Multi-Knowledge Electronic Comprehensive Journal For Education And Science Publications (MECSJ)

ISSUE (12) , Sep (2018)

ISSN : **2616-9185**

www.mecsj.com

Breast Cancer: An overview

Name: Doa'a Tantawi
Department: Medical

1. **Introduction**:

Cancer is defined as a disease in which cells have an abnormal ability to divide and invade other tissue without any control. These abnormal cells can spread to other parts of the body via blood and lymph system. There are more than 100 types of cancer cells, and the type of cancer is named according to the type of cells or organs in which they start (National Cancer Institute, 2014). Breast cancer is characterized by the uncontrolled growth of abnormal cells in the milk producing glands of the breast or in the passages (ducts) that deliver milk to the nipples (Baqutayan, 2012).

Depending on statistics, 1 in 8 women will develop breast cancer during their lifetime and breast cancer is considered as the most common type of cancer as well as the main leading cause of cancer death in women (WHO Cancer Factsheet, 2014). Each year more than one million women are diagnosed with breast cancer worldwide over half of whom will die from the disease. According to Jordan National Cancer Registry records in 2009, there is 4% increment per year in the incidence of the disease. In 2009, 926 breast cancer cases were diagnosed, accounting for 20% of the total new cancer cases. Similar to other parts of the world wide data, breast cancer in

Jordanian population is considered number one cancer in female accounting for 37% of all female cancers, and is the leading cause of cancer deaths among Jordanian women. Until now there is no specific known reason for the development of this disease, but there are several factors that increase the risk of the occurrence of breast cancer. These factors include: age, geographic location, socioeconomic status, reproductive events, exogenous hormones, lifestyle and dietary risk factors (alcohol, diet, obesity and physical activity), history of benign breast disease, familial history of breast cancer, mammographic density, bone density, ionizing radiation, height, prolactin levels and chemo-preventive agents (Dumitrescu & Cotarla, 2005).

It is well accepted that environmental and genetic factors are the two main groups of risk for breast cancer, and studies have inducted that the complex interplay of genetics, environmental exposures, hormones, and behaviors may predispose to breast cancer (Lecarpentier et al., 2015).

Breast cancer cells often spread undetected by contiguity, lymph channels, and through the blood early in the course of the disease, resulting in metastatic disease after local therapy. The most common metastatic sites are lymph nodes, skin, bone, liver, lungs, and brain (Kalinsky et al., 2015).

In light of the above, this study has been conducted with aim to study review breast cancer and associated issues.

2. Review

2.1.Breast cancer

2.1.1.**Prevalence**

Breast cancer is the most common type of cancer among females and it occurs in both developed and less developed countries with more than 50% occurring in less developed countries (Ferlay et al., 2010). According to Global Health Estimates over 508 000 women died in 2011 due to breast cancer and nearly 1.7 million new cases were diagnosed in 2012 (World Cancer Research Fund International, 2013) . There is a great increase in the incidence of this disease, but the prevalence varies from 19.3 per 100,000 women in Eastern Africa to 89.7 per 100,000 women in Western Europe. In most of developed countries the incidence rates are below 40 per 100,000 (Ferlay et al., 2010). Breast cancer occurs in both men and women, although male breast cancer is rare and it is mainly due to *BRCA2* rather than *BRCA1* germ line mutations (Guaoua et al., 2014).

2.1.1.1. Breast cancer in Jordan

According to Jordan National Cancer Registry records in 2009, there is 4% increment per year in the incidence of the disease. In 2009, 926 breast cancer cases were diagnosed, accounting for 20% of the total new cancer cases (Figure 1). Similar to other parts of the world wide data, breast cancer in Jordanian population is considered number one cancer in female accounting for 37% of all female cancers, and is the leading cause of cancer deaths among Jordanian women. Only 9 cases of breast cancer were diagnosed in males resulting in a female to male ratio of 95:1Jordan

Multi-Knowledge Electronic Comprehensive Journal For Education And Science Publications (MECSJ)

ISSUE (12) , Sep (2018)

ISSN : **2616-9185**

Breast Cancer Program (2008). Jordanian women are afflicted with breast cancer at a much younger age (median age 51) compared with women in Western countries (median age 65), when they are still raising children, caring for their families, and contributing to the growth and development of society.

