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Epidemiological Indicators in Palestinian Cohort Women Affected with Breast Cancer

By

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In Partial Fulfillment of the Requirements for the Degree
of Master of Science in Biotechnology

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The undersigned hereby certify that they have read and recommend to the Faculty of Scientific Research and Higher Studies at the Palestine Polytechnic University and the Faculty of Science at Bethlehem University for acceptance a thesis entitled:

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ABSTRACT

Breast cancer is one of the major cancers in females in Palestine. Several factors are known to have an affect on risk of breast cancer such as age, cigarette smoking, emotional stress, hereditary and reproduction. The main goal of this study is to determine the major factors that are shared among women diagnosed with breast cancer in Palestine and whether these factors contribute to breast cancer risk development. The study was carried out through questionnaires that consist of more than 24 questions relating to the patient's familial and medical history. The data was collected from the Augusta Victoria Hospital (AVH) from reported cases attending treatment and counseling, starting from November 2007 to July 2010. 334 questionnaires were filled by the patients themselves or their immediate relatives. The data was analyzed using SPSS software. The things that characterize Palestinian women with breast cancer were studied.

The age of the breast cancer patients was studied and the percent of cancer in each age group was compared with national proportions. The average age at the time of breast cancer diagnosis was 47 years with a wide age range among women. When compared with other countries, we noticed that the average age of diagnosis is lower among Palestinian women than it is in some other countries.

The results showed that the patients had a family history of malignancy. Breast cancer has been 20.3 % in 1^{st} degree relatives and 25.9% in 2^{nd} degree relatives. Moreover, most of these women had mastectomy as they were diagnosed in late stage of the disease.

The mean age at First Full-Term Pregnancy (FFTP) was 24.1 years. The age when women were diagnosed with breast cancer and age at FFTP is found to be not significant. However, the time since first birth and age diagnosed with breast cancer is found to be significant.

Although this study is only the beginning, it is a necessary step in recognizing if epidemiological factors have an impact on cancer incidence in Palestine.

Keywords: Breast cancer, Risk Factors, Hereditary Cancer, Mastectomy, Palestinian Women, Augusta Victoria Hospital.

عنوان الرسالة مترجم للعربية

المؤشرات الوبائية لمجموعة نساء مصابات بسرطان الثدي في فلسطين

يعد سرطان الثدي من أكثر أنواع السرطان انتشارا في فلسطين. وهناك العديد من العوامل التي تساهم في ظهور سرطان الثدي مثل العمر والتدخين والوراثة. تهدف هذه الدراسة إلى تحديد العوامل المشتركة بين هؤلاء النساء المصابات بسرطان الثدي في فلسطين. بنيت هذه الدراسة عن طريق استمارات بحث كانت تحوي أكثر من أربعة وعشرين سؤالاً عن التاريخ الطبي والعائلي للمريضة.وقد تم جمع المعلومات من مستشفى المطلع في القدس من مريضات مصابات في سرطان الثدي اللواتي قدمن للمستشفى للعلاج, وقد تم جمع ثلاثماءة وأربعة وثلاثون استمارة من تاريخ تشرين ثاني سنة 2007 ميلادي حتى شهر تموز سنة 2010 ميلادي. ومن ثم تم تحليل هذه المعلومات عن طريق برنامج إحصائي لمعرفة الخصائص المشتركة فيما بينهم.

لقد تم حساب الوسط العمري ودراسة الفئة العمرية لهم ومقارنتها مع النسبة العالمية للنساء المصابات بسرطان الثدي. وقد وجد أن معدل الوسط العمري لمرضى سرطان الثدي في فلسطين يقارب السبعة والأربعين عاماً, وهي أقل بكثير من معظم الدول الأخرى.

أظهرت هذه النتائج أن التاريخ العائلي للمصابات يحتوي على نسب عالية من الأمراض الخبيثة, بحيث وجد أن هناك أفراد من العائلة مصابات بسرطان الثدي من ذوي الدرجة الأولى والثانية من القربى. وأن معظم السيدات خضعن لعمليات إزالة الثديكونهن شخصن في مراحل متأخرة من المرض.

لقد وجد أن معدل عمر النساء عند الولادة الأولى يقارب الأربعة وعشرون عاماً. وقد وجد أيضاً أن هناك علاقة تربط ما بين عمر المريضة عند تشخيصها بسرطان الثدي والزمن المحسوب لها بعد أول ولادة, بينما لم توجد هناك علاقة بين عمر المريضة عند التشخيص وعمرها عند أول ولادة لها.

تعتبر هذه الدراسة خطوة أولى مهمة في تحديد العوامل المؤثرة في زيادة الإصابة بسرطان الثدي في فلسطين.

DECLARATION

I declare that the Master Thesis entitled " **Epidemiological Indicators in Palestinian Cohort Women Affected with Breast Cancer**" is my own original work, and hereby certify that unless stated, all work contained within this thesis is my own independent research and has not been submitted for the award of any other degree at any institution, except where due acknowledgment is made in the text.

Name and signature: "Mary Odeh"

Date_____ August 2011

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In presenting this thesis in partial fulfillment of the requirements for the joint master degree in biotechnology at Palestine Polytechnic University and Bethlehem University, I agree that the library shall make it available to borrowers under rules of the library. Brief quotations from this thesis are allowable without special permission, provided that accurate acknowledgement of the source is made.

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Signature: "Mary Odeh"

Date: August 2011

Dedication

I would like to dedicate this Master dissertation to my family, especially…

To My Father and My Mother who in many ways gave me support and strength to continue to the end.

To My Brothers: George, Hanna and Simon for their patience and understanding.

To Abeer and Rasha for their encouragement and support.

To My beloved Niece Jessica for her love and big heart.

Acknowledgment

Life is really simple, but we insist on making it complicated

Confucius

This dissertation would not have been possible without the guidance and the help of several individuals who in one way or another contributed and extended their valuable assistance in the completion of this study.

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Many thanks are due to the women who participated in the study because without them this work could not have been completed.

Lastly, I offer my regards and blessings to all of those who supported me in any respect during the completion of this thesis.

Abbreviations:

AJCC	**American Joint Committee on Cancer**
α	**Significance level**
AVH	**Augusta Victoria Hospital**
BRCA1	**Breast cancer gene one**
BRCA2	**Breast cancer gene two**
BRCAPRO	**BRCA mutation carrier probability prediction model**
CI	**Confidence interval**
DCIS	**Ductal carcinoma in situ**
ER	**Estrogen receptor**
FNA	**Fine needle aspirator**
FFTP	**First full-term pregnancy**
HCAs	**Heterocyclic amines**
HTR	**Hormone replacement therapy**
LCIS	**Lobular carcinoma in situ**
NATs	**N-acetyl transferase 2**
PAHs	**Polycyclic aromatic hydrocarbons**
SD	**Standard deviation**
TDLU	**Terminal duct lobular unit**
TNM	**Tumor size(t), Lymph node involvement(N), Distance metastasis (M)**
UK	**United Kingdom**
USA	**United State of America**

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CHAPTER 1

Introduction

1.1 Breast Anatomy

Despite the advancement of medical technology, nothing has been discovered that can stop cancer from invading the breast tissue of women. Its etiology and prevention are still a dilemma that needs solving and more investigation. To understand the different types of breast cancer, from where it originates or how it is developed, anatomy of the breast is briefly discussed in this research and further illustrations of the most important structures are seen in Figure 1.1.

Breast lies anterior to the chest wall between the third and seventh ribs which are supported by both the pectoral muscles and superficial fascia. Cooper's ligaments which are made up of fibrous tissue surrounds the breast glands and keep their shapes and position. Each breast is divided by these ligaments into 15-25 lobes that are divided into many lobules which is sometimes called ductal lobular unit in which the most common type of breast cancer originates (from the epithelial cells of this unit). In turn, each lobule is subdivided into 10 to 100 alveoli capable of producing milk. Ducts transport milk from alveoli to the nipple under the influence of reproductive hormones. The nipple is made up of epithelial, glandular, erectile, and nervous tissue that is surrounded by a darker area called areola [1]. Fat and fibrous tissues fill the spaces between the lobules and ducts. Reproductive hormones are important in the development of the breasts in puberty and in lactation. Estrogen promotes the growth of glands and ducts while progesterone stimulates

the development of milk producing cells. Prolactin stimulates milk production and oxytoxin is responsible for milk ejection from the lactating breast [2].

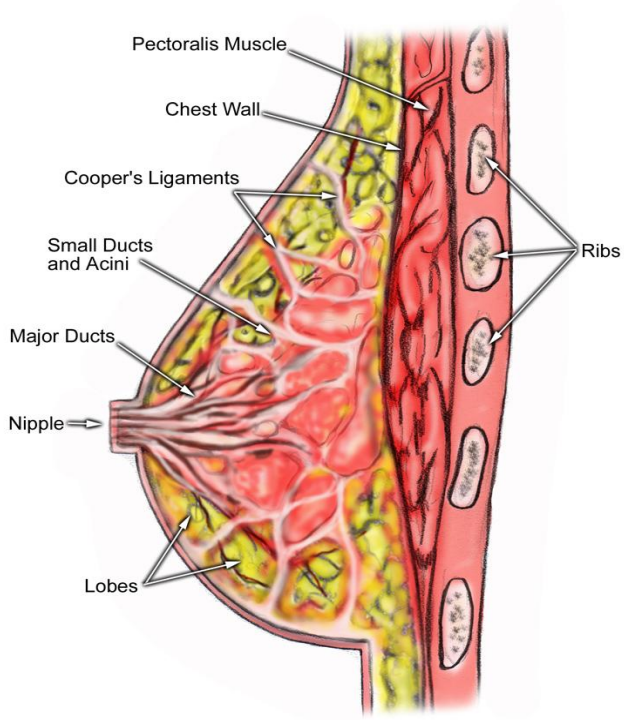

Figure 1.1: Breast anatomy: image from emedicine.medscape.com/article/346529-overview [3].

1.2 Breast Cancer

Breast cancer is considered to be the most common type of cancer in women and the second leading cause of mortality in females after lung cancer [4]; it occurs in men but it is rare. Breast cancer is a disease in which some types of cells become abnormal and start to multiply without order or control. The tumor can grow and spread to nearby tissue or the cells can break away and enter the blood or lymphatic system affecting other organs. This spread of cancer is called metastasis [5]. The most common form of cancer occurs in the ducts of the breast, so it is called ductal carcinoma. The second type is a less common

form of breast cancer and occurs in the lobules, so it is called lobular carcinoma; both of them are classified as non-invasive or invasive.

1.3 Types of Breast Cancer

The followings are the most occurring types of breast cancer among women [6]:

1. Invasive ductal carcinoma:

It is the most common type of breast cancer. Between 70-80% of cases, the cells have broken out of ducts with a chance to spread into nearby lymph nodes or other parts of the body.

2. Invasive lobular breast cancer:

It is the second most common type of breast cancer after invasive ductal carcinoma, about 10% of invasive breast cancers are invasive lobular carcinomas. It is an advanced aggressive form of cancer, which starts out in the milk ducts and proceeds to invade the tissues of the breast.

3. Ductal carcinoma in situ-DCIS:

The tumor is inside the ducts where it has not spread to the lymphatic system or the body yet.

4. Lobular carcinoma in situ-LCIS:

Although it is not considered to be a cancer, there is a tendency for some changes to occur in the lobes and eventually end up with a high risk of development into breast cancer.

5. Inflammatory breast cancer:

Only 1-2% is present of this type. When the cancer cells become inflamed, they block the smallest lymph channels in the breast.

6. Paget's disease:

It is a rare type of breast cancer that accounts for 1-2% of the cases. It starts in the nipple or areola as a red and scaly rash.

