An-Najah National University
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Breast Cancer Status In The Northern Part of West Bank

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Under the Supervision
Of

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Abstract:

The current study is an explorative and descriptive in nature. It aimed to study the status of breast cancer in northern part of the West Bank and compare it with the other parts of the area. We also aimed to evaluate the risk factors associated with the disease incidence. Previous studies on breast cancer in Palestine, Jordan and Israel were revised. The study also included all affected women (80) enrolled at Al-Watani cancer center in northern part of West Bank at the city of Nablus. The affected women were interviewed and their medical files were studied. Our findings indicate rapid increase in breast cancer incidence in West Bank in comparison with the situation among Israeli women, although the disease incidence among Jewish females is the highest. There is a geographical variation in the incidence of the disease in West Bank. These variations seem to be due to life style, socio-economical and health awareness of affected women. Our findings strongly indicate the lack of health awareness among females in this respect. Our findings also indicate that lactation, being married and having children especially at early age seems to play a protective role against breast cancer. On the other hand, smoking, oral contraceptive use specially at early age, stress, low fertility, early

menarche and family history seem to play a role in the disease etiology and its incidence at early age of breast cancer.

Chapter I

INTRODUCTION

Cancer is a group of diseases characterized by uncontrolled growth and spread of the abnormal cells. Carcinogen is any substance that causes cancer or helps cancer growth (1). Abnormal cell growth includes hyperplasia, hypertrophy, metaplasia, dysplasia and neoplasia. Hyperplasia is an abnormal increase in number of normal cells of tissues, and usually arranged in the normal fashion. Hypertrophy is abnormal increase in the cell size. Metaplasia is characterized by the replacement of one mature cell type with another mature type. Dysplasia is replacement of one mature cell type with a less mature cell type. Hyperplasia, hypertrophy, metaplasia and displease are reversible and result from stimulant while neoplasia is irreversible and autonomous (2).

Carcinoma is malignant tumor that begins in the lining epithelial cells of various organs. At least 90% of all cancer types are carcinoma (3), and almost all breast cancers are carcinoma (1).

Breast cancer is a malignant tumor that has developed from cells of the breast. The disease occurs mostly in women, however, it was reported to occur rarely in men (4,1). Abnormal growing cells usually develop into lumps and those like fibroadenoma or papilloma are usually benign (2).

Nearly all breast cancers start in the glandular tissue of the breast and, therefore, they are considered adeno-carcinomas (cancer

in glandular tissues of the body). There are two main types of breast adenocarcinomas, the ductal and the lobular carcinomas. Other subtypes include, the ductal (including in situ or infiltrating), the lobular carcinoma (in situ (LCIS) or Infiltrating), inflammatory, medullary, mucinous (Colloid carcinoma), Paget's disease of the nipple, phyllodes tumor (cystosarcoma phyllodes) and tubular carcinoma (2).

According to the presence of estrogen receptors, breast cancer is classified into either estrogen positive or negative. Normal breast cells and some breast cancer cells have estrogen and progesterone receptors. Estrogen receptors positive cells tend to have a better prognosis compared to those lacking such receptors and are more likely to respond to hormonal therapy (1,5,6,7,8,9,10,11,12,13).

1.1 Early detection of breast cancer

Early detection plays an important role in reducing mortality rate. Women aged 20 years or older should perform breast self-examination (BSE) on monthly basis and a clinical examination every 3 years. At the age of 40 it is advisable to have yearly screening mammography (1).

1.2 Diagnoses of breast cancer

Breast cancer is diagnosed by imaging tests for the breast and these include mammography, sonography, and ductogram.

Laboratory examination of nipple discharge and biopsy (fine needle aspiration biopsy, core needle biopsy, surgical biopsy) are among the most commonly used diagnostic tools (1,14).

1.3 Breast cancer stages

Clinically, five different stages ranging 0-4 are used in diagnoses. Stage 0, represent both ductal and lobular carcinoma in situ, and is considered as the earliest form of cancer. In stage I, the tumor mass has a diameter less than 2.0 cm and usually dose not spread beyond breast tissues. Individuals in stage II, have a mass larger than 2.0 cm in diameter and or it has spread to the lymph nodes under the arm on the same side as the affected breast. This stage is also characterized by loose and scattered lymph nodes. In stage III, tumor mass is either larger than 5cm in diameter or has spread to adjacent lymph nodes of the surrounding tissues. Breast cancers of any size that have spread to skin, chest wall, or the internal mammary lymph nodes are also included in this stage. Inflammatory breast cancer is usually classified as stage III, unless it has spread to distant organs or lymph nodes and in this case it is considered as stage IV. Stage IV is the state where cancer mass regardless of size, has metastasized to distant organs such as bone, lung or to other distant lymph nodes (1).

1.4 Breast Cancer Risk Factors

A risk factor is anything (condition, physical characteristic, and behavior) that may increase a person's chance of developing a disease. There are different kinds of risk factors. Some like a person's age, race and genes that can't be changed. Others are linked to cancer-causing factors in the environment such as pollutants. Still others are related to personal choices such as smoking, drinking, and diet and these factors are behavioral risk factors. Some factors influence risk more than others. Woman's risks for developing breast cancer can change over time. This change could be due to increasing age, new breast biopsy result, or a new diagnosis of breast cancer within the woman's family (1,15).

Some people with one or more risk factors never develop the disease while others may develop breast cancer without having any known risk factors. Although, there are some women who are at higher risk, in fact all women are at risk for breast cancer.

Excepting radiation, most established breast cancer risk factors are linked with total lifetime exposure to estrogen. Cumulative exposure to estrogen underlies most of the known risk factors. Thus, women have early menses, long monthly cycles, earlier and longer birth control pills and estrogen replacement therapy use, no children, or having children later in life, have substantially greater lifetime

exposure to estrogen are more likely to develop breast cancer. This may justify the reported rapid incidence of breast cancer in certain developing countries, where women reproductive life style became westernized (16,17,18,19).

