INTRODUCTION

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death in females worldwide, accounting for 23% (1.38 million) of the total new cancer cases and 14% (458,400) of the total cancer deaths. About half the breast cancer cases and 60% of the deaths are estimated to occur in economically developing countries ***(Jemal et al., 2010).***

Breast cancer rates are increasing in developing countries, including Egypt, and are largely attributed to aging of the population, delay in time of first pregnancy, decrease in number of children and in breast feeding, and a move toward high-calorie Western diets ***(Omar et al., 2001).***

Two genes linked to breast cancer have been identified. These are known as breast cancer genes BRCA1 and BRCA2. Mutation in BRCA1/2 genes are rare in most population (with prevalence of 0.3%) but they are believed to have high penetrance. These mutations account for about 5-10% of all breast cancers in general population ***(Chang-Claude, 2004).***

Women carrying gene-line Mutations in BRCA1 or BRCA2 are at risk for early- onset breast cancer. Such women currently receive annual mammograms beginning at age 25-30 years ***(Jenkintown, 2005).***

Early detection of breast cancer is the most effective way to reduce mortality, and a screening program based on mammography is considered the best method for early detection of breast cancer ***(Sanders and Baum, 2005)***.

Mammography has been proven to detect breast cancer at an early stage and, when followed up with appropriate diagnosis and treatment, to reduce mortality from breast cancer. For women at increased risk of breast cancer, other screening technologies also may contribute to the earlier detection of breast cancer, particularly in women under the age of 40 years for whom mammography is less sensitive. The American Cancer Society (ACS) guideline for the early detection of breast cancer stated that women at increased risk of breast cancer might benefit from additional screening strategies beyond those offered to women at average risk, such as earlier initiation of screening, shorter screening intervals, or the addition of screening modalities (such as breast ultrasound or magnetic resonance imaging [MRI]) other than mammography and physical examination ***(Saslow et al., 2007)***.

In a clinical setting, breast carcinoma is commonly diagnosed using a "triple test" of clinical breast examination (breast examination by a trained medical practitioner), mammography, and biopsy. Both mammography and clinical breast examination are also used for screening, they can indicate approximately that a lump is malignant, and may also identify any other lesions ***(Sheshardi and Kandaswamy, 2006).***

Breast conservation therapy has become the treatment standard for early stage breast cancer. Sentinel lymph node biopsy is a new procedure that can predict axillary lymph node dissection. The next challenge is to treat primary tumors by several new minimally invasive procedures, including radiofrequency ablation, interstitial laser ablation, focused ultrasound ablation, and cryotherapy which are under development and may provide treatment options that are psychologically and cosmetically more acceptable to the patient ***(George and Helena, 2007)***.

Multimodality approach is required for early stage breast cancer. These include surgery, radiotherapy, chemotherapy, endocrine therapies, and targeted therapy which aim both to eradicate residual cancer and prevent recurrent disease hence increased survival. Recent improvement in outcome in patients with breast cancer appears to result largely from the use of adjuvant therapies, including chemotherapy and endocrine manipulations ***(Mauriac, 2006).***

Aim of the Work

The aim of this work is to discuss the recent modalities used for diagnosis and treatment of early breast cancer that aims at improving quality of life for breast cancer patients.

BIOLOGICAL CLASSIFICATION OF BREAST CANCER

Introduction:

Breast cancer is the most common cancer affecting women globally. It is the leading cause of death from cancer in women and has age–standardized annual incidence and mortality rates of 37.4 and 13.2 per 100 000 women. The outcome of breast cancer is predicted by the extent of spread of the tumor to locoregional lymph nodes, which, in turn, predicts distant spread. Patients with advanced metastatic disease have a very poor prognosis, hence the importance of effective early diagnosis and treatment to prevent later recurrences and improve survival ***(Lonning et al., 2007).***

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The approach to increase survival in cancer breast is targeting therapy, they act by targeting the pathways that promote, sustain growth and invasion of carcinoma cells and is critical to effective treatment of breast cancer ***(Lin et al., 2008).***

The Biology of Breast Cancer

Cancer develops through a multistep process in which normal, healthy cells in the body go through stages that eventually change them to abnormal cells that multiply out of control. In most cases, cancer takes many years to develop. Normal cells in the body communicate with each other and regulate each other's proliferation (division). Cells proliferate to replace worn-out cells. When cancer occurs, cells escape the normal controls on their growth and proliferation. This escape from control can happen through a variety of pathways ***(Cooper, 2000).***

