvidtfeldt et al., 2013; S. A. Robert et al, 2004)

In Palestine, female employment, higher educational level, which can be characteristics of high socio-economic status, among north Palestinian women, increased the risk for BC (Darweesh, 2009).

2.4.5. Reproductive factors

Absolute age is not always the issue, age at menarche and menopause also affect the risk. The longer the time spent in menstruation phase, the higher the risk. Females who start menstruating earlier in life or who have a late menopause have an increased risk of developing breast cancer. Women who have their menopause before the age of 45 have half the risk than those who have it after 55 of age. Women who had done bilateral oophorectomy before the age of 35 years, had 40% of the risk of BC of women who had a natural menopause. In addition, late age at first pregnancy or first birth, increase the lifetime incidence of BC. The risk of BC in women who have their first child after the age of 30 is twice the risk among women who have their first child before the age of 20. The highest risk group are those who have a first child after the age of 35, these women have even higher risk than nulliparous women (Mcpherson et al., 2000).

Many studies showed that late age at marriage and pregnancy increases the risk (American Cancer Society, 2018). Approximately an 18% increase in the risk was reported among

women married at older age (Hirose et al, 1995). The risk was doubled when 1st pregnancy occurred after 30 (Engla, 2010), and increased by 3 folds after age of 40 (Mcpherson et al., 2000). In Gazan women, an increased risk was observed in women who had their first pregnancy after 35, (OR=11.56, 95%CI: 1.64-81.35) (Kariri et al., 2017). Among Palestinian women in the North, there was a 10% increase in the risk for females with first marriage occurred after the age of 20 years (Darweesh, 2009).

A positive dose response relationship was reported between 1st pregnancy age and BC risk. Having the 1st pregnancy after 30 had increased the risk among French women, (RR=1.17, 95%CI: 0.97-1.41) (Gauthier et al., 2004), among Chinese women (RR=2.67, 95%CI: 1.28-3.45) (H. B. Nichols et al., 2005; Yuan, Vu, Ross, Gao, & Henderson, 1988), and among American women (RR=2.18, 95%CI: 1.36, 3.49) (Ma et al., 2010). The highest risk was found among women in Spain ,(OR= 3.5 95%CI: 1.41-9.83) (Ramon et al, 1996). In addition, early age at first pregnancy in the Arab world (less than 30) (OR=0.23, 95%CI: 0.16-0.32), was negatively associated with BC (Laamiri, Bouayad, Hasswane, & Ahid, 2015).

The same applied for 1st age at delivery which increases the risk of getting BC, comparing 1st delivery after 30 to less than 20. The increase in the risk ranged from 20% to 27% (Albrektsen, Heuch, Hansen, & Kvåle, 2005; Ma, Bernstein, Pike, & Ursin, 2006). When having the first baby after the age of 40 years, RR was 1.16, (95%CI: 1.02-1.32) (Warner et al., 2014).

Age at menarche and menopause also affected the risk of BC. It was reported that an additional year for age at menarche decreased the risk by 5%. Menopause itself was not associated with an increased risk of developing cancer. However, the rate of BC increases with age. In addition, some of the drugs used to manage menopausal symptoms might increase or decrease the risk (Laura J. Martin, 2017). However, late age at menopause (more than 55) was found to increase the risk of BC (OR=2.36, 95%CI: 1.91-2.91) (Warner et al., 2014). It was suggested that early menarche and late menopause increase the risk of BC by prolonged ovarian hormone production (Andrea Z LaCroix, 1997), due to more cumulative menstrual cycles and more ovulation (Clavel chapelon et al, 2002; K. L. Terry, Willett, Rich-edwards, David, & Michels, 2008). It was reported that for every year older a woman's age at menopause, BC risk increased by about 3 percent (Lancet Oncology, 2012). On the contrary, a study held in north Palestine showed an opposite result, with

OR=0.30 when menopause occurs at 50 or more (Darweesh, 2009). The inconsistency between Palestinian results and the previous results may be due to the cutoff point, which was 55 years in European studies.

Number of full term pregnancies was negatively associated with BC risk. This result was consistent not only for one type, but all subtypes of BC, for pre and post-menopausal women (Li et al., 2013). Three or more full term pregnancies decreased the risk of BC (OR=0.76, 95%CI: 0.54-1.05) (Hirose et al, 1995). Females who had 5 full term pregnancies had half or third the risk of BC, with (RR=0.65) (Blamey et al., 2004), and (RR=0.39, 95%CI 0.19-0.80) (Yuan et al., 1988) respectively. Multiparity in Morocan women decreased BC risk (OR=0.64, 95%CI: 0.53-0.77) (Laamiri et al., 2015). Among Palestinian women in the Northern region, a 50% decrease in the risk was reported among females with 4 full term pregnancies or more (Darweesh, 2009).

Nulliparity, on the other hand, was reported as a risk factor for BC (Weir & Ali, 2007). It was estimated that the cumulative incidence of BC in developed countries would be reduced by more than half, if women had the average number of births and lifetime duration of breastfeeding that had been prevalent in developing countries until recently (Valerie Beral, 2002). Relative risk declined by approximately 9.0% for each additional parity (Weir & Ali, 2007), in addition to a decrease of 7.0% for each birth (Valerie Beral, 2002).

Abortion was suspected to be a risk factor for BC. Most studies differentiated between induced and spontaneous abortions, many studies found no connection between any type of abortions and BC incidence (American Cancer Society, 2014). On the other hand, a comprehensive review reported an increase in the risk (OR= 1.3, 95%CI: 1.2-1.4), for only induced abortion (Brind, Chinchilli, Severs, & Summy-long, 1996). An estimated 11% increase risk in BC was confirmed with each induced abortion (Blamey et al., 2004). BC risk was found to be doubled in induced abortion (OR=1.9), and increased by 50% (OR=1.5) for spontaneous abortion (Holly Howe et al, 1989). This disagreement in findings may be due to intentional recall bias by women, who wouldn't accurately tell their history of abortion, because it was illegal in many countries. Among Palestinian women in the north, history of abortion either induced or spontaneous increased the risk significantly (OR=6.69) (Darweesh, 2009).

Breastfeeding is known to be protective for breast cancer. It is clearly known that long-term breastfeeding can be linked with up to a 30% reduction in breast cancer risk (Weir & Ali, 2007). A clear dose response relationship, was noted with risk of breast cancer; BC relative risk decreased by 4·3% for every 12 months of breastfeeding. In addition, breastfeeding could account for almost two-thirds of estimated reduction in breast cancer incidence. Furthermore, it was reported that fewer parous women with cancer had ever breastfed than parous controls (71% *vs* 79%), and their average lifetime duration of breastfeeding was shorter (9.8 vs 15.6 months) (Valerie Beral, 2002). It was found that the protective effect depends on whether the cancer is hormone receptor-negative or positive. (Li et al., 2013; Ma et al., 2010; H. B. Nichols et al., 2005; Warner et al., 2014). Analysis showed a protective effect of ever breastfeeding against hormone receptor-negative BC, and this effect seemed to be several times stronger than what had been suggested by studies of all BC without stratification by receptor status. Women with the highest risk of receptor negative BC, can potentially benefit more from breastfeeding (Islami et al., 2015)**.**

Having an irregular menstrual cycle was found to increase the risk in a Jordanian study (Wasileh P Nustas et al, 2002). Other studies showed the opposite results, it was reported that longer menstrual cycles (more than 28 days) at ages 18 to 22 years were associated with a lower incidence of premenopausal BC before age 40 (Terry et al 2008), especially after adjustment for reproductive factors and family history, (OR=0.44, 95%CI: 0.22-0.86) (Den Tonkelaar et al, 1996). It is worth noting that these results were limited to longer cycles, not shorter ones.

Long-term use of hormone replacement therapy, but apparently not long-term use of oral contraceptives, was also related to increased risk of BC (Beral, Banks, Bull, & Reeves, 2003). Despite the use of mega-doses of hormones in fertility treatments, there was no evidence that these treatments are hazardous to the breast (Gauthier et al., 2004). It was reported that a history of oral contraceptive use slightly and significantly increases BC incidence (OR=1.08, 95%CI: 1.00-1.17), but the duration of use was not associated with the risk. Furthermore, it was noticed that time since last oral contraceptive use, was associated with higher risk more than recent use (Gierisch et al., 2013). The associations also depended on the receptor subtype. Association of ever use of oral contraceptives and

BC among women who are BRCA1 or BRCA2 mutation carriers were similar to those reported for the general population (OR=1.21; CI 0.93-1.58). Findings were similar when examining BRCA1 and BRCA2 mutation carriers separately (Moorman et al., 2013). On the other hand, among Moroccan females, it was revealed that oral contraceptives beyond 6 months, increased the risk of BC (OR=1.25, 95%CI: 1.01-1.55). Moroccan data reported that extensive use of contraceptives at a late age of reproductive life leaded to a significant increase of developing BC (Laamiri et al., 2015).

Hysterectomy and oophorectomy result in less number in ovarian cycles, therefore, they were found to decrease the risk of BC. Hysterectomy either with ovarian conservation or removal, was found to reduce the risk of BC (Press et al., 2011). It was reported that the risk of BC was reduced in women who underwent bilateral oophorectomy with hysterectomy (OR=0.8, 59%CI: 0.7- 0.9), or hysterectomy alone (OR=0.7, 95%CI: 0.6-0.8) (Parazzini F et al, 1997). In addition, bilateral oophorectomy was associated with more reduction of BC risk (OR=0.59, 95%CI: 0.50-0.69). It should be mentioned that hormone replacement therapy cannot be separated from these surgeries, which might suppress that effect. Medical strategies in our region start hormonal therapy just after hysterectomy or oophorectomy. Estrogen alone is usually given, which increases the risk more than any other hormone therapy (Toine Lagro-Janssen, Walter W Rosser, 2003).

2.4.6. Health status

Body mass index, history of diseases, and some chronic medication were taken into account in this section. Obesity was associated with a two fold increase in the risk of BC in postmenopausal women (RR=2) (Mcpherson et al., 2000). Furthermore, another study reported that higher body mass index (BMI) was associated with higher risk of BC, with a clear dose response relationship regardless of menopausal status, the RRs of BC in ascending order of BMI categories were 1.10 for the category (22.5-24.9) BMI, RR=1.45 for the category (25-27.4) BMI, RR=1.62 for the category (27.5-29.9) BMI, and 1.36 for the category of BMI 30 or more, when compared to BMI < 22.5 (Hormones, Cancer, & Group, 2003). A 5-unit increase in BMI was associated with a 12% increase in risk, and obese women had a 20% to 40% increase in the risk (American Institute for Cancer Research, 2017). On the other hand, obesity among premenopausal women was protective, (RR=0.7) (Mcpherson et al., 2000). The positive association between obesity and postmenopausal BC is thought to be due estrogen, which a risk factor for BC. Estrogen is

synthesized in adipose tissue. Obesity is also associated with high levels of insulin, a known mitogen. It is suggested that insulinemia is an independent risk factor for BC and may have a substantial role in explaining the obesity – BC relationship (Gunter et al., 2009).

Cardiovascular diseases, osteoporosis, auto-immune diseases, joint problems ,and many other chronic conditions are considered to be risk factors for BC (Cancer research UK, 2014a). Among chronic drugs that were taken for more than 6 months, Aspirin in almost all studies confirmed the protective role, with about 30% decrease in the risk, for all breast cancer subtypes (D. Schreinemachers et al, 1994), or for only hormone positive receptor tumors in other studies, (OR=0.74 95%CI: 0.60-0.93) (M. B. Terry, Gammon, Teitelbaum, Britton, & Neugut, 2004). Not only Aspirin, but all NSAID's (non-steroidal anti-inflammatory drugs) showed same protective role in BC (OR=0.60, 95%CI: 0.40-0.91) (Randall E Harris et al, 1996).

Digoxin, an anti-arrhythmic drug, was associated with 39% increase in the risk of BC (RR=1.39, 95%CI: 1.32-1.46) (Biggar, Wohlfahrt, Oudin, Hjuler, & Melbye, 2011). It was reported recently that the increase in the risk was higher only for hormone receptor positive tumors (Osman et al., 2017), as Digoxin chemically resembles estrogen and may have estrogenic effect (Rifka SM et al, 1976), and can cause gynecomastia (Dicky RP et al, 1975).

2.4.7. Family history

Up to 10% of BC in Western countries is due to genetics. Many families affected by breast cancer show an excess of ovarian, colon, prostatic, and other cancers attributable to the same inherited mutation (Mcpherson et al., 2000). Approximately 17% to 19% of breast cancer in the population could be attributed to family history. Women with family history of BC, even if the nearest relative with BC is a third-degree relative, are at increased risk of the disease. It was found that a threefold increase in risk of BC was reported among those with the highest family history score. Furthermore, the risk was increased for women with a first-degree relative with breast cancer (OR=2.45 95%CI: 1.84 -3.06). A greater risk was observed if the first-degree relative was a woman's mother (OR=2.44, 95%CI: 1.77-3.42) rather than a sister (OR=2.01, 95%CI: 1.66-2.43). The risk was clearer when the subject is diagnosed before the age of 50 years (Slattery & Martha, 1993).

The following categories identify women who have three or more times the population risk of developing breast cancer according to (Mcpherson et al., 2000): a woman who has one first degree relative with bilateral breast cancer or breast and ovarian cancer, **Or** one first degree relative with breast cancer diagnosed under the age of 40 years or one first degree male relative with breast cancer diagnosed at any age, **Or** two first or second degree relatives with breast cancer diagnosed under the age of 60 years or ovarian cancer at any age on the same side of the family, or three first or second relatives with breast and ovarian cancer on the same side of the family, or families with four or more relatives affected with either breast or ovarian cancer in three generations and one alive affected relative (Mcpherson et al., 2000).

2.4.8. Lifestyle

This group of risk factors includes physical activity, history of smoking, some daily habits, and nutrition.

Physically active women are at a lower risk of having breast cancer than inactive women; The average breast cancer risk reduction associated with physical activity was 12% (Wu Y et al, 2013). The reduction in the risk was reported for both premenopausal and postmenopausal women; However, the evidence for an association is stronger for postmenopausal BC (Eliassen AH et al, 2010; Fournier A et al, 2014).

Considering active and passive smoking, an increased risk was reported among only active smokers, with highest risk found for those who smoked for more than 50 years, and start smoking at teenage, but the analysis didn't show an association with passive smoking (Luo et al., 2011). On the other hand, passive smoking, as well as active smoking was a significant risk in a more recent cohort study, (HR=1.16 95%CI: 1.05-1.28) for active smokers, and (HR=1.14 95%CI: 1.04-1.25) for passive smokers (Dossus et al., 2014).

2.4.9. Nutritional factors, alcohol

The fact that diet can be a risk for breast cancer has been studied for years. Dietary fat has been the most investigated kind of food. It is believed that a high-fat diet is not directly related to the risk of breast cancer (Eunyoung Cho et al., 2003). The true relation between fat intake and breast cancer does not appear to be particularly strong or consistent (Mcpherson et al., 2000). On the contrary, it was reported that overall caloric intake, and

obesity in particular with certain weight-gain patterns, are related to increased breast cancer risk, with different effects between pre- and postmenopausal women (Endogenous Hormones Breast Cancer Collaborative Group, 2003; Harvie et al., 2005). This agrees with a proven role of regular physical activity in reducing breast cancer risk (Bardia et al., 2006). High fruit and vegetable consumption is related to decreased BC risk in most studies (S. Zhang et al., 1999). Especially, the consumption of cruciferous vegetables, which was shown in vitro and in vivo to be related to such protection. Of all food items studied, regular alcohol consumption, even at moderate levels, has consistently been found to be related to a mild increase in breast cancer risk in women (Mcdonald et al., 2004). Furthermore, it was found that consumption of a dietary pattern characterized by vegetables, fruit, fish, and soy and its derivatives, as well as patterns designated as traditional and Mediterranean, reduced the risk of breast cancer, while consumption of the alcoholic pattern was associated with increased risk of breast cancer. A positive association was observed relative to the western dietary pattern; however, most of these results were not statistically significant (Albuquerque, Baltar, & Marchioni, 2014). A significant association was found between meat consumption and risk of breast cancer (RR=1.17, (95%CI: 1.06-1.43). On the other hand, many systematic reviews identified no statistically significant findings by red meat, white meat, dairy fluid, dairy solid and egg consumption (Missmer et al, 2002). It was also reported that saturated fat intake increased the risk (RR=1.19, 95%CI: 1.06-1.35) (Boyd et al., 2003). On the contrary, saturated fat in case control studies decreased the risk (RR 0.91, 95%CI: 0.66-1.28) (Weir & Ali, 2007).

Since decades, alcohol is thought to be a risk factor for many cancers, and specifically for BC. Consumption of the “alcoholic” pattern increased BC risk by 27%. among older women (>50 years) (P. Terry, Suzuki, & Hu, 2001). Two cohort studies (Cottet et al., 2009; P. Terry et al., 2001), and four case-control studies (Bessaoud, Tretarre, Daurès, & Gerber, 2012; Nkondjock & Ghadirian, 2005; Ronco et al., 2006; Stefani et al., 2009) had identified a pattern of alcoholic beverage consumption; Findings indicated that consumption of alcoholic beverages is a significant risk factor for breast cancer in pre- and postmenopausal women (World Cancer Research Fund & American Institute for Cancer Research, 2007). However, no association between BC and alcohol consumption was identified in case control studies. An explanation might be the relative stability and homogeneity of the population’s lifestyle and dietary habits (Nkondjock & Ghadirian, 2005). Similarly, Ronco et al. did not find an association between the “alcoholic” dietary

pattern and breast cancer, even when the analysis was stratified by menopausal status. These authors suggested the absence of an effect was due to the low prevalence of alcohol consumption among women (approximately 20%) (Albuquerque et al., 2014).