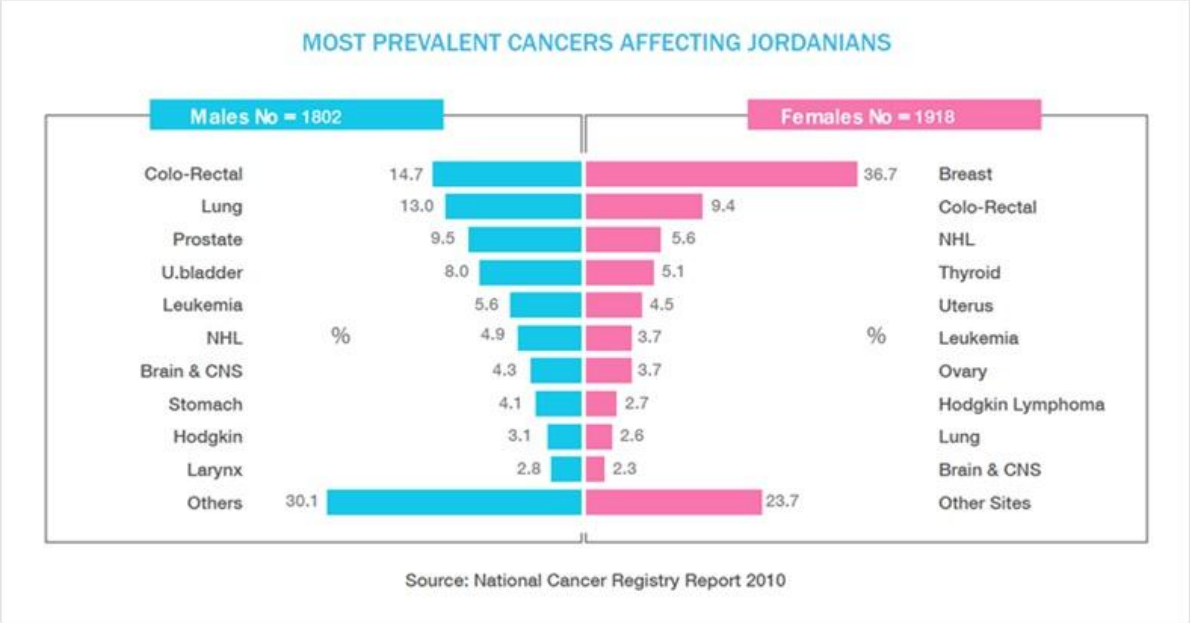

Figure 1. The percentage distribution of the most frequent types of cancer by gender (all ages) in 2010. (National Cancer Registry Report, 2010)

2.1.2. **Etiology**

Until now there is no specific known reason for the development of this disease, but there are several factors that increase the risk of the occurrence of breast cancer. These factors include: age, geographic location (country of origin), socioeconomic status, reproductive events, exogenous hormones, lifestyle and dietary risk factors (alcohol, diet, obesity and physical activity), history of benign breast disease, familial

history of breast cancer, mammographic density, bone density, ionizing radiation, height, prolactin levels and chemo-preventive agents(Dumitrescu & Cotarla, 2005).

2.1.3. Breast cancer risk factors

2.1.3.1. Gender

Female gender is the most important risk factor for breast cancer that is related to female hormones estrogen and progesterone that play an important role in the growth of cancer cells. Breast cancer can also occur in male with less than 1 % of cases and can occur at any age but is more common at the age between 60-70 years (National Cancer Institute, 2014).

2.1.3.2. Age

Age play an important role in breast cancer, the incidence increases with age. In women 40 to 49 years of age, there is one in 68 risk of developing breast cancer and in the 50 to 59 years of age risk increases to one in 37. Seventy seven percent of diagnosed women is above 50 years and more than a half of them were in age above 65 years (Costanza, 1994; Smigal et al., 2006).

2.1.3.3. Race and ethnicity

White women are slightly more likely to develop breast cancer than African American women, but African-American women are more likely to die of this cancer. However, in women before the age of ٥٠, it is more common in African- American women. Asian, Hispanic, and Native-American women have a lower risk of developing and dying from breast cancer (Smigal et al., 2006).

2.1.3.4. Benign breast conditions and dense breast tissue

There are two types of tumors benign and malignant. In benign tumor there are normal cells that grow abnormally and rapidly leading to lump formation. Women who developed benign breast tumor are at higher risk to develop breast cancer (Kunju et al., 2011).

One of the risk factors that increase the incidence of breast cancer is having dense breast tissue which means that breast contains more glandular and fibrous tissue and less fatty tissue. This characteristic is affected by a number of factors such as age, menopausal status, the use of drugs (such as menopausal hormone therapy), pregnancy, and genetics (Gold et al., 2001).

2.1.3.5. Personal history of breast cancer

A woman with cancer in one breast has a 3- to 4-fold increased risk of developing a new cancer in the other breast or in another part of the same breast. This is different from a recurrence of the first cancer (Schacht et al., 2014).

2.1.3.6. Family history of breast cancer

Family history of breast cancer increases the risk of occurrence of this disease, the exact risk is unknown but less than 15% of women with breast cancer have family history. Having one first-degree relative (mother, sister, or daughter) with breast cancer approximately doubles the woman's risk and having 2 first-degree relatives increases her risk about 3-fold. (Colditz et al., 1993).

2.1.3.7. Reproductive and hormonal risk factors

2.1.3.7.1. Menstrual periods

Risk of breast cancer increases as the number of menstrual cycles during women life increases as in women who menstruate early before the age of 12 years or in women who went through menopause later (after the age 55).This unexpected shift has been attributed to broad exposure to hormone disruptors, since rise in hormones triggers the onset of breast development and puberty (Brinton, Schairer, Hoover, & Fraumeni, 1988).