The followings are some rare types of breast cancer [6]:

1. Triple-negative breast cancer.
2. Medullary breast cancer.
3. Mucinous breast cancer.
4. Tubular breast cancer.
5. Adenoid cystic carcinoma of the breast.
6. Papillary breast cancer.
7. Metaplastic breast cancer.
8. Angiosarcoma of the breast.

9. Phyllodes or cystosarcoma phyllodes.

10. Lymphoma of the breast.

11. Basal type breast cancer.

1.4 Breast Cancer Staging

According to the American Joint Committee on Cancer (AJCC), classification of tumor is determined by using information about tumor size, how far it has spread within the breast and nearby organs (T), lymph nodes involvement (N), and the presence or absence of distant metastasis (M). Once the T, N, and M are determined, a stage of I, II, III, or IV is assigned, where stage I being an early stage and stage IV being the most advanced one [7].

An important step in evaluating breast cancer is to test a portion of the biopsy to see if it has estrogen and progesterone receptors.

Cancer cells may contain neither, one, or both of these receptors. Breast cancers that contain estrogen receptors are often referred to as *ER-positive* (or ER+) cancers, while those containing progesterone receptors are called *PR-positive* (or PR+) cancers.

1.5 Epidemiology of Breast Cancer

Epidemiology is the study of the distribution and determinants of a disease in human population. It is mostly concerned with description and analysis of the causes of a disease, discovering the relative frequencies of it, studying the causal factors and finally trying to prevent its occurrence. The main objective of epidemiology is to identify the risk factors

and to quantify their significance. A risk factor can influence the probability that a specific disease develops either through environmental influences, genetic predisposition or behavioral characteristics.

Causes of breast cancer are still unknown, but studying some of the risk factors continues to be significant in many epidemiological studies. The incidence of breast disease and mortality rates is increasing. Breast cancer could either occur by chance or by multiple factors including lifestyle, environmental and hormonal factors. Some of these factors women have little control on such as gender and age. The reason that breast cancer is also rare in men suggests directly an influence of sex steroid hormones. Table 1.1 shows the relative risk of each factor and the group of people with high risk. **Relative risk** compares the risk of disease among people with a particular exposure to the risk among people without that exposure. If the relative risk is above 1.0, then the risk is higher among exposed than unexposed persons. The relative risk can theoretically range from 0 to positive infinity, assuming no association when the relative risk being 1. Below is a description for some of these risk factors:

1.5.1 Age

Aging is one of the major risk factors for breast cancer, as the incidence rate being 0.3% for women under the age of 30, increasing rapidly around the age of 35, and then continually throughout life [8]. Although the incidence rate doubles every 10 years; it slows down around age of 50 which is the average age of menopause [9] Figure 1.2.

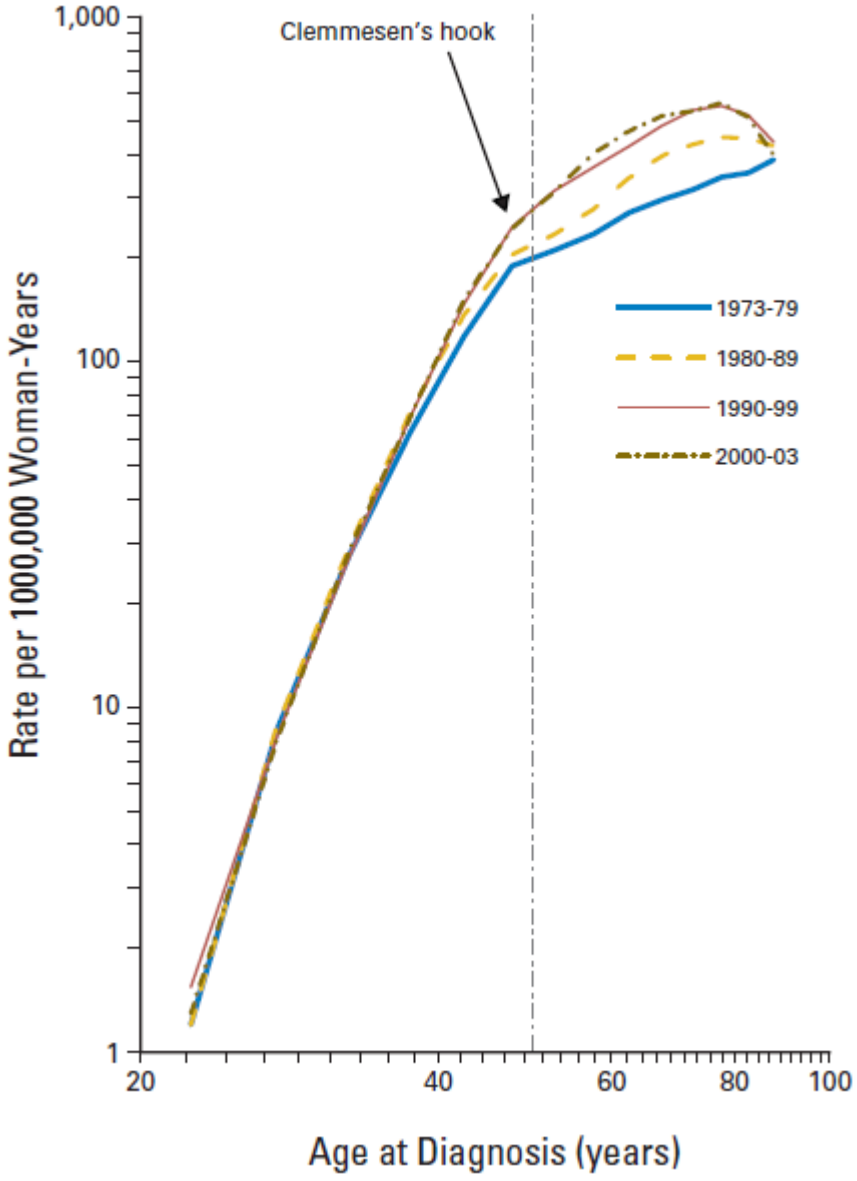

Figure 1.2: Age-specific incidence rates for the Surveillance, Epidemiology, and End Results 13 Registry Database by four calendar periods. For all time periods, age-specific rates increased rapidly until age 50 years, paused at the so-called Clemmesen's hook that has been attributed to menopause, and then rose at a slower pace [10].

Table 1.1: Risk Factors of Breast Cancer.

Factor	Relative Risk	High Risk group
Age	**>10**	**Elderly**
Reproductive Factors:		
Age at menarche	**3**	**Before age 11**
Age at menopause	**2**	**After age 54**
Age at first full pregnancy	**3**	**Nulliparous or first child in early 40s**
Family History:	**≥ 2**	**Breast cancer in 1st degree relative**
Previous benign breast disease	**4-5**	**Atypical hyperplasia**
Cancer in other breast	**>4**	**Previous breast cancer**
Breast density	**>5**	**mammographically dense**
Lifestyle:		
Diet	**1.5**	**High intake of saturated fat**
Bodyweight(post menopause)	**2**	**High body max-index**
Alcohol consumption	**1.3**	**Excessive intake**
Radiation	**3**	**Abnormal exposure after age 10**
Hormonal Status:		
Oral contraceptives	**1.2**	**Current users**
Hormonal replacement therapy	**1.66**	**Use for ≥ 10 years**
Geographical Location	**5**	**Developed countries**

Source: The table was adopted from McPherson [11].

1.5.2 Reproductive Factors

Early menarche, late age at menopause and late age at first full-term pregnancy (FFTP) increase the risk of developing breast cancer. The reason behind this increase returns to the long term exposure to estrogen levels. Estrogen has a role in stimulating ductal growth and increasing cell proliferation rates, subsequent DNA synthesis, and finally increasing the chance of mutations [12].

1.5.2.1 Menarche.

Early menarche is a risk factor for breast cancer. The relative risk is two-fold at young ages for women with menarche before the age of 12 compared with women with menarche at age 13 or more [13]. This suggests that long time exposure of the breasts to the high levels of ovarian steroids in premenopausal as well as in postmenopausal women increases the risk [14]. It was concluded that a delay of menarche of two years corresponds to 10% reduction in breast cancer risk [15].

Women with early menarche (age 12 or younger) and rapid establishment of regular cycles have an almost four-fold increased risk of breast cancer compared to women with late menarche (age 13 or older) and long duration of irregular cycles [16]. The reason behind this is that the early menarche women have in their reproductive life the higher proportion of menstrual cycles (they will get), and subsequently will be exposed to higher levels of estrogen [17]. It seems that during menstrual cycles, estradiol levels are low in the early follicular phase, peaks midcycle at about the time of ovulation. Although it declines somewhat in the luteal phase, it remains elevated until the beginning of the next cycle [18]. In the luteal phases, the epithelial cells of the terminal duct lobular unit

(TDLU) from which the vast majority of breast cancers arise undergo division by rates of twofold higher than the follicular phase. As the duration of luteum is constant in most women from month to month, a woman with regular short cycles will spend more time in luteum than women with irregular longer cycles [19].

The total duration of menstruation also appears to be important as a risk factor for breast cancer. Women who menstruate for more than 30 years are at increased risk compared with those who menstruate for less than 30 years [20].

1.5.2.2 Menopause.

Late age at menopause is associated with greater risk of breast cancer. When comparing a woman with menopause at age 45 to a woman with a menopause at age 55, risk is lowered by 30% [21]. During the postmenopausal period, epithelial-cell proliferation is greatly lower than during the premenopausal period due to the fact that serum estradiol falls to a low level and progesterone is absent [22]. Among women who stop menstruating before age 45 years, breast cancer risk is about two times lower for those whose cycle stops naturally vs. through surgery. It is approved by many studies that for every 5 years difference in age at menopause, the risk for breast cancer changes by about 17 percent [23]. Animal studies have shown repeatedly that estrogens are able to induce and promote mammary tumors and the removal of the ovaries early in life are at markedly reduced risk of subsequently developing breast cancer. The earlier it is done, the greater is the reduction [24].

1.5.2.3 Parity.

Both pregnancy and age at first full-term pregnancy (FFTP) are predictor risks for breast cancer. Many results showed that single women and nulliparous married women have a higher risk of developing breast cancer that is 1.4 times higher than parous married women [25]. Women with at least one child have lower risk factors than nulliparous women. It is estimated that for each child born, there is a decrease of breast cancer risk by an average of 7%, especially if these women gave birth early in their lives [26]. Also, young age at first birth gives a protective effect due to the fact that earlier in life cells undergo differentiation, the decreasing mammary cells proliferation. For example, women who give birth at age 20 years or earlier have about half the breast cancer risk as women who gave birth at age 30 years or above. This is due to changes in the endocrine function that occur at different times in a woman's life that effect her risk of developing breast cancer.

Abortion is not excluded from being a risk factor for breast cancer. Hormonal changes that occur during pregnancy promote breast cells differentiation and if pregnancy for some reason had not been completed; the growth and differentiation of cells would also be incomplete [27]. Estrogens stimulate the growth of the breast ducts and rushes of progesterone causing the glandular tissue to expand. So there will be a susceptibility of breast carcinogenesis development.

1.5.2.4 Lactation.

Breastfeeding plays a protective role against breast cancer. This could be due to the fact that breast-feeding lowers a woman's total number of menstrual periods and lowers

estrogen levels as doe's pregnancy. Breast-feeding may be more protective against the development of premenopausal compared to postmenopausal breast cancer. Women breastfeeding for at least one year may reduce their rate of developing breast cancer by nearly 50 percent compared to women who have never breastfed. Some studies discovered that women who breastfed for at least 13 months - or had breastfed more than three children had about half the risk of developing breast cancer than women who had never breastfed [28].

