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Al-Quds University

Factors associated with prostate cancer in the south area of West Bank: A retrospective case-control study

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Jerusalem – Palestine

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DEDICATION

To my dear parents

To my dear wife Waheebeh

To my dear children: Tyma, and the twins Ahmad and Rafeef.

To all my friends

DECLERATION

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 thesis (or any part of the same) has not been submitted for a higher degree to any other university or institution.

Yasser Naiem Qasem

Jerulsalem

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ABSTRACT

Background: In Palestine, prostate cancer accounts for 5.3% of all cancer cases. The age-standardized incidence rate is 20 per 100,000 populations. It has a mortality of 4.8% of all cancer in year 2010. Literature shows that congenital factors, lifestyle factors and environmental exposures were found to determine the risk of its occurrence.

In Palestine, there is no screening program for prostate cancer. Also, no study investigated the risk/protective factors for this serious disease. Therefore, we planned this study to be a baseline study for decision makers to help in planning for a national strategy that can help in preventing this cancer and/or its complications.

Aim and objectives: This study aimed to identify the determinants of prostate cancer in the south area of West bank. Its objectives were to determine the associations between the various lifestyles, socio-demographic, family history of malignancy, and patients' health status with the risk of developing prostate cancer.

Study methodology: This retrospective case-control study investigated 60 prostate cancer cases (study cases), and 60 study controls. All prostate cancer cases attending Beit Jala outpatients' cancer clinic and the oncology department during the study period were approached with similar number of controls from the same age group (non-cancer/ no urology patients) attending the same hospital but for other reasons. The diagnosis of prostate cancer of each case was ascertained by his medical record. All the study controls underwent a PSA test as an indicator of prostate activity that reflects no cancer presence. Both study cases and control group were interviewed while waiting in the outpatient clinic assembly of BJGH. Part of the study cases were interviewed in the day care unit while receiving their prescribed chemotherapy. A structured questionnaire was used to collect information about the Sociodemographic, lifestyle factors, health status of the participants, and there family history of malignancy. Cases medical records were reviewed to extract the confirmation of prostate cancer diagnosis, the date of diagnosis, and to get the baseline PSA test results.

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

the two groups (study cases and control group). Conditional logistic regression models were used in the multivariate analysis.

Results: Analysis of study cases data showed that the mean age of the participants was 67.7 ±9.5 (mean± SD), and 83.3% of the study cases were older than 60 years of age. Of them, 73.3% were married, and 46.7% had 5- 8 children. Of the study cases 13.3% was illiterate, and 16.7% had completed higher education and 58.3% lived in urban areas. Also, 53.3% were unemployed, 46.7% of those working in the past 10 years had office work and 68.3% had a monthly income ≤3000 NIS.

On the other hand, analysis of control group data showed that the mean age of the participants was 65.7 ±10 (mean± SD), and 71.7% of the control group were older than 60 years of age. Of them, 86.7% were married, and 60% had 5- 8 children. Of the control group 11.7% was illiterate, and 11.7% had completed higher education and 48.3% lived in urban areas. Also, 55% were unemployed, 45% of those working in the past 10 years had office work and 88.3% had a monthly income ≤3000 NIS

The multivariate analysis showed that married men are at lower risk for prostate cancer development by five folds. Also low family monthly income increased the risk by ten folds to have prostate cancer. Moreover, weekly consumption of cruciferous vegetables (AOR=0.15), homemade cheese (AOR=0.10), and processed meat (AOR=0.19) showed a significant inverse association with prostate cancer occurrence. In addition, type 2 diabetes mellitus and cardiovascular diseases appeared to increase the risk of prostate cancer by three folds and seven folds, respectively.

Conclusion: This is the first study that deals with prostate cancer epidemiology in the West Bank. The study yielded important results regarding the determinants of prostate cancer in Palestine. We were able to show how patients' lifestyle factors determined the risk/protection of prostate cancer in Palestine. These findings stress on the fact that modification of lifestyle might play an important role in this disease prevention.

This study recommends an establishment of a national program for early detection of prostate cancer. Also, give attention to the modifiable lifestyle factors that increase or decrease the risk of this type of cancer among the Palestinian population. This study stimulates the conduction of more specified studies in the field of male cancers in Palestine.

العوامل المرتبطة بمرض سرطان غدة البروستات في جنوب الضفة الغربية: دراسة استعادية دراسة الحالات و الشواهد.

اعداد: ياسر قاسم

اشراف د. نهى الشريف

ملخص الدراسة

خلفية الدراسة: يشكل مرض سرطان غدة البروستات ما نسبته 5.3% من إجمالي حالات السرطان المسجلة في فلسطين. كما ويشكل معدل الوقوع 20 حالة لكل مئة ألف من السكان. ويساهم مرض سرطان غدة البرستات ب4.8% من حالات الوفيات بسبب مرض السرطان في فلسطين. وقد وجد أن عوامل نمط الحياة والعوامل البيئية لها علاقة بحدوث هذا النوع من السرطان.

لا يوجد في فلسطين برنامج للكشف المبكر عن مرض سرطان غدة البرستات. وكذلك لا يوجد أي دراسة في فلسطين تهدف للكشف عن العوامل المساعدة على حدوثه أو العوامل التي قد تقي من حدوثه في المجتمع الفلسطيني. لذلك فقد قمنا بعمل هذه الدراسة لتكون قاعدة ارتكاز لصناع القرار لمساعدتهم في التخطيط لمنهجية وطنية تساعد على منع حدوث هذا المرض أو الحد من مضاعفاته.

أهداف الدراسة: هدفت هذه الدراسة لمعرفة محددات مرض سرطان البروستات في مناطق جنوب الضفة الغربية. كما هدفت إلى معرفة العلاقة بين نمط الحياة والعوامل الاجتماعية والسكانية وتاريخ العائلة المرضي والوضع الصحي العام وخطر الإصابة بمرض سرطان غدة البرستات.

منهجية الدراسة: دراسة استعادية (دراسة الحالات و الشواهد). حيث تم إشراك 60 حالة مصابة بمرض سرطان البروستات و60 حالة مقارنة غير مصابة بهذا المرض. المشاركون في هذه الدراسة كانوا جميعهم من المرضى المراجعين لعيادات مستشفى بيت جالا الحكومي أو من المرضى الذين تم إدخالهم لأقسام المستشفى المختلفة. خضع كافة المشاركين من مجموعة المقارنة لفحص PSA -وهو فحص يستخدم عادة للكشف عن سرطان غدة البروستات- للتأكد من خلوهم من هذا المرض. كلا المجموعتين (المصابين وغير المصابين) تمت مقابلتهم أثناء الانتظار في قاعة الانتظار في العيادات الخارجية لمستشفى بيت جالا الحكومي أو أثناء تلقيهم للعلاج الكيميائي في وحدة العناية اليومية.

وقد تم استخدام استبانة أعدت خصيصا لهذه الدراسة لجمع معلومات عن الحالة الاجتماعية السكانية ونمط الحياة والحالة الصحية العامة والتاريخ العائلي لمرض السرطان من المشاركين في هذه الدراسة. كما تم تفحص الملف الطبي للمريض للتأكد من التشخيص وتاريخ التشخيص و نتيجة فحص PSA عند التشخيص.

التحليل الإحصائي: تم إدخال جميع البيانات وتحليلها باستخدام برنامج SPSS-IBM. ففي المرحلة الأولى، تم حساب التكرارات لجميع المتغيرات، وقد عرضت البيانات في جداول وأشكال بيانية، أما في المرحلة الثانية تم فحص العلاقة بين سرطان غدة البروستات و عوامل الإختطار عند مستوى الدلالة الاحصائية ($P < 0.1$)، كما تم حساب فحص

العامل المستقل (t-test) لرصد اختلاف مستويات PSA بين حالات الدراسة والمجموعة الضابطة، كذلك تم حساب نموذج الانحدار اللوجيستي المتعدد لجميع المتغيرات عند الدلالة الاحصائية (P <0.1) في تحليل وحيد المتغير للحصول على نسبة الترجيح ودرجة الثقة (90%).

النتائج الرئيسية: بينت نتائج الدراسة أن معدل أعمار المشاركين في هذه الدراسة كان 66 عاما بانحراف معياري بلغ 9.7. وقد كان 77% من المشاركين أكبر من 60 عاما. 80% من المشاركين كانوا متزوجين وكانت أعمارهم عند الزواج بين 21 و 25 عاما. كما أظهرت الدراسة أن 53% من المشاركين كان عندهم 5-8 أولاد وأن 12% كانوا أميين و 14% قد أنهوا التعليم الجامعي و53% كانوا من سكان المدن. وكشفت الدراسة أن 54% من المشاركين كانوا من غير العاملين وأن 45.8% كانوا يعملون في وظائف مكتبية خلال العشرة أعوام الأخيرة. وكان الدخل الشهري ل 78% من المشاركين 3000 شيكل أو أقل.

وقد أظهرت تنائج تحليل نموذج الانحدار اللوجستي المتعدد أن الرجال المتزوجين كانوا أقل عرضة لخطر الإصابة بمرض سرطان غدة البروستات بخمس مرات مقارنة بغير المتزوجين. كذلك تبين أن الدخل الشهري المنخفض قد يزيد من خطر الإصابة عشر مرات أكثر من الدخل المرتفع. أما بالنسبة للعوامل الغذائية فقد تبين أن كلا من الخضروات الصليبية و الجبنة البلدية و اللحوم المصنعة قد تقلل من خطر الإصابة بمرض سرطان غدة البروستات. ومن الناحية الصحية للمشاركين فقد تبين أن مرض السكري النوع الثاني وأمراض القلب و الشرايين قد تزيد من احتمال حدوث مرض سرطان غدة البروستات 3 و 4 مرات على التوالي.

الخاتمة: تعتبر هذه الدراسة الأولى في فلسطين التي تتطرق لموضوع مرض سرطان غدة البروستات من حيث المحددات. وقد تمخضت هذه الدراسة عن نتائج هامة تخص محددات هذا المرض بين رجال المجتمع الفلسطيني. حيث تبين أن عوامل نمط الحياة للمشاركين في هذه الدراسة حددت مدى احتمال الإصابة أو الحماية من هذا المرض. وهذه النتائج تؤكد أن عوامل نمط الحياة التي يمكن التحكم بها تلعب دورا هاما في الوقاية من هذا المرض.

وتوصي هذه الدراسة بضرورة تفعيل برنامج وطني للكشف المبكر عن مرض سرطان غدة البروستات. كما توصي أيضا بأهمية الالتفات الى عوامل نمط الحياة التي يمكن التحكم بها والتي قد تحد من انتشار هذا المرض بين الرجال في المجتمع الفلسطيني. وتحث هذه الدراسة الباحثين على إجراء دراسات أكثر عمقا وتفصيلا في هذا المجال لزيادة القدرة على السيطرة على هذا المرض.

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List of abbreviations

BJGH	**Biet Jala Governmental Hospital**
CI	**Confidence Interval**
MOH	**Ministry of Health**
OR	**Odds Ratio**
PC	**Prostate Cancer**
PSA	**Prostatic Specific Antigen**
SPSS	**Statistic Package for Social Sciences**
5ARI	**5 Alpha-Reductase Inhibitor**
EPIC	**European Prospective Investigation into Cancer and Nutrition**
IGF-1	**Insulin-like Growth Factor**
ENT	**Ear, Nose, Throat**

Chapter One: Introduction

1.1 Background

Prostate cancer has the highest prevalence of any nonskin cancer in the human body, with similar likelihood of neoplastic foci found within the prostates of men around the world regardless of diet, occupation, lifestyle, or other factors. Essentially all men with circulating androgens will develop microscopic prostate cancer if they live long enough (Bostwick et al., 2004). Prostate cancer is a disease of increasing significance worldwide. In many industrialized nations such as the United States, it is one of the most common cancers and among the leading causes of cancer deaths (Jemal et al., 2006).

In developing countries prostate cancer is less common compared to developed countries, however its incidence and mortality has been on the rise (Delongchamps et al., 2007). In countries of the Middle-East, prostate cancer is already a problem, and the incidence rates in Arab countries are ranging from 4-30 per 100,000 men (Salim et al., 2009). The prevalence in Palestine is 28.9/100,000, while in Jordan is 72.9 per/100,000, and in Israel is 15.5 per 100,000 (Sharaf, 2006). In Palestine, the prostate cancer accounts for 5.3% of all cancer cases, and its mortality is 4.8% of all cancer deaths during year 2010 (PHIC, 2010).

In many countries, prostate cancer screening programs for the early detection of the disease is done by using either PSA or the digital rectal examination. Early detection of prostate cancer using screening increases the probability of cure and decreases the mortality from prostate cancer (Villers et al., 2003). In the United States, approximately 90% of prostate cancers are detected by means of screening (Hoffman, 2011). But early results from two large, randomized, controlled trials of screening were inconsistent; an European study showed a modest decrease in prostate-cancer mortality, whereas a U.S. study showed no decrease in prostate-cancer mortality (Hoffman, 2011). In Palestine, there is no screening program for prostate cancer**.**

Prostate cancer can be prevented more easily than other types of cancers. However, there is no proven prostate cancer prevention strategy. But reducing the risk of prostate cancer is possible by making healthy choices, such as exercising and eating a healthy diet. In addition to changing lifestyle with healthy food and reducing dairy and calcium intake, taking certain drugs (5ARI) may prevent cancer development (Chung, 2010).

Also, other factors such Lycopene, vegetables intake, and green tea consumption was shown to be protective factors that may decrease the risk of prostate cancer (Kamel et al., 2006, Cohen et al., 2000, Kolonel et al., 2000, Gann et al., 1999, Bettuzzi et al., 2006, Wu and Yu, 2006). Moreover, avoiding risk factors such as smoking, being overweight and lack of exercise may help prevent prostate cancer (Gong et al., 2006, Hosseini et al., 2010, Kamel et al., 2006, Putnam et al., 2000, Rodriguez et al., 1997, Tyagi et al., 2010). Increasing protective factors such as quitting smoking, eating a healthy diet and exercising may also help in preventing prostate cancer. However, in Palestine no study investigated the risk factors for prostate cancer.

1.2 Study Problem

Very few local researchers have been concerned with the determinants when discussing the epidemiology of prostate cancer. Early detection of prostate cancer indictors such as PSA testing which has been used in screening programs proved to be a good method of preventing cancer itself or progression of prostate cancer into more complicated cancer (Schroder et al., 2012).

However, protecting men at risk for prostate problems, such as smokers, obese men, alcohol drinkers, physically inactive men and others, was proved to be a tool of prevention from cancer. Therefore, it is very important to specify the factors that play a role as risk/protective factors among men in Palestine. This data is not available in Palestine, which makes it a rich area for research. Results of this research will be the baseline for any future plans in the area of prevention of prostate cancer; whether primary to avoid its occurrence or secondary such as screening for early detection.

1.3 Justification of the study

Men health and its research is a neglected area in Palestine compared to women's health research although prostate cancer counts for 5.3% of all cancer cases, and located in the sixth rank among cancer types affecting Palestinian population, and the third among men(PHIC, 2010). Remarkably, the incidence rate in Palestine is higher than the surrounding countries. For example in Egypt the age-standardized incidence rate is 4.4 per 100,000 populations (Baade et al., 2009,Salim et al., 2009). While in Jordan the age-standardized incidence is 11.2 per 100,000 populations (Salim et al., 2009). In Palestine the age-standardized incident rate is 20 per 100,000 populations (Salim et al., 2009). Prostate cancer mortality in Palestine is 4.8% of all cancer deaths during 2010(PHIC, 2010). The incidence of prostate cancer was fluctuated in the last decade showing unstable decrease until the year 2004, and then was stabilized until year 2008, but increases dramatically until 2011. Figure 1 shows the distribution of percentages of the reported cases of prostate cancer in Palestine between years 2000-2011.