Long exposure to estrogen seems to increase cell proliferation thus, increasing the chance of DNA damage (20,21). On the other hand, such exposure promotes estrogen responsive cancer cell growth by stimulating the release of insulin-like growth factors (22). Estrogen metabolite types play an important role in the determination of estrogen effects on breast tissues. Metabolites resulted from the 2-hydroxylation process has weak estrogenic activity, while hydroxylation of 16-alpha position or oxidation of the 4^{th} position has strong estrogenic activity as they can bind covalently to estrogen receptors. Elevated levels of 4-hydroxy-estrogen could increase breast cancer risk, perhaps by causing direct genetic damage through the formation of free radicals. The 16-alpha-hydroxy-estrogen metabolite is an initiator of preneoplastic transformation and induces DNA damage. Furthermore, it has been accused in decreasing cell gap junction communication which is an integral component involved in the regulation of cell proliferation. It was also found to induce hyper-proliferation in mammary epithelial cell (20, 23,24).

Variations in the ratio of 16-alpha- to 2-hydroxyestrone may explain disparities in breast cancer incidence across geographic borders. Asian women have been found to have high levels of 2-hydroxyestrone compared to 16-hydroxyestrone, and this might be behind the finding of lower incidence rates of breast cancer (20).

1.4.1 Environmental Factors

A great deal of research has been reported in the field of environmental influences on breast cancer risk. The goal of these researches is to determine possible relationships between environmental factors and breast cancer. Given the widespread dissemination of organo-chlorine insecticides in the environment and the food chain, environmental contamination with these organo-chlorine residues may be an important etiologic factor in breast cancer (25). Exposure to these exogenous estrogen analogs could affect the level of sexual hormones in serum and increase the ratio of 16-alpha to 2-hydroxyestrone. This may accelerates DNA duplication and induces atypical hyperplasia of mammary gland(26). Many of these harmful xeno-estrogens do not bind at all with sexual human binding globulin (SHBG) but do bind potently with the estrogen receptor. In addition, many of these potentially hazardous xeno-estrogens are lipophilic, which means that they tend to persist in women fatty tissue including breast tissue. Women with the

highest serum concentration of DDT metabolites had a four-fold higher risk of developing breast cancer than did women with the lowest concentration (20, 27).

Not all-exogenous estrogens are harmful, some like Genistein and indole-3-carbinol, which are found in soy products and vegetables, appear to reduce the risk of breast cancer, by decreasing the ratio of 16-alpha-esteron to 2-hydroxyestrone. Interestingly, many of the protective xeno-estrogens bind directly with sex hormone binding globulin, and they are rapidly excreted reducing the risk of such compounds (20).

1.4.2 Effect of Oral Contraceptive

It is still not clear what role oral contraceptives might play in breast cancer as a risk factor. Whether hormonal contraceptives cause breast cancer is important health question, as well as one of great importance to women and men choosing their method of family planning. Use of hormonal contraceptive is also common and is expected to increase worldwide. Thus, even a small increase in the risk of breast cancer in women using oral contraceptive would be important because of frequency of exposure.

The exposure-response relationship between duration of oral contraceptive use and risk of breast cancer depends on the age at first use. Given a fixed duration of oral contraceptive use, the risk

increased with younger starting age of oral contraceptive use. The early reproductive years following the beginning of menses or before first pregnancy are of great importance as risk determinants for breast cancer after oral contraceptive use (28, 29, 30, 31, 32, 33, 34, 35, 36). This might be due to the possible DNA damage in breast epithelial cell at the time of high breast cell proliferation (37). Evidence in support for this assumption came from the findings among those exposed to oral contraceptives use at early age as they were found with aggressive cancer (38). Long-term oral contraceptive use was also found to increase risk in individuals carrying mut-BRCA compared to non-carriers of this mutation (39).

1.4.3 Effect of Menarche Age

Age of first menstruation progressively decreased in different parts of the world. Women who started menstruating at an early age (before age 12) or who went through menopause at a late age (after age 50) have a slightly higher risk. Women whose menarche occurs early not only have a longer duration of exposure to estrogen but their exposure are at higher levels during years after puberty which are probably important in initiation of breast cancer and probably at later ages also (40,41,42). Women with early menarche have lower concentration of SHBG so they have higher levels of free estrogen in their blood (43,44).

1.4.4 Having children

Women who have had no children or who had their first child after age 30 seems to have a slightly higher risk for breast cancer. Full term pregnancy inhibits the initiation of neoplastic process through the induction of complete differentiation of mammary gland. While the breast of null porous women retain those undifferentiated cells, which increase predisposition of organ to undergo malignant transformation (45, 46,47, 48). Prolactin seems to have inductive role in breast cancer incidence. Parity was found to be inversely related to Prolactin level (49). There was a considerable reduction in Prolactin concentration after first pregnancy (50). Pregnancy has dual action, transient increase in risk due to increase proliferation of mutant breast cells and long term protective effect as result of breast cell complete differentiation (51). Full term pregnancy or treatment of virgin rats with a placental hormone, human chorionic gonadotrophin(HCG), prior to the administration of carcinogens was found to protect the mammary gland from tumor development.(52). It was also reported that alpha–fetoprotin (AFP), a major serum protein produced during fetal development, has anti-estrotrophic activity that can be used as therapeutic agent to treat existing estrogen dependent breast cancer

or to prevent pre-malignant foci from developing into breast cancer(53).

1.4.5 Effect of Lactation

Several mechanisms have been postulated for the protective effect of lactation which include hormonal changes, such as reduced estrogen; removal of estrogens through breast fluid; excretion of carcinogens from breast tissue through breast-feeding; physical changes in the mammary epithelial cells, reflecting maximal differentiation; and delay of the re-establishment of ovulation (16, 54, 55, 56). Non-lactating women have higher blood concentration of organochloride than lactating women. Some studies suggest that poly-organochlorines exposure increase the risk of breast cancer in post menopausal women and is restricted to porous women who had never breast-fed infants (57).

Lactation protective effect seems to be restricted to pre-menopausal women (58,59). However, other studies showed that lactation regardless of duration and timing is associated with slight reduction of breast cancer among younger and older porous women(60).

1.4.6 Family History of Breast Cancer

Family history accounts for small proportion of breast cancer cases among women up to 70 years of age. Nevertheless, Breast

cancer risk is higher among women whose close blood relatives (mother, sister or daughter) have this disease. Women whose first-degree relative diagnosed at pre-menopausal or before the age of 40 have more risk of developing breast cancer than did women with no maternal history of cancer. Mother's age, at the time of diagnosis, determines the risk degree, which increased with decreasing age (14, 61, 62, 63).

Women with a first-degree family history of breast cancer have a much better survival rate if they do get breast cancer than do women with no such family history. The improved survival rate may be due in part to the less aggressive nature of the type of tumors common in genetically predisposed women (64).