1.5.3 Family History

Having a first-degree relative who has breast cancer doubles the risk of the woman having breast cancer. If two or more first degree relatives have breast cancer, the risk is increased further [29]. The number of relatives affected, bilateral, relatedness of the affected cases, and age of onset of breast cancer are important factors to consider when relating to family history [30]. There are several patterns of inheritance, one that might be described as hereditary and another, as a familial aggregation. The former implies a direct inheritance of a specific genetic defect and the later, a predisposition dependent on interaction with environmental factors [31].

Genetic breast cancer constitutes a small percentage of all breast cancers, most likely less than 5-10%. Out of these percentages 80-90% of hereditary breast cancer cases are caused by mutations in the BRCA1 and BRCA2 genes. Other important clinical genetic predispositions include Cowden syndrome, Li-Fraumeni syndrome, Peutz-Jeghers syndrome, and ataxia- Telangiectasia [32]. At least three generation of family history including ethnic background is needed in order to identify hereditary breast cancer. Both

BRCA1 and BRCA2 are inherited as autosomal dominant with incomplete penetrance. The major causes are believed to be life time exposure to environmental and lifestyle factors, acting either alone or in combination with susceptibility genes of lower penetrance [33].

1.5.4 Exogenous Hormones

The use of exogenous hormones, either as hormone replacement therapy (HTR) or as oral contraceptives, have become an important issue in human carcinogenesis because the number of case reports suggesting its relation to hormone use is increasing due to the increased hormone consumption from various medical treatments [34].

1.5.4.1 Hormone Replacement Therapy

The use of combined HRT decreased sharply in the United States after the HRT part of the Women's Health Initiative study was stopped in 2002. Millions of women had been taking menopausal estrogen and progesterone (hormone therapy, HT) for prolonged periods, so as to lessen menopausal symptoms, prevent osteoporosis and prevent coronary heart disease, which contributed to estrogen exposure and increased the risk of breast cancer development [35]. The incidence of breast cancer, including all histological types combined, was increased by 60 to 85% in recent long-term users of HRT, whether estrogen alone or estrogen plus progestin [36].

1.5.4.2 Oral Contraceptives

Women currently using combined oral contraceptives or who had stopped using them within the last 10 years had an increased risk of breast cancer [37]. Increasing the duration of use and age at first use had little effect on relative risks, although the first use of oral contraceptives under the age of 20 did increase the relative risk for breast cancer in women being diagnosed at a young age. It is also found that oral contraceptives which were used in the 1930's by millions of women contributed to 1.3-1.5% increase in breast cancer before the age of 40-50 years [38].

1.5.5 Lifestyle

1.5.5.1 Obesity

A two-fold increase in the risk of breast cancer in post menopausal women is associated with obesity. This is done by two mechanisms. The first one occurs when circulatory estrogens are produced from adipose tissue via the enzyme aromatase, so excess adipose tissue in postmenopausal women increases serum estradiol levels. The other mechanism occurs through leptin, Leptin levels are increased due to obesity, and they have been shown to stimulate growth of estrogen receptor (ER) positive breast cancer cell lines [39].

1.5.5.2 Alcohol

Alcohol intake by itself is a risk factor for breast cancer as reported by many studies. Over 70 studies showed direct relationship in premenopausal and postmenopausal women in breast cancer risk increase by 7% for every 10 grams of alcohol consumed per day [40].

1.5.5.3 Diet

Breast cancer is a heterogeneous disease, and dietary factors may differentially affect certain breast cancer subtypes [41].

The role of specific dietary factors in the etiology of breast cancer has not completely been determined. Results from prospective studies do not support the concept that fat intake in middle life has a major relation to breast cancer risk. However, weight gain in middle life contributes substantially to breast cancer risk [42]. A Link between dietary fat and breast cancer has been reported, as specific types of fat could differentially affect risk for breast cancer. In most animal studies, it was seen that diets high in polyunsaturated fat but typically at levels beyond human exposure, have clearly increased the occurrence of mammary tumors.

On the other hand, polycyclic aromatic hydrocarbons (PAHs) and heterocyclic amines (HCAs) are carcinogens formed in or on the surface of well-done meat, cooked at high temperature. These results support the accumulating evidence that consumption of meats cooked by methods that promote carcinogen formation may increase risk of postmenopausal breast cancer [43].

1.5.5.4 Smoking

The epidemiological studies concerning smoking and breast cancer risk have been inconsistent, but recent studies have proved that smoking increases breast cancer risk. This comes from three recent meta-analysis and a pooled analysis, which found increases of 35% to 50% in breast cancer risk for long-term smokers who have one of several N-acetyltransferase 2 (NAT2) slow acetylation genotypes [44]. Among slow acetylators,

smoking intensity rather than smoking duration is the most greatly affected breast cancer risk. Among rapid acetylators, neither intensity nor duration of smoking increased the risk [45].

Exposure to tobacco smoke at a young age either by direct or passive smoking may be related to an increased breast cancer risk [46]. Animal experiments and *in vitro* studies have shown that compounds found in tobacco smoke, such as polycyclic hydrocarbons, aromatic amines, and *N*-nitrosamines, may induce mammary tumors [47].

1.5.5.5 Physical Activity

Exercise is a protective against breast cancer in both premenopause or after menopause. The reduction in breast cancer risk reaches 20-40% among the most physically active women, regardless of menopausal status, type or intensity of activity [48].

1.5.6 Mammogram Density

Women with dense breasts in more than 75% of the breast have four - to six-fold increased risk of developing breast cancer compared to those with little or no density.

Density is influenced by age, parity, body mass index, and menopause. Age and BRCA1 and BRCA2 mutations increase the risk of developing breast cancer even more [49]. Mammographically dense breast tissue is associated both with epithelial proliferation and with stromal fibrosis. The relationship between these histological features and the risk of breast cancer may be explained by the known actions of growth factors that are thought to play important roles in breast development and carcinogenesis. Mammographically dense

tissue differs from most other breast cancer risk factors in the strength of the associated relative and attributable risks for breast cancer because it can be changed by hormonal and dietary interventions. This risk factor may be most useful as a means of investigating the etiology of breast cancer and of testing hypotheses about potential preventive strategies [50].

1.5.7 Benign Breast Disease.

Fibrocystic disease is associated with increased risk for breast cancer development. The histological studies from biopsy of different specimens taken from benign breast diseases showed to have cellular proliferation. While simple hyperplasia doubles the risk, atypical hyperplasia increases the risk by four to five folds [51]. A number of clinical factors appear to modify the risk associated with these lesions including the time since biopsy, menopausal status, and family history of breast cancer. The recent trend is going to focus on the potential of biological, molecular, and genetic markers in assessing breast cancer risk in patients with benign breast disease.

1.5.8 Geographic and Socio-economic Variations.

Both geographic and socio-economic variations play a role in increasing the incidence and mortality for breast cancer occurrence. Incidence rates vary by 5 folds among countries. However, the incidence is higher among women of upper rather than lower social class. It is more common in Jewish women rather than non-Jewish women. Rates are lowest in Asia and the Third World Counties than in North America and Europe. The

American white and black populations have the highest incidence rates. These variations are due to social and environmental factors rather than genetic factors [52].

1.5.9 Ionizing Radiation

Exposure of teenage girls to ionizing radiation during rapid breast formation allows an increased risk in breast cancer formation [53]. The exposure of female breasts to ionizing radiation can cause genetic damage for normal cells and thus contributing significantly to breast cancer development.

1.6 Trends in Breast Cancer Occurrence

Female breast cancer is the most common cancer among women in both developing and developed areas. Globally, it is the principal cause of death from cancer among women. It accounts for over one-fifth of the estimated annual 4.7 million cancer diagnoses in females, and the second most common tumor after lung cancer in both sexes [54].
More than one million new cases of breast cancers are diagnosed annually. The outcome incidence rates of these cases depend on geographical variation, socioeconomic status, race, and ethnicity. Much of these variations were reflected through the changes that occurred to reproductive status, such as delayed childbearing and having fewer children, which are recognized as risk factors for breast cancer [55].

Generally the highest incidence rates are found in Switzerland, U.S. whites, Italy, and many other European countries, whereas low rates are found in Africa, Asia, and South America [56]. According to Globocan database 2008 the incidence rate differs from 19.3 per 100,000 women in Eastern Africa to 89.7 in Western Europe. In the developed region

of the world, the incidence rate reaches 80 per 100,000 population while in most of the developing countries the incidence rate accounts for less than 40 per 100,000 population. On the other hand the highest incidence rates occurred in northern Europe, northern America, Australia and New Zealand, while Southern and Eastern Europe have lower incidence rates Figure 1.2. There is an upward trend in incidence of breast cancer occurrence in developing countries consistent with the adoption of unhealthy westernized lifestyles such as smoking, physical inactivity, consumption of calorie-dense food, changes in childbearing and breast feeding, and exogenous hormonal intake [57].

Trends of breast cancer occurrence differed from the year 1980 to 2006 for invasive breast cancer. While the highest peak of incidence is seen in 1999, during the administration of mammography screening, rising rates of obesity and menopausal hormone usage [58], a sharp decrease in breast cancer incidence rates have been recorded between 2002 and 2003 among women aged 50-69 years due to menopausal hormone use. However, breast cancer incidence rates have remained relatively stable since 2003.

Looking at in situ breast cancer incidence rates, a rapid increase during the 1980s and 1990s occurred for the reasons mentioned earlier. Above all, the increase was observed in all age groups, although it was highest in women aged 50 years and above. Since 1999 the incidence rates of in situ breast cancer decreased among women aged 50 years and older, but continued to increase in younger women [59].

Comparing the age of American women, it was found that after the age of 40, White women have higher incidence rate while before the age of 40 years the African American women have higher incidence rates of breast cancer [60].

The incidence of small tumors (≤ 2 cm) and localized disease was consistently higher in White women, whereas the incidence of larger tumors (> 5 cm) and distant-stage disease was higher in African American women [61].

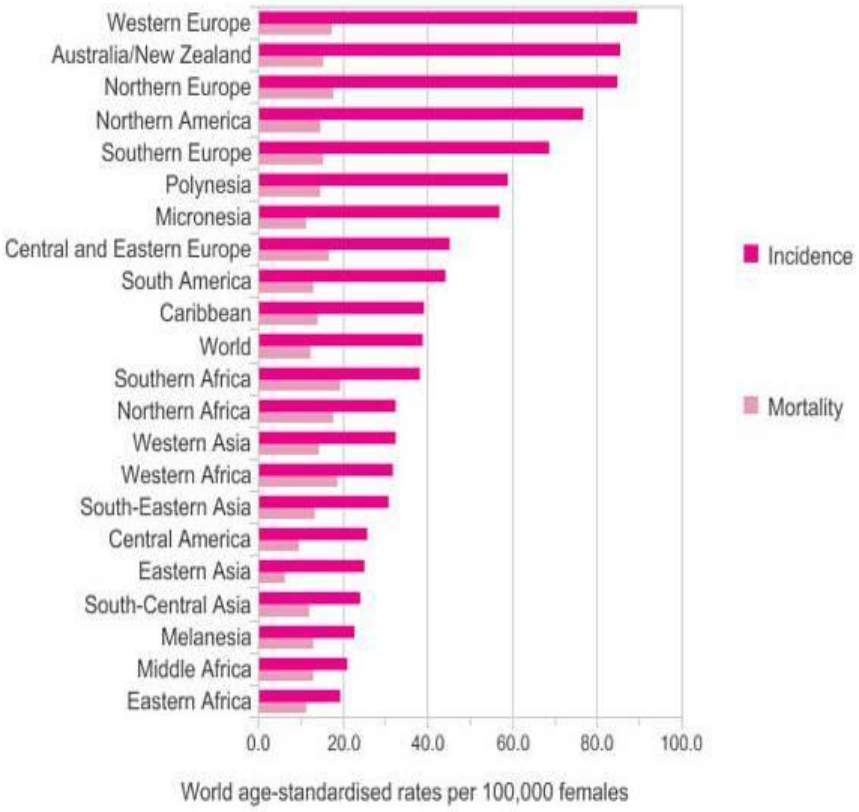

Figure 1.3 Breast Cancer incidence rate worldwide [62].