Part of the multistep process to cancer includes acquiring damage to genes that normally regulate cell proliferation. A series of permanent mutations in tumor suppressor genes and proto-oncogenes are needed before cancer develops. Buildup of damage in these genes can result in uncontrolled cell proliferation. In some cases, further damage can lead to cells that can break away from the primary tumor and form cancers at other sites in the body ***(Nigg, 2000).***

Breast tissue is particularly sensitive to developing cancer for several reasons. The female hormone estrogen stimulates breast cell division. This division can increase the risk of making damage to DNA permanent. Furthermore, breast cells are not fully matured in girls and young women who have not had their first full-term pregnancy. Breast cells that are not fully mature bind carcinogens (cancer causing agents) more

strongly and are not as efficient at repairing DNA damage as mature breast cells ***(Dairkee and Smith, 2000).***

Development of Breast Cancer

When cancer develops it is because of a change in the cells of the body. In the breast tissue of young women and girls, cells are especially sensitive to DNA damage from cancer causing agents ***(Norbury, 2000).***

Mutations in DNA

In every one of the trillions of cells in the body, there is an "operations manual" made up of DNA molecules. The information in the manual is separated into chapters, called genes which are made up of small units of DNA. Genes are written in a DNA code that must be transcribed and translated in order for the cell to make the protein signals specified in each gene. These proteins are signals which tell the cell how to function. A change in the genetic code is a mutation. Mutations can happen by subtracting from, adding to, or rearranging the original code. Mutations can happen randomly within the cell's DNA, but they can also be induced. A substance that causes mutations in DNA is called a mutagen. Mutations in a gene may interfere with its ability to make a functional signal, or cause it to code for a protein that sends an incorrect signal to the cell ***(Lee et al., 2002).***

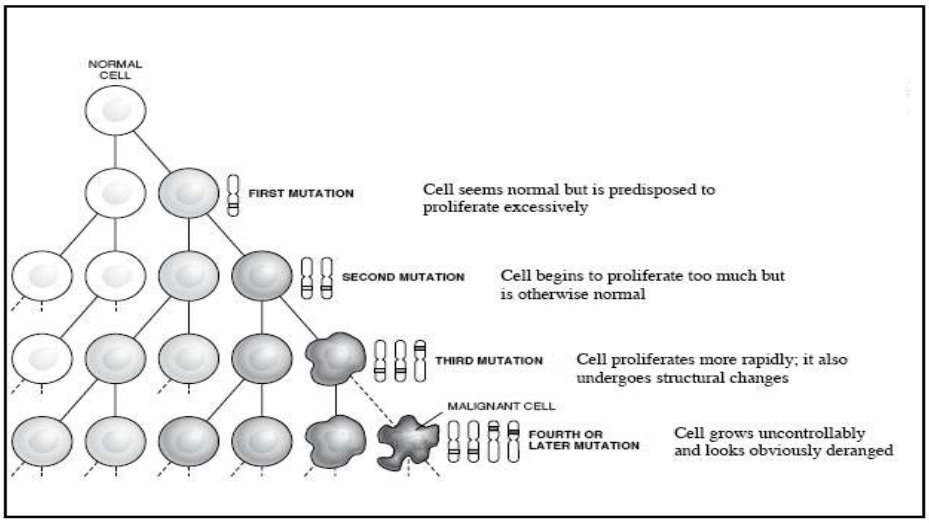

Figure (1): Emergence of a cancer cell from a normal one (white) is thought to occur through a process known as clonal evolution. First, one daughter cell (light grey) inherits or acquires a cancer-promoting mutation and passes the defect to its progeny and all future generations. At some point, one of the descendants (medium grey) acquire a second mutation, and a later descendant (grey) acquires a third, and so on. Eventually some cell (dark grey) accumulates enough mutations to cross the threshold to cancer ***(Lee et al., 2002).***

Most mutations are repaired by the cell, but in rare cases mutations do not get repaired. If a mutation is not repaired before a cell copies its DNA and divides into two cells, then the mutation is passed on to the two new daughter cells and becomes permanent. Rare genetic disorders (e.g., Ataxia Telangiectasia) are one way that cells are deprived of the ability to repair DNA, and may experience buildup of mutations in cells ***(Clarke, 2012).***