As seen above, evidence of all of the previous risk factors of breast cancer are not consistent in all literature, table 2.5 reviews a summary of these risk factors and their evidence differences.

Furthermore, T2DM and breast cancer share some common risk factors. A review of modifiable and non-modifiable risk factors for both T2DM and breast cancer are summarized in table 2.2 and 2.3 respectively.

2.5. Diabetes and breast cancer

T2DM is associated with an increased risk of breast cancer. Three mechanisms are thought to contribute to the association between T2DM and BC: activation of the insulin pathway, activation of the insulin-like-growth-factor pathway, and impaired regulation of endogenous sex hormones. But the exact mechanism of T2DM association with cancer remains uncovered and needs to be examined in further studies (Dankner, Shanik, Keinan-Boker, Cohen, & Chetrit, 2012). A statistically significant 20% increased risk of breast cancer was reported among women with T2DM (RR=1.20, 95%CI: 1.12-1.28). The increase in the risk has ranged from 1.2 to 2.5 folds. Insulin blood levels are high among T2DM patients, and were positively associated with the risk of breast cancer, (HR=1.46, 95%CI: 1.00-2.13). High insulin level was associated with BC among nonusers of hormone therapy (HR=2.40, 95%CI: 1.30-4.41), and among obese women (HR for BMI $\geq$ 30 kg/m^2 =2.12, 95%CI: 1.26-3.58); However, this association was attenuated by adjustment for insulin. This tells that hyper-insulinemia is an independent risk factor for breast cancer and may have a substantial role in explaining the obesity – breast cancer relationship (Gunter et al., 2009). When insulin is taken as a treatment, the risk of BC is increased dramatically (OR=2.98, 95%CI: 1.26-7.01) (García-Esquinas et al., 2015). Pre-diabetes also was found to increase the risk of BC in postmenopausal women (adjusted OR=2.08, 95%CI: 1.10-3.96) as does diabetes (adjusted OR=2.85, (CI 1.55-5.26). A history of diabetes preceding BC by $\geq$7 years and <7 years were both associated with an increased risk for BC (adjusted OR=2.80, 95%CI: 1.40-5.60) and (OR=3.00, 95%CI: 1.50–5.90), respectively (Salinas-Martínez et al., 2014).

On the other hand, no significant association was found between T2DM and breast cancer in other studies (OR=1.09, 95%CI: 0.82-1.45). T2DM was only linked to the risk of developing TN tumors (OR=2.25, 95%CI: 1.22–4.15) (García-Esquinas et al., 2015).

2.5. Metformin and breast cancer

Many studies have suggested that Metformin decreases the incidence of several common cancers. The mechanism is not clearly understood, but the most probable mechanism is that Metformin acts as a growth inhibitor for human BC cells (Zakikhani, Dowling, Fantus, Sonenberg, & Pollak, 2006). In a clinical experiment it was found that Metformin inhibits breast cancer cell growth, colony formation and induces cell cycle arrest in vitro, Metformin reduces levels of cell cycle promoters and inhibits signaling in breast cancer cell lines (Alimova et al., 2009). A dose response relationship is noted with the use of Metformin as protective factor, a study showed that among diabetics, the risk of developing HR/HER2- tumors decreased with longer Metformin use (OR per year of use= 0.89, 95% CI: 0.81-0.99) (García-Esquinas et al., 2015). Compared with other antidiabetic drugs, a 30% decrease in the risk was found among Metformin users (RR=0.69, 95%CI: 0.61-0.79) (DeCensi et al., 2010).

When taken as an independent variable, Metformin users were less likely with a diagnosis of breast cancer OR=0.77; (CI; 0.61-0.99) than non-Metformin users (Bosco, Antonsen, Sørensen, Pedersen, & Lash, 2011). Long-term use of more than five years of Metformin was also associated with decreased risk of breast cancer (adjusted OR= 0.44, 95%CI: 0.24-0.82) (Bodmer, Meier, Krahenbuhl, Jick, & Meier, 2010). Furthermore, postmenopausal women with diabetes receiving medications other than Metformin, had a slightly higher incidence of BC (HR=1.16, 95%CI: 0.93-1.45) (Chlebowski et al., 2012).

Metformin not only reduces the risk of BC, but also might reduce the development of multidrug resistance in vitro in breast cancer cells and may reverse resistance once it has occurred. People with T2DM and cancer who take Metformin have been reported to have a 31% reduction in the occurrence of new cancers. Also, Metformin has been suggested to benefit all-cause survival in those with breast cancer (H. Nichols, 2017).

2.6. Insulin replacement therapy, other oral hypoglycemic drugs and breast cancer

Long acting Insulin Glargine was associated with increased BC risk in many cohort studies (Jennifer W Wu, 2017), and the risk was higher when it was taken after other kinds of insulin (Peeters, Bazelier, Leufkens, Auvinen, & Staa, 2016). On the other hand, it was found that Glragine non-significantly decreased the risk of BC (HR=0.59 95%CI: 0.28-1.25). And adjusted HRs for death or cancer associated with insulin Glargine compared with human insulin was (HR=0.58, 95%CI: 0.32-1.06) (Blin et al., 2012).

The odds ratio of BC increasing evidence shows that insulin sensitizers such as Thiazolidinediones (TZDs) are associated with prostate cancer and HER2-positive BC among diabetic patients (Dankner, Balicer, et al., 2012). The diabetic patients who are treated with insulin or insulin secretogogues are more likely to develop cancer than those with Metformin (Blin et al., 2012).

Sulfonyureas are usually prescribed with Metformin in a combination therapy, so the slightly elevated risk for breast cancer associated with Sulfonyureas is not seen (Currie et al., 2009). Glucose lowering agents were shown to have an effect on cancer risk, as indicated by the higher rates seen in patients using Sulfonylurease relative to those using Metformin (Bowker, Majumdar, Veugelers, & Johnson, 2006).

An overall review of sugar lowering drugs, their mechanism of action, and a comparison of their advantages and disadvantages is summarized in table 2.4.

Finally, and according to this review, the study conceptual framework will be presented.

Table 2.2: Non Modifiable Risk Factors of Type 2 Diabetes and Breast Cancer

Compared Risk Factors	Type 2 Diabetes Mellitus	Breast Cancer
Age	26.9 % of adults age ≥65 yrs or older have been diagnosed or have undiagnosed diabetes compared to 3.7% in adults aged 20-44.*	The older an individual is, the more likely she or he will develop BC. Rate of BC increases after age 40 and are highest over age 70.
Gender	11.8 % of all men ≥ 20 yrs of age have diabetes vs. 10.8 % of all women.* Men are more likely to have undiagnosed diabetes	Being female is the most common risk factor for BC. BC is 100 times more common in women than in men.
Having a family history of the disease	If your siblings or parents have diabetes, you have a higher risk.*	A family history of certain types of cancer can increase your risk of BC. This increased risk may be due to genetic factors (known and unknown) and lifestyle.
Race	Compared to non-Hispanic whites, the risk of diagnosed diabetes was 18% higher in Asian Americans, 66 % higher among Hispanics and 77% higher among non-Hispanic blacks. *	Non-Hispanic white women have the highest BC incidence overall. African American women have the highest BC mortality overall.

Table 2.3: Modifiable Risk Factors of Type 2 Diabetes and Breast Cancer

Risk factors:	**Type 2 Diabetes Mellitus**	**Breast Cancer**
High blood pressure	2 out of 3 people with diabetes report having high blood pressure (140-90 or higher).*	No association
Physical inactivity	Being active helps maintain normal levels of blood sugar and keeps your body sensitive to insulin.(D. E. R. Warburton, C. W. Nicol, and S. S. D. Bredin, "Health benefits of physical activity: the evidence.," *CMAJ*, vol. 174, no. 6, pp. 801–9, Mar. 2006.)	Regular exercise appears to lower BC risk by about 10-20 %. This benefit is most clearly seen in postmenopausal women.
Overweight or obesity	Being overweight raises the risk. * For most people, losing weight can reverse T2DM.	Before menopause, being overweight or obese modestly decreases risk. After menopause, being overweight or obese increases risk.
Unhealthy diet	Diets low in red and processed meats and high in vegetable, fruit, whole grains cereals and dietary fiber may protect against T2DM by improving insulin sensitivity. Note: While low carbohydrate, high protein and fat diets have been shown to reduce weight and lower insulin levels, large randomized clinical trials have only been performed on low fat, low calorie diets to date.	Studies now show that eating vegetables may slightly lower the risk of some breast cancers. ("Fruit and vegetable intake and risk of breast cancer by hormone receptor status," *J. Natl. Cancer Inst.*, vol. 105, no. 3, pp. 219–36, Feb. 2013.) Eating a high fat diet during adolescence may be associated with increased risk of premenopausal BC.
Smoking	May be an independent risk factor for developing T2DM. Smoking increases risk for complications from diabetes, such as – cardiovascular disease, damage to the retina of the eye and other diabetes-related health outcomes. ("Diet, Lifestyle, and the Risk of Type 2 Diabetes Mellitus in Women - NEJM." http://www.nejm.org/doi/full/10.1056/NEJMoa010492.)	Smoking's effect on breast cancer is still under study. Although there is growing evidence that smoking may slightly increase the risk of breast cancer, overall, study findings remain mixed.

Risk factors:	Type 2 Diabetes Mellitus	Breast Cancer
Alcohol	Excessive alcohol consumption has been associated with increased risk for T2DM. However, moderate alcohol (about 2 drinks per day) consumption appears to lower risk slightly. ("Moderate Alcohol Consumption Lowers the Risk of Type 2 Diabetes: A meta-analysis of prospective observational studies," Diabetes Care, vol. 28, no. 3, pp. 719–725, Mar. 2005.)	Studies show that women who had more than two alcoholic drinks per day had a 20 % higher risk of BC. However, drinking low to moderate amounts of alcohol may lower the risks of heart disease, high blood pressure and mortality.
Pre-diabetes	If pre-diabetes is left untreated, it often progresses to T2DM.*	Increases the risk of BC in postmenopausal women (AOR=2.08, 95%CI: 1.10-3.96) (Salinas-Martínez et al., 2014).
Gestational Diabetes	If you had gestational diabetes, your risk for developing T2DM later on increases by about 35-65%. *	No association
Metabolic Syndrome or insulin resistance syndrome	A diagnosis of metabolic syndrome can result in up to a 5 fold increase risk for developing T2DM. (E. S. Ford, C. Li, and N. Sattar, "Metabolic syndrome and incident diabetes: current state of the evidence.," *Diabetes Care*, vol. 31, no. 9, pp. 1898–904, Sep. 2008.)	Associated with a moderately increased risk for postmenopausal BC. ("Metabolic syndrome and postmenopausal BC: systematic review and meta-analysis.," *Menopause*, vol. 20, no. 12, pp. 1301–9, Dec. 2013.). Still an area of investigation.

* (Centers for Disease Control, 2011)

- Note: of course there are other known risk factors for breast cancer, such as age at first pregnancy and age at menopause, which will be discussed in our objectives and conceptual framework

Table 2.4: Comparison of Anti-diabetic Medications

Agent**	Mechanism***	Advantages*	Disadvantages**
Sulfonylurea (Glyburide, Glimepiride, glipizide)	Stimulating insulin release by pancreatic beta cells by inhibiting the K_{ATP} channel	• Inexpensive • Fast onset of action • No effect on blood pressure • No effect on low-density lipoprotein • Lower risk of gastrointestinal problems than with Metformin • More convenient dosing	• Causes an average of 5–10 pounds weight gain • Increased risk of hypoglycemia • Glyburide has increases risk of hypoglycemia slightly more as compared with Glimepiride and Glipizide • Higher risk of death compared with metformin*(http://news.yahoo.com/metformin-outperforms-common-class-diabetes-drugs-study-160405357.html*)
Metformin	Acts on the liver to reduce gluconeogenesis and causes a decrease in insulin resistance via increasing AMP Kinase signaling	• Not associated with weight gain • Low risk of hypoglycemia as compared to alternatives • Good effect on LDL cholesterol • Decreases triglycerides • No effect on blood pressure • Inexpensive	• Increased risk of gastrointestinal problems • Contraindicated for people with moderate or severe kidney disease or heart failure because of risk of lactic acidosis due to Alcoholism • Increased risk of Vitamin B12 deficiency • less convenient dosing Metallic taste
Alpha-glucosidase inhibitor (Acarbose, Miglitol, Voglibose)	Reduces glucose absorbance by acting on small intestine to cause decrease in production of enzymes needed to digest carbohydrates	• Slightly decreased risk of hypoglycemia as compared to sulfonylurea • Not associated with weight gain • Decreases triglycerides • No effect on cholesterol	• Less effective than most other diabetes pills in decreasing glycated hemoglobin • Increased risk of GI problems than other diabetes pills except Metformin • Inconvenient dosing • Expensive
Thiazolidinediones (Pioglitazone, Rosiglitazone)	Reduce insulin resistance by activating PPAR-γ in fat and muscle	• Lower risk of hypoglycemia • Slight increase in high-density lipoprotein • Actos linked to decreased triglycerides	• Increased risk of heart failure • Causes an average of 5–10 pounds weight gain • Higher risk of edema • Higher risk of anemia

		• Convenient dosing	• Increases low-density lipoprotein • Avandia (Rosiglitazone) linked to increased triglycerides and risk of heart attack • Actos linked to increased risk of bladder cancer • Slower onset of action • Requires monitoring for hepatotoxicity • Increased risk of limb fractures • Expensive
Agent**	**Mechanism*****	**Advantages***	**Disadvantages****

Cambon-Thomsen, A.; Rial-Sebbag, E.; Knoppers, B. M. (2007). "Trends in ethical and legal frameworks for the use of human biobanks". European Respiratory Journal **30 (2): 373–382. doi:10.1183/09031936.00165006. PMID 17666560.*

** (Drugs, 2012) (*"The Oral Diabetes Drugs: Treating Type 2 Diabetes" (PDF). Best Buy Drugs (Consumer Reports): 20. Retrieved September 18, 2012.*,)

*** Table entries taken from page 185 in: *Elizabeth D Agabegi; Agabegi, Steven S. (2008). Step-Up to Medicine (Step-Up Series). Hagerstwon, MD: Lippincott Williams & Wilkins. ISBN 0-7817-7153-6.*

Table 2.5: Breast Cancer Risk Factors

Increases risk ('sufficient' or 'convincing' evidence)	May increase risk ('limited' or 'probable' evidence)	Decreases risk ('sufficient' or 'convincing' evidence)	May decrease risk ('limited' or 'probable' evidence)
• Alcoholic beverages • Diethylstilbestrol • Estrogen-progestogen contraceptives • Estrogen-progestogen menopausal therapy • X radiation and Gamma radiation • Body fatness* • Adult attained height*	• Digoxin • Hormone replacement therapy • Ethylene oxide • Shift work involving circadian disruption • Tobacco smoking • Adult attained height** • Greater birth weight** • Abdominal fatness* • Adult weight gain* • Total dietary fat*	• Breastfeeding	• Body fatness** • Physical activity

* Post-menopausal breast cancer only. ** Pre-menopausal breast cancer only.

International Agency for Research on Cancer (IARC) and The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) classifications. Find out more about IARC and WCRF/AICR classifications.

(Parkin, Boyd, & Walker, 2011)

Chapter 3

Conceptual Framework

3.1. Introduction

In this chapter, the mechanism that describes the association between diabetes and BC is presented. The study model will be shown and explained too.

3.2. Association between diabetes and breast cancer

The association between T2DM and breast cancer was firstly investigated about 50 years ago. The exact mechanism behind this correlation is not clearly understood yet, but three main mechanisms were suggested to explain this association (Wolf, Sadetzki, Catane, Karasik, & Kaufman, 2005).

3.2.1. Activation of the insulin pathway:

The insulin pathway: The first step in activation of the insulin pathway is the binding of insulin to the insulin receptor, which is a tyrosine kinase composed of two α subunits and two β subunits. Healthy breast tissue and breast-cancer cells express insulin receptors as many well as other tissues in the body like liver, adipose tissue and skeletal muscles. The binding of insulin to insulin receptor (IR), leads to auto-phosphorylation of tyrosine residues in the intracellular subunits and activation of the tyrosine kinase. Once activated, several intracellular proteins are phosphorylated, including members of the insulin receptor family and this activates phosphatydylinositol 3-kinase, which in turn activates the pathway, leading to activation of extracellular-signal-regulated-kinase cascade, one of the mitogen-activated protein kinase pathways (Wolf et al., 2005). Insulin signaling has a metabolic role, but enzymes in the pathway also have important roles in tumorigenesis

(Frenso Vara JA et al, 2004). Also, insulin was found to stimulate cell-cycle progression in a kind of breast-cancer cells by itself or synergistically with estradiol (Lai, Sarcevic, Prall, & Sutherland, 2001). Furthermore, overexpression of insulin receptor can induce malignant transformation in breast epithelial cell lines (Lucia Frittitta et al, 1995). Stimulation by progestins, or the activity of oncogenes can lead to overexpression of IR in breast cancer, by contrast with adipose tissue, breast-cancer tissue showed diminished down regulation of insulin receptors in response to insulin (Papa et al., 1990).

The binding of insulin to insulin receptors in breast cancer cells was higher than any tissue, in 22 of 23 samples of breast cancer (Humanmammarycarcinoma, Benson, & Holdaway, 1982). The binding of insulin in breast cancer was not reduced, even in the presence of high serum concentrations of insulin, furthermore, the concentration of insulin receptor was six-fold higher in 159 samples of breast cancer than in 33 samples of healthy breast tissue; concentrations of insulin receptor were also higher in breast -cancer tissue than in other healthy tissue, including the liver. And it was correlated with tumor size, grade, and estrogen-receptor concentration (Papa et al., 1990). Not only cancer incidence was related to high insulin concentrations, but also with cancer recurrence and death (Giudice et al., 1998).