1.4.7 Genetic risk factors

The pattern of breast cancer occurrences in families with breast cancer history is most consistent with an autosomal dominant mode of inheritance. The location of a gene that could explain the pattern of transmission of the breast cancer trait in families averaging early (pre-menopausal) onset of breast cancer was first reported in 1990. Since then, two genes have been identified: BRCA1 and BRCA2. These two gene account for significant proportion of hereditary breast cancer (43). Other hereditary breast cancer forms have been associated with germ-line mutations in TP53, PTEN, and ATM.

There may be other genetic factors that contribute to hereditary breast cancer, since not all families with multiple cases of breast cancer harbor of these germ-line mutations (65,66).

1.4.8 Effect of Diet

Fatty acids seem to increase the incidence of breast cancer due to several factors. These include, decrease cell lysis, enhancement of the growth of tumor cells, increase the synthesis of prostaglandin, increase the formation of free radical, increase the fluidity of cell membrane, increase the synthesis of prolactin, induction of cell division and proliferation and decrease concentration of SHBG. Breast cancer rates were highly correlated with the intake of animal fats. Intake of fat from fish on the other hand, appeared to have a protective effect. The detrimental effects were greatest in women over 50 years old. A lag time of about 10 years between breast cancer incidence and changes in fat intake or consumption was observed (67). Increased adiposity and weight gain in decade preceding diagnoses suggest that excess weight may function as late stage promoter (68,69).

High intake of mono-unsaturated fats (e.g. olive oil) is protective against breast cancer while a high intake of poly-unsaturated fats significantly increases the risk of developing breast cancer (70).

Vitamin E succinate (VES) is considered as a potent inhibitor of breast cancer. Estrogen responsive breast cancer cells were more susceptible than non-estrogen responsive cells. This form of vitamin E induces DNA synthesis arrest as well as programmed cell death (apoptosis). In contrast, the acetate derivative of vitamin E does not exhibit in *vitro* growth-inhibitory effects (71).

1.4.9 Abortion:

Abortion in the first trimester may increase the risk of breast cancer due to rapid increase in estrogen. Full term pregnancy seems to protect against breast cancer due to the fact that differentiation of breast stem cells, which make them less susceptible to carcinogen, occur later in pregnancy. Interruption of pregnancy results in proliferation of breast cells without the possible differentiation (72).

1.4.10 Adverse Life Events

Cancer of breast is probably present microscopically more than five years before it is clinically detectable. Hence, sever life events during this time may increase growth and multiplication of cancer cells through alteration of natural immune surveillance processes. This is presumably mediated through the endocrine system. Women, who have a long history of adverse life events, may indeed predate the onset of cancer. Life events may be confounded by

other, genuine risk factors, either environmental or constitutional, which can be associated with both life stress and cancer (73).

1.4.11 Smoking

Smoking has carcinogenic effects. Postmenopausal women have reduced capacity to detoxify the body of tobacco carcinogen. Up to 55% of white women have genetically slow N-acetyl transferase 2, which help body to get ride off tobacco carcinogen. Postmenopausal women who have slow acetyllators and heavy smokers are 4 times at risk to develop breast cancer compared to non smoking women. Slow acetyllator are found in 10-20% of Asians, 35% in African Americans and 65-90% in Middle East women. It was also found that women who started to smoke at or before 16 and were slow acetylator have 4-time higher risk than those with rapid acetylators (74,75).

1.4.12 Free radicals

There is substantial evidence that free radical attacks on DNA are one of the major factors in the initiation of cancer. Women with metastasized breast cancer exhibit twice as much free-radical damage to the breast tissue DNA than do women with localized cancer. There is clear correlation between the growth of metastatic tumors and the extent of radical-induced DNA damage (76).

1.4.13 Physical activity

Exercise and cancer is a relatively new area of research. Recent studies indicate that strenuous exercise in youth might provide life-long protection against breast cancer, and that even moderate physical activity as in adult can lower breast cancer risk. Physical exercises decrease cumulative lifetime exposure to circulating ovarian hormones. There is currently no scientific consensus on the critical time period of exposure or on the intensity or frequency of physical activity needed to influence the risk of breast cancer (77,78,79).

1. 5 Incidence of breast cancer

Breast cancer is one of the most frequently occurring cancers in women. At present, breast cancer incidence in the West Bank is 3-4 times greater than that reported during 1970's (4,80). Such increase is much greater than those reported in other countries. In the USA, breast cancer incidence showed 25% increase during 1973-1991 and approximately leveled during 1990's (81).

The estimated age standardized incidence (ASI) for female breast cancer all over the world is 33 per 100,000.(4). The estimated ASI in Palestine was estimated at 22per 100,000 in 1992(80).

In terms of number of new cases, breast cancer is the most common female malignancy in the West Bank and all over the

world. Breast cancer represents about 13% of the new registered cancer cases in both sexes and about 26% of female cases in the West Bank, while it represents 21% of all the new cancer cases world wide (4, 82).

1.6. Study objectives

Although, previous studies on breast cancer are limited, there seems to be a high incidence rate of breast cancer among Palestinian females. Such situation motivated us to study this disease in more detailed epidemiological approach. The current study aimed at:

1- Assess the status of breast cancer in the northern part of the West Bank within Palestine.

2- Comparing the status and the incidence of breast cancer in the West Bank with near by countries mainly, Jordan and Israel.

3- Identifying the risk factors associated with the disease as a first step towards better disease monitoring and prevention.

Determination of incidence rate and assessing cancer trends are essential for identifying resources necessary to provide effective and efficient health services for breast cancer patients. Accurate determination of incidence is very important for decision-maker to plan health services to provide the most cost effective health services to prevent the disease or at least decrease incidence rate.

Chapter II

Methodology

The current study is an explorative and descriptive in nature. Quantitative data about breast cancer patients in the West Bank were collected from Palestinian cancer registry and published data under the title "Palestinian Cancer Statistics 1976-1992" by Al-Quds University (80). Qualitative and quantitative data were collected about breast cancer in northern West Bank to determine risk factor associated with breast cancer.

