

Breast Cancer: Detection Markers, Prognosis, and Prevention

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ABSTRACT: Breast cancer is the common invasive cancer with high mortality worldwide. High incidence of breast cancer in South and central America, Southren, Northren, Westren Europe, Ocenia and North America. Lowest breast cancer incidence in Africa and Asia. Risk factors includes: female sex old age, lifestyle, oral contraceptive, hormone replacement therapy, mutations in the breast cancer susceptibility genes BRCA1 or BRCA2, alcohol intake, hereditary factors, and exposure to chemicals. Breast cancer occurs because of an interaction between external factor and genetically susceptible host. Frequent symptoms of breast cancer is typically a lump and lumps found in the lymph node in the armpits. Diagnosis by physical examination of the breast and mammography. Further tests include histopathological examination, breast cells grading by TNM systeme.g., Zero stage a precancerous or marker condition, stage 1- 3 within the breast and regional nodes, and stage four is metastatic stage. Management of breast cancer depends on the stage of the cancer and age of the patient. Usually treated with surgery, chemotherapy or radiation therapy or both. A multidisciplinary approach is preferable. Metastatic cancer has less favorable prognosis. Prognosis is usually the probability of progression-free survival (PFS) or disease free survival (DFS). Prevention include change in life style, maintaining healthy weight, less alcohol consumption, and intake of marine omega-3 and soy-based foods Prophylactic mastectomy (removal of both breasts) helps in people with BRCA1 and BRCA2 mutations. Early detection of breast cancer has better prognosis.

Keywords: Breast cancer, Risk factors, Diagnosis, Prognosis

I. Introduction

Breast cancer is cancer that develops from breast tissues[1]. Early signs of breast cancer may include a lump in the breast, a change in breast shape, dimpling of the skin, fluid coming from the nipple, or a red scaly patch of skin[2]. Worldwide breast cancer is the most common invasive cancer in women[3]. Breast cancer comprises 22.9% of invasive cancers in women[4]. In 2012, it comprised 25.2% of cancers diagnosed in women making it the most common female cancer[5]. In 2008, breast cancer caused 458,503 deaths worldwide, 13.7% of cancer deaths in women and 6.0% of all cancer deaths for men and women together[4]. In 2012, it resulted in 1.68 million cases and 522,000 deaths[6]. Incidence of breast cancer varies greatly around the world: it is lowest in the less-developed countries and greatest in the more-developed countries. In the twelve world regions, the annual age-standardized incidence rates per 10,000 women are :in Eastern Asia, 18, South Central Asia, 22, sub-Saharan Africa, 22, South-Eastern Asia, 26, North Africa and Western Asia, 28, South and Central America, 42, Eastren Europe, 49, Southern Europe, 56; Nothern Europe, 73; Ocenia, 74, Wstern Europe, 78, North America 90[7]. In 2006, Malaysia reported 3525 cases of breast cancer, and 16.5% of all cancer registered with peak age of 50 years to 59 years age group[8]. Breast cancer is strongly related to age with only 5% of all breast cancers occurring in women under 40 years old[9]. Risk factors for developing breast cancer include: female sex, obesity, lack of physical exercise, drinking alcohol, hormone replacement therapy, ionizing radiation old age and family history[2,]. Diagnosis of breast cancer is confirmed by biopsy of the concerning lump, with further tests to determine if the cancer has spread beyond the breast[2]. Outcomes for breast cancer vary depending on the cancer type, extent of disease, and person's age[10]. Survival rates in the developed world are high, with between 80% and 90% of those in England and the United States alive for at least 5 years[11,12]. Management mainly by surgery, medication, and radiation. Prevention by life style changes, maintaining healthy weight and less consumption of alcohol[13]. The paper reviews the risk factors, diagnosis, and current management of breast cancer.

II. Historical Perspectives

The oldest evidence of breast cancer was discovered in Egypt in 2015 and dates back to Sixth Dynasty [14]. The study of a women's remains from necropolis of Qubbet el-Hawa showed the typical destructive

damage due to metastatic spread[14].The Edwin Smith Papyrus describes 8 cases of tumors or ulcers of the breast that were treated by cauterization.The writing says about the disease, “There is no treatment”[15].Ancient medicine, from the time of the Greeks through the 17th century, was based on humoralism,and thus believed that breast cancer was generally caused by imbalances in the fundamental fluids that controlled the body, especially an excess of black bile[16].Alternatively. Patients often saw it as divine punishment [17].

