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BREAST CANCER ASSOCIATED RISKS AND DIAGNOSIS

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Abstract: More than 277 distinct forms of cancer disease are referred to as cancer in the broadest sense. Researchers have discovered various cancer stages, suggesting that a number of gene alterations have a role in the genesis of cancer. Anomalous cell proliferation results from these gene alterations. Millions of people worldwide are still impacted by the complicated and common health issue that is breast cancer. In this paper, the complex field of breast cancer is thoroughly examined, with a focus on the wide range of risk factors that contribute to the disease's occurrence and the developments in diagnostic techniques. Many risk variables, including genetic predispositions such mutations, hormone effects, lifestyle factors, and reproductive patterns, have been found by a thorough review of the literature published recently. The complex web of elements that contribute to breast cancer etiology also includes age, family history, and environmental factors. New technologies such as genetic testing and magnetic resonance imaging complement mammography, the mainstay of breast cancer screening, to improve the sensitivity and specificity of breast cancer diagnosis. Even with these developments, it is still difficult to guarantee that screening programs are widely accessible, especially in environments with low resources. To sum up, this review highlights the significance of comprehending many risk variables in the emergence of breast cancer and stresses the vital role that developing diagnostic methods have in improving early detection. The goal of this review's synthesis of the available data is to further our understanding of the complex nature of breast cancer and provide guidance for future investigations, screening methods, and preventative measures.

Index Terms **- Cancer, mutation, hormones, mammography, biopsy**

I. INTRODUCTION

Worldwide, cancer is the second most common cause of death. Overall, the incidence of cancer has increased; by 2014, there were over 1,665,540 cancer patients in the United States alone, and 585,720 of them had passed away from the illness.[37]. Breast cancer is one of the many and common malignant tumors that harm women. Numerous internal and external variables can contribute to the development and occurrence of breast cancer.[1-3] Its incidence is associated with poor lifestyle choices, environmental conditions, and social-psychological factors. Research indicates that between 5% and 10% of breast cancer cases are related to genetic abnormalities and family history, while 20% to 30% of cases are related to potentially modifiable variables.[4] Breast cancer begins in the cells of the breast. A malignant tumor is a cluster of cancer cells that can spread and kill surrounding tissue. It can also spread across the entire body. Changes that impair the ability of breast cells to proliferate or function normally can occasionally occur. These alterations may lead to atypical hyperplasia, cysts, and non-cancerous breast diseases. They could also lead to benign malignancies such as intraductal papillomas.[5]

Alterations to breast cells can occasionally lead to breast cancer. The cells lining the ducts—the tubes that transport milk from the glands to the nipple—are where breast cancer usually starts. One name for this subtype of breast cancer is ductal carcinoma. Cancer can also develop from the cells in the lobules, which are groups of glands that produce milk.[6,7] This particular type of cancer is called lobular carcinoma. It is

possible for both ductal and lobular carcinomas to be in situ, meaning that the cancer is still located in the original site and has not migrated to other tissues. Additionally, they could be invasive, meaning that they have penetrated into the surrounding tissues.[8]. There are many less prevalent ways that breast cancer might present itself. These consist of Paget disease, inflammatory breast cancer, and triple-negative breast cancer. Two rare types of breast cancer include soft tissue sarcoma and non-Hodgkin lymphoma.[9].

II. Risk factors for developing breast cancer

Personal history of breast cancer

Women who have had breast cancer before are more likely to face a recurrence. The second breast cancer could develop in a different breast or the same breast as the first. While the majority of women with breast tumors that are detected in situ (ductal carcinoma in situ or lobular carcinoma in situ) do not experience recurrence, these women are more likely to do so.[16]