2.1 Study population

Study population was breast cancer patients registered at the cancer center based at Al-Watnee Hospital in the city of Nablus. This center is one of two centers for the treatment of the cancer patients in West Bank. Al-Watanee hospital cancer center serves the northern area of West Bank, which include the districts Nablus, Tulkarem, Jinin, Tubas, Qalqilya and Salfeet. While the other center, which is based at Biet Jala hospital serves the patients of the southern area of West Bank. We interviewed all referable patients during the period of January 1st 1999 to 1st of November 1999 and we were we able to interview 80 patients.

2.2 Data collection

A specially designed questionnaire was prepared for this purpose (appendix I). It contains demographic, reproductive and family history data. This questioner includes most of the known risk

factors indicated by the previous mentioned literature such as age, marital status, family history, age of menarche, time of first pregnancy, smoking lactation and use of oral contraceptives. In addition, the medical files and the cancer registration forms (appendix II) of these patients were also reviewed for other related clinical data. The raw data available at the cancer registry at Al-Watanee hospital were analyzed also. The oncologist interviewed the patients in order to make them more confident and comfortable.

2.3 Study limitations:

Small size of the population relative to the law incidence rate and small size of population in West Bank limits the statistical significance of our data. Although, the registered cases were 125 for the last three years (1999-1997) we managed to include only 80 cases. This was mainly due to the fact that some of the registered patients seek treatment in neighboring countries, after diagnosis. There is no follow up for patients' survival so it's difficult to know if the remaining patients are still alive or not. Lack of follow up to the survived cases is another factor that adds another limitation for obtaining accurate prevalence estimates. Lack of published data about female situation in the West Bank specially in the northern part limits our ability to compare our results with general female population in northern part West Bank. Absence of good recording

Variation in lifestyle, health awareness, environmental and socioeconomic factors within the various localities seems to influence the incidence rates within the different geographical districts of West Bank. The highest incidence was reported in the central region of West Bank (table 2) and this could be due to the above mentioned factors. The following is a summary of some of these variations that may account to the observed geographical differences in the incidence of breast cancer according to the Central Bureau of Statistics 1996 (87,88). The percentage of women smokers in the northern of the West Bank was 2.2% compared to 1.3% in Hebron district and to 5.8% in the central districts of the West Bank (Ramallah, Jericho, and Bethlehem). It was also reported that the fertility rate was the lowest in Bethlehem district (4.97) and the highest in Tulkarem and Qalqeelia (6.63). An association was observed between breast cancer incidence and participation of women in labor force, the use of contraceptive pills and the percent of weaned child within the first three-month after birth.

Table 2. Breast cancer incidence rate in West Bank according to various regions during the period 1998 –1999 (4)

District	No cases 1998	IR*1998	No cases 1999	IR* 1999
North West Bank	42	25	46	29
Central West Bank	50	59	26	31
South West Bank	25	33	25	33

* Incidence Rate Per 100,000

During the period of 1997-1999, the number of yearly new reported cancer cases in the northern of the West Bank districts was estimated around 300 cases, of which 47% were female cases. Breast cancer accounts for around 30% of reported female cancer cases and 14% of all new reported cases as shown in table 3.

Table 3: Reported female breast cancer cases in the northern areas of West Bank:

Year	Total cases	Female cases	% female	NO Breast cancer	%Breast Cancer in female cancer cases
1997	272	142	52%	55	39%
1998	320	151	47%	38	25%
1999	296	123	42%	32	26%

* This data was tabulated from Al-Watanee cancer center.

The mean age of diagnosis of female breast cancer was 52 years. Diagnosis of breast cancer was rare among the age group <30 year and 75% of the cases were diagnosed after age of 40 years as shown in table 4.

Table 4. Breast cancer cases in the northern areas of the West Bank according age group.

Age group	1997	%	1998	%	1999	%
>60	14	25.5	12	32	10	31
50-59	14	25.5	8	21	7	22
40-49	14	25.5	9	24	9	28
30-39	10	18	6	15	5	16
20-29	3	5.5	3	8	1	3
20>	0	0	0	0	0	0
Total	55		38		32	

* This data was tabulated from Al-Watanee cancer center.

It is indicated by literatures that the risk of breast cancer increases with age (1). It was found that among the female inhabitance in the northern parts of the West Bank, the risk was 1 in 20,000 at the age of 20-29 and it increased to 1 in 2,000 among women over 60 years (table5).

Table 5. Female breast cancer risk by age in the northern of the West Bank

Age group	Risk
>60	1 in 2,000
50-59	1 in 2,200
40-49	1 in 2,500
30-39	1 in 7,000
20-29	1 in 20,000

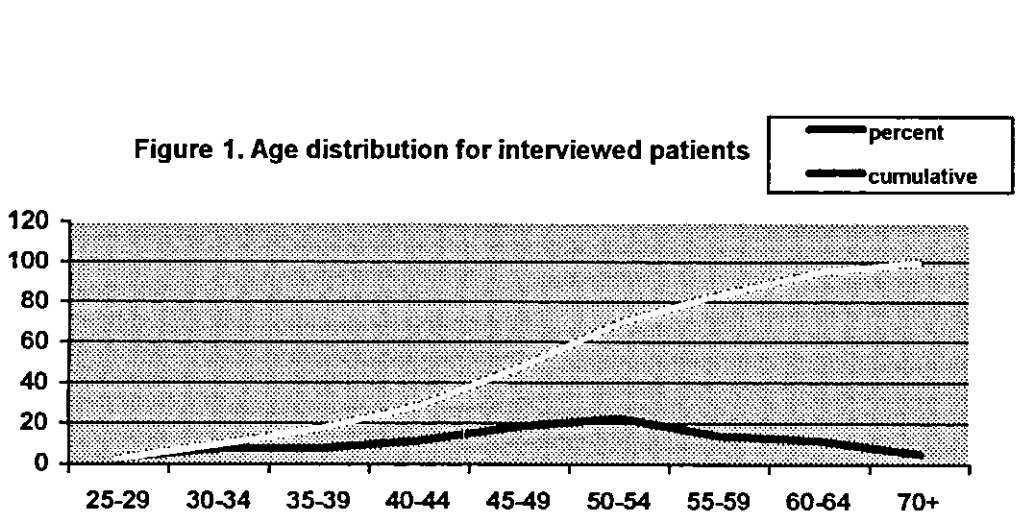
Chapter IV

Results and Discussion

4.1 Result and discussion

The current study included 80 breast cancer patients with a mean age of 52 years and with 50 years mean age of diagnosis. Data analysis showed that 63% of the studied cases were over 50 years old and 35% were in the age group 50-59year. It also shows that 53% of the interviewed patients were diagnosed at age over 50 years and 41% of patients are diagnosed at the age of 45-54 years.