2.1.3.7.2. Age at the first childbirth and number of childbirth

The effect of the first pregnancy is like a weapon with two sides. At first, it increases short-term risk and then it lowers long-term risk. These effects interact depending on a woman's age (Nelson et al., 2012). Women who give birth to their first child at age 35 or younger tend to get a protective benefit from pregnancy. Breast cancer risk is increased for about 10 years after a first birth, and then it drops below the risk of women who don't have children(Rosner, Colditz, & Willett, 1994). The younger you are when you have your first child, the sooner you get the protective effect of pregnancy. Women that gave birth to their first child at later ages are at increased risk of breast cancer compared to women who have their first child at younger ages. For example, women who give birth for the first time after age 35 are 40 percent more likely to get breast cancer than women who have their first child before age 20 (Ewertz et al., 1990). For these women, the increase in risk from the first pregnancy is never fully offset by its long-term protective benefits (Rosner et al., 1994).Women who are over age 35 when they give birth to their first child also have a small increase

in lifetime risk of breast cancer compared to those who do not give birth (Colditz & Rosner, 2000).

2.1.3.7.3. Birth control

There are no exact results in this field, results are conflicting. Studies show that current or recent use of birth control pills (oral contraceptives) increases the risk of breast cancer. Analysis of data from several studies found that women who took birth control pills had a 10 to 30 percent higher risk of breast cancer than women who had never used these pills(Moorman et al., 2013). The risk of breast cancer will decrease after stopping an oral contraceptive and it needs 10 year to return to the normal level(as in women who never use OC). Reassuring data that oral contraceptives do not increase breast cancer risk later in life have been published recently (Marchbanks et al., 2002; Vessey & Painter, 2006).

2.1.3.7.4. Hormone replacement therapy.

Estrogen plus progestin increase the risk of both developing and dying from breast cancer (Bakken et al., 2011; Colditz et al., 1995) . These hormones increase the risk of having an abnormal mammogram within the first year of use(Beral, 2003). The risk of breast cancer increases within the first five years of use (Rossouw et al., 2002) .

The U.S. Food and Drug Administration (FDA) recommended only the use of the lowest dose of hormonal replacement therapy that will alleviate symptoms and for the shortest time needed (U.S. Food and Drug Administration, 2013) .However, there is a

decreased risk of breast cancer with estrogen alone compared to placebo after an average of seven years of use (Manson et al., 2013).

2.1.3.7.5. Breastfeeding

There is a transient increase in risk of breast cancer in the first three to four years after pregnancy. Lactation reduced the risk for breast cancer. This protective effect seems greater for women who had extended periods of breastfeeding during their lifetime, particularly in case of *BRCA1* mutation. After breast cancer treatment, there is no evidence that breastfeeding increases the risk of breast cancer recurrence, nor that it carries any health risk to the newborn. Women previously treated for breast cancer and free of recurrence are allowed to breastfeed their children. Beneficial effects of breastfeeding for the mother and the newborn should lead physicians and midwives to encourage prolonged breastfeeding in their medical practice (Babita, Kumar, Singh, Malik, & Kalhan, 2014).

2.1.3.7.6. Induced abortion

A woman gains protection from breast cancer by completing a full-term pregnancy. In utero, her offspring produce hormones that mature 85 percent of the mother's breast tissue into cancer-resistant breast tissue. If the pregnancy ends through an induced abortion or a premature birth before thirty-two weeks, this increase the amount of immature breast tissue that will leave the mother with more sites for cancer initiation, thereby increasing her risk of breast cancer (Huang et al., 2014; Lanfranchi, 2014). On the other hand, several studies have provided data that neither induced abortions

nor spontaneous abortions (miscarriages) have an overall effect on the risk of breast cancer(Ilic, Vlajinac, Marinkovic, & Sipetic-Grujicic, 2013).

2.1.3.8. Life style risk factors

2.1.3.8.1. Obesity

Obesity is associated with an increased risk of breast cancer, and increased risk of recurrence in women who develop breast cancer. Evidence suggests that the risk of estrogen-receptor (ER)-positive breast cancer is increased in obese postmenopausal women, whereas in premenopausal women the risk of triple negative breast cancer is increased. Nonetheless, the presence of obesity at diagnosis, and possibly weight gain after diagnosis, may independently contribute to an individual's risk of recurrence of both pre- and postmenopausal breast cancer(Jain, Strickler, Fine, & Sparano, 2013).

Also, women who are overweight tend to have higher blood insulin levels. Higher insulin levels have also been linked to some cancers, including breast cancer(Bianchini, Kaaks, & Vainio, 2002).

2.1.3.8.2. Physical activity

Evidence is growing that physical activity in the form of exercise reduces breast cancer

risk.Lack of exercise can result in obesity, while a consistent exercise routine lowers hormone levels and boost the immune system. Brisk walking for ≥7 hours/week was associated with a reduction in breast cancer incidence similar to that for vigorous exercise. Sitting for long periods at work or watching TV was not significantly associated with breast cancer incidence (Rosenberg et al., 2014).