Mutations in the BRCA gene

Genetic mutation is the term used to describe a changed gene. Certain gene alterations may increase the risk of developing specific cancer types. Gene mutations that are inherited can be passed from one parent to the next. Only a small proportion of breast cancers (between 5 and 10%) are caused by mutations in hereditary genes. The breast cancer genes BRCA1 (breast cancer gene 1) and BRCA2 (breast cancer gene 2) are both part of normal human physiology. These genes are referred to as tumor suppressors because of their apparent role in controlling the development of cancer cells. Mutations in the BRCA1 or BRCA2 genes may impair their capacity to control the growth of cancer. Mutations like these are uncommon. Approximately 1 in 500 persons encounter them. Studies show that women with inherited mutations in either the BRCA1 or BRCA2 gene are 85% more likely to get breast cancer in their lifetime. Furthermore, women who have these hereditary abnormalities are more likely to develop breast cancer earlier in life than other women. Women with the BRCA gene mutation are more likely to develop breast cancer in both breasts. If a person has cancer in one breast, they are more likely to have cancer in the other. If a woman has a mutation in the BRCA gene, she can get ovarian cancer at any age.[19]

Dense Breasts

Dense breast tissue has more connective tissue, glands, and milk ducts than fatty tissue. Breast density is inherited. Women with dense breast tissue are more likely to develop breast cancer than those with little or no dense breast tissue. Mammograms are the sole method available for detecting breast density, and thick breasts complicate image interpretation. Thyroid-like dense tissue shows white on a mammography, whereas fatty tissue appears dark, hiding a tumor.[20]

Breast and other types of cancer in the family history

It is a sign that the disease runs in the family when one or more close blood relatives have breast cancer. Some families have a higher than expected random incidence of breast cancer cases. Determining whether a family's history of cancer is due to genetics passed down from parents to children, coincidence, a shared lifestyle, or a combination of these can be challenging.[17]

Late or No Pregnancies

During pregnancy, the exposure of breast cells to circulating estrogen is stopped. Additionally, it lessens the total number of menstruation cycles a woman may encounter in her lifetime. A woman who has had at least one full-term pregnancy before the age of thirty has a slightly increased risk of developing breast cancer. Early pregnancy is linked to a lower risk of breast cancer. The more children a woman has, the better protected she is against breast cancer. A woman's chance of breast cancer is elevated if she never gets pregnant.[22]

Late Menopause

Menopause is the end of a woman's menstrual cycle and the body's production of estrogen and progesterone declines. If a woman enters menopause later in life (after age 55), her cells are exposed to these hormones for a longer period of time, which increases her risk of breast cancer. If a woman enters menopause earlier in life, her breast tissue is exposed to these hormones for a shorter

Hormonal replacement treatment

The Women's Health Initiative (WHI) study found that estrogen raised the risk of breast cancer by approximately 1% annually, while estrogen and hormone replacement therapy (HRT) increased the risk by around 8% annually. The study also found that even with very short use of combination HRT, the risk rose when compared to a placebo. Following a few years of no HRT, the increased risk appears to have disappeared. The WHI study also showed that between 2002 and 2004, there was a discernible decrease in the number of new cases of breast cancer among Canadian women aged 50 to 69. Simultaneously with this decline was a decline in the use of combination HRT.

Estrogen

The risk of breast cancer is associated with endogenous and exogenous estrogens. The ovary normally produces endogenous estrogen in premenopausal women, and ovarian removal can reduce breast cancer risk. Exogenous estrogen is primarily obtained from HRT and oral contraceptives. Oral contraceptives have been widely used since the 1960s, and to reduce adverse effects, their formulations have been changed. However, the odd ratio for female populations in Iran and Africa is still greater than 1.5. If a woman stops taking oral contraceptives for more than ten years, her risk of breast cancer does not increase. HRT involves giving exogenous estrogen or other hormones to women who are menopausal or postmenopausal.

Studies have shown that using HRT can increase the risk of breast cancer. The UK's Million Women Study indicates that there is a 1.66 relative risk difference between individuals who have never used HRT and those who do. Hazard ratios (HRs) of 1.48 and 1.95 were discovered following the use of HRT for 4 and 8 years, respectively, in a cohort research involving 22,929 Asian women. It has been shown that there is a substantial decrease in the risk of breast cancer after two years of no HRT. The recurrence rate is also significant among breast cancer survivors on HRT, with a 3.6 HR for a new breast tumor.[25].

