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Examining The Pathology of Breast Cancer, Its Causes and Diagnosis Methods According To The Latest Studies

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Abstract
Breast cancer is the second most common cancer after skin cancer and the second leading cause of women's death after lung cancer in the world. which is discussed in this article and the impact of this cancer especially on the health of women who have a central role in the family and society, adopting effective and efficient diagnostic methods in the early stages is very important and should be the main component of the strategy Those whose aim is to improve women's health and reduce the incidence and mortality of breast cancer should be considered. In the meantime, training and raising women's awareness and recommending different screening methods for breast cancer in the early stages, according to the available guidelines, play an important role as preventive measures. In this review article, an attempt has been made to examine the prevalence, causes, pathology, and diagnosis methods according to the latest studies.

Keywords: breast cancer, causes, pathology, diagnosis methods

1. Introduction

Breast cancer is the most common cancer among women. The increase in the incidence of cancer in recent years and its impact on various physical, psychological and social aspects of human life has turned it into a major problem of the century. The incidence of this disease varies between 1 and 2% in developed countries and increases by approximately 5% in less developed countries. (1) According to estimates, more than 7 million people in the world die from cancer every year. The number of new cancer cases was predicted to increase from 10 to 15 million by 2020. (2,3)

Breast cancer is the most common cancer after lung cancer and the leading cause of cancer deaths in women. In recent years, there have been significant changes in the incidence and mortality rate of breast cancer. In Iran, the standardized incidence rate for breast cancer is about 28 per 100,000 people, which has increased in recent years. (4) Meanwhile, breast cancer is the most common type of malignant neoplasms with more than one million new cases per year. In Iran, breast cancer is the most common type of cancer among women with a prevalence of 21.4 to 32%. This disease is the main cause of death among women aged 45 to 55 and is the second cause of death from cancer. The incidence of breast cancer is approximately 1 in 8 women, which in most cases requires complete tissue removal, chemotherapy, radiotherapy and hormone therapy. (5) The primary risk factors for cancer are age, high hormone levels, race, economic status and iodine deficiency diet . Breast cancer is a multistage disease. (Figure 1-1) (6,7)

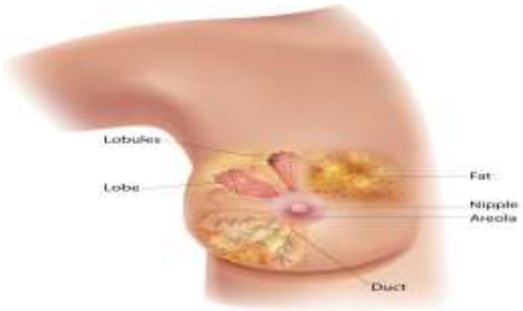

Figure 1: Schematic of breast cancer tissue (7)

A change or mutation in DNA can cause normal breast cells to turn into cancer cells. Some DNA changes are passed down from parents (inherited) and can increase the risk of breast cancer. Other factors related to lifestyle, such as what you eat, how much you exercise, etc. can increase the probability of getting this cancer. But it is still not clear exactly how some risk

factors cause the transformation of normal cells into cancer. Hormones seem to play an important role in many cases of breast cancer, but how this happens is still not fully understood.

2- Effective factors in the occurrence of breast cancer

2-1- Breast cancer and quality of life

The World Health Organization defines quality of life as a person's perception of his position in life within the framework of the culture and value systems in which he lives and in relation to his goals, expectations and standards. The main problems that affect the quality of life of patients are the mental and psychological effects of the disease, diagnostic and therapeutic measures, stress, pain, depression, and the consequences of the disease on family, marital, and social relationships, as well as the resulting economic burden. (8,9).

2-2- Relationship between breast cancer and genetic factors

Breast cancer is a very heterogeneous disease that is caused by the interaction of genetic risk factors and environmental factors and leads to the gradual accumulation of genetic and epigenetic changes in breast cancer cells. Although epidemiological evidence highlights the existence of risk factors (such as age, obesity, alcohol consumption, and lifetime estrogen exposure), a family history of breast cancer is the strongest risk factor. (10,11) Approximately 20% of all breast cancers have a familial origin, and in terms of etiology, they depend on a specific predisposing gene for that disease. (12) Cancer is generally a genetic disease, in other words, all cancers, including breast cancer, are caused by gradual genetic changes in tissue cells and the accumulation of these mutations, in such a way that these mutations cause cancer and overgrowth of that cell in several ways. which eventually lead to cancer are as follows:

1- Activating mutations in oncogenes: mutations in genes involved in cell growth pathways. Mutations in oncogenes usually confer a growth advantage to the cancer cell. In such a way that they ignore the inhibitory mechanisms and cause cancer to progress, on the other hand, the cell that has a growth advantage reproduces faster, and the mechanisms that control the cell cycle are not able to inhibit the uncontrolled growth of the tumor, because cells with primary mutations produce more offspring. and that these offspring are prone to further mutations. Therefore, with the passage of time and excessive cell proliferation and the increase of mutations, there are endless consequences.