2.1.3.8.3.Tobacco smoke

Cigarette smoking is strongly associated with various diseases including many cancers; however, evidence regarding breast cancer risk remains inconclusive with some studies reporting no association, and others showing an increased risk with long duration and early initiation of smoking. Ten prospective cohort studies involving 782 534 female non-smokers were included in the meta-analysis and 14 831 breast cancer cases were detected. The results suggest that passive smoking may not be associated with increased incidence of breast cancer. However, the present conclusion should be considered carefully and confirmed with further studies (Yang, Zhang, Skrip, Wang, & Liu, 2013).

2.1.3.8.4.Night work

Disruption of circadian rhythms by night shift work or disturbed sleep-wake cycles may lead to an increased risk of breast cancer and other diseases. Moreover, light exposure at night (LEN) suppresses the nocturnal production of melatonin that inhibits breast cancer growth (Dauchy et al., 2014). This effect is still controversial and needs further investigations (Rabstein et al., 2014).

2.1.3.8.5. Antiperspirants

Based on the available evidence, there is little if any reason to believe that antiperspirants increase the risk of breast cancer (Watson, Gies, Thompson, & Thomas, 2012).

2.1.3.8.6. Breast implants

Several studies have found that breast implants do not increase the risk of breast cancer,

although silicone breast implants can cause scar tissues in the breast.

Breast implants may be linked to a rare type of lymphoma called anaplastic large cell lymphoma. There are too few cases to know if the risk of this lymphoma is really higher in women that have implants (Adrada et al., 2014).

2.1.3.9. Dietary risk factors

2.1.3.9.1.Drinking alcohol

Many epidemiologic studies have evaluated the relationship between alcohol and breast cancer. Alcohol is the only dietary factor that has shown consistent results in clinical trials. Studies indicate both a modest positive association between alcohol and breast cancer and a dose–response relationship. The risk increases with consumption of alcohol in general, regardless of the beverage type or woman's menopausal status. Potential biologic mechanisms for this association include increased levels of estrogen or other reproductive steroid hormones; increased production of insulin-like growth factors by the liver; and altered hepatic metabolism of carcinogens (Hamajima et al., 2002; Key et al., 2006).

2.1.3.9.2.Diet and vitamin intake

The available literature suggested increased risk of breast cancer with increased fat intake, while there is no reported significant relation between carbohydrate and dairy products consumption and breast cancer. Many studies evaluating and discussing the role of different diets and breast cancer risk, showed a conflicting results indicating

that further studies are needed to prove this role (Mourouti, Kontogianni, Papavagelis, & Panagiotakos, 2014; Woo et al., 2014).

2.1.3.10. Genetic mutations

More than 10% of breast cancer patients are thought to be related to hereditary causes. Most hereditary cases of breast cancer are associated with two abnormal genes: breast cancer gene 1 (*BRCA1*) and breast cancer gene 2 (*BRCA2*). Mutations in these genes are thought to account for between 5% and 10% of all breast cancer cases. Available literature suggest that other mutations in highly penetrant genes may play an important role in breast cancer susceptibility, and studies aimed at the isolation of these genes are under way (Martin & Weber, 2000).

2.1.4. **Symptoms and signs**

A painless lump is the initial sign of breast cancer in most women. The typical malignant mass is solitary, unilateral, solid, hard, irregular, and nonmobile. In small numbers of cases, stabbing or aching pain is the first symptom. Less commonly, nipple discharge, retraction, or dimpling may herald the onset of the disease. In more advanced cases, prominent skin edema, redness, warmth, and induration of the underlying tissue may be observed (Chisholm-Burns, Schwinghammer, Wells, Malone , & DiPiro, 2013).

2.1.5. **Diagnoses**

Initial workup for a woman presenting with a lesion or symptoms suggestive of breast cancer should include a careful history, physical examination of the breast, 3-D mammography, and possibly other breast imaging techniques such as ultrasonography or MRI. Most breast cancers can be visualized on a mammogram as a mass, a cluster of calcifications, or a combination (Barnett, 2014). Full radiologic testing should also be completed including a CT scan of the chest, abdomen, and pelvis, and bone scan to assess for metastatic disease types of breast cancer (Kellie L. Jones, 2013).

2.1.6. **Types of breast cancer**

Ductal and lobular carcinomas are the most common types of breast cancer. Ductal tumors may be classified either as invasive ductal carcinoma if it has invaded through the basement membrane of the duct, or ductal carcinoma in situ (DCIS), if it has not. Lobular tumors may be classified similarly (i.e., invasive lobular carcinoma or lobular carcinoma in situ [LCIS]) (Kellie L. Jones, 2013). Invasive ductal carcinoma accounts for 50 to 75 percent of all breast cancers while invasive lobular carcinoma is the next most common type and accounts for about 10 to 15 percent of cases. Tubular carcinoma and mucinous (colloid) carcinoma are less common types of invasive breast cancer that tend to have a good prognosis (Harriss, Marc, Lippman, Kent, & Monica, 2009)

2.1.7. **Staging of breast cancer**

The stage of breast cancer depends on the size of the breast tumor and whether it has spread to lymph nodes or other parts of the body. Stages of breast cancer are

described by using the Roman numerals 0, I, II, III, and IV and the letters A, B, and C.