In the 18th century, a wide variety of medical explanations were proposed, including a lack of sexual activity, too much sexual activity, physical injuries to the breast, curdled breast milk, and various forms of lymphatic blockage, either internal or due to restrictive clothing[15].in the 19th century, the Scottish surgeon John Rodman said that fear of cancer caused cancer, and this anxiety, learned by example from mother, accounted for breast cancer’s tendency to run in the families[18].Although breast cancer was known in ancient times, it was uncommon until 19thcentury, when improvements in sanitation and control of deadly infectious diseases resulted in dramatic increase in lifespan. Previously, most woman had died too young to have developed breast cancer [18].Additionally, early frequent childbearing and breastfeeding probably reduced the rate of breast cancer development in those woman who did survive to middle age [18].

Mastectomy for breast cancer was performed at least as early as AD 548,when it was proposed by the court physician Aetios of Amida of Theodora[19].It was not until doctors achieved greater understanding of the circulatory system in the 17th century that they could link breast cancer’s spread to lymph nodes in the armpit. The French surgeon Jean Petit(1674-1750) and later Scottish surgeon Benjamin Bell (1749-1806) were the first to remove the lymph nodes, breast tissue, and underlying breast muscle[20].Their successful work was carried on by William Stewart Halsted who started performing radical mastectomies in 1882.This often led to long term pain and disability, but was seen as necessary in order to prevent the cancer recurring[21].Before the advent of the Halsted radical mastectomy,20 year survival rates were only 10%,Halsted surgery raised that rate to 50%[22].Extending Halsted work, Jerome Urban promoted super radical mastectomies, taking even more tissue, until 1963,when ten –year survival rates proved equal to the less damaging radical mastectomy[21].

Breast cancer staging systems were developed in the 1920s and 1930s[21].During the 1970s,a new understanding of metastasis led to perceiving cancer as a systemic illness as well as a localized one, and more sparing procedures were developed that proved equally effective. Modern chemotherapy developed after World War II[23].In 1926,Janet Lane-Clayton published a comprehensive study of 500 breast cancer cases and 500 control patients of the same background and lifestyle for the British Ministry of Health[24].In the 1980s and 1990s,thousands of women who had successfully completed standard treatment then demanded and received high-dose bone marrow transplants, thinking this would lead to better long-term survival. However, it proved completely ineffective, and 15-20% of women died because of brutal treatment [25].*In 1995 reports from the Nurses’ Health Study and the 2002 conclusions of the Women’s Health Initiative trial conclusively proved that hormone replacement therapy significantly increased the incidence of breast cancer*[25].

II. Contributory Factors

Contributory or risk factors to breast cancer can be divided into two categories:[26].

- a) Modifiable risk factors-things that people can change themselves, such as consumption of alcohol beverages.
- b) Fixed risk factors-things that cannot be changed, such as age and biological sex.

The primary risk factors for breast cancer are female sex and older age[27].Other potential risk factors include: genetics, lack of child bearing or lack of breastfeeding[28,29],higher levels of certain hormones, and certain dietary patterns,and obesity[30,31].Recent studies have indicated that exposure to high pollution is a risk factor for the development of breast cancer[32].

Lifestyle factors

Smoking tobacco appears to increase the risk of breast cancer, with greater the amount smoked and earlier in life that smoking begin, the higher the risk[33].In those who are long term smokers, the risk is increased 35% to 50%[33].A lack of physical activity has been linked to 10% of cases[34].Sitting regularly for prolonged periods is associated with high mortality from breast cancer. The risk is not negated by regular exercise although it is lowered [35].

Oral contraceptives

There is an association between use of hormonal birth control and the development of premenopausal breast cancer[26,],but whether oral contraceptives use may actually cause premenopausal breast cancer is matter of debate[36].If there is indeed a link, the absolute effect is small[36].Additionally it is not clear if association exists with newer hormonal birth controls[37].In those with mutations in the breast cancer susceptibility genes BRCA1 or BRCA2,or who have a family history of breast cancer, use of modern oral contraceptives does not appear to affect the risk of breast cancer[38].

Breast Feeding

The association between breast feeding and breast cancer has not been determined, some studies have found support for an association while others have not[39].In the 1980s,the abortion-breast cancer hypothesis posited that induced abortion increased the risk of development breast cancer[40].This subject was the subject of extensive scientific inquiry, which concluded that neither miscarriage nor abortions are associated with a heightened risk for breast cancer[41].