Figure 1. Age distribution for interviewed patients

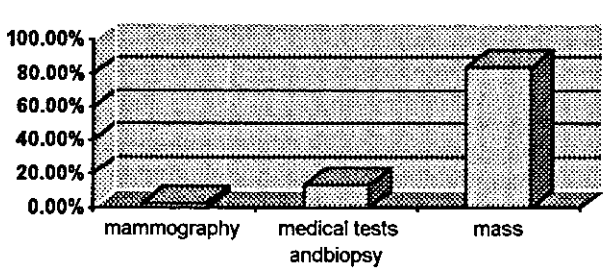


Data presented in figure 1, clearly shows that the majority of breast cancer patients are within age group 40-60 years.

4.2 Health awareness

According to the collected data (figure 2), 84% of the patients

Figure 2. Breast Cancer Detection



were diagnosed after they found an abnormal mass in breasts. None of these females consulted her physician for medical advice immediately after the discovery of the mass and it took some of them up to five years to do so. Only 2.5% of the studied patients have been detected during routine mammography screening and 13.5% were diagnosed after being advised by their physician to do biopsy and other confirmatory tests based on health complaints not related to cancer. Our findings in this respect strongly indicate the lack of health awareness among females. It also points out the inefficiency of the mammography screening programs adopted by the health sector at both governmental and private sector levels. The lack of governmentally directed educational programs specially designed for this purpose might also account for the delay in detection and diagnosis of the disease. One should also point out that physicians, especially gynecologists should play a more effective role in early detection and protective measures in this respect. Altogether, these aforementioned factors will complicate the situation and will have diverse effects on the wellbeing of the patient and the economy of the country in general.

4.3 Risk factors

With respect to occupation, 10% of interviewed patients were workers. This is very similar to the percentage of working women

in the general population (11.2%) in the West Bank. The mean age of diagnosis for this group was 46 year, while for non-working breast cancer patients it was 49 years. Such slight variation at the age of diagnosis is of no statistical significance value and could be partially explained by work stress especially during the last 5 years before diagnosis. This was explained by the fact that stress may encourage the growth of malignant cells due to immune suppression(73).

The average number of children for breast cancer population was 5.3 compared to 5.6 for normal female population in the West Bank. Increased number of children seems to play a protective role and is expected to lower breast cancer incidence rates (16). Our findings are in agreement with previous reports on the protective role of pregnancy, as normal women where with slight increase in the average number of children.

According to the collected data (see table 6), 11% of breast cancer patients were smokers compared to 2.2% of Palestinian females in the northern part of the West Bank (88). Our results in this respect indicate that high proportions of breast cancer patients were smokers, thus increasing the risk of contracting of the disease(74,75). Our results also show that smoking has no effect on the mean age of diagnoses. This seems to be due to the fact that the

capacity of women to detoxify tobacco carcinogens is reduced after menopause, thus increasing the incidence rate among the elder age groups.

Table 6: Smoking status among the studied group

Smoking Status	Frequency	Percentage
Smokers	9	11.3%
Non-smokers	71	88.8%
Total	80	100 %

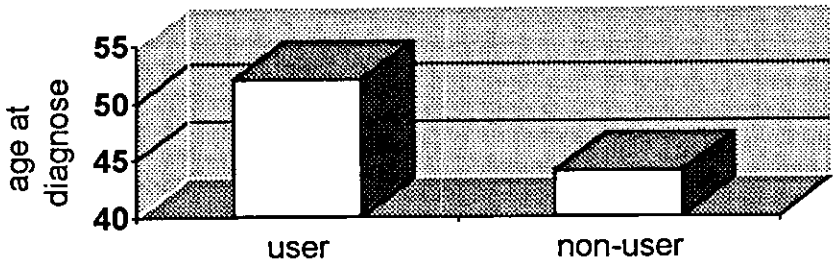
According to the collected data patients on contraceptive were represented by 70%, 38% and 21% for those diagnosed at age 35 or less, at age 36-44 and at age of 45 or more, respectively. Variations among the various age groups and the use of pills were significant with a *P* value of 0.006. Thus, indicating that earlier use of such contraceptives seems to increase the risk of breast cancer at early age among females. Data presented in table 7 shows the use of contraceptive pills among various age groups.

Table 7: Contraceptive usage among the various studied age groups

Age at diagnose	Users	Non users	Total
35 or less	7	3	10
36-44	5	8	13
45 or more	12	45	57
Total	24	56	80

Comparison of the mean age at diagnosis (figure 5) for user and non user of oral contraceptive pills breast cancer patients using T

Figure 3 Mean age of diagnosis in aasociation to oral contraceptives use



test indicates significant early incidence of breast cancer in users with mean age of diagnosis at the age of 44 year compared to 52 year for non-users ($P = 0.002$).

Our findings in this respect indicate that the use of oral contraceptive increase the incidence of breast cancer before menopause as 54% of patient use oral contraceptive and 36% of non usres were diagnosed before menopause. Data presented in Table 8 shows the association between oral contraceptive use and the menstrual status at diagnosis and the incidence of breast cancer.

Table 8: Patients on oral contraceptive and the menstrual status at diagnoses.

Use oral contraceptive	Before menopause	After menopause	Total
Users	13 (39%)	11 (23%)	24
Non –users	20(61%)	36(77%)	56
Total	33	47	80

There was no difference between proportion of oral contraceptive users in breast cancer patients (30%) and the general population in the northern part of the West Bank (32%). These results may indicate that use of oral contraceptives may not affect on the probability of female to get breast cancer but it seems to play an inductive role in the etiology of the disease at earlier age.

Early age of menarche increases probability of developing breast cancer at early age (43,44). Out of the studied cases (table 9) 72.5% of the patients had their menarche at the age of 14years or less.

Table 9. Breast cancer patients age at diagnosis in association with menarche age

	Frequency	Percent
14 or less	58	72.5
More than 14	22	27.5
Total	80	100.0

Out of the studied cases, 87% of patients were diagnosed at age of 40 years or less had the onset of menarche at 14 years or less. A percentage decrease to 65% was found among patients diagnosed at age 40-60 year. Variations between age groups at diagnosis and

menarche were of no significant value as indicated by Chi-square test (P=0.061).