2- Mutations in tumor suppressor genes, which are cell growth inhibiting mechanisms. Tumor suppressor genes produce products that are involved in cell cycle inhibition and regulation pathways. The most important of these genes are P53 and Rb genes, which are located on the short and long arms of chromosomes 17 and 13, respectively, and their products are involved in cell cycle control.

3- The third category is the genes that work in DNA repair mechanisms. The two main genes that lead to breast cancer in this category are BRCA1 and BRCA2.

4- Recently, other genes have been introduced as carcinogens that are involved in cellular metabolism activities.

Although several genetic factors have been identified as causing cancer, new factors are always added to this list, and recently RNA genes have also been included in this list. which includes micro RNA genes, genes encoding long RNAs and...

2-3- Nutritional factors and breast cancer

Among the nutritional factors, weight gain and high calorie intake are two causes of breast cancer. Researchers believe that obesity and high BMI after menopause increase the risk of breast cancer. While there is no such relationship in premenopausal women. For the first time in 1940, research findings showed that increased use of fat leads to mammary tumors in animals. A positive relationship between high fat consumption and the risk of breast cancer has been reported. On the other hand, calorie intake leads to weight gain and obesity, which causes premature menopause. Both factors can create the basis for the development of cancer in the future. (13)

Strong evidence supports a direct link between alcohol consumption and breast cancer risk, as alcohol may damage cell DNA by raising estrogen levels. Also, studies show that women who drink alcohol 3 times a week through alcoholic drinks, etc. increase the risk of developing breast cancer by 15%, and with each additional drink per day, the risk increases by 10%. .

Sugar and sugar: In 2016, a study was conducted on mice, the results of which led researchers to believe that mice fed a diet rich in sugar were more prone to mammary gland tumors similar to breast cancer in humans. In addition, with this style of diet, these tumors are more likely to spread or metastasize.

Fat: High fat diets are generally harmful to health. Among the types of fat, trans fat, which is mostly found in processed and fried foods such as donuts, crackers, cookies or sweets, increases the risk of various diseases, including cancer. Overall, there seems to be a connection between obesity and breast cancer. Yes, of course, this issue is more relevant in post-menopausal women.

It is worth mentioning that useful vegetable fats such as sunflower seeds, olive oil, sesame, etc., if they are present in the diet as much as needed and not more, can reduce the risk of breast cancer.

2-4- Hormonal factors and breast cancer

Hormones are proteins that act as chemical messengers in the body. They affect the function of cells and tissues in different places of the body and often reach their goals through the bloodstream. Estrogen and progesterone hormones are produced by the ovaries and some other tissues including fat and skin. Estrogen causes the growth and maintenance of female sexual characteristics and the growth of long bones, and progesterone plays a role in the menstrual cycle and pregnancy. Estrogen and progesterone also cause the growth of some breast cancers, which are called hormone-sensitive (or hormone-dependent) breast cancers. Hormone-sensitive breast cancer cells contain proteins called hormone receptors that are activated when

hormones bind to them. Activated receptors cause changes in the expression of certain genes that can stimulate cell growth. Doctors use hormonal blockade to prevent hormone-sensitive breast cancers from returning after treatment. Hormone therapy may be used to treat estrogen receptor (ER) and progesterone receptor (PR) positive cancers.
Doctors usually give hormone blocking therapy after surgery, but they may sometimes use it to shrink the tumor. The main risk factors of non-genetic breast cancer are of hormonal origin. For example, gender, age of menstruation and menopause, history of fertility, breastfeeding and use of exogenous estrogen (of external origin) can be mentioned. In most cases, nongenetic breast cancer occurs among postmenopausal women who have high estrogen receptor expression. Estrogen has at least two main roles in the development of breast cancer: (1) estrogen metabolites can induce mutations or generate DNA-damaging free radicals, and (2) estrogen can damage cells in precancerous and cancerous lesions through Increase your hormonal activity. In addition, since an important part of breast carcinoma is estrogen receptor negative, other mechanisms are also involved in the development of breast cancer. (14)