Overweight

Obesity raises the risk of breast cancer in postmenopausal women. Studies show that women who have never undergone hormone replacement therapy (HRT) and have a body mass index of 31.1 or above are 2.5 times more likely to develop breast cancer than women who have a body mass index of 22.6 or lower. Specifically, ovaries' estrogens are a major contributor to breast cancer. The cumulative dosage of estrogen that the breast tissue absorbs over time is regarded to be the cause of several breast cancer risk factors. The ovaries generate most of the body's estrogen, but after menopause, adipose tissue only produces a little quantity of estrogen. Having more fat tissue can lead to a greater estrogen level and an increased risk of breast cancer.[24].

III. DIAGNOSED USING THE TECHNOLOGIES THAT ARE CONNECTED

Breast tumors usually begin as benign tumors and sometimes even spread to other parts of the body as a result of ductal hyperproliferation that is continuously triggered by different carcinogenic stimuli. The initiation and progression of breast cancer are contingent upon the tumor's microenvironment, including the presence of macrophages or stromal effects. Neoplasms could be produced in the rat mammary gland when carcinogens were only exposed to the stroma, not the extracellular matrix or the epithelium. Macrophages have the ability to generate a mutagenic inflammatory milieu that promotes angiogenesis and shields cancer cells from immunological rejection. Observations of distinct DNA methylation patterns between the usual and tumor-associated microenvironments imply that carcinogenesis may be promoted by epigenetic modifications inside the tumor microenvironment.

Recently, a novel subclass of dangerous cells found inside tumors called cancer stem cells (CSCs - cancer stem cells) has been discovered and connected to the beginning, escape, and recurrence of malignancies. This little number of cells can replenish itself and is resistant to conventional treatments like radiation and chemotherapy. It may have come from progenitor cells or stem cells in healthy tissues. Breast cancer stem cells, or bCSCs (breast cancer stem cells), were initially identified by Ai Hajj, and as low as 100 bCSCs could cause new tumors to grow in immunocompromised mice. Luminal epithelial progenitors are more likely to be the source of bCSCs than basal stem cells. Wnt, Notch, Hedgehog, p53, PI3K, and HIF are among the signaling pathways that mediate the self-renewal, proliferation, and invasion of bCSCs.[19].

There are two conjectural explanations for how breast cancer begins and spreads: the CSC theory and the stochastic theory. The notion pertaining to CSCs states that all tumor subtypes are descended from a common stem cell or transit-amplifying cell. Acquired genetic and epigenetic alterations in stem cells or progenitor cells lead to a wide range of tumor characteristics. The stochastic theory states that all tumor subtypes originate from a single type of cell. Any breast cell has the potential to progressively acquire random mutations, and if enough of these mutations build up, the breast cell has the ability to change into a tumor cell. Despite the overwhelming evidence supporting both theories, none is able to provide a complete explanation for the genesis of human breast cancer.[26]

IV. PREVENTION OF BREAST CANCER THROUGH BIOLOGY

Monoclonal antibodies for the disease, or biological prevention, have recently been created to improve the quality of life for individuals with breast cancer. One of the main targets of these monoclonal antibodies is human epidermal growth factor receptor 2 (HER2). In roughly 20% to 30% of cases of breast cancer, there is an overexpression of the HER2 protein or an amplification of the HER2 gene. The FDA has approved trastuzumab (Herceptin), a recombinant humanized monoclonal antibody, as the first HER2-targeted drug. It has the ability to directly engage with the extracellular portion of HER2's C-terminal domain IV region. The entire anti-tumor mechanism of trastuzumab is still unknown. By blocking the MAPK and PI3K/Akt

pathways, enlisting ubiquitin to internalize and degrade HER2, and stimulating the immune system against cancer cells through an effect known as antibody-dependent cell-mediated cytotoxicity, trastuzumab may prevent the growth and multiplication of cancer cells. In the beginning, trastuzumab was used to treat metastatic breast cancer, with an objective response rate of 26%. Based on in vitro studies, trastuzumab interacts favorably with other anti-tumor drugs such as nimotuzumab, carboplatin, 4-hydroxycyclophosphamide, docetaxel, and vinorelbine. The adjuvant trastuzumab plus chemotherapy administered for a year can prolong disease-free survival in patients with HER2+ breast cancer (HR = 0.76), according to the HERA and TRAIN studies.