3.2.2. Activation of Insulin like growth factor pathway:

This pathway consists of a network of ligands (IGF1 and IGF2), insulin-like growth factor binding proteins (IGFBP), and the IGF1 receptor (IGF1R). IGF1 and IGF2 are highly homologous to insulin and IGF1R shares 55% homology with IR. IGF1R and IR can form hybrid receptors, which have high affinity with IGF1 and low affinity with insulin. Activation of IGF1R by IGF1 activates the same proteins and pathways that are activated by insulin and insulin receptors. Therefore, the specificity of the IGF pathway depends mainly on the ligand and its receptor and not on the downstream parts of the cascade. The insulin-like-growth-factor system is thought to be a key regulatory pathway in breast cancer (Siddle K et al, 2001). High circulating concentrations of IGF1 and IGF-BP3 are associated with increased risk of premenopausal breast cancer and increased IGF1 is thought to be an important link between obesity and increased risk of breast cancer (Wolf et al., 2005).

However, T2DM usually affects postmenopausal women and, controlled for obesity, blood concentrations of IGF1, IGF2, and their binding proteins are usually not raised in patients with diabetes, suggesting that these growth factors might not have a direct role in the

association between diabetes and breast cancer. A high concentration of insulin could stimulate the IGF pathway in T2DM through the non-specific activation of the IGF1R and the IGF1R/IR hybrid receptor. However, the importance of this mechanism in the pathogenesis of breast cancer remains to be defined (Wolf et al., 2005).

3.2.3. Impaired sex-hormone regulation:

High endogenous plasma concentrations of estrogens and androgens, as well as low plasma concentrations of sex hormone binding globulin (SHBG) are strongly associated with breast-cancer risk in postmenopausal women (Key T et al, 2002). Deregulation of plasma concentrations of sex hormones, caused by increased production of estradiol and androgens combined with decreased liver production of SHBG, has been suggested as the main mechanism that connects postmenopausal obesity and breast-cancer risk. Similar changes in concentrations of sex hormones and SHBG are found in women with diabetes, and these changes remain significant even after adjustment for obesity (Nyholm H et al, 1989).

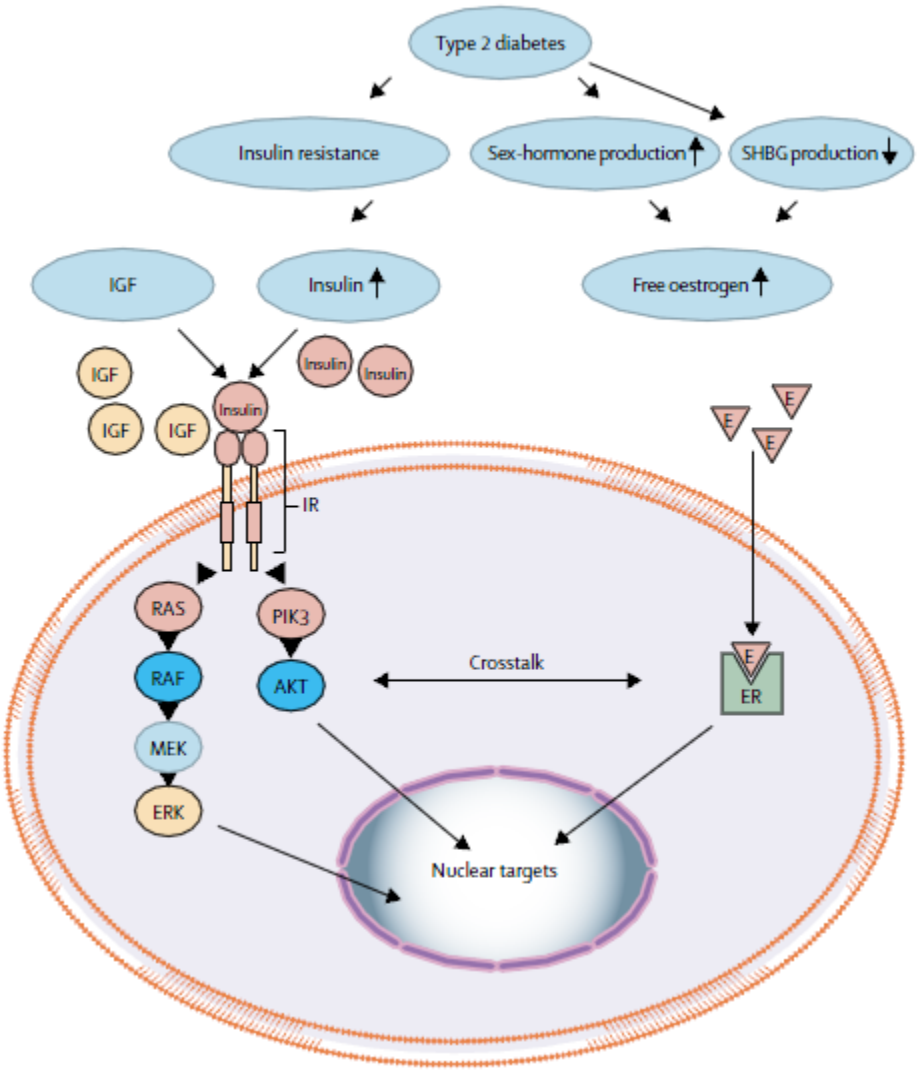

Figure 0.1: Activated signal transduction pathways in T2DM also involved in breast cancer (Wolf et al., 2005).

Insulin resistance leads to high plasma insulin concentrations, which activate the extracellular-related-kinase cascade and the AKT pathway through activation of the insulin receptor or the insulin-like-growth-factor (IGF) receptor. High expression of the insulin receptor in breast cancer augments activation of these pathways. Diabetes mellitus increases production of sex hormones and deceases sex hormone binding globulin (SHBG) production, leading to high plasma-free estrogen concentrations, which in turn activate the estrogen receptor (ER). Activation of these pathways can lead to cell-cycle progression and decreased apoptosis (Wolf et al., 2005).

3.3. Metabolic syndrome and Breast cancer

Metabolic syndrome is defined as a cluster of conditions- increased blood pressure, high blood sugar, excess body fat around the waist, and abnormal cholesterol or triglyceride levels - that occur together, which is linked to obesity, less physical inactivity, and insulin resistance. Altogether increase the risk of heart disease, stroke and diabetes. Any of these conditions alone can increase the risk of serious disease (Mayo Clinic, 2018**).**

Many theories have explained it by using the concept of metabolic syndrome, and studied its association with breast cancer risk. According to these theories, obesity is the mediator for this association. Metabolic syndrome, variously called as insulin resistance syndrome or syndrome X or Reaven syndrome, consists of a group of metabolic abnormalities which include central obesity, hyperglycemia, hyperinsulinemia, hypertension, hyper-triglyceridemia, low high-density lipoprotein (HDL) cholesterol, hyperuricemia, and increased levels of fibrinogen that confer increased risk of cardiovascular disease and diabetes mellitus (WHO, 1999). Metabloic syndrome has recently been proposed to play a part in breast carcinogenesis (Burhan Wani et al, 2017). The metabolic syndrome could impact the risk of breast cancer through alterations in a number of interrelated hormonal pathways, including those involving insulin, estrogen, cytokines, and growth factors (Xue F et al, 2007).

Metabolic syndrome is also associated with increasing levels of inflammatory cytokines and Leptin, which can stimulate cell proliferation through various mechanisms, and is inversely associated with adiponectin, which down-regulates tumor cell proliferation and up-regulates apoptosis (Xue F et al, 2007). Insulin itself is an inflammatory agent, which may induce carcinogenic reactions on a chronic basis (Tiberian J, 2017), so as previously seen, it is about insulin itself and not high sugar in the blood.

3.4. Diabetes medications and breast cancer

3.4.1. Metformin and breast cancer

Metformin (1,1-dimethylbiguanide hydrochloride) is a biguanide commonly used in the treatment of T2DM mellitus. It is frequently referred to as an ‘‘insulin sensitizer’’ because in settings of insulin resistance and hyperinsulinemia, it lowers circulating insulin levels (Witters, 2001). There is some evidence that suggests that the mechanism of action of Metformin involves enhancement of signaling through the insulin receptor, leading to

improvement of insulin resistance, followed by reduction in insulin levels (Stith, 2014). However, recent work provides evidence that the key action of Metformin is the inhibition of hepatic glucose output by inhibition of gluconeogenesis, with a secondary decline in insulin levels, in the absence of a major effect on insulin signaling (R. J. Shaw et al., 2005). There is strong evidence that in the liver, this mechanism involves the activation of AMP kinase (Zakikhani et al., 2006). Metformin is an AMP kinase- dependent growth inhibitor for breast cancer cells (Zakikhani et al., 2006). In vitro, Metformin showed biological activity against all estrogen receptor (ER) positive and negative, normal and abnormal breast cancer cell lines tested. It inhibited cellular proliferation, reduced colony formation and caused partial cell cycle arrest, so it inhibits breast cancer cell growth, colony formation, and induces cancer cells arrest (Alimova et al., 2009).

3.4.2. Synthetic insulin, insulin analogues and breast cancer

As explained above, long and short acting synthetic insulin, are associated with increased risk of breast cancer for the same reason that insulin levels are increased in the body, so the same effect of hyperinsulenemia, which consists a great part of metabolic syndrome. Long acting insulin has a stronger association, because it is in contact with insulin receptors either in the normal tissue or cancer cells for a longer time (Suissa et al., 2011).

3.5. Study conceptual model

Risk factors of BC other than T2DM were investigated in our study, due to their overlapping effects; for example, socio demographic factors, is related to health status, family history, and reproductive factors, which all together are associated with BC risk. The same applies to T2DM, which is strongly associated with health status and lifestyle.

The following figure (figure 3.2), major groups of variables are presented. Our study is a case-control study in which BC is the dependent factor, and other groups of variables are the independent variables. The study model was built on the Mayo Clinic (Mayoclinic staff, 2015), and British cancer research organization (Cancer research UK, 2014b). Risk factors of BC are categorized in this model into major 6 groups; Socio-demographic factors which include age, family size, type of living place, educational level, employment information, consanguinity, and marital status; Reproductive factors, which include pregnancy, delivery, breastfeeding, hormonal use, oral contraceptives, and reproductive organ surgeries; Health status, which includes chronic diseases, chronic medication and

BMI; T2DM factors, which include period, age at diagnosis, T2DM medication and their regimen; Family history, which includes relatives with breast cancer or other cancers; Lifestyle factors, which includes physical activity, daily habits, and food intake.

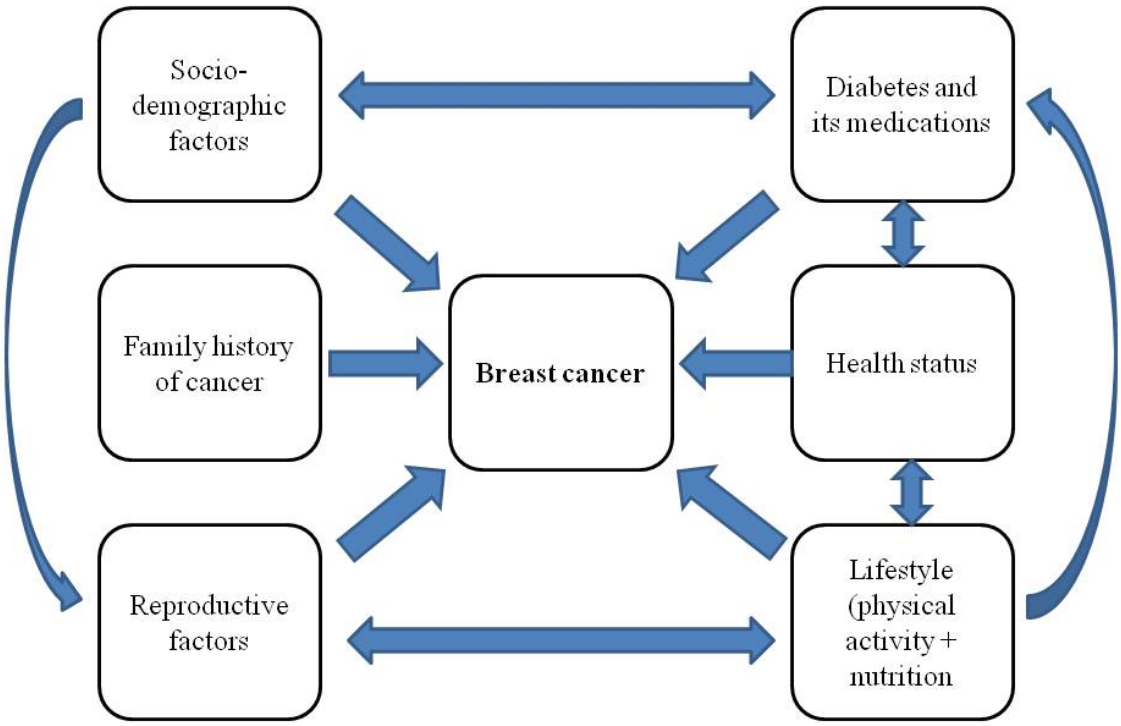

Figure 3.2: Study conceptual framework, breast cancer is the dependent variable and all other group of variables in the figure are the independent variables in our study.

Chapter Four

Methodology

In this chapter, study setting, sample frame, sampling methods and sample size are presented. Also, study tools, and statistical analysis.

4.1. Study Design

This study is a case control study with a ratio 1:1, matched by age groups and residency location of the study subjects.

4.2. Operational Definitions

- **Breast cancer case:** is a female who has a malignant mass in the breast confirmed by ICD10 code 'C50' (National Cancer Registry, 2018), derived from the oncology department records.
- **Breast cancer control:** is a female who had undergone mammography test and confirmed as cancer-free female by the code BIRADS1, i.e 0.00% likelihood of cancer, and so only routine screening is recommended.
- **Type 2 Diabetes mellitus patient:** is any female with fasting blood sugar (FBS) equals to or more than 110 mg/dL accessed from the females' records, which is also the criterion followed in the hospital.
- **1st degree relative:** includes mother, father, sister, brother, sun, and daughter.
- **2nd degree relative:** includes grandfather, grandmother, uncle, aunt, niece, nephew, and cousin (from both sides; father and mother).

4.3. Study Setting

There are three oncology departments in the West Bank; i.e. Al Watani Hospital at Nablus governorate, Augusta Victoria Hospital in Jerusalem, and Beit-Jala Governmental Hospital at Beit-Jala.

Since our study was all conducted in the Ministry of Health settings, approvals were confirmed before the field research get started, signed and delivered to all branches that would be included in our study (Annex 3).

The study was conducted at 2 main settings; The first was Beit-Jala Governmental Hospital, in which the daycare oncology department offers medical services for cancer patients in the middle and southern region of the West Bank, including Ramallah, Jerusalem, Bethlehem, Beit-Jala, Beit-Sahour and Hebron. The second was the primary health care mammography units which belong to Palestinian Ministry of Health, and are distributed throughout the West Bank providing diagnostic and screening services. Routine screening programs are available for any female aged 40 years or over; Regardless to her age, any female with a suspected mass is referred to these units. Mammogram and ultrasound tests are available. In our study, the major mammography units of Bethlehem and Hebron were included, due to difficulty to access all units in the southern region of the West Bank.

4.4. Sample Frame

Study cases were chosen from the daycare unit of the oncology department at Beit-Jala hospital, as reported in their records.

Controls were chosen from cancer-free females who had mammography testing at the primary health care units in Bethlehem and Hebron, chosen only among females who were available for screening and not for diagnostic purposes.

4.5. Study Sample Size

Sample size was calculated by the online calculation software called “Epitool” (Australian biosecurity CRC, n.d.); For a case control study sample size determination, the following calculations parameters were used: an 80% power, an estimated odds ratio of 2.0 for the association between diabetes and BC with 95% confidence (Boyle, 2012; Salinas-Martínez

et al., 2014). Therefore our target sample was about 500 (250 study cases and 250 control group).

Table 0.1: Sample Size Calculation Results

	P= 0.005	P= 0.01	P= 0.02	P=0.03	P= 0.04	P= 0.05	P=0.1
OR=2	4749	2395	1218	826	630	513*	280
OR=3	1586	801	409	279	213	174	97
OR=4	882	446	228	156	120	98	56
OR=5	596	302	155	106	82	67	38
OR=10	217	110	57	39	30	25	15

*the least needed sample size for our study

4.6. Selection of Study Sample

Selection of study cases: 237 BC patients that were chosen while attending the day care clinic or receiving chemotherapy.

Control group: 237 female controls were chosen from the mammography units in Bethlehem and Hebron primary health care clinics.

Study cases inclusion-exclusion criteria:

1. Cases should be females confirmed with BC using the code "C 50".
2. BC should be the primary cancer diagnosed, and not secondary to other malignancy.
3. The participant was considered diabetic, if two conditions were satisfied, when FBS was ≥110 mg/dL, and when T2DM was diagnosed at least one year before cancer. Those who were diagnosed with T2DM after BC were excluded.
4. Only those who were 40 years or older were included, as controls, who had done mammography screening test in the governmental sector program, were at least 40 years old.
5. Only alive patients were included (no proxies).

Control group inclusion-exclusion criteria:

1. Controls should be cancer-free females according to the BI-RADS1, confirming they had never been diagnosed with any malignancy.
2. Only females who came for screening purposes were chosen, those who were referred by a physician were excluded, because they have suspected tissue abnormality.