A cancer that is Stage I is classified as an early-stage breast cancer, and a cancer that is Stage IV is advanced cancer that has metastases and spread to other parts of the body, such as the liver, and brain. The stage often is not known until surgery is done to remove the tumor in the breast and one or more underarm lymph nodes (Singletary et al., 2002).

2.1.8. **Treatment**

Breast cancer treatment options vary depending on the stage of the cancer, its size, position, whether it has spread to other parts of the body and the physical health of the patient. Current treatments for breast cancer include surgery, radiotherapy, and chemotherapy, hormonal and targeted therapies. These therapies may be used alone or in combination depending on the stage of the disease(Yang, Swennenhuis, Rho, Le Gac, & Terstappen, 2014).

2.1.8.1. **Surgery**

This is the main treatment option for patients whose breast cancer has not spread to other parts of the body and is also an option for more advanced stages of the disease. The types of breast cancer surgery differ in the amount of tissue that is removed with the tumor; this depends on the tumor's characteristics, whether it has spread, and the patient's personal feelings (Fisher et al., 2002; He et al., 2012; Litière et al., 2012)

2.1.8.2. Radiotherapy

Therapy with radiation is often used to reduce the chances of the cancer recurring in addition to surgery and chemotherapy. It can be given after surgery (adjuvant treatment) or in conjunction with chemotherapy prior to surgery (neoadjuvant therapy) to shrink the tumor size. Radiotherapy can also be used without surgery in patients with advanced metastatic breast cancer to help alleviate symptoms (Lalani et al., 2014).

2.1.8.3. Chemotherapy

Chemotherapy may be given prior to surgery (neo-adjuvant) with the aim of reducing tumor size and the need for extensive surgery, or after surgery (adjuvant) to reduce the chances of the cancer coming back. When the cancer has spread to other parts of the body (metastatic), chemotherapy may be used to reduce symptoms, improve quality of life and extend survival. Chemotherapy drugs can be given intravenously, or orally in a tablet. Chemotherapy is typically associated with adverse side effects such as fatigue, nausea and diarrhea; this is because of its toxic nature and non-specific mode of action (Hassan, Ansari, Spooner, & Hussain, 2010).

2.1.8.4. Hormonal therapy

Hormonal therapy is an effective treatment for breast cancer in women that is estrogen receptor positive (ER positive or ER+) and progesterone receptor positive (PR positive or PR+). The most commonly used hormonal therapies are

anti-estrogens, aromatase inhibitors, ovarian ablation, progestins, and androgens (Bachelot et al., 2012; Hershman et al., 2010).

2.1.8.5. Targeted therapy

Targeted (also called biological) therapies are a relatively new approach to cancer treatment and target specific biological processes that are often essential to tumor growth. Targeted therapy can include use of monoclonal antibodies, vaccines and gene therapies (Slamon et al., 2011; Witkiewicz, Cox, & Knudsen, 2014).

References:

Adrada, B. E., Miranda, R. N., Rauch, G. M., Arribas, E., Kanagal-Shamanna, R., Clemens, M. W., . . . Yang, W. (2014). Breast implant-associated anaplastic large cell lymphoma: sensitivity, specificity, and findings of imaging studies in 44 patients. *Breast cancer research and treatment, 147*(1), 1-14. doi:10.1007/s10549-014-3034-3

Babita, Kumar, N., Singh, M., Malik, J. S., & Kalhan, M. (2014). Breastfeeding reduces breast cancer risk: a case-control study in north India. *International journal of preventive medicine, 5*(6), 791-795 .

Bachelot, T., Bourgier, C., Cropet, C., Ray-Coquard, I., Ferrero, J. M., Freyer, G., . . . Pujade-Lauraine, E. (2012). Randomized phase II trial of everolimus in combination with tamoxifen in patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer with prior exposure to aromatase inhibitors: a GINECO study. *Journal of Clinical Oncology, 30*(22), 2718-2724. doi:10.1200/jco.2011.39.0708

Bakken, K., Fournier, A., Lund, E ,.Waaseth, M., Dumeaux, V., Clavel-Chapelon, F., . . . Berrino, F. (2011). Menopausal hormone therapy and breast cancer risk: impact of different treatments. The European Prospective Investigation into Cancer and Nutrition. *International journal of cance* .156-144 ,(1)128 ,doi:10.1002/ijc.25314

Baqutayan, S. M. S. (2012). The Effect of Anxiety on Breast Cancer Patients. *Indian Journal of Psychological Medicine*

.123-119 ,(2)34doi:10.4103/0253-7176.101774

Barnett, C. M., et al. (2014). *Pharmacotherapy: A Pathophysiologic Approach* (g1, Trans. e. a. Joseph T. DiPiro Ed. 9e ed. Vol. Chapter 105. Breast Cancer). b: New York, NY: McGraw-Hill.

Beral, V. (2003). Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet, 362*(9382), 419-427 .

Bianchini, F., Kaaks, R., & Vainio, H. (2002). Overweight, obesity, and cancer risk. *The lancet oncology, 3*(9), 565-574 .