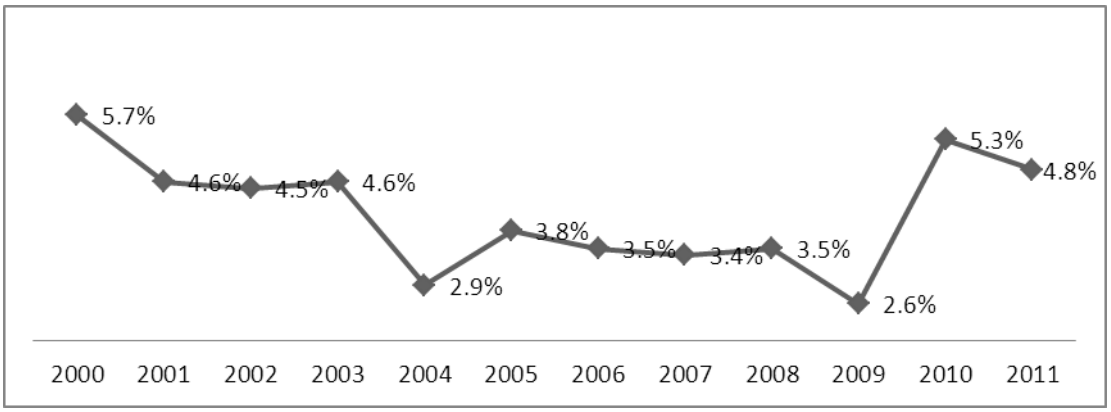

Figure1: Distribution of the reported Prostate Cancer between years 2000-2011 (MOH reports 2000-2011)

The American cancer society, the Cancer research in the United Kingdom, and Mayo clinic showed similar models of risk factors for prostate cancer. These risk factors are divided into two main categories: endogenous factors, and exogenous factors (Bostwick et al., 2004). Endogenous factors such as family history of malignancy, especially prostate and breast cancers (Ghadirian et al., 1997,Hayes et al., 1995,Lesko et al., 1996a), race (Haas et al., 2008,Bostwick et al., 2004,Thompson et al., 2006), age (Haas et al., 2008,Bostwick et al., 2004,Thompson et al., 2006), and hormones (Barba et al., 2009,Bostwick et al., 2004). Exogenous factors such as lifestyle factors including diet, smoking, and physical activity (Tyagi et al., 2010,Severson et al., 1989,Kolonel et al., 2000,Kamel et al., 2006,Gann et al., 1999,Cohen et al., 2000), environmental exposure to certain agents like endocrine disrupting chemicals (EDCs) and cadmium, and occupation especially in farming and rubber industry (Fritschi et al., 2007,Sass-Kortsak et al., 2007,Zeegers et al., 2004). Also diseases and health status were included in the models of risk factors for prostate cancer. Obesity (Fritschi et al., 2007,Gong et al., 2006,Putnam et al., 2000) and diabetes (Giovannucci et al., 1998,Gong et al., 2006,Kasper et al., 2009,Rodriguez et al., 2005). Other factors that may influence the occurrence of prostate cancer include: energy intake, marital status, anthropometry, sexual activity, and vasectomy (Hosseini et al., 2010,Rodriguez et al., 2007,Park et al., 2007,Holt et al., 2008).

Till to date, no study in Palestine investigated the risk factors for developing prostate cancer among men.

Services presented to prostate cancer patients such as treatment and follow up are mainly offered in the cancer care centers distributed along the West Bank. BJGH in the central and the southern districts, and Al Watani Governmental Hospital in the northern districts are the two MOH governed cancer care centers. On the other hand Augusta Victoria Hospital in Jerusalem is a private referral hospital where limited services are presented to the prostate cancer patients. Treatment services including surgery, chemotherapy, and hormone therapy are delivered in the MOH governed cancer care centers. Since the radiation therapy is not available in the MOH governed cancer care centers, the prostate cancer patients who need such a treatment are referred to Augusta Victoria Hospital. Prostate cancer patients follow up are presented in the oncology clinics of the MOH governed cancer care centers. In some limited cases the patient may be referred to neighboring countries to get the needed services.

However, there is no active screening or preventive program dealing with prostate cancer in the Palestinian community. Hence, any research that focuses on the issue of prostate cancer determinants would be of great value to help start establishing national programs dealing with the risk and protective factors of prostate cancer. This study is a baseline study for decision makers to help in planning for a national strategy that can help in preventing this cancer and/or its complications.

1.4 Aim of the study

To identify the determinants of prostate cancer in the south area of West Bank.

1.5 Objectives

- To determine the relationship between lifestyle factors and prostate cancer.
- To relate the sociodemographic factors with prostate cancer.
- To determine the association between family history of malignancy and prostate cancer.
- To determine the association between health status and prostate cancer.

1.6 Expected outcome

The study of the determinants of prostate cancer would increase the knowledge about these determinants and reveals the specific risk and protective factors in the Palestinian community, as well as address the groups at risk. Thereafter, programs are made focusing directly on these at risk groups and working on the specific risk and protective factors in the large community.

1.7 Thesis chapters

The thesis consists of six chapters. Chapter one is the introductory chapter, it contains a background of the study, study justification and problem statement, aim and objectives. Chapter two includes the literature review of the international and local studies and research that were conducted concerning prostate cancer epidemiology and risk/protective factors. Chapter three includes the study theoretical and conceptual frame work. In chapter four the study setting, methods, tools, sampling methods, field work, design, statistical analysis and ethical considerations are included. In chapter five all study results are presented. Finally, in chapter six the study findings are discussed and compared to the reviewed literature, and also the study conclusion and recommendations are presented.

Chapter Two: Literature review

2.1 Introduction

In this chapter the epidemiology of prostate cancer and the literature related to prostate cancer epidemiology will be presented.

2.2 Epidemiology of prostate cancer

2.2.1 Prostate cancer epidemiology worldwide

Prostate cancer is a disease of increasing significance worldwide. In many industrialized nations such as the United States, it is one of the most common cancers and among the leading causes of cancer deaths (Jemal *et al*., 2006). In developing countries it may be less common, however its incidence and mortality has been on the rise (Delongchamps *et al*., 2007).

The International Agency for Research on Cancer (IARC) represents the most up to date information on the incidence of prostate cancer around the world. The highest rates are from the United States with 124.8 per 100,000 where African American men have an incidence rate of 185.4 per 100,000 and White Americans have an incidence rate of 107.8 per 100,000. China has some of the lowest incidence rates (1.7 per 100,000). Among European countries, the incidence in Austria (region of Tyrol) is the highest (100.1 per 100,000) compared to those reported from the eastern region (66.4 per 100,000). Tyrol has an organized, very thoroughly conducted screening program for prostate cancer (Haas *et al*., 2008).

The clinical incidence, mortality, and prevalence of prostate cancer varies among various geographical regions of the world. The approach to screening, early detection initiatives and availability of treatment modalities has a major impact on disease epidemiology (Haas *et al*., 2008).

2.2.2 Prostate cancer epidemiology in Arab world

Cancer is already a major problem in the Arab community, and the changing in the lifestyle and aging will raise the burden of this disease otherwise corrective strategies are adopted including reliable screening and early detection methods.

The age-standardized incidence rates were ranging from 3 per 100,000 in Egypt to 20 per 100,000 in Palestine (Salim *et al*., 2009). An Egyptian case-control study pointed to sausages, butter and natural ghee as risk factors, while vegetables were protective (Kamel *et al*., 2006).

Screening for prostate cancer is not regular in most Arab countries. However, in some public awareness campaigns the PSA test offered as a screening method. More efforts should be done to minimize the burden of prostate cancer in the Arab communities.

2.2.3 Prostate cancer epidemiology in Palestine

In Palestine, prostate cancer accounts for 5.3% of all cancer cases. The age-standardized incident rate is 20 per 100,000 populations. It has a mortality of 4.8% of all cancer in year 2010 (PHIC, 2010).

Screening for prostate cancer is not a common practice in the Palestinian health care system like other Arab countries although the incidence of prostate cancer among Palestinians is higher than most neighboring communities.

2.3 Dietary factors and prostate cancer risk

In table 2.1, we reviewed studies that were concerned with foods and dietary items that might be associated with prostate cancer among different populations worldwide.

A case-control study in USA revealed that legumes negatively associated with prostate cancer (Kolonel et al., 2000b). A prospective cohort study in Hawaii-USA showed that rice and tofu were both associated with decreased risk of prostate cancer (Severson *et al*., 1989).

Similar finding were shown in studies in less economically developed countries. In Egypt a case control study concluded that vegetables were protective factors from prostate cancer. When comparing the amount of vegetables consumed weekly, eating three or more

servings of vegetables per week had an inverse significant association with prostate cancer (OR= 0.59) compared to eating less than one serving per week. Eating tomatoes and cruciferous vegetables (OR=0.41) were found to have the greatest effect among all vegetables (Kamel *et al*., 2006).

Meat and fat was shown in several studies as risk foods for prostate cancer. In two case-control studies in India (Kamel *et al*., 2006) and Egypt (Kamel *et al*., 2006,Tyagi *et al*., 2010), meat, fish, and fat appeared to be positively associated with prostate cancer risk. Similarly, in a prospective cohort study in USA red and processed meat consumption found to be risk factors for prostate cancer (Kamel *et al*., 2006,Sinha *et al*., 2009). On the contrary, prospective cohort study in Europe found no association between dietary fat and prostate cancer risk(Crowe et al., 2008a). Another randomized placebo-controlled trial in USA and Canada no association of any nutrient or supplement with prostate cancer risk were found (Kristal *et al*., 2010).

2.4 Tobacco smoking and prostate cancer risk

Table 2.2 shows a summary of studies that investigated the association of smoking and prostate cancer.

A case-control study in Iran showed a non-significant increased risk for prostate cancer by seven times among cases using pipe smoking compared to controls (Hosseini *et al*., 2010). Another population-based case-control study conducted in Delhi, India suggested that the odds ratio of current and past filter cigarette smoker had higher risk for development of prostate cancer but the association was statistically significant only in the case of past smokers (OR: 5.16, 95% CI: 2.13-12.51) (Tyagi *et al*., 2010).

In a prospective cohort study in USA (Hsing *et al*., 1990) the authors concluded that tobacco may be a risk factor for prostate cancer. As the relative risk for smokeless tobacco users in form of shewing was (RR=2.1 95% CI, 1.1-4.1), and the smoking relative risk (RR=1.8 95% CI, 1.1-2.9). While as, in two case-control studies in Egypt (Kamel *et al*., 2006) and in USA (Yu *et al*., 1988) there were no differences in smoking habits between cases and controls.

In the studies that dealt with the effect of smoking on survival of prostate cancer patient, a prospective mortality study in USA (Rodriguez *et al*., 1997) suggested that cigarette smoking was associated with fatal prostate cancer with a rate ratio (RR=1.34 95% CI,

1.16-1.56). Another prospective cohort study in USA (Hsing *et al*., 1990,Watters *et al*., 2009) reported an increased risk of fatal prostate cancer (hazard ratio=1.69, 95%CI: 1.25, 2.27). That mean smoking may adversely affect survival in prostate cancer patient.

2.5 Alcohol consumption and prostate cancer risk

Table 2.3 shows a summary of studies that studied the effect of alcohol consumption on prostate cancer risk.

A prospective cohort studies in USA (Kalish *et al*., 2000,Watters *et al*., 2010) revealed that the risk of non-advanced prostate cancer was 25% higher for men consuming six or more drinks daily (hazard ratio=1.25, 95% CI, 1.13, 1.37), 19% higher for men consuming three to six drinks daily, and 6% higher for men consuming up to three drinks daily, compared with nondrinkers. This study found no association between alcohol consumption and advanced prostate cancer, but an inverse association with fatal prostate cancer was found.

Another Prospective cohort study in USA reported that moderate liquor consumption was associated with a significant 61-97% increased risk of prostate cancer(Sesso *et al*., 2001). While as, beer and wine were not associated with prostate cancer risk. And a case-control study conducted in Canada (Sharpe and Siemiatycki, 2001) reported that the risk of prostate cancer increased with increasing cumulative consumption of alcoholic beverages (beer, wine, and spirits) adjusted odds ratio was (OR=1.8 95% CI, 1.2-2.7). Beer consumption showed the strongest association with increased prostate cancer risk adjusted odds ratio (OR=1.6 95% CI, 0.9-2.5).

In contrast, there were two case-control studies in USA (Schoonen *et al*., 2005,Yu *et al*., 1988), and one prospective cohort study in Europe (Rohrmann *et al*., 2008) concluded that there was no association between alcohol consumption and risk of prostate cancer. Nevertheless, a case-control study in USA (Schoonen *et al*., 2005) suggested that the red wine consumption may be associated with reduced relative risk of prostate cancer Each additional glass of red wine consumed per week showed a statistically significant 6% decrease in relative risk (OR=0.94 95% CI, 0.90–0.98).

2.6 Physical activity and prostate cancer risk

Table 2.4 shows a summary of some studies that investigated the relation between physical activity and risk of prostate cancer.

A prospective cohort study in Norway (Nilsen *et al*., 2006) suggested that recreational physical activity was associated with reduced risk of advanced and fatal prostate cancer. The relative risk of those who reported high physical activity compared to those with no physical activity was (RR=0.64 95% CI, 0.43-0.95) for advanced prostate cancer, and (RR=0.67 95% CI, 0.43-0.95) for fatal prostate cancer.

While as, a prospective cohort study conducted in the Netherland (Zeegers *et al*., 2005) showed no association between physical activity and risk of prostate cancer. Neither in non-occupational physical activity for more than 90 minutes daily versus less than 30 minutes daily the rate ratio was (RR=1.01 95% CI, 0.81-1.25), nor for history of sport participation versus never participated (RR=1.04 95% CI, 0.90-1.22). And in another prospective cohort study in USA (Liu *et al*., 2000) the authors reported that the relative risks for prostate cancer associated with exercise vigorous enough to work up a sweat were 1.0 (referent) for frequency less than once per week, 1.02 (95% CI : 0.82–1.26) for once per week, 1.07 (95% CI : 0.90–1.27) for 2–4 times per week, and 1.11 (95% CI : 0.90–1.36) for 5+ times per week.

In a prospective cohort study in USA ((Liu *et al*., 2000,Patel *et al*., 2005) findings suggested that the risk of overall prostate cancer between men who reported high physical activity and men who reported no physical activity was not different, the hazard rate ratio was (RR=0.90, 95% CI, 0.78-1.04). But the increased incidence among those who reported no physical activity was observed in aggressive prostate cancer (RR=0.69 95% CI, 0.52-0.92).

Similarly, in a case-control study in Sweden (Wiklund *et al*., 2008) which reported that comparing the most active with the least active men, total physical activity was not associated with either localized disease (OR = 0.95, 95% CI = 0.67–1.34) or advanced disease (OR = 1.19, 95% CI = 0.83–1.71). Another case-control study in Italy (Pierotti *et al*., 2005) revealed similar results as the odds ratio for prostate cancer for the highest level of physical activity men compared with the lowest level men was (0.94 95% CI, 0.75–1.17). In addition, a case-control study in Canada (Friedenreich *et al*., 2004) provided inconsistence evidence for the association between physical activity and prostate cancer risk.

2.7 Occupational factor and prostate cancer risk

Table 2.5 summarizes some studies that investigated the correlation between occupation and risk of prostate cancer.

a prospective study in Sweden (Dich and Wiklund, 1998) revealed that pesticides applicator are at increased risk of prostate cancer with incidence ratio (IR=1.13 95% CI, 1.02-1.24). Likewise, a retrospective study (Sharma-Wagner *et al*., 2000) also in Sweden revealed the same result. In addition, this retrospective study (Sharma-Wagner *et al*., 2000) suggested that exposure to cadmium, herbicides, and fertilizers during the occupational activity increase the risk of prostate cancer.

On the other hand, two case-control studies in Australia (Fritschi *et al*., 2007) and in Canada (Sass-Kortsak *et al*., 2007) did not provide strong evidences for significant occupational risk factors for prostate cancer. Likewise, a prospective study in Netherland (Zeegers *et al*., 2004) found that the association between occupation and risk of prostate cancer can not be confirmed with confidence. (See table 2.5 for more details).

2.8 Family History of prostate cancer and prostate cancer risk

In table 2.6 shows the summary of studies that investigated the relation between family history of prostate cancer and the risk of prostate cancer.

Two case-control studies one in Massachusetts, USA (Lesko *et al*., 1996a) and another in Maryland (Steinberg *et al*., 1990) reported that prostate cancer risk was two times more among those who had father or brother with prostate cancer, odds ratio was (OR=2.3 95% CI, 1.7-3.3) and relative risk was (RR=2 95% CI, 1.2-3.3) respectively. Moreover, the risk was increased when two or more relatives had a history of prostate cancer (OR=3.9 95% CI, 1.7-52). Another population based case-control study in Canada (Ghadirian *et al*., 1997) revealed that 15% of the cases reported at least one relative with history of prostate cancer, compared with 5% of the controls, giving a relative risk (RR=3.3 95% CI, 2.18-5.05). Likewise, in USA case-control study (Hayes *et al*., 1995) the odds ratio was (OR=3.2 95% CI, 2.0-5.0) among those with first degree relatives with history of prostate cancer.

Similarly, two prospective cohort studies conducted in USA (Cerhan *et al*., 1999,Kalish *et al*., 2000) concluded that the family history of prostate cancer was a strong risk factor of

prostate cancer. Where the relative risk values of prostate cancer associated with family history were (RR=3.2 95% CI, 1.8-5.7) for both studies. (See table 2.6 for more details).

2.9 Obesity and prostate cancer risk

Table 2.7 shows studies that aimed to find the relation between obesity and prostate cancer risk.

A randomized placebo-controlled trial in the USA (Gong *et al*., 2006) suggested that obesity increase the risk of high grade prostate cancer (OR=1.29 95% CI, 1.01-1.67), but decreases the risk of low grade prostate cancer (OR=0.82 95% CI, 0.69-0.98). Two retrospective studies in the USA (Putnam *et al*., 2000) and in Japan (Masuda *et al*., 2012) found that the obesity is a risk factor for more clinically significant prostate cancer.