3. Women who had their mammography screening test done before January 2016 were excluded, to have a time start line.
4. The participant was considered diabetic if FBS was ≥110 mg/dL,

4.7. Study Tools

– Patients' medical records: Cases' records were accessed through oncology registry system at Beit-Jala Hospital, and also through registry department or the central data system of the hospital. Controls' records were accessed through the data system of the mammography unit itself.

– Questionnaires: The questionnaire was built on previous validated questionnaire: i.e. the Cancer Research UK (Cancer research UK, 2014a). Questions which were unique for our community were taken from previous master thesis (Qasem,2013); (Barham, 2013; Rabadi, 2012). The questionnaire was administered through a face to face interview with the study participants.

Questionnaire parts: The questionnaire consisted of 105 questions, categorized into 7 main parts (Appendix 1). Each part of the questionnaire contained a group of the main risk factors of BC including the following:

Part 1: Socio-demographic factors, (Question1 to Question 16)
Part 2: Reproductive health factors, (Question 17 to Question 43)
Part 3: Health Status, (Question 44 to Question 52)
Part 4: Family History, (Question 53 to Question 57)
Part 5: Type 2 Diabetes Mellitus (T2DM), (Question 58 to Question 61)
Part 6: Lifestyle factors: physical activity, food intake, (Question 62 to Question 98)
Part 7: Breast Cancer characteristics -only for study cases-, (Question 99 to question 105)

4.8. Questionnaire Validation

The questionnaire was validated by an oncologist, a medical doctor "radiologist" who reads the mammography tests, a radiology technician with expertise in cancer scanning and epidemiology, and an endocrinologist. They evaluated the content of the questionnaire and the survey methodology. The questionnaire was modified according to their suggestions and edition, especially in cancer treatment methods and diabetes medication.

4.9. Data Collection

1- Data collected form patients' medical records: Data were collected from cancer patients' medical records included: date of diagnosis, stage at diagnosis, type of cancer, and therapy strategy. We also could retrieve information regarding, patients' diseases and medication history, and family history of cancer, but these data were not available in all patients' records.

2- Interview questionnaire: The questionnaires were administered face to face or by phone call interview. Phone calls were done through the hospital staff, who explained the study and its objectives to the participants, and asked for their permission to fill the questionnaire. After getting the acceptance, the study researcher continued the survey at the phone.

Cases were recruited by being available at the daycare unit of Beit-Jala Hospital. An interview was conducted by the researcher to have the questionnaires filled, after signing the consent form by the patient.

Controls were accessed through records of mammography units of Ministry of Health either in Bethlehem or Hebron. Controls were chosen as confirmed cancer-free females who had their mammography test done not before January 2016. Hard copy files were manually checked in order to only select the normal mammography results, which are (BIRADS 1), and their contact information were derived from these files, due to their unavailability at the mammography unit. Controls were chosen to be frequency- matched to the cases in terms of age group and region.

During the interview, emphasis was made in recalling BC risk factors before the disease and not after, to ensure the reliability of the answers. For Diabetes Mellitus status of the participants were determined by the last fasting blood sugar (FBS) result derived from their records.

4.10 Ethical Considerations

The project was ethically approved by the institutional review board (IRB) committee of Al-Quds University. In addition, Ministry of Health approvals were confirmed as the study was conducted in their settings (Appendix 3). Furthermore, participants signed a consent

form (Appendix 2) that confirmed their willingness to be included, after they were informed about the aim of the study.

4.11 Statistical Analysis

Data were coded, then entered and analyzed using the Statistical Package for the Social Sciences version 20 (SPSS). Descriptive statistics were represented to show frequencies, percentages for categorical variables, and means and standard deviation for continuous variables. Chi-square test and T-test were used as needed to calculate the difference between cases and controls regarding all variables in the study. A P-value <0.05 was considered statistically significant. Variables that showed a significant difference between cases and controls were included in our multivariate model for risk estimation. Conditional forward logistic regression was used to get odds ratios. Our principal measure of association was the Adjusted Odds Ratios (AORs) with 95% confidence intervals (95% CI).

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Chapter Five

Results

5.1. Introduction

In this chapter results are presented in three parts: description of study cases, the univariate analysis and finally the multivariate analysis.

5.2. Descriptive Analysis

Our study consisted of 474 participants, 237 women were confirmed BC cases, and 237 females were cancer free females confirmed by mammography test results done during the last year before the interview date.

Table 5.1 shows the characteristics of the study cases. The mean age of the study cases at recruitment was 55 (±SD 10.9), while the mean age at diagnosis was 52 (±SD 10.90). About 88% of the study cases attending Beit-Jala Hospital were from the southern region of the West Bank. Most of the study cases were diagnosed at stage 2 and 3 of cancer with a percentage of (35%), and (30%), respectively. The vast majority of the cases (82%) were diagnosed with BC after having an obvious lump, while only 17% were diagnosed by screening. More than the half of study cases had ductal carcinoma (58%). It should be mentioned that 30% of the study cases were diagnosed before the year 2014, i.e before electronic cancer registry system was implanted in the hospital, therefore, did not have any reporting for their BC type. Almost all cases had chemotherapy treatment (98%). Regarding surgery treatment, about 83% of cases had undergone partial mastectomy, while about half of them had undergone full mastectomy. Furthermore, 75% of cases had surgery as the first line treatment, and didn’t receive neo-adjuvant therapy. Cases were classified

into 7 age groups, with a 5 year- interval for each group, but the oldest age group, consisted of any female aged 70 years or more.

Table 0.1: Description of study cases' characteristics, disease status and treatment

Variable	Description	Frequency N (%)
Age at diagnosis	Mean (SD) Min-Max	51.62 (10.90) 31-99
Cancer type	Missed	71 (30)
	Ductal	138 (58.2)
	Lobular	19 (8)
	Follicular	5 (2.1)
	Mixed (ductal, lobular)	4 (1.7)
Cancer stage at diagnosis	Missed	16 (6.7)
	1^{st}	29 (12.3)
	2^{nd}	84 (35.4)
	3^{rd}	71 (30)
	4^{th} (metastasis)	37 (15.6)
Breast Cancer detection	Obvious lump	195 (82.3)
	Screening	40 (16.9)
	By chance	2 (0.8)
Therapy	Radiotherapy	92 (38.8)
	Hormonal therapy	76 (32)
	Surgery	203 (58.7)
	Chemotherapy	233 (98)
Neo – adjuvant therapy	Yes	60 (25.3)
	No	177 (74.7)
Place of living	Southern region*	208 (87.8)
	Northern region**	29 (12.2)
Weight before diagnosis (kg)	Mean (SD) Min- Max	79.19 (14.32) 41-120
Weight change after treatment (kg)	Mean (SD) Min- Max	1.35 (10.86) -39 - 43
Breast surgeries done	Biopsy	237 (100)
	Partial mastectomy	126 (53.1)
	Full mastectomy	111 (46.8)
Age at recruitment (years)	Mean (SD) Min- Max	54.62 (10.91) 39-100
Age groups at recruitment (years)	40-44	50 (21.1)
	45-49	40 (16.9)
	50-54	37 (15.6)
	55-59	40 (16.9)
	60-64	19 (8.0)
	65-69	27 (11.4)
	≥ 70	24 (10.1)

*Southern region: Hebron, Bethlehem, Beit-Jala, Beit-Sahour

**Northern region: Jerusalem, Ramallah, Jericho

5.3. Univariate Analysis

5.3.1. Socio-demographic factors and breast cancer

The vast majority of the control group (98.7%), and the study cases (87.8%) were from the Southern region. Study cases were significantly more educated than the control group ($p<0.05$), and a higher percentage of the study cases were living in private houses ($p<0.05$). Study cases' current family size was significantly smaller than that of the control group ($p<0.05$). Moreover, approximately 58% of the study cases, and 46% of the control group had parents who are 1st degree relatives ($p<0.05$) (table 5.2).

Table 0.2: Socio-demographic characteristics of the study subjects

Variable	Description	Control Group N=237 (%)	Study Cases N=237 (%)	Chi-square P-value
Region	Southern region *	234 (98.7)	208 (87.8)	<0.01
	Northern region **	3 (1.3)	29 (12.2)	
Educational level	1-6 years	117 (49.3)	81 (34.2)	<0.01
	7-9 years	62 (26.2)	59 (24.9)	
	10-12 years	44 (18.6)	49 (20.7)	
	>12 years	14 (5.9)	48 (20.2)	
Type of living place	Separate house	147 (62)	198 (83.5)	<0.01
	Apartment	90 (38)	39 (16.5)	
Monthly income	Less than 1000	55 (23.2)	78 (32.9)	0.09
	1000 to 2000	121 (51.1)	103 (43.5)	
	2001 or more	61 (25.7)	56 (23.6)	
Work	Yes (now or then)	23 (9.7)	35 (14.8)	0.09
	No	214 (90.3)	202 (85.2)	
Period of work (years)	Less than 15	15 (65.3)	16 (45.7)	0.31
	15-30	7 (30.4)	15 (42.9)	
	More than 30	1 (4.3)	4 (11.4)	
Marital status	Single	10 (4.2)	19 (8.0)	0.20
	Married	189 (79.7)	185 (78.1)	
	Divorced or widowed	38 (16.1)	33 (13.9)	
Parental consanguinity	No Relation	123 (51.9)	100 (42.2)	<0.01
	1st Degree Relation	52 (21.9)	102 (43.0)	
	2nd Degree Relation	62 (26.2)	35 (14.8)	

*Southern region: Hebron, Bethlehem, Beit-Jala, Beit-Sahour
**Northern region: Jerusalem, Ramallah, Jericho

5.3.2. Reproductive health and breast cancer

In table 5.3, the reproductive health characteristics of married women are presented. Women in the control group were shown to be significantly married earlier, they got pregnant and had their first child at an age more before 18 years. However, and since study cases got married at an older age, they had more full term pregnancies than controls ($p<0.05$). In addition, about 2/3 of married women in both groups had 5 or more children. Moreover, there was a significant difference among breastfeeding mothers; control group seemed to breastfeed their children for a longer period.

Table 0.3: Reproductive health characteristics of married study subjects

Variable	Description	Control Group N= 228 N (%)	Study Cases N= 218 N (%)	Chi square P-value
Age at first marriage (years)	≤18	124 (54.4)	95 (43.6)	0.02
	>18	104 (45.6)	123 (56.4)	
Age at first pregnancy (years)	≤18	105 (46.5)	63 (30.9)	<0.01
	>18	121 (53.5)	141 (69.1)	
Age at first Delivery (years)	≤18	81 (36)	54 (26.9)	0.04
	>18	144 (64)	147 (73.1)	
Current pregnancy	Yes	2 (0.9)	3 (1.4)	0.62
	No	226 (99.1)	215 (98.6)	
Number of full term pregnancies	No pregnancies	3 (1.3)	17 (7.8)	<0.01
	1-4	47 (20.7)	61 (28.0)	
	≥5	177 (78.0)	140 (64.2)	
Abortion	Yes	125 (55.8)	119 (58.6)	0.56
	No	99 (44.2)	84 (41.4)	
Number of abortions	No abortion	99 (44.2)	84 (41.3)	0.24
	1	61 (27.2)	46 (22.7)	
	>1	64 (28.6)	73 (36)	
Breastfeeding	Yes	217 (96.4)	187 (93)	0.11
	No	8 (3.6)	14 (7)	
Age at 1st breastfeeding* (years)	≤18	77 (35.5)	48 (25.7)	0.03
	>18	140 (64.5)	139 (74.3)	
Overall breastfeeding duration (all children) (years)	Didn't breastfeed	4 (1.8)	8 (3.7)	<0.01
	≤ 3	19 (8.4)	51 (23.4)	
	4-6	32 (14.1)	58 (26.6)	
	7-9	59 (26.0)	48 (22.0)	
	>9	113 (49.8)	53 (24.3)	

In table 5.4, it is shown that age of menarche was significantly higher among study cases than control group ($p=0.002$). Also, study cases tended to use oral contraceptive pills and hormone replacement therapy significantly more than control group ($p<0.05$). More than

the half of both cases and controls were postmenopausal females with no significant difference between the two groups.

Table 0.4: Reproductive health characteristics of study subjects

Variable	Description	Control Group N= 237 N (%)	Study Cases N= 237 N (%)	Chi square P-value
Age at menarche (years)	<13	58 (24.5)	32 (13.5)	0.002
	≥13	179 (75.5)	205 (86.5)	
Rhythm of menstrual cycle	Regular	103 (43.5)	91 (38.4)	0.21
	Irregular	7 (3)	14 (5.9)	
	Stopped	127 (53.6)	132 (55.7)	
Age at menopause (years)	≤44	12 (9.4)	20 (15.2)	0.26
	45-49	41 (32.3)	34 (25.8)	
	≥50	74 (58.3)	78 (59.1)	
Hysterectomy	Yes	5 (2.1)	7 (3.0)	0.56
	No	232 (97.9)	230 (90.0)	
Oophorectomy (one ovary or both)	No oophorectomy	233 (98.3)	231 (97.5)	0.82
	Unilateral removal	2 (0.8)	3 (1.3)	
	Bilateral removal	2 (0.8)	3 (1.3)	
Use of hormone replacement therapy	Yes	8 (3.4)	36 (15.2)	<0.05
	No	229 (96.6)	201 (84.8)	
Past oral contraceptive use for ≥ 2 months	Yes	25 (10.5)	47 (19.8)	0.005
	No	212 (89.5)	190 (80.2)	
Recent use of Oral contraceptives**	Yes	3 (1.3)	00 (0.0)	0.08
	No	234 (98.7)	237 (100)	
Age at 1st use of Oral contraceptives**	<30	13 (52)	27 (57.4)	0.66
	≥30	12 (48)	20 (42.6)	
Total period of oral contraceptive use (years)**	<2	13 (52)	14 (29.8)	0.07
	≥2	12 (48)	33 (70.2)	

**Among those using oral contraceptive pills only

5.3.3. Health status and breast cancers

Table 5.5 shows the history of breast examination patterns done for study subjects. Study cases tended to have their first breast examination at a younger age, and had done the examination more frequently than controls.

Table 0.5: Breast examination pattern among study subjects

Variable	Description	Control Group N=237 (%)	Study Cases N=237 (%)	Chi square P-value
1st Breast examination Age (years)	Mean (SD)	52.04 (11.2)	49.36 (12.4)	0.01
Number of breast tests in the last 5 years	Mean (SD)	1.42 (0.7)	1.8 (1.4)	<0.01
Last Breast Test Age	Mean (SD)	53.47 (10.5)	52.77 (11.3)	0.48

Results in table 5.6 indicate that cases were significantly having a greater BMI than controls ($p<0.05$). Regarding history of diseases, study cases suffered from osteoporosis, cardiovascular diseases, joints problems, and auto-immune diseases more than the control group. Almost 40% of both cases and controls were on aspirin as a prophylactic drug, as they were all over 40 years old.

Table 0.6: Medical history of the study subjects

Variable	Description	Control Group N=237 (%)	Study Cases N=237 (%)	Chi Square P-value
Body Mass Index	Normal	29 (12.3)	44 (18.8)	<0.01
	Overweight	112 (47.2%)	56 (23.1)	
	Obese	56 (23.4)	70 (29.5)	
	Morbid obesity	40 (17)	67 (28.6)	
Medication ≥6 months	Aspirin	103 (43.5)	97 (40.9)	0.58
	Digoxin	2 (0.8)	6 (2.5)	0.15
Chronic diseases	No diseases	93 (39.2)	87 (36.7)	0.59
	Hypertension	109 (46)	98 (41.4)	0.35
	Cardiovascular diseases	22 (9.3)	60 (25.3)	<0.01
	Allergy	16 (6.8)	27 (11.4)	0.08
	Glandular diseases	10 (4.2)	18 (7.6)	0.12
	Osteoporosis	25 (10.5)	42 (17.7)	0.02
	Joint problems	57 (24.1)	81 (34.2)	0.01
	Hyperlipidemia /Hypercholesterolemia	54 (22.8)	69 (29.1)	0.11
	Auto-immune disease*	0.00	12 (5.1)	--

*Auto immune disease: includes Celiac disease, dermatomyositis, Hashimoto disease, Myasthenia Gravis, Systemic Lupus Erythematous, type 1 diabetes, Multiple Sclerosis, pernicious anemia.

5.3.4. Family history and breast cancer

There was a significant difference between study cases and control group for having a relative with a BC or any other cancer. Almost one third (n=73) of females in the study cases, and only 10 percent (n=23) of females in the control group had at least one relative with BC ($p <0.05$). In addition, almost 41% of the study cases (n=84) had at least one relative with other type of cancer than BC, compared to only 20% in the control group (n=50) ($p <0.05$) (Table 5.7).

Table 0.7: Family history of cancer of the study subjects

Variable	Relative Degree	Control Group N= 23 (%)	Study Cases N= 73 (%)	Chi-Square P value
Relative with breast cancer	1st degree	8 (35)	27 (37)	0.44
	2nd degree	15 (65)	46 (63)	
Relative with other cancer	1st degree	12 (5.1)	29 (12.2)	0.19
	2nd degree	45 (19)	102 (43)	

5.3.5. Type 2 diabetes mellitus (T2DM) and breast cancer

As shown in table 5.8, prevalence of T2DM among controls was significantly lower (14.8%, n=35) when compared to study cases (24%, n=57) ($p<0.05$). No significant difference was found between study cases and controls in diabetes age of diagnosis (mean age 49.6 (±SD 9.4) in study cases, 50.8 (±SD 10.3) in control group, p=0.52), nor in duration of T2DM (p= 0.93). Table 5.9 shows the T2DM medication among diabetics in study subjects. Among blood sugar lowering agents, Metformin and Lantus (Insulin Glargine) use were significantly different between study cases and control group.