Mutations in most of a cell's DNA have no effect on whether the cell will become cancerous. However, the protein signals coded by a very small proportion of the total genes in each cell regulate cell growth and division. These regulatory genes include the two groups of genes called proto-oncogenes and tumor suppressor genes. A series of mutations in the DNA of either and/or both groups of these growth controlling genes can eventually lead to cancer. Buildup of these mutations may take years to develop ***(Clarke, 2012).***

Breast Biology and Susceptibility to Cancer

Cells that divide are at a higher risk of acquiring mutations than cells that don't divide. Cancer is generally rare in tissues in which cells don't divide, like nerve tissue. Alternatively, cancer is more common in tissues in which cells divide frequently such as with breast, skin, colon, and uterine tissues.

Young women and girls have breast tissue that is especially sensitive to carcinogens. Unlike other tissues in the body like the liver and heart that are formed at birth, breast tissue in newborns consists only of a tiny duct. At puberty, in response to hormones (like estrogen that is secreted by the ovary), the breast duct grows rapidly into a tree-like structure composed of many ducts. Most breast development occurs between puberty and a woman's first pregnancy. The immature breast cells, called

"stem cells", divide rapidly during puberty. The cells in the immature, developing breast are not very efficient at repairing mutations, and they are more likely to bind carcinogens. Therefore it is important to reduce the exposure of young women and girls to carcinogens that might damage DNA during this phase of rapid breast development. For example, Japanese infants and young women exposed to ionizing radiation from atomic bombing during WWII had high rates of breast cancer as adults. It is also important to reduce exposure to environmental estrogens during these critical times. Environmental estrogens (estrogen 'mimics') are synthetic chemicals that can act like human estrogen in a woman's body, and may stimulate cell division in the breast ***(Simon et al., 2001).***

After a woman's first full-term pregnancy, hormonal influences transform a high proportion of her breast cells into mature, differentiated cells which make milk. Milk producing cells are fully mature and less sensitive to DNA damage than immature undifferentiated cells. Therefore, susceptibility to mutations declines in the breast cells of women who have had an early full-term pregnancy. Some evidence also suggests that breast feeding further reduces the breast cells' sensitivity to mutations. Though much of what we know about the biology of breast tissue susceptibility to cancer is based on research in animals, it is believed most of this knowledge can be applied to human biology ***(Russo et al., 1995).***

Proto-oncogenes and oncogenes

"Go" genes Proto-oncogenes are normal genes that code for the "go" signals controlling the cell cycle. These signals tell a cell to enter the cell cycle and code for how long it should stay there and divide. If a proto-oncogene loses the ability to regulate the cell cycle, the cell may reproduce uncontrollably because it stays in the cell cycle and continues to divide. A mutated proto-oncogene that has lost control of its "go" signal is called an oncogene.

Oncogenes code for protein signals that stimulate the cell to enter or continue in the cell cycle. This leads to inappropriate cell division and growth of a developing tumor. For example, a mutation in a proto-oncogene may cause the over expression of certain growth factors, and lead to inappropriate division of cells. That is why some growth factors are seen at higher levels in many breast tumors. The **erb-B2 receptor gene**, an oncogene which codes for a receptor protein. The receptor in normal cells must be bound to a certain growth factor before it can stimulate the cell to enter the cell cycle and divide. But in faulty versions of the erb-B2 receptor gene, the receptors specified by this gene can release a flood of signals to stimulate increased cell division without being bound to the growth factor. Researchers have shown that up to 30% of primary breast cancers have too many copies of the erb-B2 gene ***(Cavanee et al., 2006).***

Other oncogenes that researchers have found to be related to breast cancer include the **tyrosine kinase family of growth factor receptors**, the c-myc oncogene, cyclin D-1, and the cyclin regulator, CDK-1 ***(Kues et al., 2000).***