Dietary factors

A number of dietary factors have been linked to the risk for breast cancer. Dietary factors which may increase risk include a high fat diet, high alcohol intake, and obesity related high cholesterol levels [42-44].Dietary iodine deficiency may also play a role[45].Evidence for fiber is unclear. A 2015 review found that studies trying to link fiber intake with breast cancer produced mixed results [46].In 2016 a tentative association between low fiber intake during adolescence and breast cancer was observed [47].

Role of Genetics

Some genetic susceptibility may play a minor role in most cases [48].Overall however,genetics is believed to be the primary cause of 5- 10% of all cases[49].Women whose mother was diagnosed before 50 have an increased risk of 1.7 and those whose mother was diagnosed at age 50 or after has an increased risk of 1.4[50].In those with zero,one or two affected relatives, the risk of breast cancer before the age of 80 is 7.8%,13.3% and 21.1% with a subsequent mortality from the disease of 2.3 %,4.2% and 7.6% respectively[51].In those with a first degree relative with disease the risk of breast cancer between the age of 40 and 50 is double that of the general population.[52].

In less than 5% of cases, genetics plays a more significant role by causing a hereditary breast-ovarian cancer syndrome[48].This includes those who carry the BRCA1 and BRCA2 gene mutation[48].These mutations account for up to 90% of the total genetic influence with a risk of breast cancer of 60 -80% in those affected[49].Other significant mutations include *p53*(Li-Fraumeni syndrome),*PTEN*(Cowden syndrome) and *STK11*(Peutz-Jeghers syndrome),*CHEK2*,*ATM*,*BRIP*,and *PALB2*[49].In 2012, researchers said that there are four genetically distinct types of the breast cancer and that in each type, hallmark genetic changes lead to many cancers[53].

Miscellaneous factors and Medical issues

Other risk factors include radiations, and shift work[54,55].A number of chemicals have also been linked including polychlorinated biphenyls,(PCB),polycyclic aromatic hydrocarbons, organic solvents[56].*Although the radiation from mammography is a low dose, it is estimated that yearly screening from 40 to 80 years of age will, cause approximately 225 cases of fatal breast cancer per million women screened*[57].

Breast changes like atypical ductal hyperplasia, and lobular carcinoma in situ found in benign breast conditions such as fibrocystic breast, are correlated with an increased breast cancer risk[58,59].Diabetes mellitus might also increase the risk of breast cancer[60].

IV. Pathophysiology

Breast cancer, like other cancers, occurs because of an interaction between an environmental (external) factor and a genetically susceptible host. Normal cells divide as many times as needed and stop. They attach to other cells and stay in place in tissues. Cells become cancerous when they lose their ability to stop dividing, to attach to other cells, to stay where they belong, and to die at the proper time.

Normal cells will commit cell suicide (programmed cell death) when they are no longer needed. Until then they are protected from cell suicide by several protein clusters and pathways. One of the protective pathways is the P13K/AKT pathway is the RAS/MEK/ERK pathway. Sometimes the genes along these protective pathways are mutated in way that turns them permanently “on”, rendering the cell incapable of committing suicide when no longer needed. This is one of the steps that cause cancers in combination with other mutations. Normally, the PTEN protein turns off the P13K/AKT pathway when cell is ready for programmed cell death. In some breast cancers, the gene for the PTEN protein is mutated, so the P13K/AKT pathway is stuck in the: on” position, and the cancer cell does not commit suicide [61].Mutations that can lead to breast cancer have been experimentally linked to estrogen exposure[62].Abnormal growth factor signaling in the interaction between stromal cells and epithelial cells can facilitate malignant cell growth[63].In breast adipose tissue, overexpression of leptin leads to increased cell proliferation and cancer[64].

In the United States,10 to 20 percent pf people with breast cancer and people with ovarian cancer have first or second degree relative with one of these diseases. The familial tendency to develop these cancers is

called hereditary breast-ovarian cancer syndrome. The best known of these *BRCA* mutations, confer a life time risk of breast cancer of 60 and 85 percent and a life time risk of ovarian cancer of between 15 and 40 percent. Some mutations associated with cancer, such as *p53*, *BRCA 1* and *BRCA2*, occur in mechanisms to correct errors in DNA. These mutations are either inherited or acquired after birth. Presumably, they allow further mutations, which allow uncontrolled division, lack of attachment, and metastasis to distant organs [54].