1.7 Breast Cancer Prevention

Both earlier detection and better treatment of breast cancer are contributing to the recent decline in breast cancer mortality. Different strategies are used to reduce breast cancer incidence. Chemoprevention and breast cancer risk-assessment models are some of them:

1.7.1 Chemoprevention

Chemoprevention is the use of drugs to reduce the incidence of breast cancer. Among these are the followings [63, 64]:

1. Tamoxifen: is a drug that blocks some of the effects of estrogen on breast tissue. It has been used to reduce the risk of recurrence in localized breast cancer and also as a treatment for advanced breast cancer when the tumor is estrogen-receptor positive.
2. Raloxifene: it blocks the effect of estrogen on breast tissue that is used to reduce the risk of invasive breast cancer as well as non-invasive cancer (DCIS or LCIS).
3. Aromatase inhibitors: these drugs are used to prevent breast cancer recurrences. They work by blocking the production of small amounts of estrogen that post-menopausal women normally produce.
4. Retinoids: Vitamin A analogs or retinoids were shown to inhibit the in vitro and in vivo growth of breast tumor cells.

1.7.2 Breast Cancer Risk-Assessment Models

Breast cancer risk assessment provides a guide to estimate a woman's risk of developing invasive breast cancer through her lifetime. A woman's risk of developing breast cancer occurs through two pathways: the first includes the chance of developing breast cancer over the lifespan of her lifetime, and the second through the chances of having a mutation in known genes such as BRCA1 or BRCA2, as both of these genes accounts to 80-90% of the hereditary breast cancer cases [65]. To overcome this problem,

different models are produced to reduce a woman's chance of developing or dying from breast cancer. Some of these models are the following [66, 67]:

1. Gail Model: This model focuses on non genetic risk factors and is based on statistical tool of using personal reproductive history as age at menarche, age at first live birth, and number of previous breast biopsies. History of atypical hyperplasia, and the number of 1^{st} degree relatives diagnosed with breast cancer, age and race are also included. The model has limitation of being incapable of predicting breast cancer risk for a woman with hereditary breast cancer family and for a woman with a paternal family history of breast cancer [67].

2. Claus Model: This tool is applied on families with breast cancer and focuses on family history, age at breast cancer diagnosis, and also incorporates either a maternal or paternal family history of 1^{st} and 2^{nd} degree relatives. It is applicable to women who do not have a personal history of breast cancer [67].

3. Couch Model: This tool is used to identify the BRCA1 gene. The predictive factors included average age at breast cancer diagnosis in the family less than 55 years, ovarian cancer in the family and Ashkenazi Jewish ancestry. The model estimates the probability of finding a mutation within a family with at least two cases of breast cancer based on best-fit multivariate logistic regression [66].

4. Frank Model: It is based on logistic regression analysis to predict the risk of a mutation in either the BRCA1, or BRCA2 genes for a woman diagnosed with invasive breast cancer before the age of 50 years or with ovarian cancer at any age [66].

5. Shattuk Eiden: Uses logistic regression to predict the probability of carrying a BRCA1 mutation; it takes age of patient at diagnosis, total number of relatives diagnosed with either breast cancer or ovarian cancer and Ashkenazi Jewish ancestors [66].

6. BRCAPRO: Uses mendalian genetics with Bayesian methodology to calculate risk mutation of BRCA1 and BRCA2 on personal and family history of breast cancer and ovarian cancer and includes information on both affected and unaffected relatives.

Besides the preventive strategies mentioned above; preventive surgery is used for women with very high breast cancer risk, of these preventive (prophylactic) mastectomy and prophylactic oophorectomy [67].

1.8 Breast Cancer in Palestine

Female breast cancer among Palestinian population is the most common type of cancers. Breast cancer in the Palestinian women is continuously increasing; it occurs at younger age at onset and advanced stage at presentation. According to the registry center in Gaza Strip, the incidence of breast cancer is 60 per 100,000 population making it the most prevalent type of cancer (16.4%) [68]. The Palestinian health ministry reports showed that 60% of women in Gaza Strip were diagnosed after the disease had already spread to other parts of the body, in particular 42.2% of these cases the disease had spread to the lymph nodes at the time of diagnosis [69].Tumors in the Palestinian women tended to be large, as they are detected late by physical examination and not by screening mammography. A study was made among Palestinian women who are resident in the West Bank to evaluate the use of screening method and mammography for the detection

of breast cancer. The study revealed that more than 70% had never undergone mammography or clinical breast examination and 62% done self breast examination [70]. Large tumors are diagnosed in advanced stages because most women fear of cancer and fear of social withdraws that affects woman's standing in the community and affects her daughter's chances of being married. Adding to this, the ignorance about the disease itself and the difficulty of access to the breast health care centers.

Currently, there is a trend of modernization of life style. This includes dietary habits, lack of physical activity and urbanization, even smoking of narghilea and delay of ages at marriage and first pregnancy from the late teens and early twenties to the late twenties as seen in many Arab countries [71].

Unfortunately the epidemiological studies concerning Palestinian population are hardly available which make this study to be one of the scarce studies done in Palestine concerning epidemiological risk factors of breast cancer among Palestinian women. The fact that there is a general lack of central registry of all cancer cases in Palestine and accurate data of cancer is one of the limitations made to this study. Therefore, the incidence rates about breast cancer cases are difficult to obtain accurately. The West Bank and Gaza Strip have two registries for registration that follow-up with all cancer cases. These cancer data are underestimated because some of the patients use services outside this country or in Israel.

Palestine has been undergoing a rapid demographic, industrialized and epidemiologic transition in the last decades. This transition affected the age group of the Palestinian population. Approximately 71% of the population is now under the age of 30 years and

about 3% of the population is aged above 65 years [72], while in many countries 15-25% of the population is above 65 years.

The history of breast cancer cases reported that in 1998 and 1999, a total of 3474 cancer cases were registered across Gaza Strip and the West Bank. The crude incidence rate for breast cancer in females was 17.3 per 100,000 population, in comparison with Jordan which was 21.3 per 100,000 in 1997. The mean age for female breast cancer in the West Bank was 51 years and in Gaza Strip it was 50 years. Histopathological distribution of these cases showed that 70% were infiltrating duct carcinoma, and 3.6% were lobular carcinoma. The highest incidence rates for breast cancer in general were registered in Bethlehem followed by Khan Younis, Jericho, Salfit and Gaza city. This disease caused the highest cancer-related mortality rate in Palestinian women and reported in 1998-1999 to be 30% [73].

The reported breast cancer cases among all other reported cancers in the West Bank, Palestine in the years 2000-2009 are illustrated in Table 1.2, which shows that the incidence rate for breast cancer is increasing [74].

Table 1.2 Distribution of Reported Breast cancer Cases by Year, West Bank, Palestine 2000-2009.

Year	Reported Breast cancer cases	All Reported Cancer Cases	Percent
2000	118	1069	**11.0**
2001	169	1230	**13.7**
2002	156	1078	**14.5**
2003	155	1186	**13.1**
2004	190	1330	**14.3**
2005	147	1179	**12.5**
2006	126	1168	**10.8**
2007	175	1210	**14.5**
2008	170	1292	**13.2**
2009	206	1312	**15.7**
Total	1612	12054	**13.4**

For instance the crude incidence rate was 43.1 per 100,000 population in 2005. In particular 49.2 per 100000 in the West Bank and 32.7 per 100,000 in Gaza strip [75]. By 2010 breast cancer cases reported to represent 18.8 % of all types of cancer in both males and females which made breast cancer to be the most prevalent cancers among the Palestinian population Figure 1.4 [76].

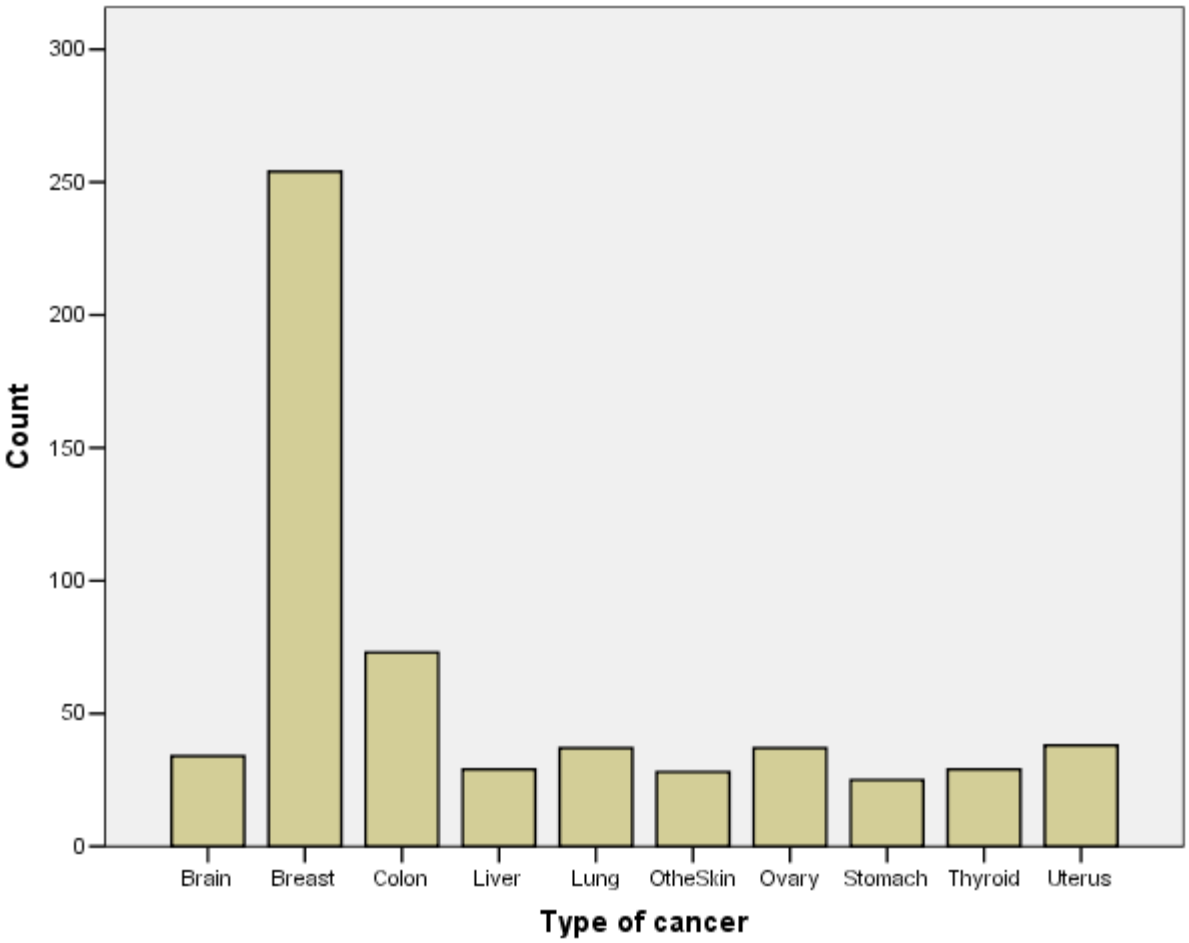

Figure 1.4 Distribution of Top Ten Repoted Cancer Among Females, West Bank, Palestine, 2010

In 2010 there had been 1350 new cancer cases reported in the West Bank, 719 cases were in females. Among these values 251 cases were for breast cancer and this accounts for 18.8% of all reported cancers in both males and females cancers in the West Bank.