A prospective study conducted in USA (Rodriguez *et al*., 2007) reported that BMI was inversely associated with low grade prostate cancer risk (RR=0.84 95% CI, 0.66-1.06). But BMI was positively associated with high grade and fatal prostate cancer risk (RR=1.2 95% CI, 0.96-1.55) and (RR=1.54 15% CI, 1.06-2.23).

A prospective study in USA (Hernandez *et al*., 2009) reported that men who gained more than 10 lb have an increased risk of advanced prostate cancer with relative risk (RR=2.12 95% CI, 1.19-3.78). Likewise, another prospective cohort study in Europe (Pischon *et al*., 2008) concluded that abdominal adiposity may increase the risk of advanced prostate cancer. (See table 2.7 for more details).

Weak positive effects were observed for high body mass index on prostate cancer risk was the conclusion of a case-control study (Yu *et al*., 1988) conducted in USA.

2.10 Diabetes and prostate cancer risk

Table 2.8 shows the summary of studies that investigated the relation of diabetes and prostate cancer risk.

In prospective cohort study in USA (Kasper *et al*., 2009) the authors concluded that the risk of prostate cancer was reduced among diabetic men comparing with non-diabetic men with a hazard ratio (HR=0.83 95% CI, 0.74-0.94). This study also concluded that the protective effect of diabetes is more obvious as the time since the diabetes diagnosis is longer, in men who diagnosed since 6-15 years ago the hazard ratio (HH=0.75 95% CI, 0.61-0.93), and since more than 15 years ago (HH=0.78 95% CI, 0.63-0.96). Similar

results was revealed from another prospective cohort study in USA (Rodriguez *et al*., 2005) where the risk of prostate cancer was reduced in men who diagnosed as diabetics since 4 years and more (Rate Ratio=0.67 95% CI, 0.60-0.75). But another prospective cohort study in USA (Giovannucci *et al*., 1998) reported that the significant reduction in risk of prostate cancer was among diabetic men who diagnosed as diabetic since more than 10 years (RR=0.54 95% CI, 0.37-0.78).

A randomized placebo-controlled study in USA (Gong *et al*., 2006) revealed that diabetes was associated with a 47% (OR=0.53 95% CI, 0.34-0.83) reduced risk of low-grade prostate cancer and a 28% (OR= 0.72 95%- CI, 0.55-0.94) reduced risk of high-grade prostate cancer. Likewise in another prospective cohort study in USA (Waters *et al*., 2009b) where the risk of prostate cancer was reduced among diabetic men compared with non-diabetic (RR=0.81 95% CI, 0.74-0.87). (See table 2.8 for more details).

2.11 Sexually transmitted diseases and prostate cancer risk

Table 2.9 summarizes studies that deal with the relation between sexually transmitted diseases and prostate cancer risk.

A case-control study in USA (Dennis *et al*., 2009) reported that herpes simplex virus-2 (HSV2) was associated with increased risk of prostate cancer (OR=1.6 95% CI, 1.05-2.44), the association was increased more obviously if the HSV2 was diagnosed before 60 months before prostate cancer diagnosis (OR=2.04 95% CI, 1.26-3.29). Another two case-control studies one in USA (Huang *et al*., 2008) and one in Cuba (Fernandez *et al*., 2005) both revealed an association of sexually transmitted disease and increased risk of prostate cancer in cases with one or more STDs (OR=1.3 95% CI, 1.0-1.6), (OR=1.7 95% CI, 1.1-2.5) respectively. A case-control study in USA (Sarma *et al*., 2006) concluded that the previous diagnosis of gonorrhea and prostatitis in black men increased the risk of prostate cancer (OR=1.78 95% CI, 1.13-2.79) and (OR=4.93 95% CI, 2.79-8.74) respectively.

A meta analysis study (Taylor *et al*., 2005) reported that significant elevated odds ratios for prostate cancer were demonstrated for any STDs (1.48, 95% confidence interval [CI] 1.26–1.73), gonorrhea (1.35, 95% CI 1.05–1.83), and human papillomavirus (1.39, 95% CI 1.12–2.06).

On the other hand, a prospective cohort study in USA (Sutcliffe *et al*., 2006) concluded that there is no statistically significant association between gonorrhea and syphilis and risk of prostate cancer. Although, a positive association was observed between prostatitis and risk of prostate cancer in younger group of men aged less than 59.

Table 2.1: Studies on dietary factors and risk of prostate cancer.

Authors	Location and date	Study design	Sample size	Conclusion
(Kristal *et al*., 2010)	USA & Canada	Randomized placebo-controlled trial	9559	No associations of any nutrient or supplement with prostate cancer risk overall.
(Tyagi *et al*., 2010)	Delhi 1998-2000	Population based case-control	303:606	Cigarette smoking, alcohol consumption and dietary items like meat and fish to be considered as potential risk factors for PC.
(Sinha *et al*., 2009)	USA 1995-2003	Prospective cohort study	175343	Red and processed meat positively associated with PC.
(Crowe et al., 2008b)	Europe 2008	Prospective cohort study	142520	No association between dietary fat and PC risk.
(Kamel *et al*., 2006)	Egypt, 2004	Hospital based case-control study	50:50	Fats in the form of butter/natural ghee, sausages might induce PC. Regular consumption of vegetables has a protective effect from PC.
(Cohen *et al*., 2000)	Seattle, WA.	Population based case-control study	628:602	High consumption of vegetables, particularly cruciferous vegetables, is associated with a reduced risk of prostate cancer.
(Kolonel et al., 2000a)	USA & Canada	Multicenter case-control study	1619:1618	Legumes (not limited to soy products) and certain categories of vegetables may protect against PC.
(Gann *et al*., 1999)	USA 1982-1995	Nested Case-Control Study	578:1294	Increased consumption of tomato products, as part of a diet generally rich in fruits and vegetables, might reduce PC risk.
(Severson *et al*., 1989)	Hawaii 1965-1986	Prospective cohort study	7999	Increased consumption of rice and tofu might decrease risk for PC Consumption of seaweeds was associated with an increased for PC No relationship with total fat and total protein.

Table 2.2: Studies on tobacco smoking and prostate cancer risk.

Authors	Location and date	Study design	Sample size	Conclusion
(Hosseini *et al*., 2010)	Iran 2005-2008	Population based case-control study	137:137	Potential risk factors for prostate cancer in exploratory analysis included family history of prostate cancer, history of other cancer, prostatitis, alcohol consumption, pipe or hookah smoking, walking to work, duration of occupational physical activity, intensity of occupational physical activity, body mass index, and older age.
(Tyagi *et al*., 2010)	Delhi 1998-2000	Population based case-control study	303:606	Past smoking and current alcohol consumption significantly increased the risk of prostate cancer.
(Watters *et al*., 2009)	USA 2009	Prospective cohort study	283312	Current and former smokers may be at decreased risk of being diagnosed with prostate cancer, and current smokers are at an increased risk of dying from prostate cancer
(Kamel *et al*., 2006)	Egypt, 2004	Hospital based case-control study	50:50	The present study did not reveal any significant differences in smoking habits between cases and controls
(Rodriguez *et al*., 1997)	USA 1982-1991	Prospective mortality study	450,279	Suggest that smoking may adversely affect survival in prostate cancer patients
(Hsing *et al*., 1990)	USA 1966-1986	Prospective cohort study	17,633	The findings add to limited evidence that tobacco may be a risk factor for prostate cancer
(Yu *et al*., 1988)	USA 1988	Case-control Study	1162:3124	Cigarette smoking and alcohol consumption were not related to the risk of prostate cancer.

Table 2.3: Studies on alcohol consumption and prostate cancer risk

Authors	Location and date	Study design	Sample size	Conclusion
(Watters *et al*., 2010)	USA 1995-2005	Prospective cohort study	294707	Higher consumption of alcohol modestly increases non-advanced prostate cancer risk.
(Rohrmann *et al*., 2008)	Europe 1992-2000	Prospective cohort study	142607	No association between the consumption of alcohol and prostate cancer in this cohort of European men.
(Schoonen *et al*., 2005)	USA	Case-control study	753:703	The consumption of beer or liquor is not associated with prostate cancer. There may be, however, a reduced relative risk associated with increasing level of red wine consumption.
(Sharpe and Siemiatycki, 2001)	Montreal Canada 1979-1985	Case-control study	399:476	The result was consistent with an increase in the risk of prostate cancer due to alcohol consumption.
(Sesso *et al*., 2001)	Harvard USA 1988-1993	Prospective cohort study	7612	The study found a positive association between moderate alcohol consumption and risk of prostate cancer.
(Yu *et al*., 1988)	USA 1988	Case-control study	1162:3124	Cigarette smoking and alcohol consumption were not related to the risk of prostate cancer.

Table 2.4: Studies on physical activity and prostate cancer risk.

Authors	Location and date	Study design	Sample size	Conclusion
(Wiklund *et al*., 2008)	Sweden 2001-2003	Population based case-control study	1449:1118	These findings do not support the hypothesis that physical activity uniformly protects against prostate cancer development.
(Nilsen *et al*., 2006)	Norway 1984-2001	Prospective cohort study	29110	Recreational physical exercise is associated with reduced risk of advanced prostate cancer and prostate cancer death
(Zeegers *et al*., 2005)	Netherland 1986-2005	Prospective cohort study	58279	The results of this current study do not support the hypothesis that physical activity protects against prostate cancer in men
(Pierotti *et al*., 2005)	Italy 1991-2002	Case-control study	1294:1451	No significant association was found between leisure-time physical activity and prostate cancer risk.
(Patel *et al*., 2005)	USA 1997-2002	Prospective cohort study	72,174	No association between recreational physical activity and overall prostate cancer risk but suggest physical activity may be associated with reduced risk of aggressive prostate cancer
(Friedenreich *et al*., 2004)	Alberta Canada 1997-2000	Case-control study	988:1063	This study provides inconsistent evidence for the association between physical activity and prostate cancer risk
(Liu *et al*., 2000)	USA	Prospective Study	22071	This study do not support the hypothesis that increased physical activity reduces the risk of prostate cancer

Table 2.5: Studies on occupational factor and prostate cancer risk.

Authors	Location and date	Study design	Sample size	Conclusion
(Fritschi *et al*., 2007)	Australia 2001-2002	Population-based case–control study	1066:1272	The association of prostate cancer with several occupational exposures, including metals, PAHs, oils, pesticides, fertilizers and wood were examined in this study. No evidence that any of these exposures were found strong occupational risk factors for prostate cancer.
(Sass-Kortsak *et al*., 2007)	Ontario, Canada 1995-1998	Population-based case-control study	760:1632	This study does not provide strong evidence for significant occupational risk factors for prostate cancer.
(Zeegers *et al*., 2004)	The Netherlands 1986-1993	Prospective cohort study.	58,279	None of the previously investigated associations between occupation and prostate cancer risk could be confirmed with confidence in this prospective study.
(Sharma-Wagner *et al*., 2000)	Sweden	Retrospective Cohort Study	36269	Our results suggest that farmers; certain occupations and industries with exposures to cadmium, herbicides, and fertilizers; and men with low occupational physical activity levels have elevated prostate cancer risks
(Dich and Wiklund, 1998)	Sweden	Prospective cohort study	20025	An increased risk among pesticide applicators was found. Pesticide applicators are more exposed to pesticides than farmers in general

Table 2.6: Studies on family history of prostate cancer and prostate cancer risk.

Authors	Location and date	Study design	Sample size	Conclusion
(Kalish *et al*., 2000)	Massachusetts 1987-1997	Prospective cohort study	1149	An association was found between prostate cancer incidence and a family history of prostate cancer.
(Cerhan *et al*., 1999)	Iowa 1999	Prospective cohort study	1557	Family history of prostate cancer is a strong prostate cancer risk factor, and also family history of breast cancer may be a prostate cancer risk factor.
(Ghadirian *et al*., 1997)	Canada 1989 - 1993	Population-based case-control study	640:639	This study provides further evidence of familial aggregation of prostate cancer.
(Lesko *et al*., 1996b)	Massachusetts 1992-1994	Population-based case-control study	563:703	Prostate cancer risk was increased among men who reported a history of this cancer in either their fathers or brothers.
(Hayes *et al*., 1995)	USA 1986-1989	Population-based case control study	981:1315	A genetic component to prostate cancer is suggested by the familial tendency to prostate cancer observed in our case-control study.
(Steinberg *et al*., 1990)	USA 1982-1989	Case-control study	691:640	The male relatives of men with prostate cancer are at increased risk for development of the disease

Table 2.7: Studies on obesity and prostate cancer risk.

Authors	Location and date	Study design	Sample size	Conclusion
(Masuda *et al*., 2012)	Japan	Retrospective cohort study	3966	Japanese men within the overweight body mass index range who have an elevated prostate-specific antigen level have a significant risk of harboring prostate cancer, especially high-grade disease
(Hernandez *et al*., 2009)	USA 2009	Prospective cohort study	83879	Adiposity and changes in adiposity between younger and older adulthood influence the development of prostate cancer.
(Pischon *et al*., 2008)	Europe 1992-2000	Prospective cohort study	129,502	Abdominal adiposity may be associated with an increased risk of advanced prostate cancer. This association may be stronger among individuals with lower BMI
(Rodriguez *et al*., 2007)	USA 1982-2003	Prospective cohort study	69991	Obesity increases the risk of more aggressive prostate cancer and may decrease either the occurrence or the likelihood of diagnosis of less-aggressive tumors.Men who lose weight may reduce their risk of prostate cancer
(Gong *et al*., 2006)	USA	Randomized placebo controlled trial	18880	Obesity increases the risk of high-grade but decreases the risk of low-grade prostate cancer.
(Putnam *et al*., 2000)	Iowa USA 1989-1995	Retrospective cohort study	1572	Obesity is a risk factor for more clinically significant prostate cancer.
(Yu *et al*., 1988)	USA 1988	Case-control study	1162:3124	Weak positive effects of borderline statistical significance were observed for high body mass, low physical exercise on prostate cancer risk.

Table 2.8: Studies on Diabetes and prostate cancer risk.

Authors	Location and date	Study Design	Sample size	Conclusion
(Kasper *et al*., 2009)	USA 1988-2004	Prospective cohort study	4511	Diabetes is associated with reduced prostate cancer risk.
(Waters *et al*., 2009a)	USA 1993-2005	Prospective cohort study	86303	Diabetes is a protective factor from prostate cancer across population.
(Gong *et al*., 2006)	USA	Randomized placebo-controlled trial	18880	Diabetic men are at lower risk of prostate cancer.
(Rodriguez *et al*., 2005)	USA1992-2001	Prospective cohort study	72670	Diabetes is associated with reduced risk of prostate cancer but only several years after diagnosis of diabetes.
(Giovannucci *et al*., 1998)	USA 1986-1994	Prospective cohort study	1401	Diabetes is associated with reduced prostate cancer risk.

Table 2.9: Studies on sexually transmitted diseases and prostate cancer risk.

Authors	Location and date	Study design	Sample size	Conclusion
(Dennis *et al*., 2009)	USA 1993-2003	Nested Case-control study	267:267	An association between prostate cancer and HSV-2 infection in sera collected 7 years before diagnosis.
(Huang *et al*., 2008)	USA 1993-2001	Nested Case-control study	868:1283	No consistent association with specific STIs and a borderline association with any versus none.
(Sarma *et al*., 2006)	USA, Michigan 1996-2001	Case-control study	129:703	A history of gonorrhea infection and prostatitis increased the odds of prostate cancer.
(Dennis *et al*., 2009,Sutcliffe *et al*., 2006)	USA 1992-2002	Prospective cohort study	36033	Gonorrhea, Syphilis, and clinical prostatitis do not seem to be risk factors for prostate cancer.
(Fernandez *et al*., 2005)	Cuba 2998-2000	Case-control study	273:254	The study supports the hypothesis that an infectious factor related to sexual behavior could be involved in the occurrence of prostate cancer.
(Taylor *et al*., 2005)		Meta-analysis		Significant elevated ORs for prostate cancer were demonstrated for any STDs, gonorrhea, and human papillomavirus

Chapter Three: Conceptual Framework

3.1 Introduction

In This chapter the study major definitions, international prostate cancer models, and study conceptual framework will be presented.

3.2 Prostate Cancer Definition

Prostate cancer is a disease in which cells in the prostate gland become abnormal and start to grow uncontrollably, forming tumors (Carroll, 2001). Along with the testicles and the seminal vesicles, the prostate secretes the fluid that makes up semen. The prostate is about the size of a walnut and lies just behind the urinary bladder. A tumor in the prostate interferes with proper control of the bladder and normal sexual functioning. Often the first symptom of prostate cancer is difficulty in urinating. However, because a very common, non-cancerous condition of the prostate, benign prostatic hyperplasia (BPH) also causes the same problem, difficulty in urination is not necessarily due to cancer.