V. DIAGNOSIS OF BREAST CANCER

Ultrasound

With the use of high-frequency sound waves, an ultrasound can provide images of different bodily parts. It is employed to ascertain whether a breast mass is a cyst or a solid tumor. Medical practitioners can also use ultrasonography to guide them to the biopsy site. When a woman has advanced breast cancer, an ultrasound may be done to check for liver metastases.[28]

Biopsy

A biopsy is the only procedure that can reliably identify breast cancer. A biopsy is performed to obtain tissues or cells from the patient's body for analysis in a lab. It will be determined by the pathologist's report whether or not cancer cells were found in the sample. Whether a lump is palpable, or something can feel, or non-palpable, or something can't, will determine what kind of biopsy is done. The doctor may use mammography or ultrasound to locate the area that needs to be checked. After most biopsies are finished, able to return home. Most biopsies are done in a hospital.[29]

Mammography

Diagnostic mammography is a low-dose radiography technique that produces a picture of the breast. It is employed to investigate unanticipated results from screening mammograms or clinical breast exams. Mammography can also be used to detect an abnormal spot during a biopsy.[27]

Fine needle aspiration

Extracts a little sample of tissue out of a bulge with a very fine needle and a syringe. It aids medical professionals in determining if a lump is a solid tumor or a cyst. Fine needle aspiration (FNA) cannot identify an invasive or non-invasive malignancy.[31] Using ultrasound or palpation as guidance, a medical expert inserts a small needle into the breast lump during the treatment. The lump is suctioned of cells or fluid using a syringe that is fastened to the needle. A pathologist will next look at these cells or fluid samples under a microscope to identify if they are malignant (cancerous) or benign (not cancerous). A minimally invasive technique called FNA can reveal important details regarding the type of breast lump. By examining the properties of the cells, assisting in the identification of malignant cells, and directing additional diagnostic or therapeutic processes, it facilitates the diagnosis of breast cancer. For a more thorough assessment, however, other procedures such as a surgical biopsy or core needle biopsy might be advised depending on the circumstances.

VI. PREVENTATIVE MEASURES

Promoting routine mammograms and screenings for risk factors and age can help with early detection and improve treatment results.[32] Breast cancer risk can be decreased by encouraging a healthy lifestyle that includes eating a balanced diet, getting regular exercise, cutting back on alcohol, quitting smoking, and keeping a healthy weight. One preventive strategy that can be implemented is to encourage breastfeeding, as it has been demonstrated to have protective effects against breast cancer.[33]

Giving people thorough and easily accessible information about the dangers of breast cancer, its symptoms, and the value of early detection can encourage them to take preventative action and seek prompt medical assistance. Genetic counseling and testing can assist people with known genetic mutations (such as BRCA1 or BRCA2) or family histories in determining their risks and determining the best course of action for prevention.[34] It's critical to comprehend the dangers of specific hormone treatments and to explore other options with medical professionals, especially when it comes to menopausal symptoms.

VII. CONCLUSION

Breast cancer continues to be a major worldwide health concern, affecting millions of people annually. The complexity of breast cancer has been emphasized by this review, which has also highlighted several risk factors and diagnostic techniques that are essential to comprehending and treating this illness. Furthermore, early detection and treatment outcomes have been markedly enhanced by advances in diagnostic technology. When combined with other cutting-edge technologies like molecular testing and magnetic resonance imaging, mammography is essential for detecting breast cancer early on, allowing for timely treatment and possibly improving patient outcomes. It continues to be crucial to conduct research to find

new risk factors, improve screening techniques, and provide tailored treatments. In addition, raising awareness, pushing for easier access to screening, and encouraging international cooperation between researchers and medical professionals are all critical in the continuous battle against breast cancer. In order to combat breast cancer and lessen its effects on people and societies around the world, a comprehensive strategy that incorporates research, education, early detection, and easily available healthcare services is crucial.

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