In general, cancer is reported to be the third leading cause of death in Palestine in 2010, with death rate of 10.8% compared to 10.3% in 2007 from the total deaths in West Bank. Lung cancer ranked one (17.9%) then colorectal and breast cancer ranked second (11.3%) in cancer death rates.

Breast cancer incidence rates in Palestine seem to be similar to that in the nearby countries except Lebanon (Table 1.3) [77].

In the Arab population breast cancer patients tend to be young and almost half of them are below the age of 50, with a median age of 49-52 years compared to the age of 63 in industrialized nations. Epidemiological findings point to the same risk factors as in the Western world. A positive family history of breast cancer, young age at menarche, late age at last full term pregnancy and wide inter-birth interval were significant predictors for occurrence in Egypt [78]. Post-menopausal obesity is a significant risk factor in Jordan, along with number of pregnancies (more than 4) [79].

Table 1.3 Site-specific (breast cancer) proportions in Palestine and in neighboring countries.

	West Bank	**Israeli Arabs**	**Israeli Jews**	**Jordan**	**Lebanon**
Year	**2005**	**2000**	**2002**	**2002**	**1998**
Breast: site-specific proportions of all cancers	31.4%	27.7%	31.5%	32.5%	46.7%

1.9 Objectives of the Study

1. To define and understand the size of breast cancer problem and the pattern of its occurrence in Palestine.
2. To identify breast cancer risk factors in Palestine.
3. To show how to use breast cancer data as an important source of epidemiological and clinical studies.
4. To utilize data on breast cancer incidence and prevalence as a tool for cancer prevention and control in a cost-effective manner.
5. To evaluate trends in breast cancer incidence in Palestine by age group.
6. To study the relationship between breast cancer and different demographic factors, hormonal and reproductive factors contributing to the disease.

CHAPTER 2

Data Collection and Methodology

2.1 Data Collection

The purpose of this research was to study the epidemiological indicators of breast cancer cases among the Palestinian women. In order to do that a questionnaire developed primarily by Mary-Claire King, a PhD professor in the University of Washington School of Medicine in the United States was used. The questionnaire was translated and modified according to the traditions and behaviors of the Palestinian population. The questionnaire was designed to contain details about the general profile of the present and past health experience, demographic characteristics, selected personal and family medical history, questions about menstrual and reproductive history and lactation, and the presence or absence of known risk factors for breast cancer.

The questionnaire consisted of 24 major questions. All filled questionnaires were given codes, and then patients names were removed and administered to the computer to maintain confidentiality. The date of birth and the date of inclusion in the study were recorded for each woman.

The overall number was three hundred and thirty four filled questionnaires. The information in the questionnaires was presented systematically as follow:

The first part of the questionnaire gave personal information (name, residence, telephone number, birth date and place). The country of origin for the ancestors for each participant was also recorded.

The second part of the questionnaire gave information about family history of cancer cases among: grandmothers, aunts and uncles from the mother's and father's side, type of cancer, age at diagnosis, date of birth and, if deceased, age at death. Information about immediate relatives in the family who had any type of cancer was also recorded.

Information about the father, mother, sister(s), brother(s), daughter(s) and son(s) were recorded regarding presence or absence of cancer, type of cancer, age at diagnosis, age, if deceased and the age at death.

The third part was concerning other diseases that are genetically inherited and occurred frequently in the family.

The forth part of the questionnaire concentrated on the reproductive factors of the participants, such as, the first time menarche, if it was started by itself, and if not, what was the reason, and questions about how regular the periods have been.

Questions about the Current menstrual status were also asked and classified according if the female was: still menstruating (premenopausal), pregnant, breast feeding, had chronic amenorrhea, had irregular periods if beginning menopause (perimenopausal), had hysterectomy or oophorectomy and the age at surgery, had natural menopause and age of menopause, and other conditions.

The participants were asked about the number of pregnancies they had. Out of these pregnancies, how many live births, still birth, ectopic pregnancies, miscarriage and therapeutic or elective abortions they had. For each pregnancy, the months of pregnancy, year of birth, sex, and breast feeding period were recorded.

To complete the forth part of the questionnaire, participants were asked if they had tried to get pregnant and could not for one straight year or more. If they had problems getting pregnant, what were the causes.

Women who had problems in getting pregnant were asked whether they ever took any medication(s) to help them get pregnant, and if so , they were asked to provide information about the treatment they took including the brand, age of taking drugs, the dates of starting and ending of treatment and specify the reason for taking them.

In the fifth part of the questionnaire all participating women were asked if they were taking or had ever taken oral contraceptives to prevent pregnancy or for any other medical reasons, such as regulation of menstrual cycles. If yes, they were asked at what age they did first took oral contraceptives and for how long. If used, the hormone replacement therapy (HRT) brand and duration was recorded.

Women were asked if they had ever taken Tamoxifen or Nolvadex as a treatment of breast cancer or as a part of preventive measures.

The sixth part of the questionnaire asked was regarding hormone imbalance or endocrine problems.

The seventh part investigated the medical history of women with breast cancer, first by asking questions about the doctor's diagnosis of breast cancer, what was done for each breast and age at surgery (including biopsy).

When studying breast cancer, it is important to know information about each surgery (including biopsy), date and type of surgery, hospital and city, which breast, and the result of surgery or biopsy (benign, malignant, or prophylactic).

The last part of the questionnaire asked about some of the known risk factors for breast cancer such as alcohol consumption.

Cigarette smoking has been linked to the development of many cancers. Therefore the patients were asked if they had ever (in the past and currently) smoked cigarettes. X-ray and radiation exposure are also a risk factor for the development of breast cancer. Hospitals, clinics, dentist's office or research laboratory are places that could expose women to radiation. Women were asked if they were ever exposed to X-ray and radiation in the work place and treatment of cancer.

The questionnaire also included questions aimed at assessing the patient's exposure to chemicals around their residences and in occupational settings. The patients were asked to record the types of chemicals, under what circumstances they were exposed, and when it happened.

2.2 Human Research Ethics and Consent

The research conducted was developed in conjunction with the oncology centre of the Augusta Victoria Hospital (AVH) at Jerusalem with the help of the radiation centre.

Consent for each patient's involvement in the study was obtained by signing a patient declaration form. Completion of the form was achieved either by the patient herself or by any other relatives accompanying her. In addition to patient consent, a signed letter from the doctor who followed up their treatment was also obtained.

2.3 Interviews

The administration of the questionnaire was done by an interview, the 334 consenting patients were asked to answer the questions through a half hour interview with an oncology nurse working at the radiotherapy unit of the AVH. Whereby these patients were asked the questions in sequence and their answers were written on the questionnaire and sent to Bethlehem University to the Hereditary Research Lab, where these questionnaires were given codes and filed for later investigation.

2.4 Setting

The subjects used in this study were women having breast cancer and attending AVH for treatment with radiotherapy. The duration of this study was from November, 2007 to July, 2010. Women were treated at the AVH in the oncology department as it is the only hospital in Palestine that has a radiotherapy unit. So, women from the Gaza strip and West Bank were admitted to the hospital to get their therapy.

2.5 Subjects of the Study

Women diagnosed with breast cancer were the subject of this study. These women were undergoing radiotherapy at the AVH. Old women were represented with their relatives who followed up their answers to the questions.

2.6 Methodology

The questionnaires were first moved to paper sheets then entered to the computer after omitting the names and specifying codes for them. All data from questionnaires were statistically analyzed using SPSS computer software. Descriptive statistics was used to determine frequencies and the associated variance of each variable. A box blot was used to determine extreme values and outliers to be removed so as not to affect study. These values were then handled so as to avoid distortion of the data.

Means and standard deviations (SD), confidence intervals (CI) and statistical testing were done using SPSS computer software. Frequencies and percentages for categorical variables were also calculated.

CHAPTER 3

Results and Discussion

3.1 Results

Three hundred and thirty four cases of women with breast cancer were analyzed from different districts of Palestine. These patients were Palestinians from both the mother's and father's side. The distribution of breast cancer cases according to district, number of cases and percentages per district is demonstrated in Table 3.1. The table shows that the largest frequencies were from Gaza and Ramallah districts 30.5% and 18.6%, respectively. So, many patients getting treatment at AVH were from these two districts.

Table 3.1 Distribution of breast cancer cases to district and number of patients.

District	Frequency	Percent (%)
Bethlehem	17	5.1%
Jerusalem	22	6.6%
Ramallah	62	18.6%
Nablus	27	8.1%
Salfit	1	0.3%
Tolkarim	27	8.1%
Hebron	36	10.8%
Jenin	28	8.4%
Jericho	8	2.4%
Qalqelia	4	1.2%
Gaza	102	30.5%
Total	334	100%

Figure 3.1 represents breast cancer cases according to the incidence rate per 100,000 population according to the residence and gender, [72] which indicates that Ramallah (17.1) then Jericho (14.7) per 100,000 population had the highest incidence rate.

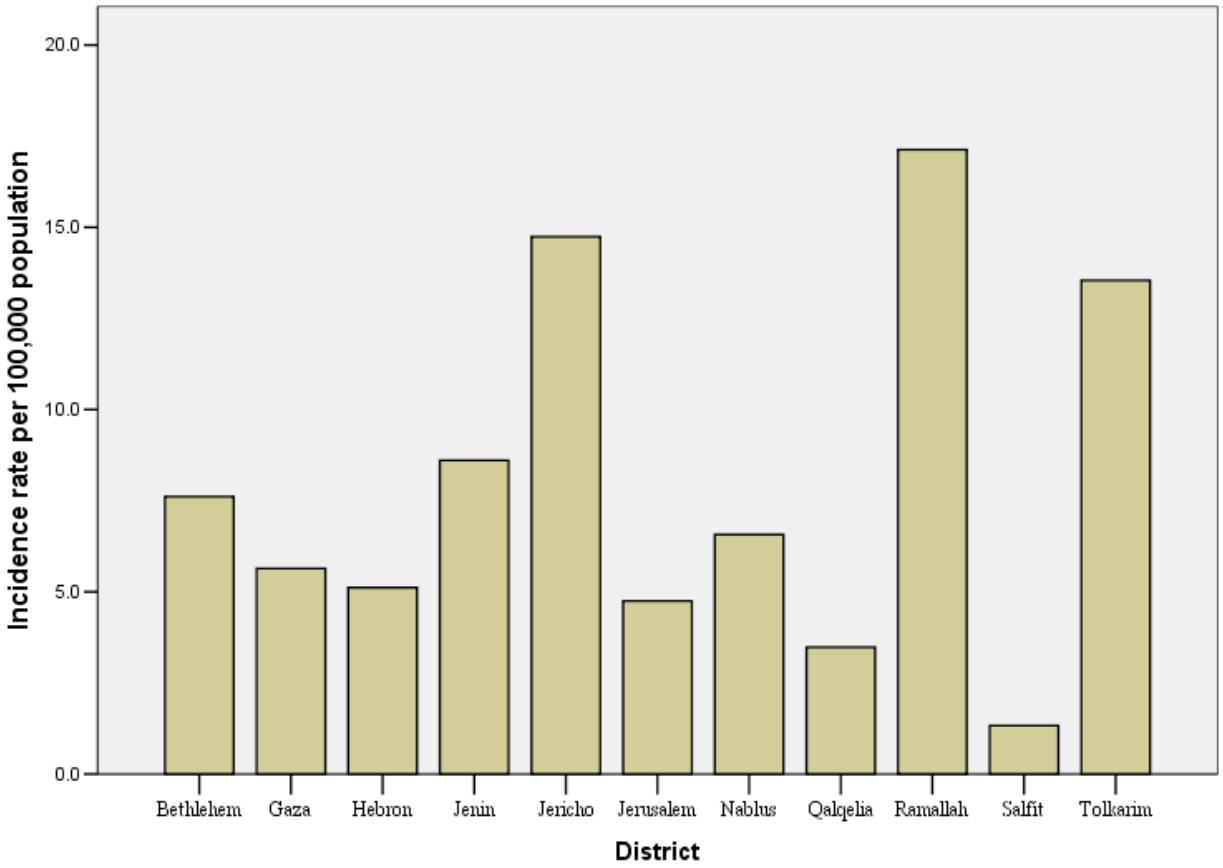

Figure 3.1 Incidence rate of breast cancer cases according to residence per 100,000 population.