Cancerous cells within the prostate itself are generally not deadly on their own. However, as the tumor grows, some of the cells break off and spread to other parts of the body through the lymph or the blood, a process known as metastasis. The most common sites for prostate cancer to metastasize are the seminal vesicles, the lymph nodes, the lungs, and various bones around the hips and the pelvic region. The effects of these new tumors are what can cause death (Beers, 2004).

As of the early 2000s, prostate cancer is the most commonly diagnosed malignancy among adult males in Western countries. Although prostate cancer is often very slow growing, it can be aggressive, especially in younger men. Given its slow growing nature, many men with the disease die of other causes rather than from the cancer itself.

3.3 Prostate cancer determinants models

The American cancer society, the Cancer research in the United Kingdom, and the Mayo clinic showed similar models of risk and protective factors for prostate cancer. These determinants are divided into two main categories: endogenous factors, and exogenous factors (Bostwick et al., 2004).

Endogenous factors such as family history of malignancy, race, hormones, and age. Exogenous factors such as lifestyle factors including diet, smoking, and physical activity, environmental exposure to certain agents like endocrine disrupting chemicals (EDCs) and cadmium, and occupation especially in farming and rubber industry. Also diseases and health status especially diabetes mellitus and obesity were included in the models of determinants for prostate cancer. Other factors that have been included in some models are: energy intake, marital status, anthropometry, sexual activity, and vasectomy (American cancer society, 2012).

Figure 3.1 illustrates the study conceptual model which built upon the above theoretical models for prostate cancer determinants and beholds:

- Lifestyle factors include: smoking, diet, physical activity, alcohol consumption.
- Socio-demographic factors include: age, occupation, marital status, and education.
- Health status factors include: diabetes mellitus, obesity, history of other malignancy, and history of sexually transmitted diseases.
- Family history of malignancy factors include: family history of prostate cancer, family history of breast cancer, and family history of other malignancy.

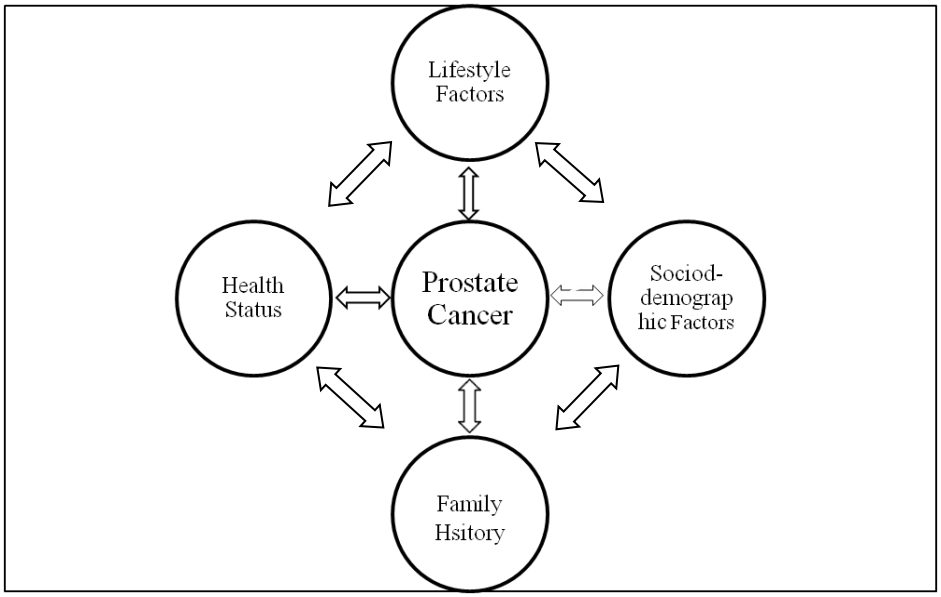

Figure 3.1: Study conceptual framework

3.4 Prostate Cancer risk factors

3.4.1 Age

The strongest known risk factor for prostate cancer is age, with very low risk in men under 50 years of age and increasing risk with increasing age. The older the man the higher the risk and this ties in the post-mortem results that showed an approximately 80% of men by age 80 were shown to have cancer cells in their prostate (Sakr et al., 1996).

A widely accepted paradigm in cancer research holds that the development of cancers is rate limited by the occurrence of oncogenic mutations. In particular, the exponential rise in the incidence of most cancers with age is thought to reflect the time required for cells to accumulate the multiple oncogenic mutations needed to confer the cancer phenotype.

In the United States, >70% of all cases of prostate cancer are diagnosed in men>65 years of age. It is relatively rare for prostate cancer to be diagnosed in men <50 years of age, but after this age, the incidence and mortality rates increase exponentially(Haas et al., 2008). The probability of developing prostate cancer increases from 0.005% among individuals aged<39 years to 2.2% (1 in 45) for those aged 40 to 59 years and 13.7% (1 in 7) for those aged 60 to 79 years. Overall, the lifetime risk of developing prostate cancer is 16.7% (1 in 6) (Crawford, 2003).

3.4.2 Family history and ethnicity

Individuals from the same family and ethnicity share part of their genetic makeup and some of their environmental exposures (e.g., diet, carcinogens, socioeconomic status, and lifestyle) during part of their lives. Except for a common variant found in 3 case-control series of European ancestry (Hayes et al., 1995), no other major susceptibility genes for prostate cancer have been consistently found across populations.

Many cancers begin when one or more genes in a cell are mutated, creating an abnormal protein or no protein at all. The information provided by an abnormal protein is different from that of a normal protein, which can cause cells to multiply uncontrollably and become cancerous.

A person may either be born with a genetic mutation in all of their cells (germline mutation) or acquire a genetic mutation in a single cell during his or her lifetime. An acquired mutation is passed on to all cells that develop from that single cell (called a somatic mutation). Most prostate cancers (about 75%) are considered sporadic, meaning that the damage to the genes occurs by chance after a person is born. Prostate cancer that runs in a family, called familial prostate cancer, is less common (about 20%) and occurs because of a combination of shared genes and shared environmental or lifestyle factors. Hereditary (inherited) prostate cancer is rare (about 5%) and occurs when gene mutations are passed within a family from one generation to the next

A family history of prostate cancer is one of the strongest known risk factors for this disease. It has been estimated that 5-10% of all prostate cancer cases and 30-40% of early-onset cases (men diagnosed <55 years) are caused by inherited susceptibility genes (Bratt, 2002).

Risk increases two to three times for men with a first-degree relative diagnosed with prostate cancer. If the relative is <60 years old at diagnosis or more than one relative is affected (at any age), the individual's risk is four times the average. These factors combine so that if more than one relative is affected by early-onset prostate cancer, the risk is increased by seven-fold (Johns and Houlston, 2003).

A strong family history of breast cancer may also affect a man's risk of prostate cancer, particularly if the family members were diagnosed under the age of 60. In particular, germline mutations in the breast cancer susceptibility gene, BRCA2, can predispose men to prostate

cancer, increasing the risk of developing prostate cancer up to five times in men overall, and more than seven times in men aged under 65 (Hemminki and Chen, 2005).

3.4.3 Diet

Fat is the dietary component most frequently associated with PC risk. The fatty acids in dietary fats can be divided into essential and non-essential fatty acids. The essential fatty acids are all unsaturated and derived directly from diet. These essential fatty acids can be divided into omega-6 and omega-3 fatty acids(Meyer and Gillatt, 2002).

At a cellular level the essential fatty acids thought to influence cellular proliferation, the immune system and the potential of tumor to invade locally and metastasize(Rose and Connolly, 1991).They are also reported to affect prostoglandin synthesis and sex hormone levels; Androgenic stimulation may be a causative factor in the development of prostate cancer. Testosterone is converted to its active form DHT by 5α-reductase, DHT is necessary for the continuing growth and development of PC(Meyer and Gillatt, 2002). Different fatty acids have been shown to have beneficial and detrimental effects on the growth of prostate cancer cells. For example omega-6 fatty acid stimulates the growth of an androgen-unresponsive PC line, whilist the omega-3 fatty acid inhibits the growth of this PC cell line(Rose and Connolly, 1992,Pandalai et al., 1996).

The association between vitamin D deficiency and PC was initially noted in a study which showed a correlation between exposure to sunlight and rates of prostate cancer death(Schwartz and Hulka, 1990). Calcitriol; the biologically active compound of vitamin D significantly inhibits PC cell lines(Skowronski et al., 1993).

3.4.4 Alcohol

The mechanisms by which alcohol consumption exerts its carcinogenic effect have not been defined fully, although plausible events include: a genotoxic effect of acetaldehyde, the main metabolite of ethanol; increased estrogen concentration, which is important for prostate carcinogenesis; a role as solvent for tobacco carcinogens; production of reactive oxygen species and nitrogen species; and changes in folate metabolism (Boffetta and Hashibe, 2006).

3.4.5 Smoking

A higher risk of fatal prostate cancer in smokers compared to non-smokers has been shown in some studies (Rohrmann et al., 2007,Gong et al., 2008). However, no clear trends were shown with number of cigarettes smoked per day or between current, ex- and never-smokers. Two

large studies concluded that smoking is not likely to be linked to either the incidence or mortality of prostate cancer (Doll et al., 2005).

3.4.6 Bodyweight

Obesity is a major health problem worldwide and has been linked to several major cancers. However, it is not yet proven to be an important risk factor for prostate cancer.

A recent meta-analysis reported a small borderline significant increase in prostate cancer risk with increasing body mass index (BMI). Some cohort studies indicate that obese men are at greater risk of dying from prostate cancer while others have reported a reduced risk of localized prostate cancer in men with a high BMI. Although the evidence is far from clear for prostate cancer, general health advice would be for men to maintain a healthy BMI.

3.4.7 Medications

Aspirin use appears to slightly reduce the risk of prostate cancer, several meta-analyses and large studies show. NSAIDs in general (including aspirin) may have a small protective effect, but overall the evidence is not clear. Ibuprofen does not appear to have a protective effect. Because of the potential adverse consequences of high intake of aspirin, such as gastrointestinal hemorrhage, it would not be recommended as a prophylactic measure.

In the laboratory, cholesterol-reducing statins have shown possible chemopreventive properties against cancers. However, a systematic review of observational studies and randomized controlled trials found that statin-use was not associated with short-term cancer risk but an association with reduced longer-term risk cannot yet be ruled out. Further research on the effects of statin-use on prostate cancer risk or the course of the disease is needed.

3.4.8 Sexually transmissible diseases

Sexually-transmitted diseases and prostatitis may increase the risk of prostate cancer with a 2005 meta-analysis reporting a 40% increased risk of prostate cancer in men with a history of gonorrhea or human papilloma virus infection.

3.4.9 Endogenous hormones

It has long been suggested that high circulating levels of sex hormones are associated with an increased risk of prostate cancer as most prostate cancers respond favorably to androgen-deprivation and castrated men do not develop prostate cancer. However, the most recent

worldwide re-analysis of 18 prospective studies, including the EPIC study, has shown no association between endogenous sex hormones and risk of prostate cancer overall.

Insulin-like growth factor (IGF-1) is an easily measurable protein that is involved in normal cell proliferation and death. Both a recent meta-analysis and a large Swedish study found that higher concentrations of IGF-1 were associated with an increased risk of prostate cancer with a clear dose-response relationship, as did a large case-control study.

However, other studies including EPIC have shown no association. IGF-1 levels may mediate the effects of many environmental exposures as its levels are regulated by other cancer risk factors such as bodyweight, diet and physical exercise. The relationship between several components of the IGF system and prostate cancer is undergoing further investigation.

3.5 Prostate Cancer Protective Factors

3.5.1 Tomatoes

Epidemiologic and case-control studies suggest that intake of tomatoes and tomato products is associated with a lower risk of prostate cancer (Giovannucci et al., 2002). It has been suggested that lycopene, a compound in raw and processed tomato products, may be responsible for the lower risk, although other carotenoids and phytochemicals in these products may also contribute to the benefit(Crawford, 2003). In a study of 2481 men, high levels of lycopene consumption were associated with a 16% lower risk of prostate cancer as compared with consumption of small amounts of lycopene (Giovannucci et al., 2002). A controlled dietary intervention study is needed to confirm the benefit of lycopene and tomato products. In addition, the mechanism by which lycopene may reduce risk remains to be established(Crawford, 2003).

3.5.2 Selenium

Several studies suggest that selenium, an essential trace element found largely in grains, fish, and meat, may also protect against prostate cancer(Vogt et al., 2003). In a population-based, case-controlled study of white and African American men, serum selenium was inversely associated with prostate cancer risk(Vogt et al., 2003). Men with the highest quartile of serum selenium had 29% lower risk than those in the lowest quartile. This pattern was similar for both whites and African Americans. The strongest relation was found for men with low serum

-tocopherol concentrations, suggesting that the benefit may relate to an antioxidant mechanism(Crawford, 2003).

3.5.3 Diabetes Mellitus

Men with diabetes mellitus appear to have a lower risk of developing prostate cancer. In a population-based cohort study conducted in Sweden, men hospitalized for diabetes had a 9% lower risk of prostate cancer, and those hospitalized for a diabetic complication had an 18% lower risk than men in other population-based registers (Weiderpass et al., 2002). In a hospital-based, case-control study, diabetes was associated with a 40% lower risk of prostate cancer overall and a 53% lower risk of regional or advanced prostate cancer (Rosenberg et al., 2002). This effect was found mainly in whites and Hispanics, but not in African Americans. Obesity and hyperinsulinemia are associated with diabetes, and both may reduce IGF-1 levels and alter endogenous steroid metabolism (Crawford, 2003).

Chapter four: Methodology

4.1 Introduction

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

4.2 Study setting

BJGH is a central hospital in the southern part of the West Bank. It has many vital medical specialties such as orthopedic, cardiovascular, ENT, surgery and oncology departments. Each medical specialty has an in-patient ward and out-patient clinic. All patients' records are kept in the paper filling archives presented within the hospital.

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

4.3 Study Design

This is a retrospective case-control study. The participants of this study are patients attending Biet Jala Governmental Hospital (BJGH). The ratio of study cases to control group was 1:1.

4.4 Study population

Study cases were patients attending BJGH oncology clinic and/or admitted in the oncology ward and diagnosed as having prostate cancer of any grade during the time of the study data collection period, i.e. February 2013to May 2013.

Study control group were patients attending BJGH clinics except oncology and urology clinics, and/or admitted in any ward except oncology or urology wards during the time of data collection for this study. Control group had the same ages of the study cases.

4.4.1 Study cases inclusion and exclusion criteria

- **Inclusion criteria:**

- Any male patient diagnosed with prostate cancer and the diagnosis is documented in his medical record.
- Visiting the oncology out-patient clinic and/or admitted in the oncology ward as a case of prostate cancer.
- Participants' consent to participate in the study was required.

- **Exclusion criteria**

- Any male patient diagnosed as prostate cancer case but this diagnosis is not presented in the hospital archive.
- Any male patient diagnosed as prostate cancer case but refused to sign the study consent form.

4.4.2 Control group inclusion and exclusion criteria

- **Inclusion criteria**

- Any male patient attending BJGH for receiving health care.
- Any male patient reported not to have prostate cancer or any type of malignancy and this approved by his medical record and PSA test.
- Participants' consent for the participation in the study was required too.

- **Exclusion criteria**

- Any patient reported to have any recent or previous diagnosis of any type of cancer.
- Any patient visiting the urology clinic or admitted in the urology ward.
- Any patient had an elevated PSA score testing.
- Any male patient complies with the inclusion criteria but does not accept to participate in the study by signed consent.

4.5 Study period

The study was carried out in February 2013 to May 2013. The questionnaire, the consent form, Ministry of Health approval and permission, and the logistic preparation were ready by the end of January 2013. Data collection and study population interviews started in February. After four months, the number of eligible participants that were included in the study was 60 cancer cases and 60 controls.

4.6 Sampling and sample size

Before the study implementation, when reviewing patients files of the year 2012 about 70 prostate cancer cases were seen in the oncology department. Those patients have to attend the clinics for follow up and chemotherapy sessions at least once monthly. Therefore, we expected to see at least 80% of these prostate cancer cases during the study period. Therefore, all prostate cancer patients attended BJGH during the study period were included in the study sample. Total number of study cases was 60 participants.

4.7 Data source and study tools

4.7.1 Participant's medical record

After selecting the study case participant, his medical record was explored to ascertain the prostate cancer diagnosis, date of diagnosis, and the PSA test score at the time of the diagnosis.

4.7.2 Structured interview questionnaire

A face-to-face interview questionnaire was developed using several previously validated questionnaires. The questionnaire was divided into sections to cover the study objectives. The full questionnaire, in Arabic is presented in Annex 1. The following sections cover the questionnaire and source of questionnaire parts.