Table 0.8: T2DM characteristics of study subjects

Variable	Category	Control Group N= 237 (%)	Study Cases N= 237 (%)	P-value
T2DM	Yes	35 (14.8)	57 (24)	0.01
	No	202 (85.2)	180 (76)	
T2DM diagnosis age (years)	<50	16 (45.7)	22 (38.6)	0.52
	≥50	19 (54.3)	35 (61.4)	
Duration of T2DM*	Mean (SD)	7.91 (8.30)	8.07 (4.41)	0.93

*For BC cases, the duration was calculated prior to BC diagnosis

Table 0.9: T2DM medication use among study subjects

Medication	Category	Control Group N= 35(%)	Study Cases N= 57(%)	Chi-Square P-value
Metformin	Yes	32 (91)	56 (98.2)	.02
	No	3 (9)	1 (1.8)	
Glibenclamide	Yes	15 (42.8)	25 (43.9)	0.92
	No	20 (57.2)	32 (56.1)	
Repaglinide	Yes	1 (2.8%)	00	--
	No	34 (79.2)	56 (100)	
Vildagliptin + Metformin	Yes	3 (9)	5 (8.8)	0.97
	No	32 (91)	52 (91.2)	
Pioglitazone	Yes	1 (2.8)	3 (5.3)	0.58
	No	34 (79.2)	54 (94.7)	
Vildagliptin	Yes	00	4 (7.0)	0.11
	No	35 (100)	53 (93)	
Glipizide	Yes	00	3 (5.3)	0.17
	No	35 (100)	54 (94.7)	
Insulin Glargine (lantus)	Yes	2 (5.7)	24 (42.1)	<0.01
	No	33 (94.3)	33 (57.9)	
Insulin aspart novorapid)	Yes	2 (5.7)	2 (3.5)	0.62
	No	33 (94.3)	55 (96.5)	
Insulin human	Yes	5 (14.3)	12 (21.5)	0.86
	No	30 (85.7)	45 (78.5)	
Insulin novomix	Yes	00	1 (1.8)	0.43
	No	35 (100)	56 (98.2)	
Liraglutide	Yes	1 (2.8%)	00	0.19
	No	34 (97.2)	57 (100)	

Although Metformin use among study cases was significantly higher (98%) compared to control group (91%) (table 5.9), but the dosage was higher in the control group (mean=2.1 ±SD 0.57) compared to study cases (mean=1.6 ±SD 0.68), p <0.05). In addition, a significant difference was shown between cases and controls regarding Lantus (Insulin Glargin) use (table 5.9), but the dosage didn't show a significant difference between the two groups (table 5.10).

Table 0.10: T2DM medication dosage among study subjects

Variable		**Control Group n=35 n (%)**	**Study Cases n=57 n (%)**	**P-value**
Metformin daily dose	Once daily	3 (8.5)	28 (50)	<0.01
	2 times/ day	21 (60.0)	22 (38.5)	
	3 times/ day	8 (22.8)	6 (10.5)	
Metformin total period	Mean (SD)	7.39 (7.33)	7.46 (5.72)	0.96
Metformin start age	Mean (SD)	50.75 (9.25)	54.55 (10.28)	0.09
Metformin stopping age	Mean (SD)	58.15 (8.55)	62.01 (10.16)	0.07
Insulin Glargine total period	Mean (SD)	3 (1.41)	9.83 (6.72)	0.17
Insulin Glargin start age	Mean (SD)	51 (12.72)	54 (5.98)	0.42
Insulin Glargine stopping age	Mean (SD)	54 (14.14)	64 (6.83)	0.06

5.3.6. Lifestyle and breast cancer

As shown in table 5.11, there was a significant difference between the cases and controls regarding total weekly physical activity; Control group seemed to be more physically active (p<0.05). On the contrary, no difference was seen regarding the hours of rest per day among both groups (p=0.17). Electric blanket was used more among study cases than control group (p<0.05).

Table 0.11: Daily activity characteristics of study subjects

Variable	**Category**	**Control Group N=237 (%)**	**Study Cases N=237 (%)**	**P-value**
Total score of physical activity per week* (METs)	Mean (SD)	1755.05 (1677.3)	1367.63 (1331.8)	<0.01
Number of rest hours per day	Mean (SD)	3.24 (1.94)	3.51 (2.25)	0.17
Using electric blanket	Yes	14 (5.9)	39 (16.5)	<0.01
	No	223 (94.1)	198 (83.5)	

* An equivalent combination of moderate- and vigorous-intensity physical activity achieving at least 600 MET-minutes. - derived from WHO (World Health Organization, 2010).

Regarding smoking profile represented in table 5.12, there were significant differences between cases and controls; Past cigarette smoking was higher among cases ($p<0.05$), in contrast, controls had smoked Nirgela more than cases ($p<0.05$). Having a smoker parent was significantly higher among study cases ($p<0.05$).

Table 0.12: Smoking history among study subjects

Variable	**Category**	**Control group N= 237 (%)**	**Study cases N= 237 (%)**	**Chi square P-value**
Current Smoking	Yes/ no	3 (1.3)	9 (3.8)	0.07
Past smoking	Yes/ no	00	10 (4.2)	<0.01
Nirgela smoking	Yes/ no	5 (2.1)	3 (1.3)	<0.01
Smoker parent	Yes/ no	99 (41.8)	131 (55.3)	<0.01

Food intake was different between cases and controls as seen in table 5.13; most kinds of food showed significant differences between cases and controls, including milk ($p <0.05$), chips and popcorn ($p =0.02$), nuts ($p =0.01$), diet soft drinks ($p =0.01$), regular soft drinks ($p =0.02$), red meat ($p <0.05$), fish and tuna ($p <0.05$), chicken ($p <0.05$), salad ($p <0.05$), eggs ($p =0.01$), cheese ($p =0.003$), white bread ($p =0.01$), wheat bread ($p <0.05$), and butter ($p =0.001$). More than 70% of our sample in both groups had low intake of milk, cake, chips, nuts, low sugar soft drinks, and butter (once weekly or less). On the other hand, chicken, salads, eggs, cheese, white bread, and soft drinks were taken more than once weekly by about 2 thirds of both groups.

Table 5.13a: Food intake among study subjects

Variable	Category	Control Group N=237 (%)	Study Cases N= 237 (%)	Chi-Square P value
Milk	≤ once/week	124 (52.3)	159 (67.1)	<0.01
	2-6 times/week	95 (40.1)	43 (18.1)	
	≥ once daily	18 (7.6)	35 (14.8)	
Cake pastry	≤ once/week	170 (71.7)	167 (70.5)	0.31
	2-6 times/week	64 (27)	62 (26.2)	
	≥ once daily	3 (1.3)	8 (3.4)	
Biscuits	≤ once/week	157 (66.2)	143 (60.3)	0.05
	2-6 times/week	74 (31.2)	77 (32.5)	
	≥ once daily	6 (2.5)	17 (7.2)	
Chips & Pop-corn	≤ once/week	166 (70.0)	181 76.4)	0.02
	2-6 times/week	68 (28.7)	47 (19.8)	
	≥ once daily	3 (1.3)	9 (3.8)	
Nuts	≤ 3 times/month	204 (86.1)	180 (75.9)	0.01
	≥ once/week	33(13.9)	57 (24.1)	
Diet soft drinks	Never	213 (89.9)	191 (80.6)	0.01
	1-3 times/month	16 (6.8)	25 (10.5)	
	≥ once/week	8 (3.4)	21 (8.9)	
Soft drinks	Never	70 (29.5)	73 (30.8)	0.02
	1-3 times/month	26 (11)	26 (11)	
	1-6 times/week	137 (57.8)	120 (50.6)	
	≥ once/day	4 (1.7)	18 (7.6)	
Red meat	Never	24 (10.1)	32 (13.5)	<0.01
	1-3 times/month	107 (45.1)	65 (27.4)	
	≥ once/week	106 (44.7)	140 (59.1)	
Fish & tuna	never	49 (20.7)	33 (13.9)	<0.01
	1-3 times/month	113 (47.7)	76 (32.1)	
	≥ once/week	75 (31.6)	128 (54)	
Chicken	≤ once/week	27 (11.4)	58 (24.5)	<0.01
	>once/week	210 (88.6)	179 (75.5)	
Peanuts	Never	56 (23.6)	55 (23.2)	0.26
	1-3 times/month	40 (16.9)	54 (22.8)	
	≥ once/week	141 (59.5)	128 (54)	
Potato	Never	19 (8)	29 (12.2)	0.24
	1-3 times/month	35 (14.8)	39 (16.5)	
	≥ once/week	183 (77.2)	169 (71.3)	
Salad	< 3 times/month	3 (1.3)	31 (13.1)	<0.01
	1-6 times/week	185 (78.1)	162 (68.3)	
	≥ once/day	49 (20.6)	44 (18.6)	
Eggs	< 3 times/month	55 (23.2)	59 (24.9)	0.01
	1-6 times/week	170 (71.7)	149 (62.9)	
	≥ once/day	12 (5.1)	29 (12.2)	
Cheese	< 3 times/month	41 (17.3)	61 (25.7)	<0.01
	1-6 times/week	184 (77.6)	151 (63.7)	
	≥ once/day	12 (5.1)	25 (10.5)	

Table 5.13b: Food intake among study subjects

Variable	Category	Control Group N=237 (%)	Study Cases N= 237 (%)	Chi-Square P value
White bread	< 3 times/month	30 (12.7%)	27 (11.4%)	0.01
	1-6 times/week	16 (6.8%)	33 (13.9%)	
	Once/day	81 (34.2%)	96 (40.5%)	
	≥2 times/day	110 (46.4%)	81 (34.2%)	
Wheat bread	< 3 times/month	130 (54.9%)	140 (59.1%)	<0.01
	1-6 times/week	14 (5.9%)	38 (16%)	
	Once/day	64 (27%)	35 (14.8%)	
	≥2 times/day	29 (12.2%)	24 (10.1%)	
Butter	< 3 times/month	213 (89.9%)	188 (79.3%)	<0.01
	≥ once/week	24 (10.1%)	49 (20.7%)	

5.4. Multivariate Analysis

In this section of analysis, one model was developed, in which all significant risk factors revealed in Chi-Square and T-Test results were included. As seen in the table, higher educational level, living in a separate home, 1st degree parental consanguinity, older age at menarche, oral contraceptive and hormone replacement therapy, family history of breast cancer, being underweight, cardiovascular diseases, joints' problems, insulin Glargine, electric blanket use, and some kinds of food all increased the risk, while longer period of breastfeeding and chicken intake were associated with lower risk of breast cancer (table 5.14).

Table 0.14: Multivariate model for breast cancer risk

Variable	Category	Sig. Of AOR	AOR	95%C.I. for AOR	
				Lower limit	Upper limit
Educational Level	1-6 years	.000	Ref.	-	-
	7-9 years	.063	1.89	.97	3.70
	10-12 years	.067	1.94	.95	3.93
	More than 12 years	.000	8.43	3.44	20.64
Type of living place	Separate home	.000	Ref	-	-
	Apartment	.001	.37	.20	.68
Parental Consanguinity	No Relation	.001	Ref.	-	-
	1st Degree Relation	.003	2.48	1.35	4.55
	2nd Degree Relation	.205	.64	.33	1.27
Total period of breastfeeding	Didn't breastfeed	.000	Ref.	-	-
	1-3 years	.276	.55	.19	1.61
	4-6 years	.520	.72	.26	1.98
	7-9 years	.066	.39	.14	1.06
	> 9	.000	.16	.06	.41
Age at menarche	<13 years	.000	Ref.	-	-
	≥13 years	.000	3.57	1.77	7.20
Oral contraceptive use	No	.000	Ref	-	-
	Yes	.031	2.23	1.08	4.61
Hormone replacement therapy	No	.000	Ref.	-	-
	Yes	.005	3.97	1.51	10.42
Have a relative with breast cancer?	No	.000	Ref	-	-
	Yes	.000	3.51	1.74	7.10
Body Mass Index	Less than 25 (Normal weight)	.000	Ref.	-	-
	25-29.99 (Overweight)	.000	.19	.08	.41
	30-34.99 (Obese)	.473	.74	.33	1.67
	35 or more (Morbid obesity)	.236	.59	.25	1.40
Cardiovascular disease	No	.000	Ref.	-	-
	Yes	.000	3.89	1.87	8.07
Joints problems	No	.000	Ref.	-	-
	Yes	.001	2.65	1.45	4.82
Insulin Glargine	No	.000	Ref.	-	-
	Yes	.001	15.51	2.95	81.59
Electric blanket use	No	.000	Ref.	-	-
	Yes	.007	3.23	1.38	7.58
Soft drinks intake	Never	.036	Ref	-	-
	1-3 times/month	.304	.63	.27	1.51
	1-6 times/week	.068	.58	.32	1.04
	≥ 1/day	.090	3.54	.82	15.25
Butter intake	<1 / day	.000	Ref.	-	-
	≥ once/day	.008	2.61	1.28	5.32
Chicken intake	< once weekly	.000	Ref.	-	-
	≥ once weekly	.017	.43	.22	.86

Conditional forward logistic regression model includes: diabetes status, educational level, type of living place, parental consanguinity, number of full-term pregnancies, age at first marriage, pregnancy, delivery and breastfeeding, total period of breastfeeding, age at menarche, oral contraceptive use, hormone replacement therapy, relative with breast cancer, relative with other cancer, body mass index, cardiovascular diseases, osteoporosis, joints' problems, Metformin use, Metformin daily dose, insulin Glargine use, smoker parent, electric blanket use, MET score, soft drinks, red meat, nuts, and butter intake.

Chapter Six

Discussion, Conclusions, Limitations and Recommendations

6.1 Discussion

Our study was a case control study conducted mainly in Beit-Jala Hospital and mammography units of the southern region of Palestine. A total of 237 study cases and 237 controls were included to study risk factors of breast cancer, including mainly its association to T2DM.

Study participants were recruited between June 2016 and October 2017. Study cases were easier to allocate than the control group; Chemotherapy daycare unit at Beit-Jala Hospital offers its medical service for cancer patients on regular and ordered basis, so it was easy to recruit patients during their chemotherapy session. As for controls, they couldn't be recruited at mammography units on that regular basis, so it was necessary to get their contact information, after official permissions were obtained, in order to access these participants by phone calls. Electronic files of study cases were accessed at the daycare unit. Some information were missed, especially for those cases diagnosed with BC before 2014, as the HIS (health information system) get in practice in 2013.

6.1.1 Characteristics of study cases

Mean age at diagnosis in our sample was 52, similar to that in other Arab countries like Jordan (Arkoob, 2010), Saudi Arabia, Egypt, Tunisia, Syria, and older Palestinian studies (El Saghir et al., 2007), and among both Jewish and Arab women in our region (Nissan et al., 2004). The age at diagnosis reported in the Arab world ranged from 43 to 52, with a mean of 48 years (Najjar & Easson, 2010), which was a decade younger than that of industrialized countries (El Saghir et al., 2007). It is worth noting that our cases were

breast cancer patients over the age of 40 years, so the real mean age at diagnosis in our region might be a younger age. Regarding age groups of the study cases, it was found that the most frequent group was that between 40 to 44 years old, same result was found among Lebanese women (Elsaghir NS et al, 2002), and Iraqi women (30% of cases were between 40 to 49 years) (Alwan, 2010), whereas global data showed different results, most studies showed an increased risk of BC with age (Weir & Ali, 2007). This may be due to the fact that Palestinian population is considered young, with elderly (over 60) accounting for only 4.8% of the population (PCBS, 2017).

Upon examining cancer subtypes, it was clearly noticeable that about two thirds (58%) of our cases were diagnosed with ductal carcinoma. Similar results were found among Egyptian and Iraqi women (Alwan, 2010; S. Omar et al, 2003). But almost 77% of Jordanian cases had ductal carcinoma (Arkoob, 2010). The results might reflect the actual number, but it also could be falsely increased due to the fact that lobular carcinoma is more difficult to detect by both physical examination or mammography (Li, Anderson, Daling, & Moe, 2003).

Most of cases were diagnosed in the 2nd and 3rd stage of the disease (65%), which indicated the detection of the mass by the patient or the physician, and not by screening examination. This finding was confirmed by the result that only 17% were diagnosed by screening, while 83% detected their own mass. The same exact percent was reported among Palestinian women in the northern region, with 84% noticed their mass by themselves (A. Z. Haj Qasem, 2000). Similar disease characteristics regarding cancer subtypes and stage at diagnosis were freported among Egyptian, Jordanian, and Iraqi females (Alwan, 2010; Arkoob, 2010; S. Omar et al, 2003)

The vast majority (88%) of the study cases were from the southern region of Palestine, as Beit-Jala Hospital is the only hospital providing service for cancer patients in the south (Bethlehem governorate, Hebron governorate); Patients in the north and in the middle seek medical intervention in other nearer hospitals. In addition, during data collection, it was noticed that there were certain places with large number of patients, like Dura and Yatta in Hebron, which might be explained by environmental hazards, genetic factors, and consanguinity, and it is worth investigation.

Several treatments have been implicated for BC. Only 25% of study cases were given neo-adjuvant therapy, which indicated surgery as the first option in our medical strategies. In

the Arab world, approximately 80% of BC cases had undergone mastectomy (El Saghir et al., 2007), compared to 68% in our study, which might indicate a better treatment strategy. Thirty percent of the study cases in our study received hormonal therapy, at least once in their treatment schedule, which is restricted for hormone responsive tumor; This finding was similar to the findings among Palestinian women in the northern region (Darweesh, 2009), and among Iraqi women (Alwan, 2010).