However, there is strong evidence of residual risk variation that goes well beyond hereditary *BRCA* gene mutations between carrier families. This is caused by unobserved risk factors [65]. This implicates environmental and other causes as triggers for breast cancers. The inherited mutation in *BRCA1* or *BRCA2* genes can interfere with repair of DNA cross links and DNA double strand breaks (known functions of encoded protein) [66]. These carcinogens cause DNA damage such as DNA cross links and double strand breaks that often require repairs by pathways containing *BRCA1* and *BRCA2* [67]. However, mutations in *BRCA* genes accounts for only 2 to 3 percent of all breast cancers [68]. Levin *et al* say that cancer may not be inevitable for all carriers of *BRCA1* and *BRCA2* mutations. About half of hereditary breast-ovarian cancer syndrome involve unknown genes. [69]. *GATA-3* directly controls the expression of estrogen receptor (*ER*) and other genes associated with epithelial differentiation, and the loss of *GATA-3* leads to loss of differentiation and poor prognosis due to cancer cell invasion and metastasis [70].

V. Clinical Manifestations

The first noticeable symptom of breast cancer is typically a lump that feels different from the rest of the breast tissue. More than 80 % of breast cancer are discovered when the woman feels a lump [71]. The earliest breast cancers are detected by a mammogram. Lumps found in lymph node located in the armpits can also indicate breast cancer [72,71]. Indications of breast cancer other than a lump may include thickening different from other breast tissue, one breast becoming larger or lower, a nipple changing position or shape or becoming inverted, skin puckering or dimpling, a rash on or around nipple, discharge from nipple/constant pain in part of breast or armpit, and swelling beneath the armpit or around the collarbone [73]. Pain (“mastodynia”) is an unreliable tool in determining the presence or absence breast cancer, but may be indicative of other breast health issues [71,72,74].

Another reported symptom complex of breast cancer is Paget’s disease of the breast. This syndrome presents as skin changes resembling eczema, such as redness, discoloration, or mild flaking of the nipple. As Paget’s disease advances, symptoms may include tingling, itching, increased sensitivity, burning, and pain. There may also be discharge from the nipple. Approximately half of women with diagnosed with Paget’s disease of the breast also have a lump in the breast [75].

Occasionally, breast cancer presents as metastatic disease—that is, cancer that has spread beyond the original organ. The symptoms of caused by metastatic breast cancer will depend on the location of metastasis. Common sites of metastasis include bone, liver, lung, and brain [76]. Unexplained weight loss can occasionally signal breast cancer, as can symptoms of fevers or chills. Bone or joint pains can sometimes be manifestations of metastatic breast cancer, such as can jaundice or neurological symptoms. These symptoms are called non-specific, meaning they could be manifestations of many other illnesses [77]. Fewer than 20% of lumps, for example, are cancerous, and benign breast diseases such as mastitis and fibroadenoma of the breast are more common causes of breast disorder symptoms [78]. Nevertheless, the appearance of a new symptom should be taken seriously by both patients and their doctors, because of the possibility of an underlying breast cancer at almost any age [79].

VI. Detection and Diagnostic Markers

Two most commonly used screening methods, physical examination of the breasts by the healthcare professional and mammography, can offer an approximately likelihood that a lump is a cancer, and may also detect some other lesions, such as a simple cyst [80]. When the examinations are inconclusive, a fine needle aspiration or fine needle aspiration and cytology-FNAC, is performed to establish the diagnosis. A finding of clear fluid makes the lump highly unlikely to be cancerous, but bloody fluid may be sent for microscopy examination for cancerous cells (cytological examination). Together with physical examination of the breasts, mammography, and FNAC can be used to diagnose breast cancer with a good degree of accuracy. Other options for biopsy include a core biopsy or vacuum-assisted breast biopsy [81].

Breast cancer Classification

Various grading systems are used to classify breast cancers:

Histopathological examination. Breast cancer is usually classified primarily by its histological appearance. Most breast cancers are derived from the epithelial lining the ducts or lobules, and these are classified as ductal or lobular carcinoma. *Carcinoma in situ* is growth of low grade cancerous or precancerous cells within a

particular tissue compartment such as mammary duct without invasion of surrounding tissue. In contrast, *invasive carcinoma* does not confine itself to the initial tissue compartment [82].