- The socio-demographic section included questions about participant's age, date of birth, marital status, age at marriage, number of siblings, profession, education, residence type, residence area, religion, and monthly income(University of Southern California Consortium, 2009).
- The lifestyle section included questions about smoking habit, alcohol drinking, physical activity, diet, and complementary diet. We used the Harvard School of Public Health food

frequency questionnaires (FFQ) with some modifications such as adding some items and removing other items that irrelevant to our study objectives (Harvard School of Public Health, 2013). For the smoking and alcohol consumption we used Steps Arabic questionnaire of the WHO (WHO, 2013).

- The health status part contains questions about the participant's chronic diseases including history of diabetes mellitus type I and type II, hypertension, cardiovascular diseases, prostatic disorders, sexually transmissible diseases, and vasectomy. Also the questionnaire asked about the usage of some medications that contains statin, or aspirin, in addition to anti-diabetic and anti-hypertension drugs (University of Southern California Consortium, 2009).
- The last part of the questionnaire contained questions regarding the history of malignancy and the family history of malignancy especially prostate cancer and breast cancer**.**

Questionnaire validity, reliability and piloting:

A- Validity

The study questionnaire and its objectives were sent to three specialists in the field of oncology and public health to be evaluated. Their comments were considered in reviewing each study question.

B- Reliability

In order to check the reliability of the study questionnaire a Cronbach's Alpha Coefficient test was done for the different sections of the questionnaire excluding the sociodemographic section. The results were as follows: lifestyle section: 62%, health status section: 68%, and history of malignancy: 55%.

C-Piloting

10% of the expected study population (six cancer cases and six non-cancer patients) filled in the study questionnaire at the Augusta Victoria Hospital cancer care center. These questionnaires data were entered to the SPSS program and analyzed. Its results were not included in the study sample. Results obtained helped us modifying some questions and modify the SPSS program.

4.7.3 Prostate Specific Antigen (PSA) test

We examined the blood serum of each participant in the control group for the score of prostate specific antigen to exclude the probability of undiagnosed prostate cancer. The blood samples were collected in the same day of the interview then sent to a certified medical laboratory to be analyzed.

At the laboratory the blood samples were centrifuged for five minutes with 3500 round per minute. The instrument used for centrifuge is (Labofuge 400) manufactured by Heraeas Instruments. In regards to PSA level measurement, the laboratory used the (Elecsys 2010) manufactured by Roch/ HITACHI. The reagent used to measure the PSA level was Elecsys and cobas e analyzers ref: 04641655 manufactured by Roch Diagnostics. The quality control procedure used the PreciControl Universal level one and two, which were measured periodically.

PSA scores were considered according to the kit manufacturer values, were they are subject age dependent. Table 4.1 shows the normal PSA limit in relation to age:

Table 4.1 Prostate Specific Antigen Normal values

Age (y)	PSA Score (ng/ml)	Result
<40	<1.4	Normal
40-49	<2.19	Normal
50-59	<3.1	Normal
60-69	<4.1	Normal
>69	<4.4	Normal

4.8 Field work

Both study cases and control group were interviewed during their waiting time for clinic visit in the out-patients clinics or during their stay in the ward if they were inpatients.

Before filling the study questionnaire, study aim and objectives were clarified for the participants. After the participant accepts to participate, he signed the consent form (Annex 2).

Height and weight of each participant were measured using the scales found at the clinic of the hospital. None of the patients we interviewed was an inpatient at the time of the study. Same interviewer was performing the interviews with the cases and the controls.

As for the controls' PSA tests, the blood samples were collected in the phlebotomy room in the same floor of outpatient clinic. A laboratory technician collected an amount of 3-5 ml of blood from the control participants who agree to participate in the study by signing the consent form specially designed for this study. The laboratory technician used an 18G winged scalp vain set, a disposable vaccutainer and a plain tube for each subject. The collected samples were stored in Ice Box and moved to a certified laboratory for analysis. The time between collecting the samples and reaching the lab did not exceed four hours.

4.9 Statistical analysis

IBM SPSS 20 was used to enter, clean and analyze the collected data.

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

To examine the binary associations, univariate analysis was done using the cross tabulation and the significance of Pearson and Fisher exact chi square-as needed- at *P*-value 0.1 was calculated.

One sample T-test was used to analyze the differences between PSA test score between the control group and the study cases at *P*-value of significance 0.05.

Multivariate analysis was done to adjust for several factors. After doing the univariate analysis, all the variables that showed significant differences between study cases and control group (p-value < 0.1) were introduced in the multivariate analysis. Logistic regression model was used. The logistic regression was used to compare odds ratio with confidence interval of 90%. p-value < 0.1 and 90% confidence interval were used due to small sample size.

The following variables were introduced into the logistic regression model: age, marital status, age at marriage, number of children, monthly income, fruit consumption, cruciferous vegetables consumption, cocked tomato consumption, homemade cheese consumption, eggs consumption, red meat consumption, processed meat consumption, type 2 diabetes mellitus,

cardiovascular diseases, history of prostitis, antidiabetic medication intake, multivitamin intake, history of prostate cancer in father, and history of prostate cancer in brother.

4.10 Ethical approval

In order to lunch this study, we got the approval from Al Quds University-School of public health research committee and Al Quds University Graduate Studies committee. We also obtained the permission to conduct this study from the MOH. Also all participants were informed about the study aim and objectives and signed a consent form before participating (Annex 2).

4.11 Variables operational definitions

Age variable: composed of three categories (40-59, 60-69, and ≥70 years).

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

Age at marriage variable: composed of three categories (15-20, 21-25, and >25).

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

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

Years of education variable: composed of four categories (illiterate, 1-6, 7-9, 10-12, and >12 years).

Employment status variable: composed of two categories (working and not working).

Career variable: composed of two main categories (office job and field job). Office job includes teacher, accountant, clerk, engineer, trader, nurse, and silversmith. Field job includes farmer, construction worker, driver, painter, and carpenter.

Religion variable: composed of two categories (Muslim, and Christian).

Participant's monthly income: composed of two categories (≤3000 NIS and >3000 NIS).

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

BMI variable: weight in kilogram divided by the height in meter square, and composed of four categories (underweight: < 18.5, normal: 18.5-24.9, overweight: ≥25-29.9, and Obese: ≥ 30).

Physical activity level variable: composed of three categories (high, medium, low)**.**

Food groups variable: composed of seven categories **(**fruits, vegetables, milk and milk products, animal products, beverages, and water).

Frequency of food intake: composed of three categories (< two times weekly, 2-4 times weekly, and > four times weekly**).**

Nutritional supplements intake variable: composed of **(**multivitamins, vitamin A, vitamin C, vitamin B complex, vitamin B6, vitamin E, vitamin D, Potassium, Calcium, Selenium, Zink, and folic acid**).**

Health status variable: composed of (diabetes mellitus, cardiovascular diseases, hypertension, prostitis, sexually transmitted infections, prostate cancer, and any other malignancy).

Medication used variable: composed of (Aspirin, anti-diabetic, anti-hypertension, and anti-hyperlipidimic).

Chapter Five: The Results

5.1 Introduction

In this chapter, study results will be presented. Study population characteristics will be shown in a descriptive analysis. Univariate and multivariate analysis will also be presented in this chapter.

5.2 Sociodemographic Variables

Table 5.1 shows that 77% of the study population was older than 60 years of age. Of them, 80% were married and their age of marriage was between 21-25 years old, and 53% had 5 to 8 children. Of the study population, 12% was illiterate, and 14% had completed higher education Also, 53.3% of study population lived in urban areas.

Of the study population, while 54% were unemployed, 45.8% of those working in the past 10 years had office work and 78.3% had a monthly income less than or equal NIS 3000 (table 5.1).

Comparing study cases and control group, table 5.1 shows that there are statistically significant differences (P <0.1) in marital status, age at marriage, number of children, and monthly income.

Table 5.1 Association between study cases and control group by socio-demographic factors

		Total N=120	Study cases N=60	Control group N=60	*P* Value
		n (%)	n (%)	n (%)	
Age (years)	40-59 years	27 (22.5)	10 (16.7)	17 (28.3)	0.243
	60-69 years	36 (30)	21 (35.0)	15 (25.0)	
	≥70 years	57 (47.5)	29 (48.3)	28 (46.7)	
Marital Status	Married	96 (80)	44 (73.3)	52 (86.7)	0.068
	Widow	24 (20)	16 (26.7)	8 (13.3)	
Age at Marriage (years)	15-20 years	29 (24.1)	20 (33.3)	9 (15.0)	0.060
	21-25 years	52 (43.3)	22 (36.7)	30 (50.0)	
	>25 years	39 (32.5)	18 (30.0)	21 (35.0)	
Number of Children (persons)	≤4	27 (22.5)	12 (20.0)	15 (25.0)	0.064
	5-8	64 (53.3)	28 (46.7)	36 (60.0)	
	≥9	29 (24.2)	20 (33.3)	9 (15.0)	
Years of Education	Illiterate	15 (12.5)	8 (13.3)	7 (11.7)	0.157
	1-6 years	39 (32.5)	19 (31.7)	20 (33.3)	
	7-9 years	37 (30.8)	21 (35.0)	16 (26.7)	
	10-12 years	12 (10)	2 (3.3)	10 (16.7)	
	>12 years	17 (14.2)	10 (16.7)	7 (11.7)	
Employment Status	Yes	55 (45.8)	28 (46.7)	27 (45.0)	0.855
	No	65 (54.2)	32 (53.3)	33 (55.0)	
Career in the Last 20 Years	Office job*	39 (32.5)	20 (33.3)	19 (31.7)	0.845
	Field job**	81 (67.5)	40 (66.7)	41 (68.3)	
Career in the Last 10 Years	Office job*	55 (45.8)	28 (46.7)	27 (45)	0.979
	Field job**	43 (35.8)	21 (35)	22 (18.3)	
	Not working	22 (18.3)	11 (18.3)	11 (36.7)	
Place of Residency	Urban	64 (53.3)	35 (58.3)	29 (48.3)	0.272
	Rural	56 (46.7)	25 (41.7)	31 (51.7)	
Residence Type	Private House	85 (70.8)	45 (75.0)	40 (66.7)	0.315
	Apartment	35 (29.2)	15 (25.0)	20 (33.3)	
Religion	Muslim	104 (86.7)	52 (86.7)	52 (86.7)	1.000
	Christian	16 (13.3)	8 (13.3)	8 (13.3)	
Monthly Income	≤3000 shekels	94 (78.3)	41 (68.3)	53 (88.3)	0.008
	>3000 shekels	26 (21.7)	19 (31.7)	7 (11.7)	

* Teacher, Accountant, clerk, engineer, trader, nurse, silversmith.

**Farmer, construction worker, driver, painter, carpenter.

5.3 Food and nutritional variables

Table 5.2 shows that 62.5% of the study population eats fruits 2-4 times weekly and 69.2% eat vegetables for more than four times weekly. Also, 83% consumes cruciferous vegetables less than two times weekly.

Comparing study cases and control group, table 5.2 reveals statistically significant differences (P<0.1) in some food intake, i.e. fruits, cruciferous vegetables, and cocked tomato.

Table 5.2 Association between study cases and control group by fruit and vegetables consuming.

		Total N=120	**Study cases N=60**	**Control group N=60**	***P*-value**
		n (%)	n (%)	n (%)	
Fruits	<2 weekly	15 (12.5)	8 (13.3)	7 (11.7)	0.082
	2-4 weekly	75 (62.5)	32 (53.3)	43 (71.7)	
	> 4 weekly	30 (25)	20 (33.3)	10 (16.7)	
Vegetables	≤4 weekly	37 (30.8)	15 (25.0)	22 (36.7)	0.166
	> 4 weekly	83 (69.2)	45 (75.0)	38 (63.3)	
Cruciferous vegetables	<2 weekly	100 (83.3)	43 (71.7)	57 (95.0)	0.001
	≥ 2 weekly	20 (16.7)	17 (28.3)	3 (5.0)	
Cocked tomato	<2 weekly	84 (70)	35 (58.3)	49 (81.7)	0.005
	≥2 weekly	36 (30)	25 (41.7)	11 (18.3)	

Table 5.3 shows that 55.8% of the study population drinks milk less than two times weekly, while 43% of the study population consumes yogurt from 2-4 times weekly. Also, 68.3% and 88.3% of the study population consumes homemade cheese and homemade butter less than twice weekly, respectively.

As for meat and animal products, 53% of the population study eats eggs 2-4 times weekly. In contrast, 50% of the study population consumes red meat less than two times weekly. Whereas, fish was eaten 1-3 times monthly in 53% of this study population.

In addition, 63.3 of the study population drink coffee more than four times weekly, compared with 20% of them drink cola more than four times weekly.

Comparing study cases and control group, table 5.3 reveals statistically significant differences (P<0.1) in some food intake, i.e. home-made cheese, eggs, red meat, and processed meat. The distribution of all studied food and nutrition variables are shown in annex (3).

Table 5.3 Association between study cases and control group by some food and drinks consuming.

		Total N=120	Study cases N=60	Control Group N=60	*P*- Value
Milk	<2 weekly	67 (55.8)	35 (58.3)	32 (53.3)	0.727
	2-4 weekly	17 (14.2)	9 (15.0)	8 (13.3)	
	> 4 weekly	36 (30)	16 (26.7)	20 (33.3)	
Yogurt	<2 weekly	35 (29.2)	22 (36.7)	13 (21.7)	0.167
	2-4 weekly	52 (43.3)	22 (36.7)	30 (50.0)	
	> 4 weekly	33 (27.5)	16 (26.7)	17 (28.3)	
Homemade cheese	<2 weekly	82 (68.3)	34 (56.7)	48 (80.0)	0.005
	2-4 weekly	21 (17.5)	17 (28.3)	4 (6.7)	
	> 4 weekly	17 (14.2)	9 (15.0)	8 (13.3)	
Homemade butter	<2 weekly	106(88.3)	51 (85.0)	55 (91.7)	0.255
	≥2 weekly	14(11.7)	9 (15.0)	5 (8.3)	
Eggs	<2 weekly	33 (27.5)	12 (20.0)	21 (35.0)	0.050
	2-4 weekly	64 (53.3)	32 (53.3)	32 (53.3)	
	> 4 weekly	23 (19.2)	16 (26.7)	7 (11.7)	
Red meat	<2 weekly	60 (50)	24 (40.0)	36 (60.0)	0.025
	2-4 weekly	49 (40.8)	27 (45.0)	22 (36.7)	
	> 4 weekly	11 (9.2)	9 (15.0)	2 (3.3)	
Processed meat	<2 weekly	93 (77.5)	41 (68.3)	52 (86.7)	0.016
	≥2 weekly	27 (22.5)	19 (31.7)	8 (13.3)	
Fish	<1 monthly	8 (6.7)	5 (8.3)	3 (5.0)	0.325
	1-3 monthly	64 (53.3)	28 (46.7)	36 (60.0)	
	once weekly	48 (40)	27 (45.0)	21 (35.0)	
Cola	<2 weekly	62 (51.7)	32 (53.3)	30 (50.0)	0.891
	2-4 weekly	34 (28.3)	17 (28.3)	17 (28.3)	
	> 4 weekly	24 (20)	11 (18.3)	13 (21.7)	
Coffee	<2 weekly	21 (17.5)	10 (16.7)	11 (18.3)	0.931
	2-4 weekly	23 (19.2)	11 (18.3)	12 (20.0)	
	> 4 weekly	76 (63.3)	39 (65.0)	37 (61.7)	

5.4 Lifestyle variables

Table 5.4 demonstrates the association between study cases and control group by their lifestyle variables. The table shows that 45% of the study population was smoker and 10% drink alcohol regularly. Moreover, 43.3% of the study population lived with high physical activity and 25.8 with low physical activity. Only 8.3% of this study population practice sport.

No statistically significant differences were seen between study cases and control group in their lifestyle factors (p>0.1). (See table 5.4).

Table 5.4 Association between study cases and control group by lifestyle variables.

		Total N=120		**Study cases N=60**		**Control group N=60**		***P*-value**
		N	(%)	N	(%)	N	(%)	
Tobacco smoking	Yes	54	(45)	30	(50.0)	24	(40.0)	0.271
	No	66	(55)	30	(50.0)	36	(60.0)	
Alcohol drinking	Yes	12	(10)	7	(11.7)	5	(8.3)	0.543
	No	108	(90)	53	(88.3)	55	(91.7)	
Physical activity level	High	52	(43.3)	26	(43.3)	26	(43.3)	0.477
	Moderate	37	(30.8)	16	(26.7)	21	(35.0)	
	Low	31	(25.8)	18	(30.0)	13	(21.7)	
Sport	Yes	10	(8.3)	5	(8.3)	5	(8.3)	0.628
	No	110	(91.7)	55	(91.7)	55	(91.7)	

5.5 Health status

5.5.1 Detection, treatment, and complications of PC in the study cases

Figure 5.1 shows the means of PC detection. Of study cases, 68% of PC cases were detected after having disease signs and symptoms. In contrast, 32% of PC cases were detected by chance or when investigated for other medical conditions. The data also present that none of the study cases have been detected during a systematic screening.