Tumor suppressor genes: "Stop" genes Just as the cell has "go" signals that tell it when to enter the cell cycle, it also has genes which control the "brakes." Cells with tumor suppressor genes that are mutated or inactivated lose control over their brakes. Brakes are important in the cell cycle. Putting on brakes at certain "check points," allows the cell to check for any damage in its DNA. Repairs must be made before the cell is allowed to go on in the cycle. Without these brakes, cells with damaged DNA would copy the mutations, divide, and pass on the damage to daughter cells. The damage is then established as a permanent mutation in subsequent generations of new cells. Therefore, an important function of tumor suppressor genes is to maintain the integrity of the DNA in cells. An example of a vital tumor suppressor ("stop") gene is the **p53 gene**. A mutation in the p53 gene is the most common genetic change found in breast cancer. One function of this gene is to keep cells with damaged DNA from entering the cell cycle. The p53 gene can tell a normal cell with DNA damage to stop proliferating and repair the damage. In cancer cells, p53 recognizes damaged DNA and tells the cell to "commit suicide" (apoptosis). If the p53 gene is damaged and loses its function, cells with damaged DNA continue to reproduce when normally they would have been removed through apoptosis. **This is why the p53 gene has been termed "The Guardian of the Genome"** ***(Kues et al., 2000).***

A small proportion of breast cancer cases (5%) are related to the inheritance of susceptibility genes. Alterations of the recently discovered "breast cancer susceptibility genes**," BRCA 1 & 2,** are involved in some inherited cases of breast cancer. If inactivated, these tumor suppressor genes can act indirectly in the cell by disrupting DNA repair. This allows the cell to accumulate DNA damage, including mutations that can encourage cancer development. Other tumor suppressor genes that researchers have found may be related to breast cancer include the Retino blastoma, Brush- 1, Maspin, nm23, and the TSG101 genes ***(Weinberg, 2001).***

The Stages of Tumor Development

Cancer develops through different stages. These stages may or may not eventually lead to invasive and metastatic cancer. In most cases it takes many years for cancer to develop. Early detection of any tumor is important because it increases the chances of removing the cancer before it becomes life-threatening.

Normal: There are trillions of cells in the healthy human body. Even though adults stop growing, the body constantly replaces worn-out cells with new ones to stay healthy. Cells must communicate and respond to each other's checks and balances to maintain the correct number of healthy cells.

Genetically altered cell(s): Tumor development begins when at least one cell has a genetic mutation which causes it to divide and proliferate when it normally would not. This leads to

more cells with the same mistake.

Hyperplasia: Cells look normal but grow too much. Further damage can lead to "dysplasia."

Dysplasia: Cells proliferate too much and look abnormal in shape and orientation. Cells are less responsive to surrounding cells and the body's signals to stop proliferating. Further damage and/or cell changes can lead to "in situ" cancer.

Atypia: Cells look abnormal. Atypia is a general term describing how cells look. For example, one cell can appear atypical, but a group of cells display "dysplasia."

Benign tumor: Although cells are not normal, they do not have the ability to travel to other parts of the body. Cells in benign tumors are typically more differentiated (mature) and organized than cells in cancerous tumors. In some cases a benign tumor may eventually become an invasive or metastatic tumor.

In situ carcinoma (cancer): Cells become even more abnormal in growth and appearance but the tumor cells have not broken through the boundary around the tumor that separates it from surrounding tissues. This boundary is like a capsule that contains the tumor. Cells may acquire additional damage and/or changes which can lead to invasive cancer.

Invasive cancer: The uncontrolled growth of cells in the tumor allow some cells to break through the capsule-like boundary and invade nearby tissues. Generally, invasive tumors

are life-threatening if the cancer cells are present within a vital organ like the kidneys, lungs, or liver. Invasive tumors in non-vital organs like the breasts are not necessarily life-threatening unless they become malignant and migrate to a vital organ. Therefore, early detection of any tumor is important because it increases the chances of removing the cancer before it becomes life-threatening. Cells from the invasive (primary) tumor gain the ability to enter the blood stream or lymphatic system and to travel to distant areas in the body (metastasize).

Metastatic cancer: Cells from the malignant primary tumor gain the ability to re-establish somewhere else in the body where they form new cancerous tumors. The secondary tumors are called metastases. Metastatic tumors can become fatal because they may disrupt the function of vital organs ***(Smith et al., 2000).***

Important receptors involved in breast cancer biology:

Estrogen receptors (ER):

Estrogens play a central role in the growth and differentiation of normal breast epithelium, stimulating cell proliferation and regulating the expression of other genes, including the progesterone receptor (PgR). In the normal pre-menopausal breast, ER(+) cells comprise the 7% of the total epithelial cell population ER(+) cells are luminal epithelial cells, evenly distributed, and seem to secrete