6.1.2 Socio-demographic risk factors and breast cancer

Several studies reported that high socio-demographic and economic status is a risk for BC (Akinyemiju, Pisu, Waterbor, & Altekruse, 2015), with an overall estimation of 20% increase in the risk for higher socio-economic factors (95%CI: 1.05–1.37) (S. A. Robert et al, 2004). This positive association was clearer among Hispanic and Asian women (Ysot K et al, 2001), and not only for BC, but for colon, ovary and melanoma cancers (Faggiano et al, 1997). Our analysis reported similar results, where high educational level and living in a separate house increased the risk for BC. Regarding educational level in our study, it showed a positive association with the risk of BC, with a well-established dose response relationship. Those who studied for more than 12 years have 8 fold increased risk than those who studied for 6 years or less. In north Palestine, the increase was by 4 folds for high educated women compared to low educated ones (Darweesh, 2009). Same result was reported among Egyptian women (El Saghir et al., 2007). In Europe, a direct dose response association was reported between education level and postmenopausal BC incidence (Hvidtfeldt et al., 2013). Considering type of living place in our results, it was found that living in an apartment significantly decreased the risk of getting BC to the third when compared to living in a separate home (OR=0.37). The same association was observed in a study of 47,586 females held in 2015 (Akinyemiju et al., 2015). It is worth mentioning that living in a separate house in our community doesn't necessarily mean a better socioeconomic status, as most of Palestinian families living in rural areas have their own separate houses, and not apartments.

A suggested explanation for the association between socio economic level and BC can be better diagnosis; Higher knowledge increases the awareness and so increases the screening strategies, and medical access. Alternatively, a real higher incidence might be responsible for this association, where hormonal factors, due to late marriage age, late pregnancy age, decreased breastfeeding, and lower parity which are characteristics of higher socio-

economic factors, might mediate this association (Blamey et al., 2004; Hvidtfeldt et al., 2013; Li et al., 2013; Ma et al., 2010).

On the other hand, the opposite relation was found in other studies, where lower socioeconomic status increased the risk of BC, as females had less awareness toward screening techniques and diagnosis (Malley et al 2000). In our study, monthly income was lower among study cases. However, it is worth noting that mammography is available to almost all females above 40 in our community, as a free service provided by the Ministry of Health.

Discussing consanguinity is an issue only in the developing countries; In our study, daughters of unrelated parents showed a decreased BC risk, whereas those with 1st degree relative parents had increased risk by 2.5 folds. Similar finding was reported in UAE in which unrelated parents of the subjects decreased the risk to the half (RR=0.5, 95%CI: 0.27- 0.93) (Denic & Bener, 2001). This genetic issue was investigated in a very recent study conducted in Palestine, which showed a real genetic mutation among BC females who had related parents, but the study revealed that although the consanguinity rate is high in the Palestinian population, no significant difference exists between consanguinity in BC and control groups, but the sample size was very low (N. Herbawi, 2016).

6.1.3 Reproductive health factors and risk of breast cancer

Most of the reproductive health characteristics in our study went with the general reproductive characteristics of the Palestinian society, such as young marital age, multiparity, and high breastfeeding practice. According to PSBC 2016, the mean age for the 1st marriage was 19.8 years in the southern region of Palestine; Consequently, they were at a young age at 1st pregnancy, 1st delivery and breastfeeding. In our analysis, the age of 18 years was considered as a cutoff point. Our multivariate results showed no significant risk regarding age at first marriage or pregnancy. On the contrary, among Palestinian women in the North, there was a 10% increase in the risk when the 1st marriage was at the age of 20 or more (Darweesh, 2009). And the OR among Gazan women who had their first pregnancy after the age of 35 years was 11.56 (95%CI: 1.64-81.35) (Kariri et al., 2017). Our results were different due to the inconsistency in the cutoff point.

To study the effect of number of full term pregnancies in our study, five full term pregnancies was considered as a cutoff point, as it was the mean of live births in Palestine

(PCBS 2016). Our results revealed no significant association between full term pregnancies and the risk of BC. However, number of full term pregnancies was negatively associated with BC risk in almost all studies, even in the western world. This result was consistent not only for one type, but all subtypes of BC, for pre and post-menopausal women (Li et al., 2013). The reduction in the risk ranged from 18% to 60% (Blamey et al., 2004; Hirose et al, 1995; Ma et al., 2010; Yuan et al., 1988). Even in the Northern region Palestine, a 50% decrease in the risk was reported among women with 4 full term pregnancies or more (Darweesh, 2009). In addition, multi-parity was shown to be protective among Moroccan women (Laamiri et al., 2015).

One of the well established protective factors against BC is breastfeeding (Islami et al., 2015). In our results, almost all women who had children had practiced breastfeeding, but the protective effect in our analysis wasn't in breastfeeding itself, but in its period. Previous studies found that breastfeeding itself was protective; A Saudi study reported that never having breastfed had doubled the risk (OR=1.89, 95%CI: 1.19-2.94) (Nasser Elkom et al, 2014). Furthermore, breastfeeding decreased the risk of having BC by almost 60% in an Israeli study in our region, (OR=0.39, 95%CI: 0.26-0.59) (Shema L et al, 2007). Similar result was reported in Morocco with a 35% risk reduction (OR=0.65, 95%CI: 0.55-0.78) (Laamiri et al., 2015). Other results even in USA confirmed this association with 14% increased risk among women who had never breastfed, (RR=1.14, 95%CI: 0.17-1.38) (Warner et al., 2014). Breastfeeding has been proposed to protect against BC through hormonal mechanisms that include postponing the resumption of ovulatory menstrual cycles after a pregnancy (Russo, 1994), reducing estrogen levels in the breast (Petrakis et al, 1987), and having fully differentiated breast tissue which is less susceptible to the hormones (Russo et al, 2000). In addition, it has been proposed that breastfeeding also has a direct mechanical effect by which carcinogenic agents are excreted from the breast ductal tissue (Ma et al., 2010).

Upon examining period of breastfeeding, results of studies were inconsistent. A study that summarized findings from developed countries showed that for every year a woman breastfed, her risk of developing BC was reduced by 4.3% (Collaborative Group on Hormonal Factors in Breast Cancer, 2002). Similar results were reported in an American study for different age and ethnic groups (Furberg H et al, 1999). In China, the risk was reduced to the half in those who breastfed more than 3 children compared to those who never lactated (OR=0.53, 95%CI: 0.27-1.04) (T. Zheng et al., 2001). An article review

showed that OR was 1.37 for never breastfed compared to 16 months or more of breastfeeding (Engla, 2010). In our study, a very clear inverse dose response relationship was found, with AOR=0.39 for the group of 9 years or more of breastfeeding, compared to never breastfed, with a decrease the risk by 25% to 30% for additional 3 years of breastfeeding. Among Palestinian women in the north, the risk for those who never breastfed was doubled compared to those who had lactated for 4 years or more (Darweesh, 2009). It was found that the reduced risk was only for hormone negative disease (Li et al., 2013). On the contrary, no association was found between breastfeeding period and the risk of BC (Ramon et al, 1996), either in developed or developing countries (Collaborative Group on Hormonal Factors in Breast Cancer, 2002). It was found that 1 year of breastfeeding increased the risk (OR=1.27, 95%CI: 0.78-2.06) compared to no breastfeeding (Hirose et al, 1995).

Older age at menarche in our results was associated with increased risk of BC. The risk was increased by three folds by menarche at the age of 13 or more (AOR=3.56). On the contrary, older age at menarche was inversely associated with BC risk in many studies, even in the Arab world. The high risk group were females with menarche before age of 12 years (OR =1.5) (Engla, 2010), or 11 years (Mcpherson et al., 2000), whilr the protection was in females who had menarche after 14(OR=0.84, 95%CI: 0.65-1.09) (Hirose et al, 1995). Furthermore, it was found among 117 studies that BC risk was increased by a factor of 1.050 for every year younger at menarche (Lancet Oncology, 2012), and a delay of 2 years at menarche had led to a 10% reduction in BC all around the world (Hsieh CC et al, 1990). This protection applied for all cancer subtypes (OR=0.72) (Ma et al., 2006). Similar results were found among Moroccan women; Age at menarche less than 13 were significantly associated with BC, in Morocco (P=0.002), and north Palestine (OR=6.50) (Darweesh, 2009; Laamiri et al., 2015). The protective result of older age at menarche, was explained by decreasing the cumulative number of ovulatory cycles, which is negatively associated with the risk, so with younger age at menarche, and with older age at menopause, a female would have more cycles, and so increased risk (Clavel chapelon et al, 2002; K. L. Terry et al., 2008). Consistent to our findings , was a Chinese-Vietnamese study which showed a slight increase in the risk of BC with older age at menarche (OR=1.11, 95%CI: 0.8-1.35) (H. B. Nichols et al., 2005).

Oral contraceptive pills (OCP) use for 2 months or more have significantly doubled the risk in our results (AOR=2.22). Similar result were revealed among Jordanian females

(Wasileh P Nustas et al, 2002), and among Palestinian females in the northern region with OR=2.54 (Darweesh, 2009). Some studies reported that the increase in the risk was for oral contraceptive use only before full term pregnancy, (OR=2.2) (Pike, Rosario, & Gray, 1981). However, almost all studies found a slight increase in the risk (Moorman et al., 2013). Other studies reported that the increased risk was only for the next 10 years just after the last OCP use (Gierisch et al., 2013; Jr, 1996). Some studies on the other hand, found a decreased risk among women but at least after 10 years of the last use of OCPs (England, 2002).

Hormone replacement therapy (HRT) was very strongly associated with risk of BC in our results (AOR=3.97). Similar results were reported among Saudi and jordanian women, (OR=2.25, 95%CI: 1.65-3.08) (Nasser Elkom et al, 2014; Wasileh P Nustas et al, 2002). The increase in the risk could be attributed to the influence of HRT on reducing the effectiveness of mammography by creating denser breast tissue (WIH JAMA, 2002). Our results were similar to almost all previous studies, even Europen; The increase risk among HRT users ranged from 30% in past users, to 60% in current users, revealing a dose response relationship with duration of use (Andrea Z LaCroix, 1997; Toine Lagro-Janssen, Walter W Rosser, 2003). Furthermore, it was reported that estrogen alone in HRT had reduced BC risk in young women, and increased the risk in older women (Howel A et al, 2011).

6.1.4 Health status and risk of breast cancer

In this group of factors, Body Mass Index (BMI), chronic diseases history, and chronic medication were included in our study.

BMI and the risk of BC depended on menopausal status and hormone receptor nature. In our analysis, surprisingly, being underweight was associated with increased risk. Different results were found among women in the middle east; where obesity (BMI $\geq$ 30) was associated with increased risk for BC in Gaza Strip (OR=4.70, 95%CI: 1.62-13.69), in Egypt, in Saudi Arabia (OR=2.29 95%CI: 1.68-3.13), and in Iran (OR=3.21 95%CI: 1.15-8.47) (Amin, 2016; Kariri et al., 2017; Montazeri et al., 2008; Nasser Elkom et al, 2014). However, being obese was a risk only among postmenopausal women in Tunisia (OR=2.1 95%CI: 1.1-3.9) (Msolly Awatef et al, 2011). Same results were reported in a study included more than 13000 women with BC, where obesity in premenopausal women was protective (adjusted hazard ratio=0.82), but in postmenopausal women led to a

statistically significant increase in the risk, (adjusted hazard ratio=1.65) (Chen et al., 2016). Postmenopausal obesity was associated with 20% to 40% increase in risk of developing BC, but in premenopausal women, overweight and obesity were associated with a 20% decreased risk in hormone positive tumors (Mark Munsell et al, 2014).

BMI and T2DM together with their relation to cancer in general were recently studied all over the world, it was reported that 4.5 % of cancer cases around the world were attributed to being overweight (BMI >25 kg/m^2) and having T2DM together. Overweight alone was responsible for twice as many cancer cases as T2DM alone (Pearson-Stuttard et al., 2017). It is suggested that obesity creates multiple pathways of chronic inflammation in the body and the breasts, as it enlarges fat cells, spurring inflammation. Obesity also creates insulin resistance, causing the body to produce more insulin in order to control blood sugar levels. It is well known that insulin is an inflammatory agent which creates a snowball effect of inflammation and enlarged fat cells; Since fat cells produce estrogen, obesity and insulin resistance can result in an overproduction of estrogen, raising not only the risk of BC, but also increases metastasis and recurrence of the disease (Tiberian J, 2017).

History of chronic diseases was strongly associated with BC risk in our study. The association was most obvious in cardiovascular diseases (AOR =3.88). In addition, joint problems doubled the risk of having BC. The percentage of females who had auto immune diseases was higher among study cases, but didn't show a significant risk due to their low frequency in the control group in our study. Joint problems and osteoporosis were found to be associated with postmenopausal hormonal changes. Our result regarding higher risk among females with joint problems were confirmed by the inverse association found between bone mineral density and the risk of BC, in which the mean bone mineral density Z-score was significantly lower among BC cases among south population in an Israeli study (Fraenkel et al., 2013). On the other hand, the opposite result was reported in a different study, but it was due to Bisphoshponate treatment for osteoporosis, like Raloxifen or Tamoxifen (Martino et al., 2004), which both were responsible for a reduction in BC risk among women (Powles T J et al, 2012).

Considering cardiovascular diseases (CVDs), which were a significant risk in our results, most studies analyzed them as a side effect of BC treatment, but not as a risk predisposing BC. An overlap between BC and CVDs risk factors was reported in many studies; Inflammation was a shared risk factor for both BC and CVDs as a mediator of both disease

processes, (Coussens LM et al, 2002; Libby P, 2006). Chronic inflammation was associated with oxidative stress, and this too is associated with both diseases processes (Koene RJ et al, 2016). Chronic inflammation not only increased the risk, but the prognosis to metastatic tumors (North Carloina Univ, 2012).

In our findings, Aspirin had no association with BC, as our sample included only women aged 40 years or over, and since Aspirin is prescribed as a prophylactic medication for women at this age, most women included in our sample were on Aspirin with no difference among cases and controls. The (no protective role) for Aspirin was confirmed only in few studies (S. M. Zhang, Cook, Manson, Lee, & Buring, 2008).

6.1.5 Family history and risk of breast cancer

Confirming previous international findings, family history of BC was significantly associated with BC risk in our results; A female who had a relative with BC of any degree was 3.5 folds more likely to have BC than those who didn't have any relative with BC. It was believed that up to 10% of BC cases in Western countries were due to genetic predisposition (Mcpherson et al., 2000), with a threefold increase in the risk of BC among those with family history of BC (Slattery & Martha, 1993). The consistent increase in the risk was when the relative is a mother or a sister (G. A. Colditz et al., 1996). The relative risk of BC ranged from 1.5 to 3.6 in a pooled analysis depending on the relative degree, with the highest risk was reported among women who had a mother or a sister with BC (Pharoah, Day, Duffy, Easton, & Ponder, 1997). Furthermore, positive family history of BC among Gazan women, increased the risk for BC (OR=2.7, 95%CI: 1.04-7.20), similar results were reported among Moroccan women (OR=11.15, 95%CI: 2.54-49) (Kariri et al., 2017; Laamiri et al., 2015)

6.1.6 Diabetes and risk of breast cancer

Results of our study revealed a significant difference between study cases and the control group regarding prevalence of T2DM. T2DM prevalence in the control group was 14.8%, the mean age of diabetics in the control group was 54 years (±SD 9.88). The prevalence of T2DM reported in PCBS in the same age group was 19.1% (PCBS, 2016), which is about 5% higher than our finding. Overall prevalence of T2DM among women aged 25 or more in southern region was 9.6% (Husseini et al., 2009b).

The main aim of our study was to investigate the association between T2DM and BC. After adjustment for covariates, the association disappeared. On the contrary, several studies reported an increased risk of BC among diabetic women, including Palestine; In a recent case control study conducted in Gaza, T2DM increased the risk of BC (OR=6.84, 95%CI: 1.77-26.36) (Kariri et al., 2017). The reported increase in the risk all over the world had ranged from 23% (Liao et al., 2011) to 27% (Boyle, 2012). This increase in the risk was limited to estrogen receptor negative BC (Palmer, 2017). However, subtypes of receptors were not available in our study, due to limited information in the registry system.

Regarding T2DM treatment in our results, it was found that almost all diabetic patients were treated with tablets, and almost 24% were treated with insulin. Previous Palestinian data reported that 21.2% of diabetes clinics' attendees were treated with insulin, while 63.0% were treated with tablets, 14.8% were treated with both tablets and insulin, only 1.0% of diabetic patients were treated by diet only (MOH, 2016). Considering T2DM treatent and BC risk in our study, Insulin Glargine was significantly associated with increased risk of BC (AOR=15.5), our findings for insulin Glargine were consistent with several studies, but the risk was higher in our findings. Glargine was associated with an increased risk of BC in several studies (HR=1.44, 95%CI: 1.11-1.85), with the risk being doubled when receiving Glargine for more than 30 months (HR=2.29, 95%CI: 1.26-4.16) (Jennifer W Wu, 2017). On the other hand, no association was found between BC and Insulin Glargine in a preclinical study (HR=1.04, 95%CI: 0.91-1.17). Furthermore, it was reported that insulin analogues (Aspart, Determir, Glulisine or Lispro), and human insulin, might induce the progression of BC by up regulating mitogenic signaling pathways, but didn’t increase the incidence (Bronsveld et al., 2015). Findings in other studies found that the risk was only elevated among insulin analogues switchers after Glargine (Peeters et al., 2016). It was suggested to switch to shorter acting insulins, especially with females having predisposing risk factors and family history (Ahmed, 2010). Other insulin analogues in our study didn’t show a significant association with BC, like Novorapid, and human insulin, since the frequency of users was limited.