Figure5.2 presents the treatment method of prostate cancer among study cases. Chemotherapy was done for 30% of study cases and radiation was the least method used.

Figure 5.3 shows the distribution of complications after having PC. The back and pelvic pain was the most common complication which was found in 28% of the study cases.

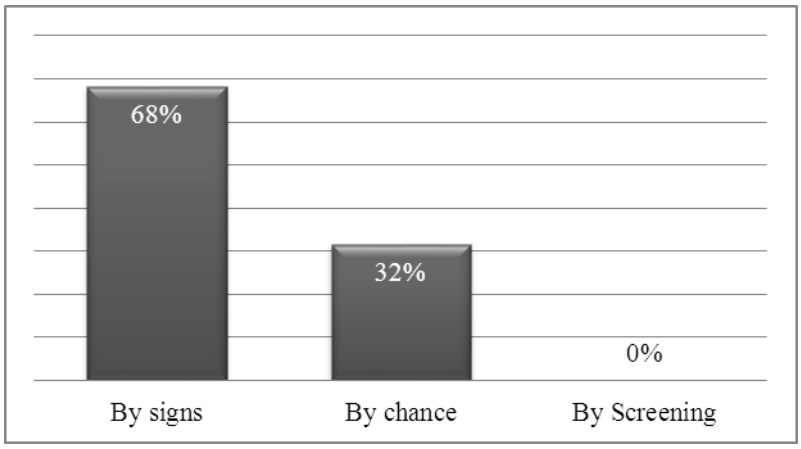

Figure 5.1 Distribution of study cases by means of PC detection

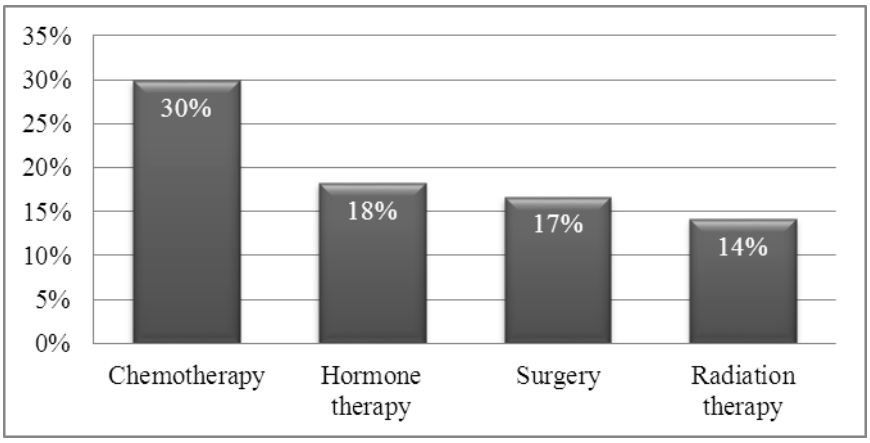

Figure 5.2: Distribution of study cases by treatment method

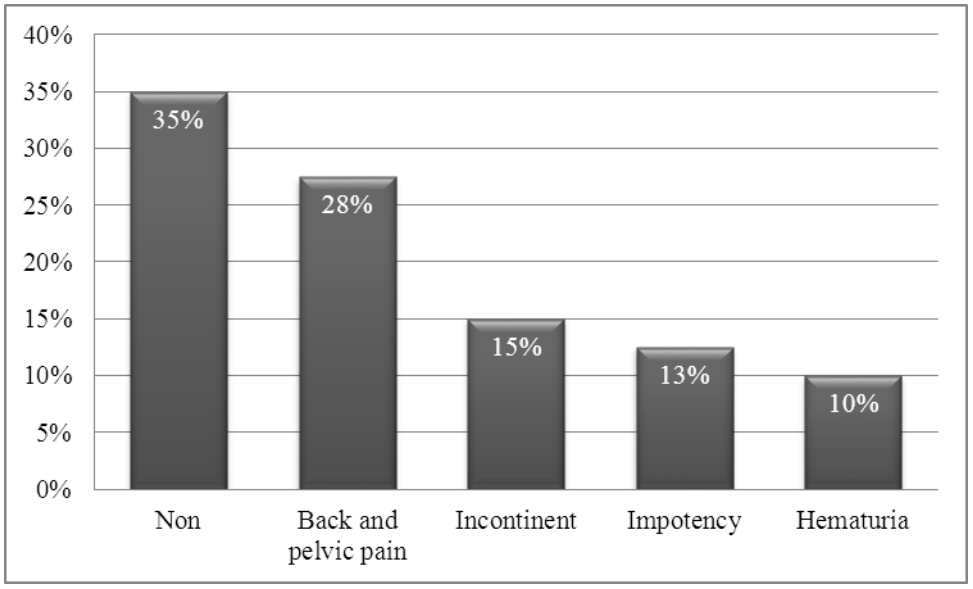

Figure 5.3: Distribution of study cases by PC complication

5.5.2 Prostate Specific Antigen (PSA) testing

The PSA results for control group were within the normal range of its level (<4.4). The mean and standard deviation was 1.51 ±1.1, ranging from 0.27 to 4.15.

The PSA levels for the study cases at time of diagnosis were available in 75% of study cases' files. The mean value and standard deviation was 37.9±38.3, ranging 5.5 to 150. Figure 5.4 shows the distribution of PSA levels among study cases at diagnosis.

Comparing study cases and control group mean levels, a statistically significant difference in PSA value (*P*=0.001) with mean difference 16.7, standard deviation 30.5, 95% CI (10.7-22.7). Figure 5.5 Boxplot distribution of PSA between study cases and control group.

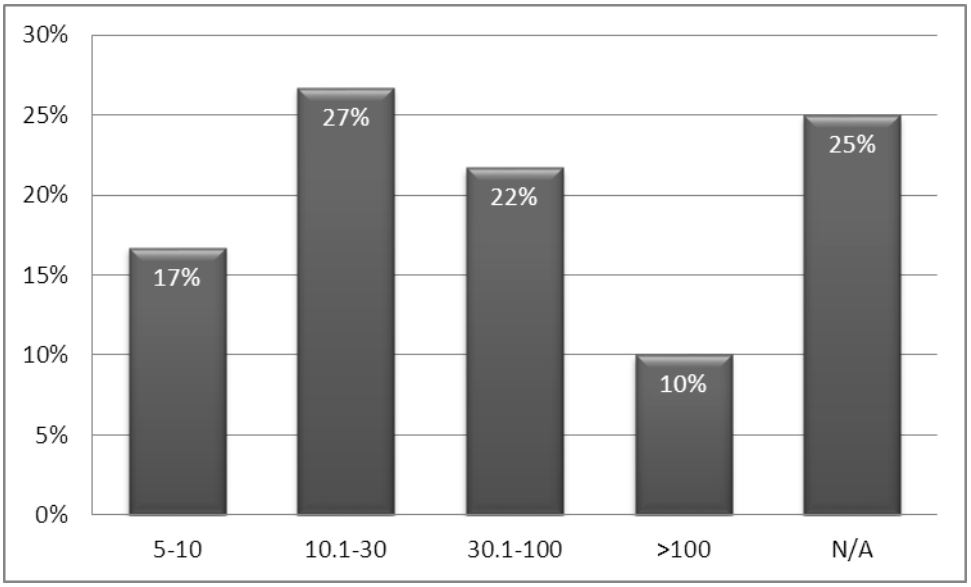

Figure 5.4: Distribution of PSA levels (ng/ml) among study cases

N/A:not available (missed data from medical records)

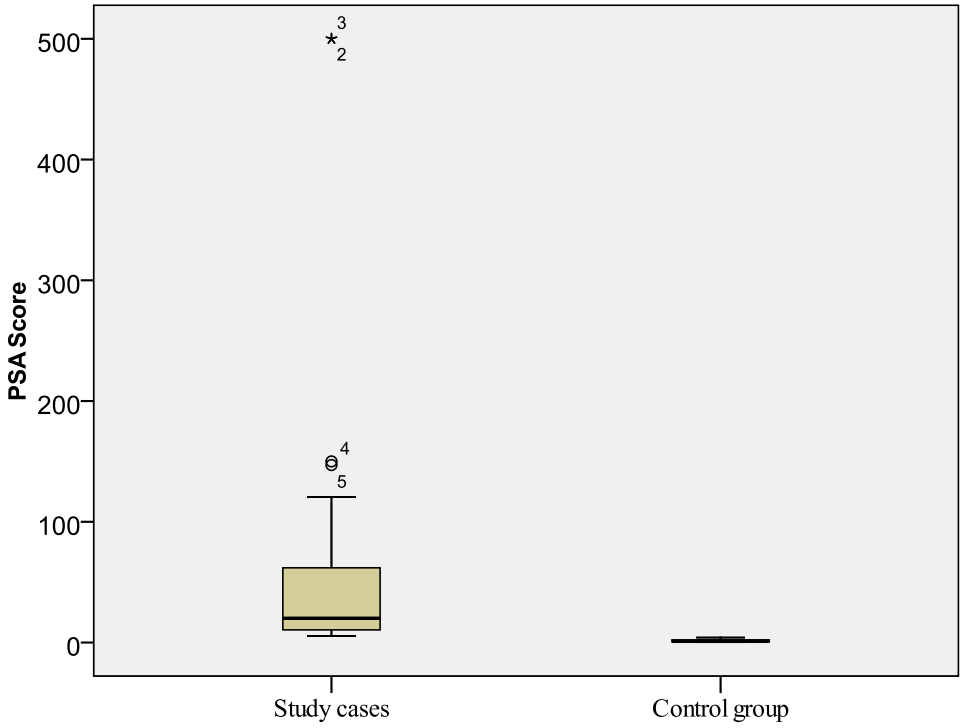

Figure 5.5: Boxplot distribution of PSA between study cases and control group

5.5.3 Univarate analysis for health status

Table 5.5 shows that 32.5% of the study population had diabetes type 2 ; 45.8% had hypertension, 25% had cardiovascular diseases, and 41.7% had prostatitis at least once in the past.

Table 5.5 Association between study cases and control group by health status

		Total N=120		Study cases N=60		Control group N=60		*P*-value
		n	(%)	n	(%)	n	(%)	
Type 2 diabetes	Yes	39	(32.5)	15	(25.0)	24	(40.0)	0.079
	No	81	(67.5)	45	(75.0)	36	(60.0)	
Hypertension	Yes	55	(45.8)	30	(50.0)	25	(41.7)	0.360
	No	65	(54.2)	30	(50.0)	35	(58.3)	
Cardiovascular diseases	Yes	30	(25)	10	(16.7)	20	(33.3)	0.035
	No	90	(75)	50	(83.3)	40	(66.7)	
Prostatitis	Yes	50	(41.7)	35	(58.3)	15	(25.0)	0.001
	No	70	(58.3)	25	(41.7)	45	(75.0)	
Other Malignancy	Yes	11	(9.2)	11	(18.3)	0	(0.0)	0.001
	No	109	(90.8)	49	(81.7)	60	(100.0)	

Table 5.6 showed that high percent (65.8%) of study population uses aspirin on daily basis, in addition to other medications for their health problems such as diabetes (45.8%). However, only 10% takes multivitamins. Of this population 47.5% was over-weight and 34.2% was obese.

The data shows statistically significant differences between study cases and control group (*P* < 0.1) in having diabetes type 2, cardiovascular diseases, prostatitis, using anti diabetic medication, and multi-vitamins intake.

Table 5.6 Association between study cases and control group by medication use.

		Total N=120	**Study cases N=60**	**Control group N=60**	
		n (%)	n (%)	n (%)	***P*-value**
Aspirin	Yes	79 (65.8)	38 (63.3)	41 (68.3)	0.546
	No	41 (34.2)	22 (36.7)	19 (31.7)	
Anti-diabetic	Yes	39 (32.5)	15 (25.0)	24 (40.0)	0.079
	No	81 (67.5)	45 (75.0)	36 (60.0)	
Anti-hypertensive	Yes	55 (45.8)	30 (50.0)	25 (41.7)	0.360
	No	65 (54.2)	30 (50.0)	35 (58.3)	
Anti-hyperlipidemic	Yes	48 (40)	27 (45.0)	21 (35.0)	0.264
	No	72 (60)	33 (55.0)	39 (65.0)	
Multi vitamins	Yes	12 (10)	9 (15.0)	3 (5.0)	0.068
	No	108 (90)	51 (85.0)	57 (95.0)	
BMI	Normal 20-25	22 (18.3)	10 (16.9)	12 (20)	0.874
	Overweight 26-30	57 (47.5)	30 (49.2)	27 (45)	
	Obese >30	41 (34.2)	20 (33.9)	21 (35)	

5.6 Family History of malignancy

Data in table 5.7 shows that 4.2% of the study population had fathers' history of PC, and 7.5% had brothers' history of PC. 10% of the study population had sisters' history of breast cancer, and 1.7% had history of mothers' breast cancer.

In the family history of malignancy, the data shows statistically significant differences between study cases and control group (*P* Value <0.1) in their family history of PC (Table 5.7).

Table 5.7 Association between study cases and control group by family history of malignancy.

		Total N=120		Case N=60		Control N=60		*P* Value
		n	(%)	n	(%)		(%)	
Father Has Prostate Ca	Yes	5	(4.2)	5	(8.3)	0	(0.0)	0.022
	No	115	(95.2)	55	(91.7)	60	(100.0)	
Father Has Other Malignancy	Yes	2	(1.7)	0	(0.0)	2	(3.3)	0.154
	No	118	(98.3)	60	(100.0)	58	(96.7)	
Brother Has Prostate Ca	Yes	9	(7.5)	8	(13.3)	1	(1.7)	0.015
	No	111	(92.5)	52	(86.7)	59	(98.3)	
Brother Has Other Malignancy	Yes	9	(7.5)	6	(10.0)	3	(5.0)	0.298
	No	111	(92.5)	54	(90.0)	57	(95.0)	
Mother Has Breast Ca	Yes	2	(1.7)	0	(0.0)	2	(3.3)	0.154
	No	118	(98.3)	60	(100.0)	58	(96.7)	
Mother Has Other Malignancy	Yes	7	(5.8)	4	(6.7)	3	(5.0)	0.697
	No	113	(94.2)	56	(93.3)	57	(95.0)	
Sister Has Breast Ca	Yes	12	(10)	8	(13.3)	4	(6.7)	0.224
	No	108	(90)	52	(86.7)	56	(93.3)	
Sister Has Other Malignancy	Yes	6	(5)	3	(5.0)	3	(5.0)	1.000
	No	114	(95)	57	(95.0)	57	(95.0)	

Multivariate analysis

Table 5.8 shows that being a widow was associated with increased risk (4 times) to develop PC compared to married men. Similarly, people with lower monthly income are associated with increased risk (8 times) to develop PC compared to people with higher income. Also, those who are consuming less amounts of cruciferous vegetables (6 times), homemade cheese (10 times), and processed meat (5 times) were at increased risk to develop PC compared to those consuming higher amounts However, diabetic persons (3 times) and those with cardiovascular diseases (7 times) were at increased risk to develop PC compared to those not having these diseases.

Table 5.8 Multivariate model analysis of the associated variables with prostate cancer *

		Sig	AOR**	90% CI***
Marital status	Widow		1.00	
	Married	0.03	0.225	0.073-0.697
Monthly income	≤3000 NIS		1.00	
	>3000 NIS	0.001	0.118	0.042-0.332
Cruciferous vegetables intake	<2 weekly		1.00	
	≥ 2 weekly	0.019	0.154	0.041-0.571
Homemade cheese intake	<2 weekly		1.00	
	2-4 weekly	0.002	0.108	0.034-0.345
	> 4 weekly	0.972	1.08	0.265-4.009
Processed meat intake	<2 weekly		1.00	
	≥2 weekly	0.011	0.192	0.066-0.557
Diabetes	Yes	0.033	3.132	1.29-7.57
	No		1.00	
Cardiovascular diseases	Yes	0.004	7.38	2.33-23.31
	No		1.00	

*All variables that were significant ($p<0.10$) in univariate analysis were included in a multivariate model (*P* value 0.1): i.e. age group, marital status, age at marriage, number of children, monthly income, fruits intake, cruciferous vegetables intake, cocked tomato intake, homemade cheese intake, eggs intake, red meat intake, processed meat intake, type II diabetes mellitus, cardiovascular diseases, history of prostatitis, antidiabetic drugs usage, multivitamins intake, history of prostate cancer of brother, and history of prostate cancer of father. **Adjusted odds ratio. ***Confidence interval.

Chapter Six: Discussion

6.1. Introduction

In this chapter, study results are summarized and compared to other studies results worldwide. Also, the results are interpreted and discussed. In the final part of the chapter study conclusions and recommendations are presented

6.2. Summary of the results

The univariat analysis of the study data showed significant differences between study cases and control group in marital status, age at marriage, number of children, and monthly income variables. Also the consumption of fruits, cruciferous vegetables, cocked tomato and home-made cheese eggs, red meat, and processed meat showed significant differences between study cases and control group.