Brinton, L. A., Schairer, C., Hoover, R. N., & Fraumeni, J. F. (1988). Menstrual Factors and Risk of Breast Cancer. *Cancer Investigation, 6*(3), 245-254. doi:doi:10.3109/07357908809080645

Chisholm-Burns, M., Schwinghammer, T., Wells, B., Malone , P., & DiPiro, J. (2013). *Pharmacotherapy Principles and Practice* (Third ed.): McGraw-Hill Medical.

Colditz, G. A., Hankinson, S. E., Hunter, D .J., Willett, W. C., Manson, J. E., Stampfer, M. J., . . . Speizer, F. E. (1995). The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. *The New England journal of medicine, 332*(24), 1589-1593. doi:10.1056/nejm199506153322401

Colditz, G. A., & Rosner, B. (2000). Cumulative risk of breast cancer to age 70 years according to risk factor status: data from the Nurses' Health Study. *American Journal of Epidemiology, 152*(10), 950-964 .

Colditz, G. A., Willett, W. C., Hunter ,D. J., Stampfer, M. J., Manson, J. E., Hennekens, C. H., & Rosner, B. A. (1993). Family history, age, and risk of breast cancer. Prospective data from the Nurses' Health Study. *Jama, 270*(3), 338-343 .

Costanza, M. E. (1994). The extent of breast cancer screening in older women. *Cancer, 74*(7 Suppl), 2046-2050 .

Dauchy, R. T., Xiang, S., Mao, L., Brimer, S., Wren, M. A., Yuan, L., . . . Hill, S. M. (2014). Circadian and melatonin disruption by exposure to light at night drives intrinsic resistance to tamoxifen therapy in breast cancer. *Cancer research, 74*(15), 4099-4110. doi:10.1158/0008-5472.can-13-3156

Dumitrescu, R. G., & Cotarla, I. (2005). Understanding breast cancer risk -- where do we stand in 2005? *Journal of cellular and molecular medicine, 9*(1 .221-208 ,(

Ewertz, M., Duffy, S. W., Adami, H. O., Kvale, G., Lund, E., Meirik, O., . . . Tulinius, H. (1990). Age at first birth, parity and risk of breast cancer: a meta-analysis of 8 studies from the Nordic countries. *International journal of cancer, 46* .603-597 ,(4)

Ferlay, J., Shin, H. R., Bray, F., Forman, D., Mathers, C., & Parkin, D. M. (2010). Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *International journal of cancer, 127*(12), 2893-2917. doi:10.1002/ijc.25516

Fisher, B., Anderson, S., Bryant, J., Margolese, R. G., Deutsch, M., Fisher, E. R., . . . Wolmark, N. (2002). Twenty-Year Follow-up of a Randomized Trial Comparing Total Mastectomy, Lumpectomy, and Lumpectomy plus Irradiation for the Treatment of Invasive Breast Cancer. *New England journal of medicine, 347*(16), 1233-1241. doi:doi:10.1056/NEJMoa022152

Gold, E. B., Bromberger, J., Crawford, S., Samuels, S., Greendale, G. A., Harlow, S. D., & Skurnick, J. (2001). Factors Associated with Age at Natural Menopause in a Multiethnic Sample of Midlife Women. *American Journal of Epidemiology, 153*(9), 865-874. doi:10.1093/aje/153.9.865

Guaoua, S., Ratbi, I., Lyahyai, J., El Alaoui, S. C., Laarabi, F. Z., & Sefiani, A. (2014). Novel nonsense mutation of BRCA2 gene in a Moroccan man with familial breast cancer. *African health sciences, 14*(2), 468-471. doi:10.4314/ahs.v14i2.25

Hamajima, N., Hirose, K., Tajima, K., Rohan, T., Calle, E. E., Heath, C. W., Jr., . . . Meirik, O. (2002). Alcohol, tobacco and breast cancer--collaborative reanalysis of individual data from 53 epidemiological studies, including 58,515 women with breast cancer and 95,067 women without the disease. *British journal of cancer, 87*(11), 1234-1245. doi:10.1038/sj.bjc.6600596

Harriss, J. R., Marc, E., Lippman, C., Kent ,O., & Monica, M. (2009). *Diseases of the Breast* (Fourth Ed.): Lippincott Williams & Wilkins.

Hassan, M. S., Ansari, J., Spooner, D., & Hussain, S. A. (2010). Chemotherapy for breast cancer (Review). *Oncology reports, 24*(5), 1121-1131 .

He, Z. Y., Tong ,Q., Wu, S. G., Li, F. Y., Lin, H. X., & Guan, X. X. (2012). A comparison of quality of life and satisfaction of women with early-stage breast cancer treated with breast conserving therapy vs. mastectomy in southern China. *Supportive Care in Cancer, 20*(10 .2449-2441 ,(doi:10.1007/s00520-011-1364-9

Hershman, D. L., Kushi, L. H., Shao, T., Buono, D., Kershenbaum, A., Tsai, W. Y., . . . Neugut, A. I. (2010). Early discontinuation and nonadherence to adjuvant hormonal therapy in a cohort of 8,769 early-stage breast cancer patients. *Journal of Clinical Oncology, 28*(27), 4120-4128. doi:10.1200/jco.2009.25.9655