Grading breast cancer cells. Grading compares the appearance of the breast cancer cells to the appearance of normal breast tissue. Normal cells in an organ like the breast become differentiated, meaning that they take on specific shapes and forms that reflect their function as part of that organ. Cancerous cells lose that differentiation. In cancer, the cells that would normally line up in an orderly way to make up the milk ducts become disorganized. Cell division becomes uncontrolled. Pathologists describe cells as well differentiated (low grade), moderately differentiated (intermediate grade), and poorly differentiated (high grade) as the cells progressively lose the features seen in the normal breast cells [83,84].

Staging breast cancer

TNM system is used in breast cancer staging, T-tumor, N, lymph nodes, and M tumor metastasized (cancer spread to other body parts). Frequently used staging are:

- a). Zero stage, is a pre-cancerous or marker condition, either ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS)
- b). Stage 1-3 is within the breast or regional nodes
- c). Stage 4 is 'metastatic' cancer that has less favorable prognosis since it has escaped into the bloodstream. In breast cancer patient with low risk for metastasis, the risks associated with PET (positron emission tomography), CT scan, or bone scans outweigh the possible benefits, as these procedures expose the patient to substantial amount of potentially ionizing radiations [83,84].

Receptor status; Breast cancer cells may or may not have three important receptors: estrogen receptor (ER), progesterone receptor (PR), and HER2 [85]. DNA testing of various types including DNA microarrays have compared normal cells to breast cancer cells [86].

VII. Therapy

Therapy or management of breast cancer depends on various factors, including the stage of the cancer and the age of the patient. Breast cancer is usually treated with surgery, which may be followed by chemotherapy or radiation therapy or both. A multidisciplinary approach is preferable [87]. Hormone receptor-positive cancers are often treated with hormone-blocking therapy over courses of several years. Monoclonal antibodies, or other immune-modulating treatments, may be administered in certain cases of metastatic and other advanced stages of breast cancer [87]. Frequently surgeries include: Mastectomy: Removal of whole breast. Quadrantectomy: Removal of one quarter of the breast. Lumpectomy: Removal of a small part of the breast [87].

VIII. Prognosis and Prevention

Prognosis is usually given for the probability of progression-free survival (PFS) or disease free survival (DFS). Survival is usually calculated as an average number of months (years) that 50% of patients survive, or the percentage of patients that are alive after 1, 5, 15, and 20 years. Prognosis is important for treatment decision because patients with a good prognosis are usually offered less invasive treatments, such as lumpectomy and radiation or hormone therapy, while patients with poor prognosis are usually offered more aggressive treatment, such as more extensive mastectomy and more chemotherapy drugs. The Nottingham Prognostic Index is a commonly used prognostic tool [88]. Breast cancer staging takes into consideration size, local involvement, lymph node status and whether metastatic disease is present. The higher the stage at diagnosis, the poorer the prognosis [88]. Younger women with an age of less than 40 years or women over 80 years tend to have a poorer prognosis than post-menopausal women due to several factors [89].

Prevention

Change in life style include maintaining health weight, consuming less alcohol, physically active and breast feeding their children [13]. These modifications might prevent 38% of breast cancers in US, 42% in the UK, 28% in Brazil and 20% in China [89]. Intake of marine omega -3 polyunsaturated fatty acids and consumption of soy-based foods may reduce risk [90,91]. Prophylactic mastectomy (removal of both breasts) may be considered in people with BRCA1 and BRCA2 mutations, which are associated with a substantially heightened risk of for an eventual diagnosis of breast cancer [92]. The selective estrogen modulators (such as tamoxifen) reduce the risk of breast cancer but increase the risk of thromboembolism and endometrial cancer [93]. Breast cancer Preventive task force recommends mammography between the ages 50 and 74 year [94]. The council of Europe recommends mammography between 50 and 69 year, with a 2- year frequency. In Canada screening recommended between ages of 50 and 74 at a frequency of 2 to 3 years [95,96]. The task force reports point out that in addition to unnecessary surgery and anxiety, the risks of more frequent mammograms include a small but significant increase in breast cancer induced radiation [97].

IX. Conclusion

Breast cancer is the most common cause of cancer in women with high mortality worldwide. Incidence of breast cancer is high in Europe and in North America and lowest in Africa and Asia. Risk factors for developing breast cancer include obesity, lack of exercise, alcohol consumption, oral contraceptive, hormone replacement therapy, and family history. Therapy mainly by surgery, medication, and radiation. Early diagnosis has better outcome. Prevention by life style changes.

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