As for the univariate analysis of the health status and family history of malignance variables, type 2 diabetes mellitus, cardiovascular diseases, multi-vitamin intake, anti-diabetic medication, father with prostate cancer, and brother with prostate cancer all showed significant differences between study cases and control group.

On the other hand the multivariate analysis of the study data showed that married men are at lower risk by five folds to develop prostate cancer. Also the study revealed that lower the family monthly income increase the risk by nine folds to have prostate cancer. More weekly consumption of cruciferous vegetables, homemade cheese, and processed meat showed to decrease the risk of prostate cancer among the study population by six, ten, and five folds, respectively. In addition, the risk of prostate cancer among diabetics was three times more than non-diabetics. Similarly, having cardiovascular diseases increased the risk of prostate cancer by seven folds.

6.3 Socio-demographic variables and prostate cancer

Marital status: In our study, marital status was found to be significantly associated with prostate cancer after adjustment. Being married was inversely associated with having prostate cancer compared to those widowed men by five folds. However, this result is inconsistent with results revealed by other studies that indicated no association between

marital status and prostate cancer risk (Tyagi *et al.* 2010; Severson *et al.* 1989; Newell *et al.* 1987). A prospective cohort study in Norway found that the risk among divorced or separated men to develop prostate cancer was 56% higher compared to married men (Lund Nilsen *et al.* 2000).

The incidence of prostate cancer is increased with older ages. In our study about 87% of the widows were older than 70 years at the time of data collection, this may explain the appearance of marital status to be associated with prostate cancer occurrence.

Monthly income: In our study, low family monthly income was found to significantly increase the risk for prostate cancer by ten folds. In a Norwegian cohort study they found that the higher the socioeconomic status the higher the risk of prostate cancer (Lund Nilsen *et al.* 2000). This could be explained by the greater medical attention among those who may have a self-paid insurance, where medical check-ups are made on a regular basis

In our study we included participants from the main cancer governmental hospital and most of its visitors, if not all, are insured patients who have no choice for other hospitals except the private hospitals or hospitals outside the country. We expect that these people cannot afford going to more expensive health facilities due to their low income. Patients from higher economic either go to private clinics and hospitals or to other advanced facilities outside the country. Moreover, asking people to report their income in a survey is not so accepted among interviewees, which leaves a space for justifying this finding by a reporting bias.

6.4 Lifestyle variables and prostate cancer

Cruciferous vegetables: Our study suggests that the consumption of cruciferous vegetables was adversely associated with the risk of prostate cancer. The participants who consumed cruciferous vegetables more than twice per week were at lower risk of developing prostate cancer by six folds compared to those consumed less. This result is supported by results from two case control studies that found people who ate greater amounts of cruciferous vegetables had a lower risk of prostate cancer (Jain *et al.* 1999; Kolonel *et al.* 2000). On the other hand, other cohort studies have examined a wide range of daily cruciferous vegetable intakes and found little or no association with prostate cancer risk (Key *et al.* 2004; Giovannucci *et al.* 2003; Schuurman *et al.* 1998).

Cruciferous vegetables contain a group of substances known as glucosinolates. During digestion the glucosinolates in cruciferous vegetables are broken down to form biologically active compounds such as indoles, nitriles, thiocyanates, and isothiocyanates. Indole-3-carbinol (an indole) and sulforaphane (an isothiocyanate) have been most frequently examined for their anticancer effects (Smiechowska *et al.* 2008). The action of these substances on the molecular level is believed to be the mechanism in which cruciferous vegetables could prevent prostate cancer development.

Home-made cheese: Home-made cheese in this study also appeared to be significantly associated with the risk of prostate cancer. Men who regularly have 2-4 portions per week of home-made cheese is at lower risk of prostate cancer by ten folds compared to those who eat less than two portions weekly. In the European Prospective Investigations into Cancer and Nutrition (EPIC) Heidelberg cohort (Nimptsch *et al.* 2008) found that the K2 vitamin (menaquinones) is adversely associated with prostate cancer risk (RR 0.65, CI 1.06-3.9). White cheese is a good source of vitamin K2, which has an antiangiogenic effect, and also kills cancer cells directly.

On the other hand, some studies revealed that dietary intake might increase the risk of prostate cancer (Bairati *et al.* 1998; Giovannucci *et al.* 1993; Kamel *et al.* 2006). This can be attributed to the presence of fat and fat affects testosterone levels which have an important role in prostate cancer development. However, these studies focused on the cheese made from full fat cow milk, which contains double amount of fat that contained in the cheese made from goat milk. In fact, the popular homemade cheese in our community is made from the domestic goats that are mainly raised locally. Therefore, goat milk homemade cheese appeared to be inversely associated with prostate cancer risk.

Processed meat: This study found that consumption of processed meat is adversely associated with prostate cancer risk. As the consumption of processed meat more than twice weekly decreases the risk of prostate cancer to 5 folds compared to less weekly consumption (OR=0.19, 90% CI 0.066-0.557).

In the reviewed literature, there are inconstancies in the results regarding the association between processed meat and risk of prostate cancer.

Koutros *et al* in Iowa and North Carolina found no association between meat type or specific cooking method and prostate cancer risk. However, they concluded that intake of

well or very well done total meat was associated with a 1.26-fold increased risk of incident prostate cancer (95% CI, 1.02-1.54) and a 1.97-fold increased risk of advanced disease (95% CI, 1.26-3.08)(Koutros *et al.* 2008).

In Washington, Rohrmann *et al* concluded that processed meat consumption was statistically insignificant associated with higher risk and total prostate cancer when comparing eating of five or more servings with eating of one or less servings of processed meat weekly(HR = 2.24; 95% CI 0.90-5.59)(Rohrmann *et al.* 2007).

On the other hand, the Cancer Prevention Study II Nutrition Cohort found that high consumption of cooked processed meats may increase the risk of prostate cancer among black men in the United States. This increase in risk was mainly due to the risk associated with consumption of cooked processed meats (sausages, bacon, and hot dogs) (RR, 2.7; 95% CI, 1.3-5.3)(Rodriguez *et al.* 2006).

The discrepancies between these results may depend on the type of the processed meat tested in each study population. In our community the most abundant processed meat in the market is made from poultry meat. In Egypt for example a study founded that sausages was a directly associated with prostate cancer risk, but these sausages was made from cow meat(Kamel *et al.* 2006).

Tobacco smoking: The univariate analysis of the smoking data collected from both study cases and control group shows that 50% of the cases were currently smokers where 40% of the controls were currently smokers, although the difference was not statistically significant (*P*-value 0.27). We merged the past smokers and smokers in the same category.

Studies worldwide revealed inconsistent results when relating tobacco smoking with prostate cancer risk. A case-control study in Iran showed a non-significant increased risk for prostate cancer by seven times among cases using pipe smoking compared to controls(Hosseini *et al.* 2010). Another population-based case-control study conducted in Delhi, India suggested that the association was statistically significant with a 5-fold increase only in the case of past smokers (Tyagi *et al.* 2010).

On the other hand, in two case-control studies in Egypt (Kamel *et al.* 2006) and in USA (Yu *et al.* 1988) there were no differences in smoking habits between cases and controls.

Alcohol consumption: Our study data showed that 11.7% of the study cases were regular alcohol drinker compared to 8.3% of the control group. The association between alcohol consumption and prostate cancer risk still a controversial issue in the literature ranging from adversely association to no association and positively association.

The relation between alcohol consumption and prostate cancer risk were always shown in the literature to depend on type, amount, and frequency of alcohol consumption. In our study the number of alcohol drinkers was too small to show the differences between study cases and control group, also the type of alcohol used was not considered during data collection. This may explain the insignificant difference between study cases and control group when alcohol consumption was the studied variable.

Schoonen *et al* suggested that red wine consumption may be associated with a reduced relative risk of prostate cancer. Each additional glass of red wine consumed per week was shown to decrease the risk by 6% (relative risk 0.94, 95% CI, 0.90–0.98)(Schoonen *et al.* 2005).

In contrast, two case-control studies in USA (Schoonen *et al.* 2005; Yu *et al.* 1988) and one prospective cohort study in Europe (Rohrmann *et al.* 2008) concluded that there was no association between alcohol consumption and risk of prostate cancer.

Moreover, a prospective cohort study in USA reported that moderate liquor consumption was associated with a significant 61-97% increased risk of prostate cancer(Sesso *et al.* 2001).

6.5 Health status variables and prostate cancer

Type 2 diabetes mellitus: Type 2 diabetes mellitus found in our study to be positively associated with prostate cancer risk (OR=3.1, 90% CI 1.29-7.57). Our result contradicts the result from a meta-analysis that provided strong evidence that people with diabetes have a significant decrease in risk of developing prostate cancer (Bonovas *et al.* 2004).

The Health Professionals Follow-Up Study confirmed by their study results the hypothesis that diabetes is associated with reduced prostate cancer risk (Kasper *et al.* 2009).

A number of theories exist to explain this protective phenomenon, but the most prevalent mechanism that diabetes mellitus may lower prostate cancer risk through a reduction of

essential serum growth factors – insulin, insulin like growth factor (IGF-1), and testosterone (Kasper *et al.* 2008). But also, the type of diabetes medications the patient use.

Metaformin was shown in literature to decrease the risk for prostate cancer (Decensi *et al.* 2010). The descriptive data of this study should that diabetes medications decreased the risk for prostate cancer but the association was not significant.

The effect of diabetes on prostate cancer risk depends on the time since diagnosis (Zhu *et al.* 2004). In our study the history of diabetes diagnosis was not traced with the participants, and this may affect our result in this aspect.

Cardiovascular diseases: Cardiovascular diseases in our study appeared to be positively associated with prostate cancer. Participants who reported to have a cardiovascular disease are at seven folds risk to develop prostate cancer compared to participants with no cardiovascular diseases. Our result is consistent with the results of a hospital based case control study in New York which concluded that patients with history of coronary heart disease are at 2-fold higher risk to develop prostate cancer (Neugut *et al.* 1998).

In contrast, a nested case control study in the United States, found that the coronary heart disease is adversely associated with prostate cancer (OR=0.72, 95% CI 0.62-0.84)(Driver *et al.* 2010).

In our study neither the specific type of the cardiovascular disease nor the history of diagnosis were investigated. This could affect the result, as most of the studies studied the relation of coronary heart disease and prostate cancer risk, which is not the scope of our study.

Obesity: The univariate analysis of our data yielded that 33.9% of the study cases were obese (BMI >30), compared to 35% of the control group (*P*-value 0.874). The difference was not significant in our study although some studies concluded that the obesity is positively associated with high grad prostate cancer risk and negatively associated with low grad prostate cancer (Gong *et al.* 2006; Masuda *et al.* 2012; Putnam *et al.* 2000; Rodriguez *et al.* 2007).

In our study, the clinical type of prostate cancer was not considered, and this may have diluted the result and set the obesity out of the association with prostate cancer risk.

6.6 Family history of malignancy and prostate cancer

Our study showed that there is no association between prostate cancer risk and family history of prostate cancer or any other type of malignancy. Lisko *et al* found in a population based case control study in Massasusetch that family history of prostate cancer was significantly affect the risk of prostate cancer, as the presence of family history of prostate cancer increased the risk of this cancer (OR=2.3, 95% CI, 1.7-3.3)(Lesko *et al.* 1996).

Lesko *et al* in their case control study found that the relation between the risk of prostate cancer and family history of prostate cancer may depend on the age of the patient and the age at diagnosis. As the prostate cancer patient getting older the effect of family history getting lesser and converted to be adversely associated if the disease diagnosed after the age of 74 (OR=0.76 95% CI, 0.38-1.5)(Lesko *et al.* 1996).

Lesko *et al* results may interpret our result as our study included 48.3% of the cases of age 70 years and older.

6.7 Limitations of the study

The contradiction of this study with other studies may be attributed to the relatively small number of the studied population. Also some biases might affect the results like information bias, recall bias, and selection bias. The study was limited in terms of time and finance, which in role prohibited more investigation and tests. Data provided from the patient's records was limited to oncological status of each patient and the lack of reporting of other medical conditions the patients have.

Some limitations of this study derived from the nature of the retrospective case-control study. The participants were asked about their lifestyle long time ago, the participants are patients who are under the effect of some medication, in addition to the old age of most of the participants, all these factors result in recall bias.

Also, the reporting bias may be presented in our study as the participants are patients trying either to deny the role of their lifestyle or to blame any other factors except themselves, so some participants answered some questions in a way to achieve their perception.

Moreover, the data of family history of malignancy in the patient record (Cancer Registry Information Form) are missed in most of the cases; therefore we could not extract reliable

family history. To compensate the defect in participant's medical record each participant was asked about his family history of prostate cancer and this might be exposed to recall bias or information bias.

6.8 Conclusion

This study is the first one in Palestine that investigated the possible association between different factors whether protective or risk and prostate cancer occurrence. A hospital based retrospective case control study design was used to answer the study question.

Most results of this study were expected and comparable to other international studies results, while some others were unexpectedly contradicted the literature. Marital status, monthly income, cruciferous vegetables consumption, homemade cheese intake, processed meat consumption, cardiovascular diseases, and type 2 diabetes mellitus appeared to be associated with prostate cancer either positively or negatively. Tobacco smocking, family history of prostate cancer, sexually transmitted infections, and tomato consumption showed no association with prostate cancer risk.

6.9 Recommendations

Recommendations for people at risk of prostate cancer

- Living in a healthy lifestyle that helps preventing the diabetes mellitus and cardiovascular diseases.
- Increase the consumption of fruits and vegetables especially cruciferous vegetables, and homemade cheese.
- Perform a screening for prostate cancer on a regular basis.

Recommendations for policy makers and health care team:

- Providing more attention for the men cancers especially prostate cancer.
- Establishing national initiatives for the encouragement of early detection of prostate cancer.
- Introducing screening methods for early detection of prostate cancer including rectal digital exam, PSA test, and biopsy.
- Modifying the national cancer registry to include more details related to each cancer type.

- Considering the prostate cancer detection when dealing with over 50 years old men.
- Giving more attention to the groups at risk of prostate cancer to enable the early detection.
- Work more on the modifiable lifestyle factors which eventually affect the risk of prostate cancer.

Recommendations for public health researchers:

- Conducting more detailed researches with larger sample size and including more hospitals and health care facilities.
- Considering the type of prostate cancer (histopathology) and the date of first diagnosis.