The distribution of these cases according to age, marital status, family history of malignancy, type of malignancy in the family and breast cancer cases according to first and second degree relatives are illustrated in Table 3.2. The age of these women at diagnosis with breast cancer ranged from 22 to 79 years old. The mean age of these patients was 47.3 years, SD = 10.708, with a 95% CI of (46.12, 48.43).

Table 3.2 Demographic distributions of breast cancer cases with its percents of occurrence.

Character	Breast cancer count	Percent (%)
Age (years)		
<40	80	24.0
40-49	131	39.2
50-59	78	23.4
> 60	45	13.5
Marital status		
Never married	29	8.7
Ever married	304	91.3
Family history of Malignancy		
Yes	197	56.2
No	137	43.8
Malignancy Type in Family		
Breast	91	46.2
Ovarian	2	1.0
Others	104	52.8
Breast cancer Relatives		
1st Degree	40	20.3
2nd Degree	51	25.9

8.7% out of these patients were women that have never been married Figure 3.2, with mean age at diagnosis of 47.9 years and SD = 9.669. These single women had an age ranging from 27-66 years.

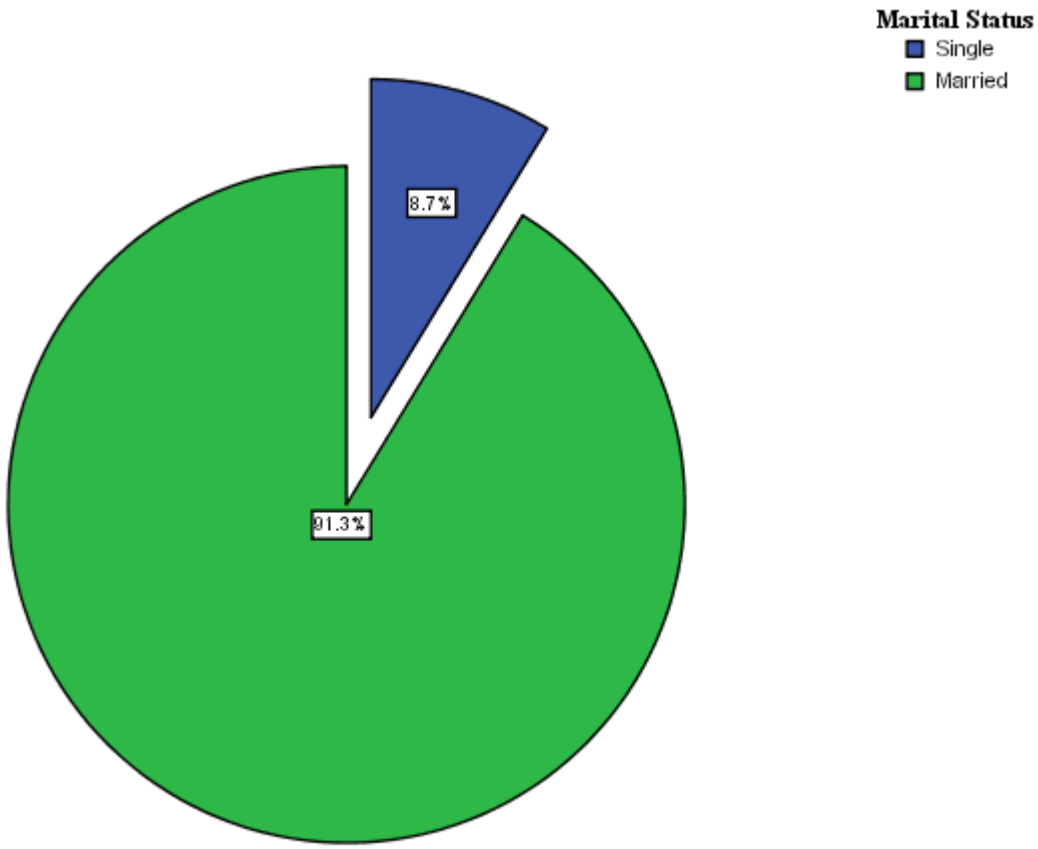

Figure 3.2 Percent of single women with breast cancer as compared to married women.

Examining the family history of these patients it was found that most of the patients had a family history of malignancy (56.2%). Breast cancer was the most prevalent among the other types of cancer cases 46.2% Figure 3.3. 20.3% of patients had family history of breast cancer in 1st degree relatives (such as the mother, daughter, and sister) and 25.9% had it in 2nd degree relatives such as grandmother, aunts, and nieces).

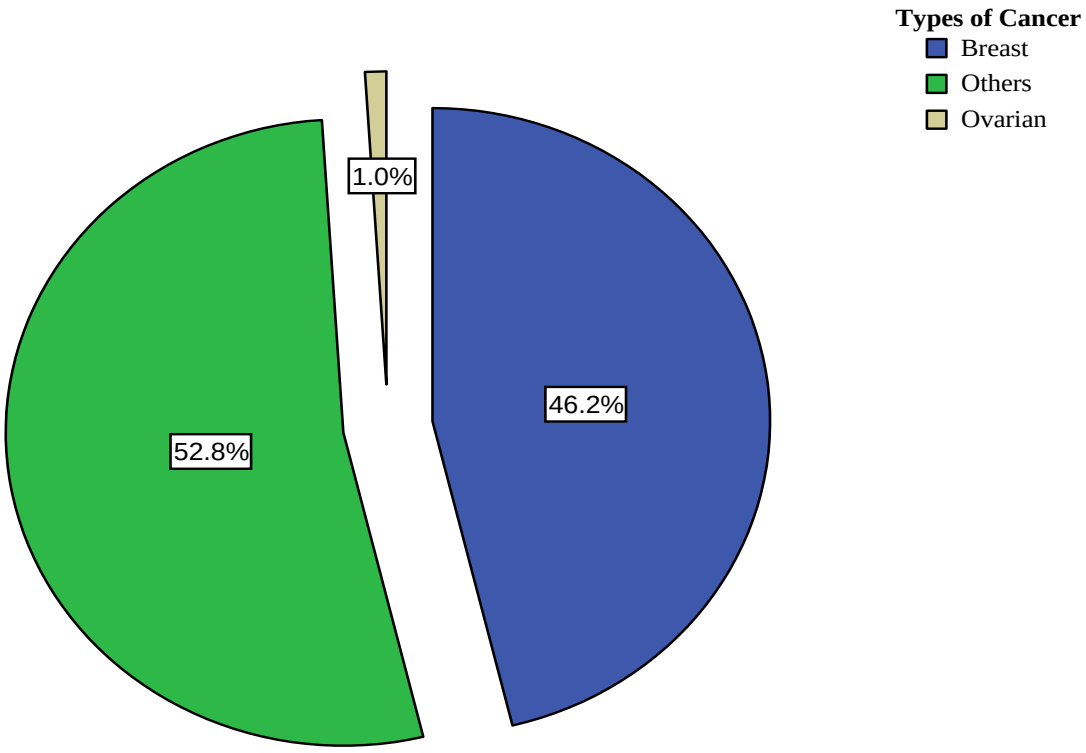

Figure 3.3 Type of cancer in the family and their percentage.

The provisional data concerning women diagnosed with breast cancer showed that the total number of breast cancer cases increased with age until 40-44 age groups and then declined (Figure 3.4). If these cases were categorized according to age-specific incidence rate based on gender per 100,000 population, it was found that the highest incidence rate was among women aged 55-59 years Figure 3.5. Age specific rates of breast cancer have been calculated using the estimated Palestine female population for the year 2009 [72].

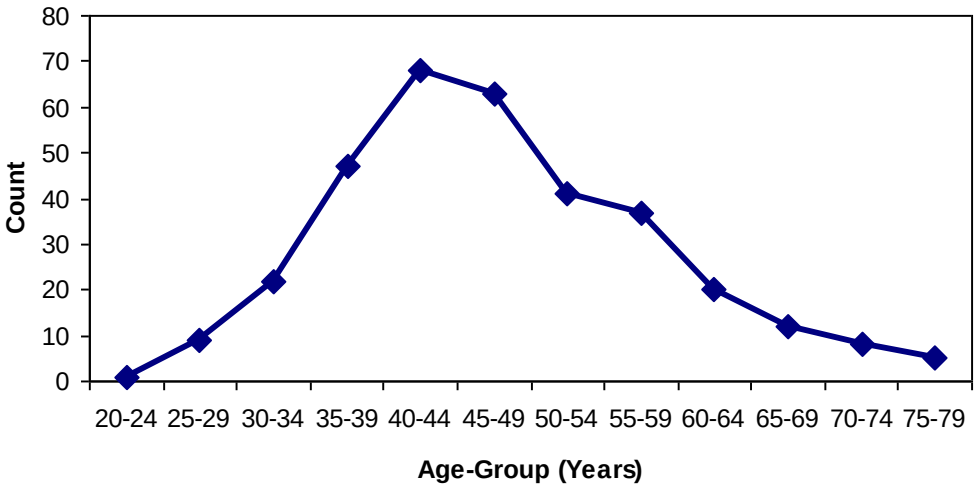

Figure 3.4 Number of breast cancer cases according to age group (years).

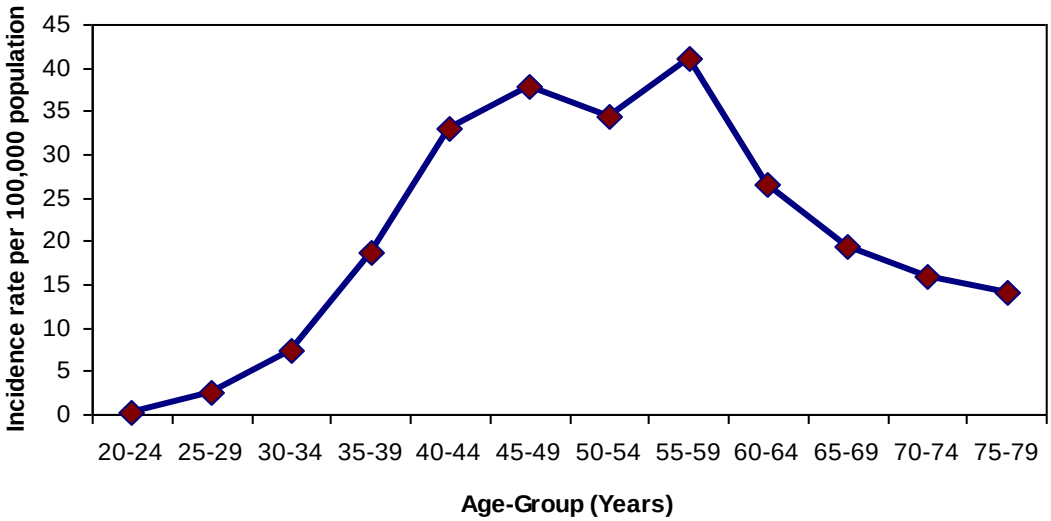

Figure 3.5 Age-specific incidence rate per 100,000 females.

Concerning reproductive factors as early and late menarche and early and late menopause, these variables epidemiologically related to breast cancer incidence. The median age for menarche was 13 years with a minimum of 10 years and maximum of 18 years. Based on that, the age of menarche was divided into two main categories, those who first menstruated before the age of 13 years old (52.9% of the cases) and those who menstruated after the age of 13 years old (47.1% of the cases) as seen in Table 3.3. The mean age was calculated to be 13.53 years with a SD of 1.477 years the values are within 95% CI of (13.37,13.69).