The most prescribed diabetes medication, Metformin, didn’t show an association with BC in our findings. Many studies on the other hand, showed that Metformin was protective. Some studies investigated T2DM as an independent risk factor from receiving Metformin, and reported that T2DM itself is a significant risk factor, but Metformin alone was protective (Armstron, George, & Halabi, 2013). In our study, Metformin couldn’t be

studied alone, as almost all diabetic females were on Metformin as a general 1st line strategy to treat T2DM in our country (98% of diabetic cases, and 91% of diabetic control group were on Metformin therapy). Reduction in the risk among Metformin users had ranged from 25% to 50% (Chlebowski et al., 2012; Nananda F Col et al, 2012). Decreased risk was reported either for long term use (>5 years) of Metformin (OR=0.44, 95%CI: 0.24-0.82) (Bodmer et al., 2010), or short term use (OR=0.63, 95%CI: 0.53–0.75) (Libby G, Donnelly LA, Donnan PT, 2009). Furthermore, Metformin was protective in physiological preclinical studies (Zakikhani et al., 2006), (Alimova et al., 2009), by inhibiting BC stem cells (Hirsch, Iliopoulos, Tsichlis, & Struhl, 2009).

On the other hand, fewer studies found that Metformin had no significant reduction in the risk for BC (Franciosi, Lucisano, Lapice, Strippoli, & Nicolucci, 2013), nor with BC incidence (Noto, Goto, Tsujimoto, & Noda, 2015). Metformin, according to those studies, was found to be associated with decreased mortality and recurrence only in BC patients, but not with the risk (Heckman-stoddard, Decensi, Sahasrabuddhe, & Ford, 2017).

6.1.7 Lifestyle and risk of breast cancer

In general, physical activity in our results was not significantly different between control group and study cases. The only factors that were found to be significantly different between cases and controls in univariate analysis, were metabolic equivalent score (MET score), having a smoker parent, and the use of electric blanket.

Women who practiced regular recreational or occupational activities were few compared to our sample size. The same applied for smoking, with suspected under-reporting, due to the fear from stigma reasons.

According to many previous studies, high recreational physical activity was inversely associated with BC risk, with a significant 20% to 25% decrease in the risk. It was reported that body mass index (BMI) might play a confounding role (Bardia et al., 2006). The associations were the strongest for recreational activity, lifetime activity, activity done after menopause, and for activity that is of moderate to vigorous intensity performed regularly, confirming that BMI was a confounder for the association (Lynch BM et al, 2011). In some studies, the decreased risk was reported not only for one subtype of BC, but for all subtypes (Lope V et al, 2017).

Electric blanket use, was found to be a significant risk for BC in our analysis; According to scientific hypothesis, electric blanket use increased the risk of BC by increasing the exposure to electric magnetic field (Feychting M et al, 2006). On the contrary, no difference in exposure to magnetic fields was found between cases and controls among the users of electric blankets (Kabat & Leske, 2004). In addition, in a larger epidemiological study, the relative risk for electric blanket use was not elevated (RR=1.08, 95%CI: 0.95, 1.24) after controlling for other breast cancer risk factors (Ladn F et al, 2000). Same results applied for pre and post-menopausal women, with no difference for increased period of the electric blanket use (Gammon et al., 1998).

6.1.8 Food intake and risk of breast cancer

Our results regarding food intake showed a significant difference between cases and controls, regarding some kinds of food when comparing the highest intake category to the lowest one. Soft drinks and butter were found to increase BC risk, while chicken significantly decreased the risk.

Results of many previous studies representing food intake were inconsistent, due to the lack of homogeneity of assessment method, or to type of food processing in each country. Most studies had classified food into 3 major patterns, Healthy Mediterranean (high oil, vegetables, and fish), which is the nearest to our food pattern, Western- High fat (Canned fish, meat products, pizza/pies, eggs, alcoholic beverages, cakes, and butter), and Drinker (high alcohol) pattern. The Mediterranean diet was confirmed to be protective, (HR=0.85 95%CI: 0.75-95) (Cottet et al., 2009), especially with high vegetable consumption, (RR=0.75, 95%CI: 0.66-0.85) (S. Gandini et al, 2000). On the other hand, it was reported that the protection was only in fresh fish (OR=0.77, 95%CI: 0.58–1.01), whereas an excess of raw vegetables and olive oil increased the risk significantly (OR=1.22, 95%CI: 1.06-1.32) (Bessaoud et al., 2012). A positive association with BC was observed regarding Western dietary pattern; However, most of these results were not statistically significant (Albuquerque et al., 2014). Drinker diet, which is not familiar in our country, was the only significant pattern which increased the risk of BC according to other studies (P. Terry et al., 2001).

In our study, fish and canned Tuna were categorized together, with their consumption was higher among study cases. An explanation might be heterocyclic amines, which are by-products of meat and fish cooking, which are mutagens and can cause cancer according to

clinical studies on animals (David W Layton et al, 1995). Furthermore, butter, which is a fat rich item, was a risk factor for BC in our study. High fat intake was found to elevate the risk, and even doubling it in some studies, (OR=2.72, 95%CI: 1.16-6.37) (Boyd et al., 2003; Ronco et al., 2006). In addition, cheese, eggs, and chips intake was higher among cases, which all contain a kind of fat.

Red meat intake was reported to increase the risk of BC (RR=1.17, 95%CI: 1.06-1.29) (Boyd et al., 2003), confirming a dose response relationship (E Cho et al., 2006). The increased risk was highest for well-done bacon, beef, and hamburger (W. Zheng et al., 1998), which are not the kind of meat consumed in our country. Red meat consumption in our findings was not associated with BC; Meat processing in our country is different than that in western countries. In addition, high meat intake in our community might be an indicator for better living standards, and higher health awareness.

Chicken intake was associated with a decreased risk in our results. Chicken is an excellent dietary source of niacin, vitamin B6, choline, selenium and tryptophan, and also contains vitamin B-12, vitamin D, iron, and zinc. Chicken is far lower in saturated fat and cholesterol than red meat. Chicken consumption has been found in numerous studies to be associated with lower risk of BC. Consumption of white meat was associated with lower breast density, a strong BC risk factor. Another explanation might be food substitution, i.e. eating chicken rather than red meat which reduces the proportion of red meat in the diet (Warren et al., 2017).

In this study, we were able to show higher prevalence of T2DM among BC cases than controls. Several risk factors associated with BC risk were found, including medication of Diabetes, oral contraceptive pills, hormone replacement therapy. In addition, we identified several health factors associated with BC risk, like cardiovascular diseases, joint problems, and BMI. Food intake, physical activity, and some daily habits affected the risk of BC significantly. Furthermore, consanguinity, positive family history, and higher educational level increased BC risk.

6.2 Conclusions

This is the first study of its type in Palestine. The study had some consistency with the published research that investigated the association between T2DM, its medication and BC risk. Most studies were performed on datasets that were collected from patients' medical

records. Our study used the classical matched case-control, which made it unique in its results.

After controlling for several factors, T2DM itself was not found to increase the risk for BC, whereas its medication the long acting Insulin Glargine was shown to significantly increase the risk for BC by 14 folds.

Other non-modifiable risk factors were associated with BC in our study, which were family history, consanguinity, reproductive health factors, and other chronic diseases such as cardiovascular diseases and joints' problems. Modifiable risk factors for BC revealed in our study were breastfeeding, oral contraceptive pills, hormone replacement therapy, female weight, electric blanket use and intake of some kinds of food.

6.3 Study limitations

Our study, although included a large sample size, but only represented the Southern region of Palestine. To a large extent, our results were consistent with previous studies conducted in the Northern region of Palestine.

Data collection in our study included interviews as the main source, and to a lesser extent, access to patients' medical records at the Ministry of Health. These records were electronically registered through the "Avicenna program" for all study cases. However, due to some program limitations, there was a gap in some information and search options.

Controls couldn't be recruited from the same hospital, as they should be confirmed as BC free females. Therefore, it was decided to match study cases by residence location; Controls were chosen from the two main mammography units in Hebron and Bethlehem, which might cause a selection bias.

Regarding study cases' characteristics, some information were missing in the registry system, like cancer subtypes or receptor status of the tumor cells. The same applied to T2DM history and treatment. Therefore, we depended on the participants recall and answers, which exposed our data to recall bias.

Women included in our sample were at the age of 40 years or older. Cases couldn't be included from other age groups since women who had done mammography were only 40 years or over. Therefore, our results can only be generalized for this age group.

6.4 Recommendations

For Patients and general population

T2DM is, to an extent, a modifiable disease. It can be controlled by having healthy diet, being physically active, and by being adherent to the proper medication/s. Regarding breast cancer, screening and prevention are the best ways to avoid the disease. It is recommend for all women to respond to the advice of doing self-breast examination and mammography as scheduled by the health case staff, as the earlier the diagnosis is, the better management strategies and treatment success.

For research field

- Further investigation for the association between T2DM, its medication, and breast cancer should be taken into account in other regions of Palestine. In addition, the association of T2DM with other cancer types must be investigated.
- Other new hypothesis for cancer occurrence of cancer must be done in Palestine too. For example, adiposity is nowadays is suspected to affect the success of cancer therapy. Therefore, we recommend conducting a study on nutrition and obesity on cancer control.
- In general, cancer research in Palestine is still poor and any new hypothesis must be encouraged to be investigated.

For Ministry of Health and policy makers

- To improve the hospital information system, and the registration system that is currently used at the Ministry of Health.
- Breast cancer screening is not yet mature in Palestine and women must be encouraged to perform it. More mammography units must be established to increase the access of women. Mobile mammography units are suggested as a solution for accessibility which will affect BC prognosis.
- Diabetes screening program must be initiated
- Awareness campaigns on diabetes self-care and prevention must be supported.
- Advocacy campaigns to support women with breast cancer must be initiated to help them in having better quality of life.
- Consanguinity marriage is still very common in Palestine. Advocacy programs should be conducted in Palestine to educate people on the health risks of this issue.

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Appendices

Appendix 1

Arabic Questionnaire

كلية الصحة العامة

رقم الاستمارة : _____ مكان المقابلة : _____

هل أنت مصابة بسرطان الثدي؟	A	☐ Yes	☐No
هل مضى سنة على تشخيص سرطان الثدي؟	B	☐ Yes	☐No
هل أنت مصابة بالسكري؟	C	☐ Yes	☐No
هل تم تشخيص السكري قبل سنة على الاقل من سرطان الثدي؟	D	☐ Yes	☐No
هل تم تشخيصك بأي سرطان آخر قبل سرطان الثدي؟	E	☐ Yes	☐No

_____	SD .1	رقم الملف
_____	SD .2	اسمك الرباعي
_____	SD .3	رقم التلفون أو الجوال
_____	SD .4	رقم الهوية
__/__/____	SD .5	تاريخ ميلادك؟
|___|	SD .6	ما هو تحصيلك العلمي الأعلى؟ 1- اساسي (0- 6) 2- أعدادي (7-10) 3- ثانوي (11-12) 4- كلية 5- جامعي
____ محافظة	SD .7	أين تقيمين حاليا؟
	SD .8	ما نوع السكن؟ 1-بيت مستقل 2- شقة في عمارة 3- بيت شعر 4- بيت صفيح
|___|___|	SD .9	ما عدد أفراد الأسرة المقيمة في منزلك الحالي؟ (بما فيهم انت)
|___|	SD .10	ما دخل الأسرة الشهري ؟ (بالشيكل) 1- أقل من 1000 2- (1000 – 2000) 3- (2001 – 3000) 4- (3001 – 5000) 5- أكثر من 5000
☐نعم ☐لا	SD .11	هل عملت أو تعملين خارج البيت ؟
	SD .12	ما هو العمل و ما مدنه؟
☐نعم ☐لا	SD .13	هل عملت بدوام ليلي ؟
|___|	SD .14	ما مدة دوامك الليلي بالسنوات؟

	المهنة 1	المهنة 2	المهنة 3
أ. نوع المهنة			
ب. مدة العمل			

|__|	SD .15	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
|___|	SD .16	ما هي حالتك الاجتماعية؟ 1- عزباء -- **انتقل للسؤال** 28 2- متزوجة 3- مطلقة 4- أرملة
|__|	RH .17	كم كان عمرك عندما تزوجت أول مرة؟
☐نعم ☐لا	RH .18	هل أنت حامل حاليا ؟
|___|___|	RH .19	كم عدد المرات التي حملت بها؟ (شامل الحمل العادي والخداج الإجهاض و فقدان الجنين و الحمل في القنوات و الحمل الحالي إن وجد) . **ملاحظة : عدد (صفر) ، انتقل للسؤال28**
|___|___|	RH .20	كم عدد الأحمال التي أدت إلى إنجاب أطفال أحياء؟
|___|___|	RH .21	كم عدد ما أنجبت من ذكور؟
|___|___|	RH .22	كم عدد ما أنجبت من إناث؟
|___|___|	RH .23	كم كان عمرك في أول حمل ؟ (مهما كانت نتيجته، إجهاض أو حمل كامل أو خداج)
|___|___|	RH .24	كم كان عمرك في أول ولادة ؟ (سواء حمل كامل أو خداج)
☐نعم ☐لا	RH .25	هل أرضعت الأطفال رضاعة طبيعية؟ **الجواب (لا) ، انتقل للسؤال** 28
|___|___|	RH .26	كم كان عمرك عندما أرضعت أول طفل؟
|__| سنة	RH .27	لو جمعنا كل فترات الرضاعة لجميع الأطفال ، كم فترة إرضاعهم مجموعة ؟ (بالسنوات)
☐نعم ☐لا	RH .28	هل استخدمت حبوب مانعة للحمل لمدة شهرين أو أكثر لأي سبب (تنظيم دورة ، حب شباب ، منع حمل) ؟ **الجواب (لا) ، انتقل للسؤال** 33
|___|___|	RH .29	كم كان عمرك في أول استخدام لحبوب منع الحمل؟
☐نعم ☐لا	RH .30	هل تستخدمين حبوب منع الحمل حاليا؟ **الإجابة (نعم) ، انتقل للسؤال** 32
|__|__|	RH .31	كم كان عمرك عندما توقفت عن استخدام حبوب موانع الحمل؟
|__|__|	RH .32	لو جمعنا الفترة التي استخدمت فيها حبوب منع الحمل ، ما طول الفترة؟ **بالسنوات**
|__|__|	RH .33	في أي عمر بدأت عندك الدورة الشهرية؟ سن البلوغ
|___|	RH .34	طبيعة دورتك الشهرية : 1- منتظمة 2- ليست منتظمة 3- أستعمل هرمونات بديلة 4- توقفت الدورة الشهرية نهائيا -- **أنتقل للسؤال 35**
|___|	RH .35	كم كان عمرك عندما توقفت دورتك الشهرية؟
☐نعم ☐لا	RH .36	هل تعرضت لعملية إستئصال رحم؟ **الإجابة (لا) ، انتقل للسؤال** 40
|___|___|	RH .37	كم كان عمرك عندما تم استئصال الرحم؟

|___|	RH .38	هل تعرضت لعملية استئصال أحد المبايض أو كليهما؟ 0- لم أتعرض -- **انتقل للسؤال 40** 1- نعم، أحد المبايض تم استئصاله 2- نعم، كلاهما
|___|___|	RH .39	كم كان عمرك عندما استئصال المبايض او احدهما؟
☐نعم ☐لا	RH .40	هل استخدمت هرمونات أنثوية بديلة لمدة شهرين أو أكثر لعلاج هبات انقطاع الدورة أو لتخفيف أعراضها؟ **الإجابة (لا) ، انتقل للسؤال44**
|___|___|	RH .41	كم كان عمرك عندما بدأت استخدام الهرمونات البديلة؟
|__|__| سنة	RH .42	لو جمعنا الفترة التي استخدمت فيها الهرمونات البديلة ما مجموع الفترة ؟
|___|___|	RH .43	كم كان عمرك عندما توقفت عن استعمال الهرمونات البديلة؟
	HS .44	هل سبق أن أجريت أي من فحوصات الثدي التالية ؟ **(متعدد الإجابات)** **0- لم أجر أي فحص – انتقل للسؤال 49** **1- فحص ثدي شعاعي (ماموغرافي)** **2- أولتراساوند** **3- فحص ذاتي** **نعم** / **لا**
|___|	HS .45	ما هو سبب إجراء الفحص؟ (مفتوح) ----------
|___|___|	HS .46	كم كان عمرك في أول مرة أجريت فيها فحص الثدي؟
|___|___|	HS .47	كم عدد مرات فحص الثدي التي قمت بها خلال الخمس سنوات الماضية؟
|___|___|	HS .48	كم كان عمرك عندما أجريت آخر فحص للثدي؟
|___|	HS .49	هل خضعت لأي من العمليات التالية: **(متعدد الإجابات)** **0- لم أتعرض** **1- خزعة من الصدر** **2- إزالة كتلة من الصدر** **3- إزالة كاملة للثدي** **نعم** / **لا**
|__,__|	HS .50	ما هو طولك؟ (بالمتر)
|___|___|	HS .51	كم وزنك حاليا؟ (كغم)
	HS .52	هل تناولت أيا من الحبوب التالية لمدة 6 أشهر فأكثر؟ **0- لا شيء** **1- Aspirin** **2- Digoxin** **3-Metformin** **نعم** / **لا**
☐نعم ☐لا	FH .53	هل أصيبت إحدى قريباتك بسرطان الثدي أو هي مصابة به حاليا؟ **الإجابة (لا) انتقل للسؤال55**

	FH .54	من من قريباتك مصابة بسرطان الثدي أو أصيبت؟

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

☐نعم ☐لا	FH .55	هل عانى أو يعاني أحد أقربائك من نوع آخر من السرطان؟ **الإجابة (لا) انتقل للسؤال 57**
	FH .56	من من أقربائك عانى او يعاني نوعا آخر من السرطان؟