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Annex

Annex (1): Prostate cancer determinants questionnaire

استمارة تقييم العوامل المرتبطة بسرطان غدة البروستاتا بين الرجال الذين يراجعون مستشفى بيت جالا الحكومي

A	التاريخ					
B	رقم الاستمارة					
C	نوع المشارك	1- مريض بسرطان البروستاتا	2- مريض بغير سرطان البرستاتا			
Q1	الاسم الرباعي					
Q2	العنوان					
Q3	التلفون					
Q4	العمر	|_____| سنة				
Q5	تاريخ الميلاد	|___|___|___|				
Q6	الحالة الاجتماعية	1-متزوج	2- أرمل	3- مطلق	4- أعزب	
Q7	العمر عند الزواج	|_____| سنة				
Q8	عدد الأولاد	|_____|				
Q9	هل تعمل ؟	1- نعم	2- لا			
Q10	المهنة خلال العشرة أعوام الماضية	_____				
Q11	المهنة خلال العشرين عام الماضية	_____				
Q12	عدد سنوات الدراسة	|_____| سنة				
Q13	مكان السكن	1-مدينة	2-قرية	3-مخيم	4-غير ذلك	
Q14	نوع السكن	1-بيت مستقل	2-شقة في عمارة	3- بيت شعر	4-بيت صفيح	
Q15	الديانة	1-مسلم	2-مسيحي	3-غير ذلك		
Q16	الدخل الشهري للاسرة	1-أقل من 1000 ش	2- من 1000-2000 ش	3- 2001-3000ش	4- من 3001-5000ش	5-أكثر من 5000ش
Q17	هل أنت مدخن؟ (سجائر- سيجار- غليون – الأرجيلة)؟	1.نعم	2. لا			
Q18	إذا كان الجواب نعم، هل تدخن بشكل يومي؟	1.نعم	2. لا			
Q19	كم كان عمرك عندما بدأت التدخين بشكل يومي؟	العمر (سنوات) |_____| سنة	لا أذكر			
Q20	هل تذكر منذ كم سنة وأنت تدخن؟	سنوات |____|	لا أذكر			

Q21	ماهو معدل تدخينك اليومي لأي من هذه الأنواع؟ **(متعدد الاجابات)**	سيجارة مع فلتر |____|	سيجارة بدون فلتر |____|	سيجار |____|	غليون |____|	ارجيلة |____|
Q22	هل كنت تدخن بشكل يومي ثم أقلعت عن التدخين ؟	1.نعم	2. لا			
Q23	كم كان عمرك عندما أقلعت عن التدخين؟	العمر (سنوات|____|	لا أذكر			
Q24	اذا كنت لا تذكر، فهل تذكر منذ متى أقلعت عن التدخين؟	سنوات |____|	لا أذكر			
Q25	هل يدخن أحد من افراد اسرتك اثناء وجودك في البيت ؟	1.نعم	2. لا			
Q26	هل يدخن أحد اثناء وجودك في مكان عملك؟	1.نعم	2. لا			
Q27	هل سبق وأن تناولت مشروبا كحوليا مثل البيرة أو النبيذ او الويسكي؟	1.نعم	2. لا			
Q28	اذا كنت تشرب الكحول فهل تشربها	1- يوميا	2- 1-4 مرات في الأسبوع	3- 1-3 مرات في الشهر		
		4 - أقل من مرة في الشهر				
Q29	اذا كنت تشرب الكحول، في المتوسط كم كاسا تشرب اسبوعيا؟	العدد |___|___|	لا أذكر			
Q30	منذ كم سنة وأنت تشرب الكحول؟	سنوات |___|___|	لا أذكر			
Q31	حسب تقييمك ما هو مستوى نشاطك البدني اليومي؟	1-عالي	2- متوسط	3- قليل	3- غير ذلك	
Q32	هل تمارس الرياضة؟	1- نعم	2- لا			

	نوع الرياضة	**كم مرة في الأسبوع تمارس هذه الرياضة**				**مدتها في كل مرة / ساعة**			
		مرة أو اقل	**2-3 مرات**	**4-5 مرات**	**6 أو أكثر**	**2/1 أو اقل**	**1 -2/1 ساعة**	**1-2**	**2 <**
Q33	**المشي**								
Q34	**الركض**								
Q35	**تمارين عامة بدون أجهزة (ايروبكس)**								
Q36	**تمارين باستخدام أجهزة رياضية**								
Q37	**غير ذلك:_____**								

الرجاء الاجابة عن الاسئلة التالية بوضع اشارة X في مربع الاجابة الصحيحة											
		الوحدة	لا يتناول أو يتناول أقل من مرة في الشهر	1-3 في الشهر	مرة في الأسبوع	2-4 في الأسبوع	5-6 في الأسبوع	مرة في اليوم	2-3 في اليوم	4-5 في اليوم	+6 في اليوم
Q38	الفواكة بشكل عام	½كأس									
Q39	الحمضيات (البرتقال أو الجريبفروت أو المندلينا)	حبة									
Q40	الشمام	½ حبة									
Q41	الخضروات بشكل عام	½ كأس									
Q42	الخضروات الصليبية (الملفوف، القرنبيط، الزهرة)	½ كأس									
Q43	البندورة الطازجة غير المطبوخة	حبة									
Q44	البندورة المطبوخة	½ كأس									
Q45	الجزر	حبة									
Q46	حليب كامل الدسم	كأس									
Q47	حليب منزوع الدسم	كأس									
Q48	لبن رائب كامل الدسم	كأس									
Q49	لبن رائب منزوع الدسم	كأس									
Q50	جبنة بيضاء بلدية	100 غم									
Q51	زبدة بلدية	100 غم									
Q52	بوظة	كأس									
Q53	لبن مخيض	كأس									
Q54	البيض	بيضة									
Q55	اللحوم الحمراء (الخروف، العجل)	150غم									
Q56	لحم الدجاج	150غم									
Q57	لحم الحبش	150 غم									
Q58	اللحوم المصنعة المطبوخة مثل السلامي، المرتديلا، البسطرمة	شريحة									
Q59	النقانق أو السجق	حبة									
Q60	اللحوم المدخنة	شريحة									
Q61	السمك	150 غم									
Q62	السمك المملح	150 غم									
Q63	التونا المعلبة	علبة									

Q64	المشروبات الغازية (الكولا)	كأس									
Q65	القهوة	فنجان									
Q66	الشاي العادي	كأس									
Q67	الشاي الأخضر	كأس									
Q68	الماء	كأس									
		الوحدة	لا يتناول أو أقل من مرة في الشهر	1-3 في الشهر	مرة في الأسبوع	2-4 في الأسبوع	5-6 في الأسبوع	مرة في اليوم	2-3 في اليوم	4-5 في اليوم	+6 في اليوم

Q69	هل تتناول الفيتامينات (Multi-Vitamins)	1 -نعم	2 - لا
Q70	اذاكنت تتناول الفيتامينات، فكم مرة تتناولها اسبوعيا؟		النوع

Q71	هل تتناول	1 -نعم	2 –لا	1-حبوب 2-حقن	النوع / كم مرة (في اليوم، في الاسبوع، في الشهر)
Q72	فيتامين أ؟				
Q73	فيتامين س؟				
Q74	فيتامين ب6؟				
Q75	Complex B				
Q76	فيتامين ي؟				
Q77	فيتامين د؟				
Q78	البوتاسيوم؟				
Q79	الكالسيوم؟				
Q80	السيلينيوم؟				
Q81	الزنك؟				
Q82	حامض الفوليك؟				

هل تم تشخيص أحد الأمراض التالية لديك بواسطة طبيب؟			
		1- نعم	2- لا
Q83	مرض السكري النوع الثاني		
Q84	مرض السكري النوع الاول		
Q85	ارتفاع ضغط الدم		
Q86	مرض شرايين القلب		
Q87	خلل/ التهاب في البروستاتا		
Q88	أمراض الجهاز التناسلي		
Q89	حدد نوع المرض		
Q90	ورم غير سرطاني		
Q91	حدد مكان الورم		
Q92	ورم سرطاني في البروستات		
Q93	ورم سرطاني في غيرالبروستات		
Q94	هل اجريت لك عملة قطع القنوات المنوية؟		
	هل تتناول الأدوية التالية؟	1- نعم	2- لا
Q95	الأسبرين		
Q96	علاجات السكري		
Q97	علاج ضغط الدم المرتفع		
Q98	علاج الدهنيات في الدم (Statin)		

هل أصيب أحد من افراد العائلة باحد انواع السرطانات التالية؟		أب/أم	أخ/ت	عم/ة	خال/ة	جد/ة لأب	جدة/ لأم		لا أعلم
Q99	بسرطان البروستات								
Q100	بسرطان غير البروستات								
Q101	بسرطان الثدي								
Q102	بسرطان غير الثدي								
Q103	في حال عدم وجود الإصابة بسرطان البروستات هل تقوم بعمل فحوصات وقائية (مسحية) لسرطان البروستات؟			1- نعم				2- لا	

Q104	الطول (سم)	_____| سم
Q105	كم كان وزنك (كغم) قبل التشخيص	_____| كغم
Q106	كم وزنك حاليا	_____| كغم

خاص بمرضى سرطان البروستات

Q107	كيف تم اكتشاف اصابتك بسرطان البروستات؟	1- ظهور أعراض المرض	2- بواسطة إجراء مسح وقائي	3- عن طريق الصدفة
Q108	كيف تم تشخيص الإصابة بسرطان البروستات؟	1-الفحص السريري	2- الموجات فوق الصوتية	3- أخذ عينة من البروستات
Q109	ما هو نوع العلاج الذي خضعت له منذ اصابتك بمرض سرطان البروستات؟ (متعدد الاجابات)	1-العلاج الإشعاعي	2-العلاج الهرموني	**3-عملية جراحية**
		4-العلاج الكيماوي	5- غير ذلك	
Q110	هل تعاني من احدى هذه المضاعفات نتيجة للإصابة بسرطان البروستات؟	1- ضعف في الوظيفة الجنسية	2- عدم القدرة على التحكم بنزول البول	3-آلام في منطقة الحوض أو الظهر
		4-نزول دم مع البول		

هل تود اضافة اية معلومه اخرى

للاستمارة_____

_____

النهاية

Annex (2): Study participation consent form

العوامل المساعدة للوقاية او لحدوث مرض سرطان غدة البروستاتا في فلسطين

يصيب سرطان غدة البروستات الرجال، ويعد من الامراض التي تزداد نسبة حدوثها مع تقدم العمر. ومن مضاعفات الاصابة به خلل في الجهاز البولي، فقدان الوزن، كما قد يؤدي إلى الوفاة في حالة عدم علاجه بشكل مناسب. واما الأسباب التي تسهم في حدوثه فهي غير معروفة بشكل كامل، ومع ذلك فهناك العديد من العوامل التي قد تساعد على الوقاية منه وتقلل من احتمالية الاصابة به مثل تناول الاسماك والفواكهة مع العلم ان عوامل اخرى قد تساعد على حدوثة مثل التدخين.

ومن هنا، يهدف هذا البحث إلى معرفة العوامل المرتبطة بحدوث سرطان غدة البروستات في المجتمع الفلسطيني والعوامل الاخرى التي قد تساعد على الوقاية منه. لذلك سنقوم باجراء مقابلات مع المرضى المصابين بهذا المرض والمراجعين لعيادات واقسام مستشفى بيت جالا الحكومي وعينة اخرى من المراجعين لهذه العيادات والغير مصابين به لمعرفة العوامل التي ساعدت على حدوثة عند المصابين وعدم حدوثة عند المجموعة غير المصابة، والتي قد تسهم في معرفة الاسباب التي قد تساعد في الوقاية منه والحد من مضاعفاته عند الاخرين. .

لقد قمنا بتجهيز استبانة تحتوي على أسئلة خاصة بأهداف الدراسة، لذا نرجو منكم الإجابة على أسئلة الاستبانة، آملين من حضرتكم إجابة كآفة الأسئلة بموضوعية تامة و بقراءة كل فقرة بتمعن و الإجابة عليها حسب التعليمات الواردة قبل كل سؤال. علما بأن المعلومات الواردة في الاستبانة ستستعمل لأغراض البحث العلمي فقط ونضمن لكم السرية التامة في المعلومات التي ستدلون بها. لذا نرجو منكم التوقيع بالموافقة على المشاركة لإتمام أهداف هذه الدراسة.

كما سنقوم بسحب عينة دم للاشخاص غير المصابين به لتحديد وضع غدة البروستاتا لديهم والتي يستطيعون الحصول على نتيجتها ان وافقوا على المشاركة في البحث.

شاكرين لكم حسن تعاونكم

لقد اطلعت على جميع التعليمات الواردة في هذه الاستبانة، وعليه قررت المشاركة في هذه الدراسة، وان وجود اسمي وتوقيعي هو دليل على قبولي للمشاركة في هذه الدراسة.

اسم المشارك : التوقيع_____

اسم الباحث : ياسر قاسم التوقيع_____

Annex (3): Distribution of study cases and control group by studied food intake

		Total N=120		Case N=60		Control N=60		*P* Value
		n	(%)	n	(%)	n	(%)	
Fruits	<2 times a week	15	(12.5)	8	(13.3)	7	(11.7)	0.082
	from 2-4 weekly	75	(62.5)	32	(53.3)	43	(71.7)	
	> 4 per weekly	30	(25)	20	(33.3)	10	(16.7)	
Citrus Fruits	<2 times a week	24	(20)	14	(23.3)	10	(16.7)	0.141
	from 2-4 weekly	38	(31.7)	14	(23.3)	24	(40.0)	
	> 4 per weekly	58	(48.3)	32	(53.3)	26	(43.3)	
Melon	<2 times a week	96	(80)	49	(81.7)	47	(78.3)	0.648
	from 2-4 weekly	24	(20)	11	(18.3)	13	(21.7)	
Vegetables	≤4 per week	37	(30.8)	15	(25.0)	22	(36.7)	0.166
	> 4 per weekly	83	(69.2)	45	(75.0)	38	(63.3)	
Cruciferous Vegetables	<2 times a week	100	(83.3)	43	(71.7)	57	(95.0)	0.001
	≥ 2 per week	20	(16.7)	17	(28.3)	3	(5.0)	
Fresh Tomato	<2 times a week	12	(10)	9	(15.0)	3	(5.0)	0.188
	from 2-4 weekly	27	(22.5)	13	(21.7)	14	(23.3)	
	> 4 per weekly	81	(67.5)	38	(63.3)	43	(71.7)	
Cocked Tomato	<2 times a week	84	(70)	35	(58.3)	49	(81.7)	0.005
	from 2-4 weekly	63	(52.5)	25	(41.7)	11	(18.3)	
Carrots	<2 times a week	109	(90.8)	53	(88.3)	54	(90.0)	0.769
	≥2per week	13	(10.8)	7	(11.7)	6	(10.0)	
Milk	<2 times a week	67	(55.8)	35	(58.3)	32	(53.3)	0.727
	from 2-4 weekly	17	(14.2)	9	(15.0)	8	(13.3)	
	> 4 per weekly	36	(30)	16	(26.7)	20	(33.3)	
Yogurt	<2 times a week	35	(29.2)	22	(36.7)	13	(21.7)	0.167
	from 2-4 weekly	52	(43.3)	22	(36.7)	30	(50.0)	
	> 4 per weekly	33	(27.5)	16	(26.7)	17	(28.3)	
Homemade Cheese	<2 times a week	82	(68.3)	34	(56.7)	48	(80.0)	0.005
	from 2-4 weekly	21	(17.5)	17	(28.3)	4	(6.7)	
	> 4 per weekly	17	(14.2)	9	(15.0)	8	(13.3)	
Homemade Butter	<2 times a week	106	(88.3)	51	(85.0)	55	(91.7)	0.255
	≥2 times per week	14	(11.7)	9	(15.0)	5	(8.3)	
Ice-Cream	<2 times a week	106	(88.3)	56	(93.3)	50	(83.3)	0.088
	≥2 times per week	14	(11.7)	4	(6.7)	10	(16.7)	
Butter Milk	<2 times a week	103	(85.8)	50	(83.3)	53	(88.3)	0.655
	from 2-4 weekly	11	(9.2)	6	(10.0)	5	(8.3)	
	> 4 per weekly	6	(5)	4	(6.7)	2	(3.3)	
Eggs	<2 times a week	33	(27.5)	12	(20.0)	21	(35.0)	0.050
	from 2-4 weekly	64	(53.3)	32	(53.3)	32	(53.3)	

	> 4 per weekly	23	(19.2)	16	(26.7)	7	(11.7)	
Red Meat	<2 times a week	60	(50)	24	(40.0)	36	(60.0)	0.025
	from 2-4 weekly	49	(40.8)	27	(45.0)	22	(36.7)	
	> 4 per weekly	11	(9.2)	9	(15.0)	2	(3.3)	
Chicken	<2 times a week	51	(42.5)	25	(41.7)	26	(43.3)	0.635
	from 2-4 weekly	58	(48.3)	28	(46.7)	30	(50.0)	
	> 4 per weekly	11	(9.2)	7	(11.7)	4	(6.7)	
Turkey	<2 times a week	115	(95.8)	57	(95.0)	58	(96.7)	0.648
	≥2 times per week	5	(4.2)	3	(5.0)	2	(3.3)	
Processed Meat	<2 times a week	93	(77.5)	41	(68.3)	52	(86.7)	0.016
	≥2 times per week	27	(22.5)	19	(31.7)	8	(13.3)	
Hot dogs	does not take or less than once monthly	86	(71.7)	39	(65.0)	47	(78.3)	0.098
	from 1-3 times monthly	27	(22.5)	15	(25.0)	12	(20.0)	
	once weekly	7	(5.8)	6	(10.0)	1	(1.7)	
Fish	does not take or less than once monthly	8	(6.7)	5	(8.3)	3	(5.0)	0.325
	from 1-3 times monthly	64	(53.3)	28	(46.7)	36	(60.0)	
	once weekly	48	(40)	27	(45.0)	21	(35.0)	
Canned Tuna	does not take or less than once monthly	29	(24.2)	15	(25.0)	14	(23.3)	0.932
	from 1-3 times monthly	48	(40)	23	(38.3)	25	(41.7)	
	once weekly	43	(35.8)	22	(36.7)	21	(35.0)	
Cola	<2 times a week	62	(51.7)	32	(53.3)	30	(50.0)	0.891
	from 2-4 weekly	34	(28.3)	17	(28.3)	17	(28.3)	
	> 4 per weekly	24	(20)	11	(18.3)	13	(21.7)	
Coffee	<2 times a week	21	(17.5)	10	(16.7)	11	(18.3)	0.931
	from 2-4 weekly	23	(19.2)	11	(18.3)	12	(20.0)	
	> 4 per weekly	76	(63.3)	39	(65.0)	37	(61.7)	
Tea	≤4 a week	9	(7.5)	3	(5.0)	6	(10.0)	0.298
	> 4 per weekly	111	(92.5)	57	(95.0)	54	(90.0)	
Green Tea	≤4 a week	112	(93.3)	55	(91.7)	57	(95.0)	0.464
	> 4 per weekly	8	(6.7)	5	(8.3)	3	(5.0)	
Water	≤3 daily	44	(36.7)	23	(38.3)	21	(35.0)	0.182
	from 4-5 daily	60	(50)	26	(43.3)	34	(56.7)	
	from 6+ daily	16	(13.3)	11	(18.3)	5	(8.3)	