Most of these women had their period started by itself without interference of medication. 88.8% of the patterns of cycles for these women were usually regular, 9.4% usually irregular and 1.8% always irregular as seen in Figure 3.6.

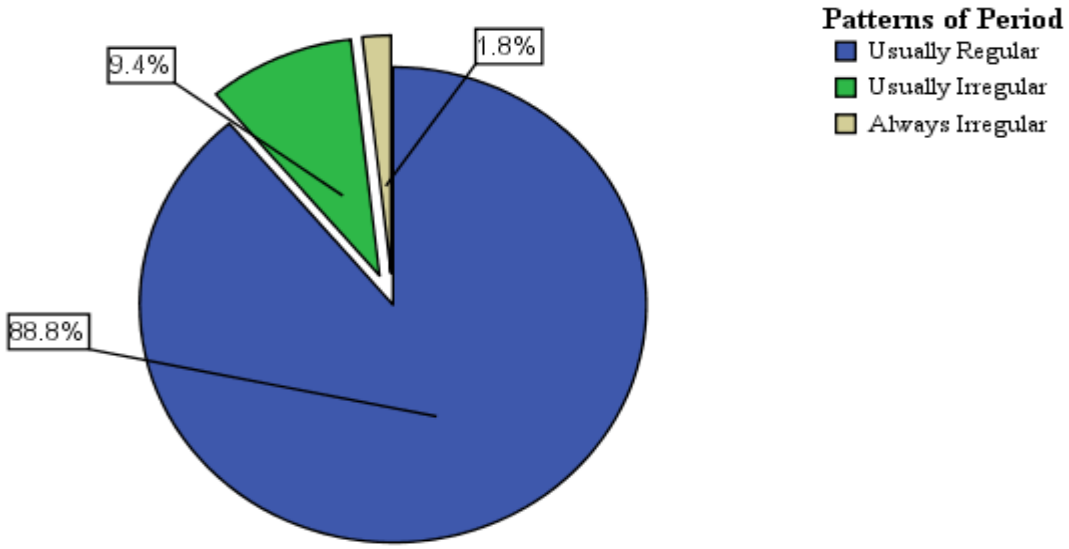

Figure 3.6 Patterns of Menstruation cycle in breast cancer cases.

Table 3.3 Age at menarche, menstrual pattern, period status and menopause with their percentages of occurrence.

Character	Number of women	Percent (%)
Age at Menarche (years)		
≤ 13	173	52.9
> 13	154	47.1
Menstrual Pattern		
Usually Regular	294	88.8
Usually Irregular	31	9.4
Always Irregular	6	1.8
Period started by itself		
Yes	324	97.6
No	8	2.4
Current Menstrual Status		
Menopause	108	32.3
Peri-menopause	8	2.4
Hysterectomy (Uterus)	19	5.7
Oopherectomy (Ovaries)	9	2.7
Chronic amenorrhea	20	6.0
Still menstruating	170	50.9
Age at Menopause		
< 45	21	19.4
45 – 49	27	25
≥ 50	60	55.6

There were 108 women that had menopause (32.3%), 5.7% of these women had hysterectomy (Uterus) and 2.7% had oopherectomy (Ovaries) and 8 women with peri-menopause. The mean age for the women with menopause was 48.58 years with a SD of

4.935, and the median age was 50 years. The age at menopause for the women was mostly above 50.

Parity is considered to be involved as a risk factor in breast cancer. Number of children, breastfeeding and abortions are illustrated in Table 3.4. Age at first full term pregnancy, age at last birth, time since first birth and time since last birth are illustrated in Table 3.4. It was seen that women who gave birth to more than 5 children represented 52.6% followed by women who gave birth to 3-4 children to be 25%. While 11.5% were women who did not get pregnant and did not have children.

It was found that 44.7% of these women had abortion during their reproductive life. 25% of these women had abortion more than once in their lives.

The majority of these women had breastfeeding during their reproductive lives according to the number of children they had.

Table 3.4 Number of birth, abortion, number of abortion and breastfeeding with percents of occurrence.

Character	Number of women	Percent (%)
Number of children		
Nulliparous	35	11.5
1-2	33	10.9
3-4	76	25
≥ 5	160	52.6
Abortion		
Yes	136	44.7
No	168	55.3
Total number of Abortion		
0	168	55.2
1	60	19.7
>1	76	25
Breastfeeding		
Yes	257	95.5
No	12	4.5

In Table 3.5 the mean age for women at First full term pregnancy (FFTP) was 24.1 years and the median was 23 years. The age for these women who gave birth between 20 - 24 years represented 38.2%, and women aged 25-29 years old 29.3%. Moreover, the age for these women at last birth ranged from 21-49 years with a median age of 35 years. Women who had their last birth after age 35 represented 53.9%.

76% of the women had their first child over 15 years ago. 54% of the women had their last birth after age 35.

Table 3.5 Age at first and last birth with time since first and last birth.

Character	Number of women	Percent (%)
Age at first Birth		
< 20	48	18.5
20 – 24	99	38.2
25 – 29	76	29.3
≥ 30	36	13.9
Age at last Birth		
< 25	7	2.7
25 – 29	35	13.6
30 – 34	77	29.8
≥ 35	139	53.9
Time since first birth (yrs)		
≥ 15	196	75.7
12 – 14	20	7.7
9 – 11	14	5.4
6 – 8	15	5.8
3 – 5	13	5.1
< 3	1	0.3
Time since last birth (yrs)		
≥ 12	125	48.4
9 – 11	42	16.3
6 – 8	44	17.1
3 – 5	22	8.5
< 3	25	9.7

There were 17.5% of these women tried to get pregnant for one straight year with 13.5% had problems in getting pregnant mostly due to problems in ovaries and ovulation. For

that 12.3% of them took medication for treatment. The duration of treatment ranged from one month to two years as seen in Figure 3.7.

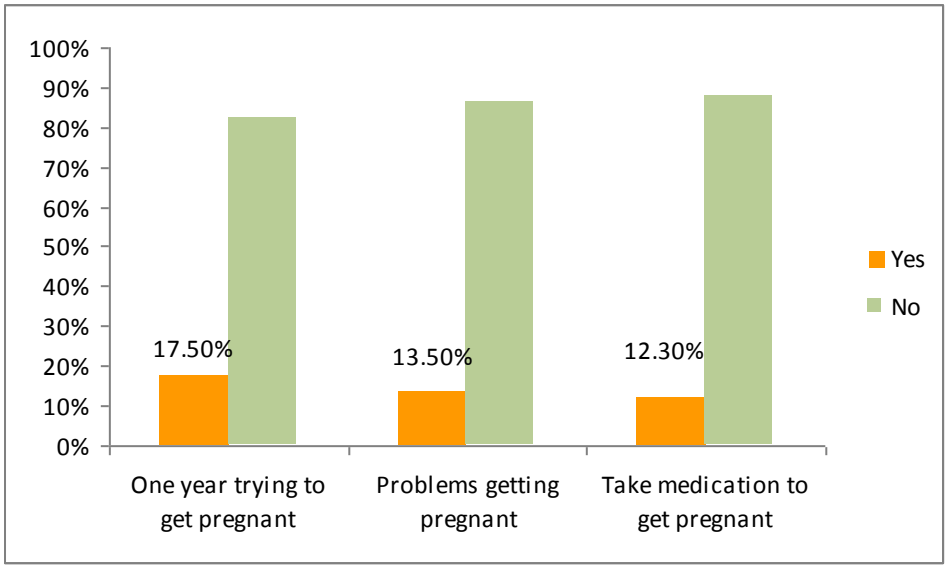

Figure 3.7 Women tried to get pregnant, had problems in getting pregnant and those who took medication.

Changing in the lifestyle such as drinking alcohol or smoking considered to be among the risk factors for breast cancer. The transient movement to urbanization in the country and nearby regions will continue to appear more prevalent in the following years. Figure 3.8 shows some of the lifestyle risk factors for those women and the percent involved. Chemical exposure, X-ray treatment and percent of genetic diseases in the family are also demonstrated. Cardiac failure, hypertension and diabetes are some of the genetic diseases involved in the family history of these patients.

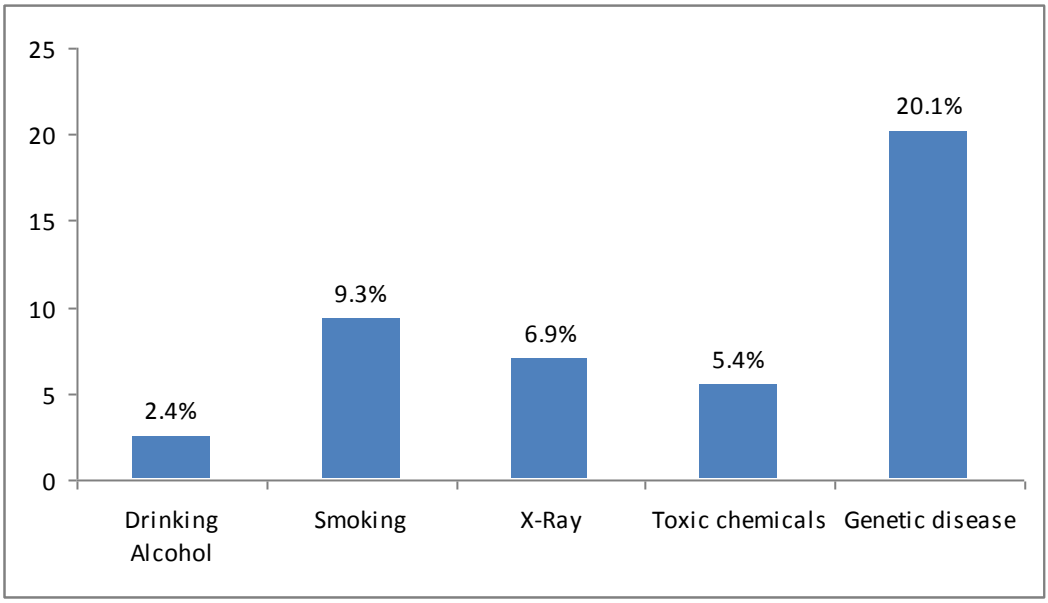

Figure 3.8 Some risk factors and percent of occurrence.

The reason for studying the epidemiology of breast cancer is to provide important clues to the etiology of its occurrence and try to overcome the problem. Most of these women used fine needle aspirator (FNA) for the first biopsy as seen from Table (3.6), then 70.1% of these women had mastectomy and 29.9% had lumpectomy and excisional biopsy. Concerning histopathological reports of these cases, it was found that among those who had reports, invasive ductal carcinoma had the highest incidence rate among patients with breast cancer (89.1%), while invasive lobular carcinoma had a rate of 7.5%. The left side of breast showed 52.1% occurrence and the right side 45.8%.

Table 3.6 Some characteristics concerning biopsy and side of breast affected.

Character	Number of women	Percent (%)
Type of biopsy		
FNA	306	91.6
After FNA		
Lumbectomy	100	29.9
Mastectomy	234	70.1
Biopsy Result		
Benign	4	1.2
Malignant	324	98.8
Histopathological Result		
Invasive ductal carcinoma	155	46.4
Invasive lobular carcinoma	13	3.9
Metastatic	6	1.8
No report	160	47.9
Breast Side		
Left	172	52.1
Right	151	45.8
Both	7	2.1

The use of oral contraceptives is considered as a risk factor for breast cancer. 33.4% of the women took these medications. The age of these women were classified to three categories: <20 years old with a percent of 4.2% , from 20 – 25 years 35.8%, and women who aged ≥ 26 years 60% as seen in Table 3.7. For the duration of taking oral contraceptives; the time was divided into three categories, 25% of these women took oral contraceptives for more than 5 years.