Our data also shows that (86%) of the patients who had their menarche at 12 years or less and 45% of patients who had their menarche after 12 years of age were diagnosed before 50 year old. Variations between age groups at time of diagnosis and the onset of menarche were significant as indicated by Chi test (P= 0.041). The average age of diagnosis for those who had their menarche before 12 years was 44 years, while the average age of diagnosis for those who had their menarche after 12years was 50 year. These results indicates that the earlier the onset of menarche the higher the risk of getting the disease due to longer exposure to estrogen and higher level of blood estrogen following puberty and low concentration of SHBG which means higher free estrogen concentration in blood.

With respect to lactation (table 10), 34% of the patients were non-lactating, 16% were lactating for 6 months or less and 3% of the patients were lactating from 6-12 months. The rest of the group (47%) lactates for more than one year. This situation was reported for each live birth.

Table 10. Patients distribution according to length of lactation period for each live birth per months

Duration of lactation	Frequency	Percent
Not lactating	25	31.3%
1-6 months	15	18.8%
6-12 months	3	3.8%
More than 1 year	37	46.3%
Total	80	100.0

Our data shows that 73% of patients were diagnosed at the age of 40years or less were either non-lactating or lactated for less than 6 months. On the other hand, the non-lactating or lactating for less than 6 months were represented by 52% for those diagnosed at age of 40-60 years and 9% for those diagnosed at 60years or more.

Only 10% of patients lactating for more than one year were diagnosed before age of 40, while 25% of non-lactating patients or who lactate for less than one year were diagnosed before the age of 40. Variation between age groups at diagnosis and lactation duration was significant as indicated by Chi-square test ($P = 0.03$). It was also found that non-lactating women had the mean age of diagnose around 47 years compared to 51 years for lactating women. Although ANOVA test indicated non-significant variations (P=0.079), lactating women seemed to acquire the disease in a later age. This finding is in agreement with several reports in this respect, where lactation seems to play a weak protective role [58,59,60].

With respect to marital status, breast cancer occurred in higher incidence among single females when compared with those married. In our study, 13% of the patients were single. 73% of single patients and 45% of married female were diagnosed before the age of 50years. Although the differences in percentages seems to be great, Chi-square test indicated that such variations had no significance (P= 0.087). One can explain this difference, which was in favor of the married women, due to the factors such as lactation and pregnancy related hormonal changes. Data presented in table 11 shows the distribution of the studied group according to marital status and age of diagnosis.

Table 11. Patients distributions in association with marital status and age at diagnosis

Age at diagnosis	Married	Single	Total
50 or less	31	8	39
More than 50	38	3	41
Total	69	11	80

Looking at the data from a different point (see table 12) where we specified three different age groups (40-60), being the most critical stage), one can see that non of the single females has been diagnosed with breast cancer after age 60 year. In comparison 16% of married female had breast cancer at that age. We also found that 27% of single females were diagnosed before the age of 40

compared with 17% among married females of that age group. Differences in the average age of diagnose for single and married women was of no significance (P= 0.087). Although, the number was quiet small for judgment, such data clearly indicated that being single is a risk factor for the development of disease. This is in agreement with previous reports where marriage, having children and lactation seems to play an important protective role against development of breast cancer (16,45,46,47,60).

Table 12: percentage of patients according to the age of diagnosis.

Age at diagnosis	Single	Married
Less than 40	27%	17%
40-60	73%	65%
More than 60	0	16%

With respect to family history as one of the major risk factors for breast cancer (1,14,61,62), our data (table 13) showed that 32% of patients have one or more cases of cancer among their relatives. It was also found that 16% of the patients have relatives diagnosed with breast cancer and 13.8% have at least one first-degree relative with breast cancer. We believe that this is an underestimated ratio. This can be attributed as mentioned before to the fact that we are suffering from the lack of good recording system in addition to the fact that socially people have low awareness and they deal with the disease with secrecy and privacy. Nevertheless, such findings are

much higher than those reported in the other regions were family history is related to less than 10% of cases(61). This is an expected observation because of being big families with a high rate of consanguinity up to 65% (89).

Table 13. Patients distribution in association with family history

Degree of relatedness	Frequency	Percent
Distant relative with breast cancer	2	2.5
Distant relative with other cancer	8	10.0
First degree relative with breast cancer	11	13.8
First degree relative with other cancer	5	6.3
No relative	54	67.5
Total	80	100.0

*First degree relative is mother, daughter, sister, brother and father.

Our findings (table 14) show that 62% of the studied cases who had relatives with breast cancer and 48% of the patients who had no previous family history were diagnosed before age of 50. Variations in the incidence rate in association with family history were significant with a *P* value of 0.043. Such variations were in favor of those with no previous family history. Our findings in this respect were in agreement with several international reports concerning family history and cancer (1,14,61,62).

Table 14. Patients distribution in association with age of diagnose and family history

Degree of Relatedness	50 or less	More than 50
First degree relative with breast cancer	6	5
First degree relative with other cancer	4	1
Distant relative with breast cancer	2	0
Distant relative with other cancer	1	7
No affected relatives	26	28

Data presented in tables 15, 16 shows the association between age of mother patient at first birth and the risk for development of cancer. The protective effects of childbirth early in a woman's life may be due to the changes that occur to breast cells as a result of pregnancy (cell differentiation) which restrict the cells' ability to grow abnormally, change its type and survive in other types of tissue. The first childbirth early in life may induce this protective effect, thereby, making the breast cells less susceptible to later changes (45,46,47,48).

Our data showed that 3 out of the studied cases had first child birth after the age of 30 and all of them were diagnosed before the age of 55. For those who had children before the age of 30, only 38% of them were diagnosed before the age of 55. Variations of the incidence among those who had children before and after the age of 30 were significant with a *P* value of 0.038. On the other hand 59%

of the cases that never had children were diagnosed before the age of 50. Out of this group, 88% were diagnosed before the age of 55. This finding indicated that early marriage and pregnancy seemed to lower the risk of acquiring the disease and in agreement with previous reports from various parts of the world.