Huang, Y., Zhang, X., Li, W., Song, F., Dai, H., Wang, J., . . . Chen, K. (2014). A meta-analysis of the association between induced abortion and breast cancer risk among Chinese females. *Cancer Causes Control, 25*(2), 227-236. doi:10.1007/s10552-013-0325-7

Ilic, M., Vlajinac, H., Marinkovic, J., & Sipetic-Grujicic, S. (2013). Abortion and breast cancer: case-control study. *Tumori, 99*(4), 452-457. doi:10.171361.15093/00

Jain, R., Strickler, H. D., Fine, E., & Sparano, J. A. (2013). Clinical studies examining the impact of obesity on breast cancer risk and prognosis. *Journal of mammary gland biology and neoplasia*

.266-257 ,(4-3)18doi:10.1007/s10911-013-93073-

Jordan Breast Cancer Program. (2008, 2008). *http://www.jbcp.jo/* .

Kalinsky, K., Mayer, J. A., Xu, X., Pham, T., Wong, K. L., Villarin, E., . . . Bischoff, F. Z. (2015). Correlation of hormone receptor status between circulating tumor cells, primary tumor, and metastasis in breast cancer patients. *Clinical & translational oncology*. doi:10.1007/s12094-015-1275-1

Kellie L. Jones. (2013). *Applied Therapeutics, The Clinical Use of Drugs* (Koda kimble and Young's Ed. 10th ed.): LIPPINCOTT WILLIAMS & WILKINS ,a WOLTERS KLUWER business.

Key, J., Hodgson, S., Omar, R. Z., Jensen, T. K., Thompson, S. G., Boobis, A. R., . . . Elliott, P. (2006). Meta-analysis of studies of alcohol and breast cancer with consideration of the methodological issues. *Cancer Causes Control, 17*(6), 759-770. doi:10.1007/s10552-006-0011-0

Kunju, L. P., Cookingham, C., Toy, K. A., Chen, W., Sabel, M. S., & Kleer, C. G. (2011). EZH2 and ALDH-1 mark breast epithelium at risk for breast cancer development. *Modern pathology, 24*(6), 786-793. doi:10.1038/modpathol.2011.8

Lalani, N., Paszat, L., Sutradhar, R., Thiruchelvam, D., Nofech-Mozes, S., Hanna, W., . . . Rakovitch, E. (2014). Long-term Outcomes of Hypofractionation Versus Conventional Radiation Therapy After Breast-Conserving Surgery for Ductal Carcinoma In Situ of the Breast. *International journal of radiation oncology, biology, physics*

doi:10.1016/j.ijrobp.2014.07.026

Lanfranchi, A. (2014). Normal breast physiology: the reasons hormonal contraceptives and induced abortion increase breast-cancer risk. *Issues in law & medicine*

.146-135 ,(1)29

Lecarpentier, J., Nogues, C., Mouret-Fourme, E., Buecher, B., Gauthier-Villars, M., Stoppa-Lyonnet, D., . . . Andrieu, N. (2015). Breast cancer risk associated with oestrogen exposure and truncating mutation location in BRCA1/2 carriers. *Cancer epidemiology, biomarkers & prevention*. doi:10.1158/1055-9965.epi-14-0884

Litière, S., Werutsky, G., Fentiman, I. S., Rutgers, E., Christiaens, M.-R., Van Limbergen, E., . . . Bartelink, H. (2012). Breast conserving therapy versus mastectomy for stage I–II breast cancer: 20 year follow-up of the EORTC 10801 phase 3 randomised trial. *The lancet oncology, 13*(4), 412-419. doi:http://dx.doi.org/10.1016/S1470-2045(12)70042-6

Manson, J. E., Chlebowski, R. T., Stefanick, M. L., Aragaki, A. K., Rossouw, J. E., Prentice, R. L., . . . Wallace, R. B. (2013). Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. *Jama, 31* .1368-1353 ,(13)0doi:10.1001/jama.2013.278040

Marchbanks, P. A., McDonald, J. A., Wilson, H. G., Folger, S. G., Mandel, M. G., Daling, J. R., . . . Weiss, L. K. (2002). Oral contraceptives and the risk of breast cancer. *The New England journal of medicine*

.2032-2025 ,(26)346doi:10.1056/NEJMoa013202

Martin, A.-M., & Weber, B. L. (2000). Genetic and Hormonal Risk Factors in Breast Cancer. *Journal of the National Cancer Institute, 92*(14), 1126-1135. doi:10.1093/jnci/92.14.1126

Moorman, P. G., Havrilesky, L .J., Gierisch, J. M., Coeytaux, R. R., Lowery, W. J., Peragallo Urrutia, R., . . . Myers, E. R. (2013). Oral contraceptives and risk of ovarian cancer and breast cancer among high-risk women: a systematic review and meta-analysis. *Journal of Clinical Oncology, 31*(33), 4188-4198. doi:10.1200/jco.2013.48.9021

Mourouti, N., Kontogianni, M. D., Papavagelis, C., & Panagiotakos, D. B. (2014). Diet and breast cancer: a systematic review. *International journal of food sciences and nutrition*

.42-1doi:10.3109/09637486.2014.950207

National Cancer Institute. (2014, june 2014). *http://www.cancer.gov/* .