The same was applied to women who took hormone therapy and they represented 10.3%. Women with imbalance and endocrine problems represented 8.1%; their problems were mostly due to hypothyroidism or hyperthyroidism.

Tamoxifen therapy is used for the treatment of estrogen positive receptor breast cancer as it was only used in 37.2% of the patients.

Table 3.7 Oral contraceptive use endocrine problems and Tamoxifen drug use.

Character	Number of women	Percent (%)
Oral Contraceptives		
Yes	105	33.4
No	209	66.6
Age at first oral contraceptives(years)		
<20	4	4.2
20-25	34	35.8
≥26	57	60
Duration of oral contraceptives (months)		
<24	60	57.7
24-59	18	17.3
≥60	26	25
Hormone Therapy		
Yes	33	10.3
No	288	89.7
Imbalance endocrine problems		
Yes	27	8.1
No	306	91.9
Tamoxifen Drugs		
Yes	124	37.2
No	209	62.8

3.2 Discussion

Breast cancer is a significant health problem as it is considered to be a multifactorial disease. The most important risk factors are being a female, advancing in age, family history and past history of breast cancer. This study is concerned mainly with the epidemiological indicators of breast cancer among Palestinian women.

The examined sample showed that Ramallah, Jericho and Tulkarem had the highest incidence rates of 17.1, 14.7 and 13.5 per 100,000 population respectively, while the ministry of health of the Palestinian National Authority points out that Nablus then Tulkarem have the highest incidence rate [80]. Nablus governorate reports the highest figures with an incidence rate (127.3) per 100,000 population while Tulkarm governorate ranked the second place with (80.8) per 100,000 population of all reported cancers.

The data concerning breast cancer is scarcely available in Palestine due to the deficiency of international cancer registry or central registry that could be applicable to the population, which is seen in the discrepancies in the geographic distribution of breast cancer cases to the region where it was collected. As a result, it does not reflect the true distribution of these cases either in the West Bank or Gaza Strip.

Breast cancer risk is strongly associated with age, 63.2% of breast cancer cases were under the age of 50 which is very different from the values obtained from the UK registry which shows that 19 % of breast cancer cases occur in women aged less than 50 [81]. Only 25% of cases in the industrialized nations are below the age of 50 [71]. The results obtained from the sample were also similar to the results obtained in the Arab population, which showed that breast cancer occurs in 65.6% in women aged less than 50 [82]. In general,

breast cancer occurs earlier in age in the Arab countries as compared to the Western countries. This may be due to other etiological factors responsible for breast cancer such as genetic or environmental factors.

The mean age for breast cancer cases in the sample was 47.3. In the Arab world, the mean age at diagnosis with breast cancer is 48.5 [82]. The median age at diagnosis is 62 in the UK and the mean age at diagnosis is 60.7 years [83]. In the USA the mean age is 64 and the median is 61 years [84]. The results obtained from the sample show that the age at diagnosis with breast cancer in Palestine is younger than in the Western countries and from the Arab countries.

Moreover, 33.0 % of the patients were found within the age group 50 – 69 years as compared to the UK, where 48% of the patients were within the age-group 50-69 years [81].

According to the demographic distribution in Palestine, single women cover one third of the population [85] hence the percentage of diagnosed with breast cancer in the sample was 8.7% which was expected. Worldwide the risk of developing breast cancer in single women increases after the age of 40 years. In the sample the average age for single women diagnosed with breast cancer was 47.9. One possible explanation is that single women as a group enter the menopausal state later, therefore remain in the more highly susceptible state longer than married women do. Also, the differences in single women are associated with factors concerning the endocrine system as child-bearing, lactation and artificial menopause which are considered as protective measures against developing breast cancer [86].

Family history is considered to be a significant risk factor in developing breast cancer. 5-10% of breast cancers is caused by hereditary causes and 80-90% is caused by BRCA1 and BRCA2 genes mutations. The risk of breast cancer is also increased if first degree relatives have the disease. The higher increase in risk is found if more than one member in the family is affected. It is already known that relatives of very early onset breast cancer patients - without mutations in the BRCA1 and BRCA2 genes – carry a four-fold increased risk of the disease than those with no family link [87]. The results showed that there were 44% of these patients had 1st degree relative with breast cancer and 56% with 2nd degree relatives. The increased number of cancer cases may be due to the consanguinity. Consanguinity was found to be a significant risk factor for reproductive wastage and found to be widely practiced in the Palestinian Territories with rates of total consanguinity reaching 45% of all marriages in 2004 [88].

It is well known that early menarche before the age of 12 years increase the risk of developing breast cancer, for every two years of delay, breast cancer risk decreases by 10% [14]. The results showed that 52.9% had their menarche before or at 13 years, 26.2% before or at the age of 12 years. The mean age for menarche was 13.5 years.

Another risk factor for breast cancer is late menopause. The results showed that 55.6% had menopause after or at age 50. The average age for menopause worldwide equals to 51.4 years [89]. This is because a late menopause exposes a woman's body to greater amounts of the hormone estrogen over her lifetime. These higher levels of estrogen increase the risk that breast cells will become cancerous. Risk increases by almost 3% for

each year of delay of menopause (natural or induced by surgery), so that a woman who has the menopause at 55 rather than 45, has approximately a 30% higher risk [20].

Child-bearing reduces the risk of developing breast cancer. The higher number of full-term pregnancies, the greater the protection will be. The results showed that women with more than 5 children were 52.6%. There is a weak relation between the age at diagnosis and the number of live children as shown using Pearson correlation coefficient ($r = 0.257$).

The mean age at FFTP was 24.1 years as there is a trend in increasing the age at FFTP from the early 20s to the late 20s and early 30s, as it is seen in most Arab countries because of the delay of marriage to the late 20s [71]. This is due to the fact that women tend to complete their higher education and go to work. In the Western countries such as the US the average age jumped from 21.4 in the 1970 to 25 in 2006 [90] and The average age for giving birth in the UK continued to rise, from 29.3 in 2008 to 29.4 in 2009 [91].

The age when women were diagnosed with breast cancer and age at FFTP is found to be not significant. However, the time since first birth and age diagnosed with breast cancer is significant as shown using Pearson correlation coefficient ($r = 0.54$). The same correlation is found since last time of birth and the age diagnosed with breast cancer. Although 46.1% of these women aged < 35 years at last birth it was shown to be significant using Pearson correlation coefficient ($r = 0.637$).

Lactation is considered to be protective against breast cancer. Although the percentage of women who breastfed exceeds 95%, the time interval for each patient in breastfeeding was not included. It is known that the longer time of a woman for lactation the lower the risk

of breast cancer. Table 3.8 shows the lower in relative risk of breast cancer for women who had lactated with different time intervals [92]:

Table 3.8 Duration of lactation and their lower relative risk.

Lactated 3 months or less	0.85
Lactated 4-12 months	0.78
Lactated 13-24 months	0.66
Lactated 24+ months	0.72
For all who lactated	0.78

Breastfeeding duration is affected mainly by women who work. There is a need for these women to get back to their work soon after delivery otherwise they will lose their jobs due to the bad economic situation in Palestine.

Women who had abortion presented 44.7% of the cases which is a high percentage. Different factors are involved in abortion. Using Pearson correlation test it was shown that there was no relation between abortion and age diagnosed with breast cancer for these patients, there was no relation found between abortion and age at menarche, and there was no association emerged with abortion and oral contraceptive use.

Changes in the lifestyle between smoking, alcohol consumption, diet, little exercises through the process of urbanization and modernization continue to be prevailed mostly in young patients.

The results showed that more than 20% of these patients had genetic diseases since diabetes and hypertension were dominant in the families of these patients.

Mastectomy was used in 70% of these patients, compared to the Europe and North America 25%. In most Arab countries, mastectomy was used in 60-80% of the cases [93]. From the percentage of histology reports of these women it was revealed that 89% of these cases had invasive ductal carcinoma which is more prominent in young women. The results showed that the left side was more affected (52.1%) than the right side which is also mentioned in the literature that left side of the breast is affected more [94].

Oral contraceptives are considered as risk factors for developing breast cancer. Oral contraceptives were used by 33.4% of these patients. They were used by 40% of the patients. Less than 25 years old. 42.3% of them used these pills for more than two years.

The use of HRT is considered as a risk factor for breast cancer. It was used by 10.3% of these patients.

Tamoxifen is anti-estrogen and used as a protective measure against developing breast cancer; it was used by only 37.2% of the cases which involved estrogen receptors.

CHAPTER 4

Conclusion and Recommendations

4.1 Conclusion

Breast cancer is ranked first among different types of cancers in the Palestinian women and is considered to be the second leading cause of death. In Palestinian, breast cancer occurs in younger women as compared in Western countries.

In young age, breast cancer is difficult to diagnose because the tissue of the breast is usually denser than that in old women, so when a lump is felt, the cancer is often found in advanced stages. The cancer in young women is found to be more aggressive and might have little chances to respond for the treatment.

Breast cancer is a disease that is life-threatening and most of women diagnosed with have fear due to the fact that it is often found in the later stages, which makes the chances of survival low. Sometimes women ignore the signs of breast cancer due to social implications and the woman's standing in the community or the thought of losing the support of her family and relatives and this leads to a second factor in addressing the tumor in later stages.

Most of the women used mastectomy from fear of cancer to invade other tissues of the body or as a preventive measure. This has an emotional and physical stress on women and keeps them in struggle with the community. Therefore, in order to relieve this burden and high treatment cost on the patient and their family from, preventive measures should be

taken into consideration to avoid difficult provision. Moreover, the guidelines that are applied to the Western countries should be modified to meet up the incidence found in Palestine. Otherwise, there will be a conflict in diagnosis and treatment.

Risk factors for breast cancer in Palestine include the hereditary factors and family history of cancer as seen from the results obtained. Early menarche, late menopause, and late age at first full-term pregnancy are also included. The changes in behavior from smoking cigarette or narghilea, to drinking alcohol, to low physical activity, diet and chemical exposure from the different gases influence the rate of breast cancer occurrence in Palestine.

Any discrepancy of results will be removed if a national registry for cancer is available and could be accessed by everyone. The lack of such resources will not reveal the true incidence and prevalence rates of the disease. Epidemiological studies of breast cancer are rare in Palestine. These studies are important to identify risk factors among different groups of the population. Therefore, a statistical platform and practical guidelines should be made and addressed to all sectors in Palestine with the help of different stakeholders to collect information regarding breast cancer.

4.2 Recommendations

The objective of epidemiological studies is to recognize and understand the risk factors of breast cancer and to reduce their effects. For that, investigations should be

continued for searching in this field for better diagnosis, control and treatment. The following should be taken into consideration while searching:

1. Staging of breast cancer according to TNM should be standardized by all pathological centers for evaluation in Palestine, including hormonal receptors status for each patient for better diagnosis and treatment.
2. Body- mass index should be evaluated, as obesity increases the risk of developing breast cancer by two-fold in post menopausal women. This was not included to this study.
3. Strategic plans for women awareness should be made for better understanding the risk factors for breast cancer. In addition to that, teaching them through demonstrations and practice how to do breast self examination monthly starting at age 20.
4. Trained health workers should be available in different parts and centers in Palestine to reach most women for physical examination starting at age 30. This should be done annually.
5. Screening Mammography should be done annually after the age of 40. These women should be registered through a system that keeps in touch with them every year for screening and evaluation.
6. Radiotherapy centers should be available in different areas of Palestine to facilitate movement and treatment for the patients.
7. Genetic testing should be carried out on all women with strong family history of breast cancer or ovarian cancer or with a relative who has BRCA1 and BRCA2 mutations.

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