Table 15. Patients distribution according to age at diagnosis and the age at first child

Age at first child birth	Less than 50	50 or more	Total
< 30	25	35	60
>30	3	0	3
Without children	10	7	17

Table 16. Patients distribution according age of diagnose and age at first child

Age at first child birth	Less than 55	55 or more	Total
< 30	38	22	60
> 30	3	0	3
Without children	15	2	17

Data presented in tables 17, 18 shows the mean average of age patients at the time of diagnosis in association with the age at first birth. A noticeable decrease in average mean age was observed among those who had children before the age of 30, thus having children, specially before the age of 30 seems to play a protective role against development of breast cancer at early age. Variations in mean age of diagnosis among those with children before and after

the age of 30 and those who never had children were of no significance and this can be attributed to the fact that we are dealing with small sample number. Our findings are in agreement with several reports in this respect (44,45).

Table 17. Average age of diagnosis and age at first full pregnancy

Age at first child birth	Mean Age of Diagnose	N
Less than30	50.8333	60
30 or more	47.0000	3
No child	46.4706	17
Total	49.7625	80

Table 18. Age at first child and mean age of diagnosis

Age at first child birth	Mean age of diagnose
18 year or less	53
19-29	50
30 or more	47
No child	46

4.4 Comparison of breast cancer status between Israel, northern of West Bank and Jordan

Breast cancer represents 30% of new yearly female diagnosed cancer cases in Israel, 27% in northern of the West Bank and 28% in Jordan. The incidence rate per 100,000 was 21.3 and 25 for Jordan and the northern of the West Bank, respectively (4,83). In Israel the incidence rate of 22 was reported among women of Palestinian origin and 82.2 for women of Jewish origin (84,85). Such variations

could be due in part to differences in the number of reported cases, presence of screening programs and degree of awareness among women. Other factors such as lifestyle, living conditions and health care services, may also account for such variations. The finding of comparatively low fertility among Jewish women (2.67) compared to (4.76) for women of Palestinian origin may also account for the observed differences in the incidence rate(86). One also should keep in mind age at first birth, as Jewish women tend to have a later marriage age and their usage of hormonal replacement therapy, which is considered high, compared to that among women of Palestinian origin (84). One might add that ethnic variation in the activity of N-acetyletransferase might also explain the differences between Arab and Jewish females' (74). Altogether, these factors may explain the variation in the observed incidence among Jewish, Jordanian and Palestinian women of the northern of the West Bank.

The mean age of diagnosis for female's breast cancer, of 49.5, 50 and 60 was reported in Jordan, northern of the West Bank and Israeli Jewish females, respectively. The lower mean age of diagnosis among Arab female population compared to those of Israeli Jewish population dose not necessarily reflect an early age of disease acquisition among Arab females, but rather reflects issues related to implementation of specially designed screening program

and in the diagnosis between the two populations. In general, Arab women are rarely diagnosed after age of 60 and they die with the disease without being reported or diagnosed. Female population in the West Bank is younger than Jewish female population and the female life expectancy among Jewish females is 80.5 (86), while that for the inhabitance of the northern of the West Bank is 73.7(87). So the proportion of old Arab female at risk is less than that reported among Jewish women. These justify the findings regarding diagnosis at early age among Arab females.

Table 19 Breast cancer incidence rate per 100,000, according to age group in Israel, Jordan and northern of the West Bank.

Age group	Israel 1995	Jordan 1997	North West Bank 1998
30-39	46.8	39.8	14
40-49	149	85	39
50-59	244	127	46
60-69	270	108	72
70-74	315.3	*	0
75+	336.4	*	68
70-79	*	109	*
85+	*	47	*

*** Data is missing**

Reports on breast cancer incidence during the period 1980-1992 indicate an increase of 30% among Israeli Jewish women and 100% among Arab women in the West Bank (80,84). Although, the incidence was much higher among Israeli Jewish women, the rapid increase among Arab females is noticeable with about three-fold

increase. This again can be explained by the facts concerning changing of life style into more westernized style and the improvement of the health sector specially screening and diagnosis programs. During the period of 1980-1990 the fertility rate decreased by 6% among Israeli Jewish women and by 8% among females in the West Bank. Fertility of Israeli Jewish women decreased by 6% during 1980-1997 and by 14% in females in of the West Bank during the same period. This is most likely due to changes in life style and to the socioeconomic status in the region.

Table 20. Increase in breast cancer incidence during 1980-1992 by the ethnic group in the region

Group	ASR*/100,000 1980	ASR/100,000 1992	Rate increase
Israeli Jewish	62	81	30%
Arab in Israel	11	22	100%
Arab in Palestine	12.8	22.1	70%

*** Age Standardized Ratio**

Recommendations and concluding remarks:

1- The current study clearly shows that late detection and lack of health awareness of the disease and its consequences are behind such high incidence at early age among Palestinian women. Thus early detection must be priority and can be achieved through:

a- Promotion of early detection using specially designed educational programs.

b- Increase effectiveness of mammography centers.

c- Increase the effectiveness of the physicians specially gynecologists in the field of early detection.

2- The Establishment of an effective National Palestinian Cancer Registry is an urgent necessity that allows necessary follow up of affected patients, identifying high-risk sub-population, determination future trends of disease incidence and tracing changing patterns in disease staging at the diagnosis.

3- Promote the protective role of lactation and pregnancy against breast cancer through educational programs.

4- It is necessary to point out the possible effects of oral contraceptive in association with disease incidence and

family planning centers should play such role.

5- It is of utmost necessity to promote the dangers of smoking in mass media and educational programs and to take strict measures to prevent smoking as it seems to be a risk factor not only for breast cancer but also for other cancer types.

6- Family history seems to be one of the major risk factors (about 14% of patients had at least one first degree relative with breast cancer), thus screening of members at risk and showing the disadvantages of consanguinity are essential.

7- Further studies are needed in order to determine the reasons of the observed regional variation within the country.

8- Estrogen metabolites, slow N-acetyl-transferas and of environmental pollutants should be evaluated in terms of their role in breast cancer.