National Cancer Registry Report. (2010). *http://apps.moh.gov.jo/MOH/arabic/publications.php* .

Nelson, H. D., Zakher, B., Cantor, A., Fu, R., Griffin, J., O'Meara, E .S., . . . Miglioretti, D. L. (2012). Risk factors for breast cancer for women aged 40 to 49 years: a systematic review and meta-analysis. *Annals of internal medicine*

.648-635 ,(9)156doi:10.7326/0003-4819-156-9-201205010-00006

Rabstein, S., Harth, V., Justenhoven, C., Pesch, B., Plottner, S., Heinze, E., . . . Bruning, T. (2014). Polymorphisms in circadian genes, night work and breast cancer: Results from the GENICA study. *Chronobiology international*

.8-1doi:10.3109/07420528.2014.957301

Rosenberg, L ,.Palmer, J. R., Bethea, T. N., Ban, Y., Kipping-Ruane, K., & Adams-Campbell, L. L. (2014). A prospective study of physical activity and breast cancer incidence in African American women. *Cancer Epidemiol Biomarkers Prev*. doi:10.1158/1055-9965.epi-14-0448

Rosner, B., Colditz, G. A., & Willett, W. C. (1994). Reproductive risk factors in a prospective study of breast cancer: the Nurses' Health Study. *American journal of epidemiology*

.835-819 ,(8)139

Rossouw, J. E., Anderson, G. L., Prentice, R. L., LaCroix ,A. Z., Kooperberg, C., Stefanick, M. L., . . . Ockene, J. (2002). Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *Jama, 288*(3), 321-333 .

Schacht, D. V., Yamaguchi, K., Lai, J., Kulkarni, K., Sennett, C. A., & Abe, H. (2014). Importance of a personal history of breast cancer as a risk factor for the development of subsequent breast cancer: results from screening breast MRI. *AJR. American journal of roentgenology, 202*(2), 289-292. doi:10.2214/ajr.13.11553

Singletary, S. E., Allred, C., Ashley, P., Bassett, L. W., Berry, D., Bland, K. I., . . . Greene, F. L. (2002). Revision of the American Joint Committee on Cancer staging system for breast cancer. *Journal of Clinical Oncology, 20*(17), 3628-3636 .

Slamon, D., Eiermann, W., Robert, N., Pienkowski, T., Martin, M., Press, M., . . . Crown, J. (2011). Adjuvant Trastuzumab in HER2-Positive Breast Cancer. *New England journal of medicine, 365*(14), 1273 .1283-doi:doi:10.1056/NEJMoa0910383

Smigal, C., Jemal, A., Ward, E., Cokkinides, V., Smith, R., Howe, H. L., & Thun, M. (2006). Trends in breast cancer by race and ethnicity: update 2006. *cancer journal for clinicians*

.183-168 ,(3)56

U.S. Food and Drug Administration. (2013). *http://www.fda.gov/ForConsumers/ByAudience/ForWomen/ucm118624.htm* .

Vessey, M., & Painter, R. (2006). Oral contraceptive use and cancer. Findings in a large cohort study, 1968-2004. *British journal of cancer*

.389-385 ,(3)95doi:10/1038.sj.bjc.6603260

Watson, L. C., Gies, D., Thompson, E., & Thomas, B. (2012). Randomized control trial: evaluating aluminum-based antiperspirant use, axilla skin toxicity, and reported quality of life in women receiving external beam radiotherapy for treatment of Stage 0, I, and II breast cancer. *International journal of radiation oncology, biology, physics, 83*(1), e29-34. doi:10.1016/j.ijrobp.2011.12.006

WHO Cancer Factsheet. (2014, February 2014). *http://www.who.int/mediacentre/factsheets/fs297/en/* .

Witkiewicz, A. K., Cox, D., & Knudsen, E. S. (2014). CDK4/6 inhibition provides a potent adjunct to Her2-targeted therapies in preclinical breast cancer models. *Genes Cancer, 5*(7-8), 261-272 .

Woo, H. D., Park, S., Oh, K., Kim, H. J., Shin, H. R., Moon ,H. K., & Kim, J. (2014). Diet and Cancer Risk in the Korean Population: A Meta- analysis. *Asian Pacific journal of cancer prevention, 15*(19), 8509-8519 .

World Cancer Research Fund International. (2013, December 2013). *http://www.wcrf.org/int/cancer-facts-figures/worldwide-data* .

Yang, Y., Swennenhuis, J. F., Rho, H. S., Le Gac, S., & Terstappen, L. W. (2014). Parallel single cancer cell whole genome amplification using button-valve assisted mixing in nanoliter chambers. *PLoS One, 9*(9), e107958. doi:10.1/371journal.pone.0107958

Yang, Y., Zhang, F., Skrip, L., Wang, Y., & Liu, S. (2013). Lack of an association between passive smoking and incidence of female breast cancer in non-smokers: evidence from 10 prospective cohort studies. *PLoS One, 8*(10), e77029 . doi:10.1371/journal.pone.0077029