	مريض1	**مريض 2**	**مريض 3**	**مريض 4**
أ. صلة القرابة				
ب.نوع السرطان				
ج.العمر عند التشخيص				

	FH .57	هل عانيت أو تعانين من التالية؟

	(نعم)	**(لا)**	**الدواء 1**	**الدواء 2**
0 - لا أعاني				
1. ارتفاع ضغط الدم				
2. امراض القلب و الاوعية				
3. امراض الحساسية				
4. امراض الغدد				
5. هشاشة العظام				
6. أمراض مفاصل				
7. دهنيات الدم				
8. أمراض مناعية				
9. ا سكري				
10. أخر				

☐نعم ☐لا	DM .58	هل أنت مشخصة كمريضة سكري؟ **الإجابة (لا) ، انتقل للسؤال** 64
|___|___|	DM .59	كم كان عمرك عندما شخصت كمريض سكري لأول مرة ؟
|____|	DM .60	آخر مرة فحصت فيها نسبة السكر في الدم ، كم كانت النتيجة؟
	DM .61	ما هي أدوية السكري التي تتناولينها أو تناولتها؟ و ما هي المدة بالسنوات ؟

نوع الدواء	**نعم**	**لا**	**كم مرة يوميا**	**متى بدأت؟ سنة**	**متى توقفت؟ سنة**
0. لا أتناول حاليا					
1. Metformin					
2. Gluben (Glibenclamide)					
3. Amaryl (Glimipiride)					
4. Novonorm (Repaglinide)					

		.5 Januent (Sitagliptin + Metformin) .6 Eucreas (Vildagliptin + Metformin) .7 Actos (Pioglitazone) .8 Galvus (Vildagliptin) .9 Gluco-Rite (Glipizide) .10 Lantus (insulin glargine) .11 NovoRapid (insulin aspart) .12 Mixtard (insulin human) .13 NovoMix (insulin aspart) .14 Victoza (liraglutide) .15 دواء آخر (حددي) **نوع الدواء** / **نعم** / **لا** / **كم مرة يوميا** / **متى بدأت** / **متى توقفت**
☐نعم ☐لا	LS .62	هل طبيعة عملك تتطلب منك القيام بنشاط بدني شاق مثل : (الحمل الثقيل والحفر ورشة بناء - التي تسبب تعرق شديد وزيادة في ضربات القلب والتنفس لمدة لا تقل عن10 دقائق في اليوم؟ **الإجابة (لا) ، انتقل للسؤال 65**
|___|	LS .63	كم يوما من أيام الأسبوع العادي تقومين بمثل هذا النشاط (البدني الشاق) كجزء من عملك؟
|___| ساعة	LS .64	كم من الوقت(ساعة) تقضينه في القيام بهذا النشاط البدني الشاق في اليوم الواحد كجزء من عملك
☐نعم ☐لا	LS .65	هل طبيعة عملك يتطلب منك القيام بنشاط بدني متوسط مثل (المشي السريع أو حمل أشياء خفيفة - التي تسبب تعرق بسيط وزيادة قليلة في ضربات القلب والتنفس) لمدة 10 دقائق على الأقل في اليوم ؟ **الإجابة (لا) انتقل للسؤال 68**
|___|	LS .66	كم يوما من أيام الأسبوع العادي تقومين بمثل هذا النشاط (البدني المتوسط) كجزء من عملك؟
|___| ساعة	LS .67	كم من الوقت (ساعة) تقضينه في القيام بهذا النشاط البدني المتوسط في اليوم الواحد كجزء من عملك
☐نعم ☐لا	LS .68	هل تذهبين مشيا على الأقدام للتنقل من والى الأماكن (الزيارات ، التسوق ، العمل). لمدة لا تقل عن 10 دقائق متواصلة على الأقل في كل مرة؟ **الإجابة (لا) انتقل للسؤال** 71
|___|	LS .69	في الأسبوع العادي كم يوما تمشين لمدة لا تقل عن 10 دقائق في كل مرة للتنقل من والى هذة الأماكن ؟
|___| دقيقة	LS .70	بالمتوسط كم من الوقت (دقيقة) تمشين في كل مرة للتنقل من والى هذه الأماكن
☐نعم ☐لا	LS .71	هل تقوم في وقت فراغك بنشاط بدني شديد شاق كالرياضة مثل: الجري بسرعة أو حمل اشياء ثقيلة ، الحفر ، العمل في المزرعة أو ورشة بناء) لمدة 10 دقائق مستمرة على الأقل؟ **الإجابة (لا) انتقل للسؤال** 74
|___|	LS .72	في الأسبوع العادي كم يوما تقومين بممارسة هذه الأنشطة البدنية الشديدة ؟
|___| ساعة	LS .73	في اليوم العادي: كم من الوقت (ساعة) تقومين بممارسة الأنشطة البدنية الشديدة ؟
☐نعم ☐لا	LS .74	هل تقومين في وقت فراغك بنشاط بدني متوسط الشدة للمحافظة علي اللياقة لمدة لا تقل عن 10 دقائق مستمرة في اليوم ؟ (المشى السريع او السباحة او ركوب دراجة او لعب الكرة الطائرة) **الإجابة (لا) انتقل للسؤال 77**
|___|	LS .75	كم يوما في الأسبوع العادي تقومين بممارسة هذه الأنشطة البدنية المتوسطة؟
|___| ساعة	LS .76	في اليوم العادي: كم من الوقت (ساعة) تقومين بممارسة الأنشطة البدنية المتوسطة.؟

|___| ساعة	LS .77	في اليوم العادي كم من الوقت (ساعة) تمضين جالسة أو مستلقية (ما عدا وقت النوم) تشمل الجلوس في العمل ، او القراءة ، او مشاهد ة التلفزيون أو التطريز أو اعمال يدوية ، أو الكومبيوتر ..الخ
☐نعم ☐لا	LS .78	هل سبق وان تناولت مشروباً كحولياً؟ (مثل البيرة ، النبيذ ، الويسكي) خلال الاثنى عشر شهراً الماضية ؟ **الإجابة (لا) ، انتقل للسؤال 82**
|___|	LS .79	في المتوسط: كم يوما تشربين المشروبات الكحولية في الأسبوع ؟
|___|	LS .80	عندما تشربين الكحول: في المتوسط كم كأسا تشربين في المرة الواحدة؟
|___|___|	LS .81	كم كان عمرك عندما تناولت الكحول للمرة الأولى ؟
☐نعم ☐لا	LS .82	هل تدخنين حاليا أي نوع من أنواع التبغ التالية مثل السجائر أو السيجار أو الغليون.....الخ ما عدا الأرجيلة سأسألك لاحقا عليها **الإجابة لا ، انتقل للسؤال 87**
☐نعم ☐لا	LS .83	هل تدخنين أيا من هذه الأنواع السابقة (السجائر أو السيجار او الغليون...) يوميا؟
|___|___|	LS .84	كم كان عمرك عندما بدأت التدخين؟
|___| سنة	LS .85	كم من الوقت مضى عليك وأنت تدخنين؟
	LS .86	في المتوسط كم من منتجات التبغ التالية تدخنين يوميا خلال الثلاثين يوما الماضية ؟ اذا كانت الاجابة انه لا يدخن نوع معين من التالي نكتب كلمة (لا شيء) او صفر كتابة وليس ارقاما

	العدد يوميا
أ- السجائر	
ب- السجائر اللف المصنعة يدويا	

	عدد المرات		
	في اليوم	**في الاسبوع**	**في الشهر**
ج- غليون			
د- سيجار			

☐نعم ☐لا	LS .87	هل يدخن أحد والديك (حاليا أو في السابق)
☐نعم ☐لا	LS .88	في الماضي هل سبق لك التدخين يوميا؟ **الإجابة لا انتقل للسؤال** 90
|___|	LS .89	كم كان عمرك عندما توقفت عن التدخين ؟
☐نعم ☐لا	LS .90	هل تدخنين الارجيلة حاليا ؟ **الإجابة لا ، انتقل للسؤال** 94
	LS .91	كم مرة تدخن الارجيلة ؟ **إجابة واحدة فقط**

	اليوم	**الاسبوع**	**الشهر**
عدد المرات			

|___|	LS .92	كم كان عمرك عندما بدأت تدخين الأرجيلة ؟
|___|	LS .93	كم سنة دخنت الأرجيلة؟
☐نعم ☐لا	LS .94	هل تلبسين حمالة الصدر (ستيانة أو صدرية) أثناء النوم؟
☐نعم ☐لا	LS .95	هل استخدمت حرام الكهرباء بشكل دوري خلال حياتك؟

	LS .96	هل تتناول أي من التالية :

	لا يتناول أو < مرة / الشهر	1-3/ الشهر	مرة / أسبوع	2-4/ أسبوع	5-6/ اسبوع	مرة / اليوم	2-3/ اليوم	4-5/ اليوم
بيتزا								
حليب								
كيك أو معجنات								
بسكويت								
شيبس او بوب كورن								
مكسرات								
مشروبات غازية دايت								
مشروبات غازية عادي								
برغر او كرات لحم								
سمك او تونا								
دجاج								
فول سوداني								
بطاطا								
سلطات								
بيض								
جبنة								
خبز ابيض								
خبز اسمر								
زبدة								

☐نعم ☐لا	LS .97	هل عندك أي فكرة عن مسببات سرطان الثدي؟
	LS .98	ماذا برأيك يسبب سرطان الثدي؟ (مفتوح) ----------

فقط للمشخصات بسرطان الثدي - من الملف المرضي

____/__	99	**ما تاريخ التشخيص؟**
	100	**ما نوع السرطان ؟**
|___|	101	**كيف تم اكتشاف الإصابة بسرطان الثدي؟** **1- ظهور أعراض المرض 2- بواسطة إجراء مسح وقائي 3- عن طريق الصدفة**
|___|	102	**في أي مرحلة من المرض تم التشخيص؟**
|___|	103	**ما نوع العلاج الذي تعرضت له ؟ (متعدد الإجابات)** **1- اشعاعي 2- هرموني 3- عملية جراحية 4- كيماوي 5- غير ذلك**
☐لا ☐نعم	104	**ان خضعت لعملية استئصال، هل تعرضت لعلاج كيماوي قبل عملية الأستئصال؟**
|___|___|	105	**كم كان وزنك قبل التشخيص؟**

Appendix 2

Consent Form in Arabic

الموافقة عن علم للمشاركة في دراسة

سرطان الثدي و علاقته بالسكري

لقد طلب مني المشاركة في دراسة تبحث في أسباب سرطان الثدي، و علاقته بمرض السكري و أدويته. حيث سأشارك كحالة (مريض الذي شُخِصَ بهذا المرض) ، أو كمجموعة ضابطة

(شخص سليم لا يعاني من هذا المرض). هذه الدراسة سوف تقارن المعطيات الشخصية ، والتاريخ الطبي ، وسبل التعرض. وذلك للناس المصابين وغير المصابين بالمرض. هذه الدراسة لديها القدرة على اكتشاف معلومات هامة عن أسباب هذا المرض.

سوف يطلب مني الإجابة على أسئلة تتعلق بنفسي ، و تفاصيلي الطبية ، والعلاج في المستشفى بالماضي ،و عائلتي ،وأين عشت ،ووظائفي التي عملت بها ، جميع المعلومات في هذا الاستبيان ستحتفظ بطابع من السرية. المقابلة ستدوم حوالي 40 دقيقة أو أقل .

أيضا سيتم الاطلاع على نتيجة فحص السكر في الدم و فحص الثدي . المعلومات من هذه الفحوصات ستبقى سرية أيضا. ولا يوجد هناك أي آثار جانبية أخرى متوقعة من المشاركة في هذه الدراسة.

الاسم:_____

أوافق على اجراء المقابلة (التوقيع) _____

التاريخ : _____

Appendix 3

Approvals from the Palestinian Ministry of Health

State of Palestine
Ministry of Health - Nablus
General Directorate of Education in Health

دولة فلسطين
وزارة الصحة- نابلس
الإدارة العامة للتعليم الصحي

Ref.: .....
Date: .....

الرقم: عبد/٨٤٦/٢٠١٧
التاريخ: ٢٠١٧/٦/١٢

الأخ مدير عام الادارة العامة للرعاية الصحية الأولية المحترم،،،

تحية واحترام،،

الموضوع: تسهيل مهمة

لاحقا لكتابنا بتاريخ 2016/5/4 والمتعلق بتسهيل مهمة **الطالبة: امتثال الخطيب – ماجستير الصحة العامة وعلم الاوبئة- جامعة القدس**، في عمل بحث الماجستير بعنوان: " **محددات/مسببات الاصابة بمرض سرطان الثدي بين النساء المصابات بمرض السكري في فلسطين**" في الحصول على المعلومات اللازمة من خلال مقابلة مريضات لتعبئة استبانة الدراسة (بعد اخذ موافقتهم على المشاركة في البحث)، ومراجعة ملفاتهن باشراف المسؤول عن الملفات في العيادة وذلك في:

- **عيادات الرعاية الأولية في منطقة بيت لحم.**
- **عيادات الرعاية الأولية في منطقة شمال ووسط وجنوب الخليل.**

علما بأنه سيتم الالتزام بمعايير البحث العلمي والحفاظ على سرية المعلومات.

البحث تحت اشراف د. لهى الشريف.

مع الاحترام،،

د. أمل أبو هولي
مدير عام التعليم الصحي

نسخة: عميد كلية الصحة العامة المحترم/ جامعة القدس

P.O .Box: 14
TelFax: 09-2333901

ص.ب. 14
تلفاكس: 09-2333901

State of Palestine
Ministry of Health - Nablus
General Directorate of Education in Health

دولة فلسطين
وزارة الصحة- نابلس
الإدارة العامة للتعليم الصحي

Ref.: .....
Date:.....

الرقم: ٢٠١٦/٦٦٧/١٦٢
التاريخ: ٢٠١٦/٥/٤

الأخ مدير عام الادارة العامة للمستشفيات المحترم،،،
الأخ مدير عام الرعاية الصحية الأولية المحترم،،،
تحية واحترام،،

الموضوع: تسهيل مهمة طلاب

تماشياً مع سياسة وزارة الصحة المتعلقة بتعزيز التعاون مع الجامعات والمؤسسات الأكاديمية بإتاحة فرص التدريب أمام الطلبة والخريجين والباحثين في المؤسسات الوطنية وإسهاماً في تنمية قدراتهم.

يرجى تسهيل مهمة **الطالبة: امتثال توفيق الخطيب – ماجستير الصحة العامة- جامعة القدس**، في عمل بحث الماجستير بعنوان: "**محددات/ مسببات الاصابة بمرض سرطان الثدي بين النساء المصابات بمرض السكري في فلسطين**"، لذا يرجى تسهيل مهمتها في الحصول على المعلومات اللازمة من خلال مقابلة مجموعة من المرضى (بعد اخذ موافقتهم على المشاركة في البحث) ومراجعة ملفاتهم وتعبئة استمارة منهم، في **مستشفى بيت جالا الحكومي**، ومقارنتها مع مجموعة غير مصابة بهذا المرض في عيادات الرعاية الصحية الأولية، **وذلك في عيادات الرعاية الصحية الأولية في منطقة الجنوب**. علما بأنه سيتم الالتزام بمعايير البحث العلمي والحفاظ على سرية المعلومات.

مع الاحترام،،

دولة فلسطين وزارة الصحة
الإدارة العامة للتعليم الصحي

د. أمل أبو عوض
مدير عام التعليم الصحي

نسخة: عميد كلية الصحة العامة المحترم/ جامعة القدس

P.O .Box: 14
TelFax: 09-2333901

ص.ب. 14
تلفاكس: 09-2333901

State of Palestine
Ministry of Health - Nablus
General Directorate of Education in Health

دولة فلسطين
وزارة الصحة- نابلس
الإدارة العامة للتعليم الصحي

Ref.: .....
Date:.....

الرقم: ٢٠١٦/٦٦٧/١٦٦
التاريخ: ٢٠١٦/٥/٤

الأخ مدير عام الادارة العامة للمستشفيات المحترم،،،
الأخ مدير عام الرعاية الصحية الأولية المحترم،،،
تحية واحترام،،

الموضوع: تسهيل مهمة طلاب

تماشياً مع سياسة وزارة الصحة المتعلقة بتعزيز التعاون مع الجامعات والمؤسسات الأكاديمية باتاحة فرص التدريب أمام الطلبة والخريجين والباحثين في المؤسسات الوطنية وإسهاماً في تنمية قدراتهم.

يرجى تسهيل مهمة **الطالبة: امتثال توفيق الخطيب – ماجستير الصحة العامة- جامعة القدس**، في عمل بحث الماجستير بعنوان: "**محددات/ مسببات الاصابة بمرض سرطان الثدي بين النساء المصابات بمرض السكري في فلسطين**"، لذا يرجى تسهيل مهمتها في الحصول على المعلومات اللازمة من خلال مقابلة مجموعة من المرضى (بعد اخذ موافقتهم على المشاركة في البحث) ومراجعة ملفاتهم وتعبئة استمارة منهم، في **مستشفى بيت جالا الحكومي**، ومقارنتها مع مجموعة غير مصابة بهذا المرض في عيادات الرعاية الصحية الأولية، **وذلك في عيادات الرعاية الصحية الأولية في منطقة الجنوب**. علما بأنه سيتم الالتزام بمعايير البحث العلمي والحفاظ على سرية المعلومات.

مع الاحترام،،

دولة فلسطين وزارة الصحة
الإدارة العامة للتعليم الصحي

د. أمل أبو عوض
مدير عام التعليم الصحي

نسخة: عميد كلية الصحة العامة المحترم/ جامعة القدس

P.O .Box: 14
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ص.ب. 14
تلفاكس: 09-2333901