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Appendix I

An-Najah National University
Faculty of Graduate Studies

Breast Cancer Status In The Northern Part of West Bank

1-Name:

2-Age:

3-Status:

a- married b- single

4-Career:

5-Ethnic:

6-Place of residence:

7-Age at the diagnose:

8-Stage at the diagnose:

9-How the disease was diagnosed:

10-are there any relatives have cancer :

a-yes b-no

If yes

Type of relation	Type of cancer	Age and stage at diagnose

11-Age at menarche:

12-Age of menopause:

13-Age at first child birth:

14-No of children she has:

15-Is she has any case of abortion:

a-yes b- no

If yes how many:

At what ages did she has them

16-did she use oral contraceptive:

a-yes b- no

How did she use them and for how long did she use them:

17-is she lactating:

a- yes b-no

If yes, how long did she lactate her children:

18-is she smoker

a- yes b- no

جامعة النجاح الوطنية

كلية الدراسات العليا

سرطان الثدي في شمال الضفة الغربية

1- الاسم

2- العمر

3- الحالة الاجتماعية:

أ- متزوجة ب- عزباء

4- المهنة:

5- الديانة:

6- مكان الإقامة:

7- العمر عند التشخيص

8- المرحلة التي تم تشخيص المرض عندها

9- كيف تم اكتشاف المرض ؟

10- هل يوجد أقارب مصابين بالسرطان

أ- نعم ب- لا

اذا كانت الإجابة نعم

طبيعة القرابة	نوع السرطان	العمر عند التشخيص

11- العمر عند بدء الدورة

12- العمر عند سن اليأس

13- عدد الأبناء

14- العمر عند إنجاب أول طفل

15- هل توجد حالة إجهاض

أ- نعم ب- لا

إذا كنت الإجابة نعم حدد عدد الحالات و العمر عند كل حالة

16- هل استخدمت حبوب منع الحمل

أ- نعم ب- لا

إذا كانت الإجابة نعم حدد العمر عند بدء استخدام حبوب منع الحمل و مدة استخدام حبوب منع الحمل

17- هل أرضعت

أ- نعم ب- لا

إذا كانت الإجابة نعم حدد مدة إرضاع كل طفل

18- هل دخنت (سجائر، ارجيلة)

أ- نعم ب- لا

ملخص:

هذه دراسة وصفية هدفت إلى التعرف على وضع سرطان الثدي في الضفة الغربية خاصة في منطقة الشمال و مقارنته مع كل من الأردن و إسرائيل. كما هدفت هذه الدراسة إلى التعرف على عوامل الخطورة التي من الممكن أن تتسبب بهذا المرض.

من اجل ذلك تمت مراجعة الدراسات و الأبحاث السابقة عن المرض في الأردن و إسرائيل و فلسطين . وتم كذلك مقابلة 80 مريضة سرطان من اصل 125 حالة تم تشخيصها في السنوات الثلاث الأخيرة في شمال الضفة الغربية كما تمت دراسة الملفات الطبية الخاصة بهن.

لوحظ ان الإصابة بسرطان الثدي تزداد بشكل كبير بين النساء العربيات مقارنة باليهوديات على الرغم من أن معدلات الإصابة لدى اليهوديات كانت أعلى منها عند الفلسطينيات. ولوحظ كذلك وجود اختلاف في معدلات الإصابة بين المناطق المختلفة في الضفة قد يكون السبب فيها الاختلاف في طبيعة الحياة و الظروف الاقتصادية و الاجتماعية والوعي الصحي.

وكما أظهرت نتائج هذه الدراسة أن الإرضاع و الإنجاب قبل سن الثلاثين يلعبان دورا وقائيا من الإصابة بسرطان الثدي. ومن جهة أخرى كان للتدخين وانخفاض معدلات الخصوبة والتوتر وحبوب منع الحمل والبلوغ المبكر وكذلك التاريخ العائلي للمرض دورا في الإصابة بالمرض.

Appendix II

Palestinian National Authority
Ministry of Health
National Cancer Registry
B.J.G.H
E-Mail: salhbpna@p-ol.com

السلطة الوطنية الفلسطينية
وزارة الصحة
السجل الوطني الفلسطيني للأورام
مستشفى بيت جالا الحكومي
تلفاكس: ٩٧٢-٢-٢٧٧٦٣٩٩ TelFax

First name:_____ Father_____Grandfather: _____ Last name:_____ Husband_____
ID#_____ Birth Date:___/___/_____ Sex: M _____ F _____
Martial Status 1) Single 2) Married 3) Divorce 4) Widowed 5) Unknown

Address: City_____, Village_____ Tel._____ *Place of Birth*_____

Religion: 1) Christian 2) Jewish 3) Moslem 8) Other 9) Unknown

Smoker 0) Never Smoked 1) Present Smoker 2) Past Smoker 9) Unknown

Occupation :01)Clerical 02) Petrol./Chem. Ind. 03)Agriculture 04) Manufacture 06)Housewife 99) Unknown
Incidence date:___/___/____

*Basis Diagnosis:*0)Death certificate only1)Clinical only2) Clin. Invest/Ult.Sound 3)Surgery/ utopsy 4)La
5) Cytology 6) Histology of metastasis 7) Histology of Primary 8) Autopsy with Histology 9) Unknown

*(Topography)Primary Site*_____
_____
(Morphology) Histopathologyical Dig. _____
_____
_____

Behavior 0) Bengin
1) Uncertain ben/ malig
2) In Situ
3) Malignant

Stage:
1) In Situ
2) Localized
3) Regional: direct ext.(adjacent)
4) regional: Lymph node
5) Regional: direct ext. & Lymph node
6) Distant metastasis
7) Not applicable
9)Unknown

Grade: 1- Grade I Well diff.
2- Grade II Mode. Diff.
3- Grade III Poorly diff.
4- Grade IV Undiff/ Anapl.
5- T- Cell
6- B- Cell
7- Mull Cell
8- Killer Cell
9 - Unspecified

Laterality : 0- Not a paired site 1- Right 2- Le
3- Unilat. Side unspec. 4- Bilteral 9- Unknow

Place of diagnosis _____Medical Record no. _____ Referring Hospital _____
Referred to _____ Physician _____

Treatment:

Surgery:	*Radiotherapy:*	*Chemotherapy:*	*Immuntherapy:*	*Hormonal therapy*
0) None given	0) None given	0) None given	0) None given	0) None given
1) Given	1) Given	1) Given	1) Given	1) Given
7)Patient refused	7)Patient refused	7)Patient refused	7)Patient refused	7)Patient refused
8)Recomd.UnkRecd.	8)Recomd.Unk.Recd	8) Recomd.Unk. Recd	8)Recomd.Unk.Recd	8)Recomd.Unk.Rec

Follow Up:
Status0) Alive 1) Dead Date last Contact ___/___/_____ Cause of death 0) Alive 1)Cancer
2) Other 9) Dead Un