5-2- Immune system and breast cancer
The immune system is capable of fighting tumors and many immune parameters using cytokines, for example IL-12 and IFN-γ, play the main role in this field. IL-12 is also the main cytokine responsible for the differentiation of TH1 cells, which are strong producers of IFN-γ, which in turn has a strong enhancing effect on the ability of phagocytes to produce IL-12 and also has an important role in the cellular immune response. . (15,16)

3- Pathology of breast cancer
Most breast cancers are epithelial tumors that arise from cells lining the ducts or lobules. Non-epithelial cancers of the supporting stroma are less common (such as angiosarcoma, primary stromal sarcoma, phyllodes tumor). Cancers are divided into two categories: localized cancer and invasive cancer. (18)

3-1- ductal carcinoma in situ
About 85% of in situ cancers are usually diagnosed only with mammography. It may involve a small or large area of the breast. If a large area is involved, microscopic invasive foci may develop over time. (19)

3-2- Lobular carcinoma in situ
Lobular carcinoma generally has two types: classic and pleomorphic. This non-palpable lesion is usually diagnosed through biopsy and is rarely visible with mammography. Invasive carcinoma is primarily adenocarcinoma. About 80% of it is the type of infiltration channel. Rare types include medullary, mucinous, metaplastic and tubular carcinomas. Mucinous carcinoma occurs in older women and grows slowly. Women with most of these rare types of breast cancer have a much better prognosis than women with other types of aggressive breast cancer. However, the prognosis for women with metaplastic breast cancer is significantly worse than for other types of breast cancer. (20) Inflammatory breast cancer is a fast-growing, particularly aggressive, and often fatal cancer. Cancer cells block the lymphatic vessels of the breast skin. As a result, the breast looks inflamed and the skin is thick. Usually, inflammatory breast cancer spreads to the axillary lymph nodes. (21)

3-3- Invasive cancer
Invasive cancer is a term that describes cancer that has grown from the original tissue or cells in which it has grown and spread to surrounding healthy tissue.
According to the US National Cancer Institute, invasive cancer is also called invasive cancer. When cancer cells reach this point, they can secrete a substance that ruptures the cell membrane, allowing the cancer to spread from its point of origin. Research says that penetration is the first step in the process of metastasis. Invasive cancer can be classified as follows:
Local: The cancer has invaded the surrounding tissues, but is limited to the breast.
Regional: It means that the cancer has invaded the tissues near the breasts, such as the chest wall or lymph nodes.
Metastatic: This means that the cancer has spread from the breast to other parts of the body.
Invasive ductal carcinoma starts from the milk ducts, but it penetrates the wall of the ducts and attacks the surrounding breast tissue, it can also spread to other parts of the body and accounts for about 80% of invasive breast cancers.
Invasive lobular carcinoma begins in the milk-producing glands of the breast, but invades the surrounding breast tissue and spreads to other parts of the body. It is more likely to occur in both breasts than other types of breast cancer and constitutes most of the other invasive cancers. (19,21)

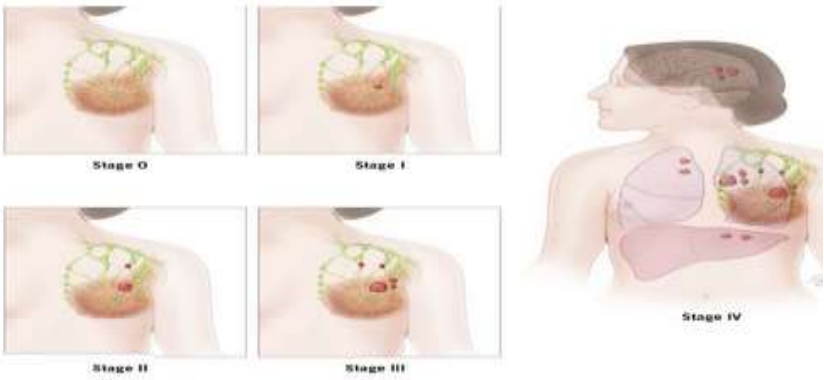

Figure 2: Staging form of breast cancer

3-4- Pathophysiology of breast cancer

Breast cancer attacks locally and spreads through regional lymph nodes, blood stream or both. Metastatic breast cancer may affect almost any part of the body. Most skin metastases occur near the breast surgery site.

Some breast cancers may recur earlier than others. Recurrence can often be predicted based on tumor markers. For example, metastatic breast cancer may occur within 3 years in patients who are negative for tumor markers or more than 10 years after initial diagnosis and treatment in patients with estrogen receptor-positive tumors. (22) (Figure 3)

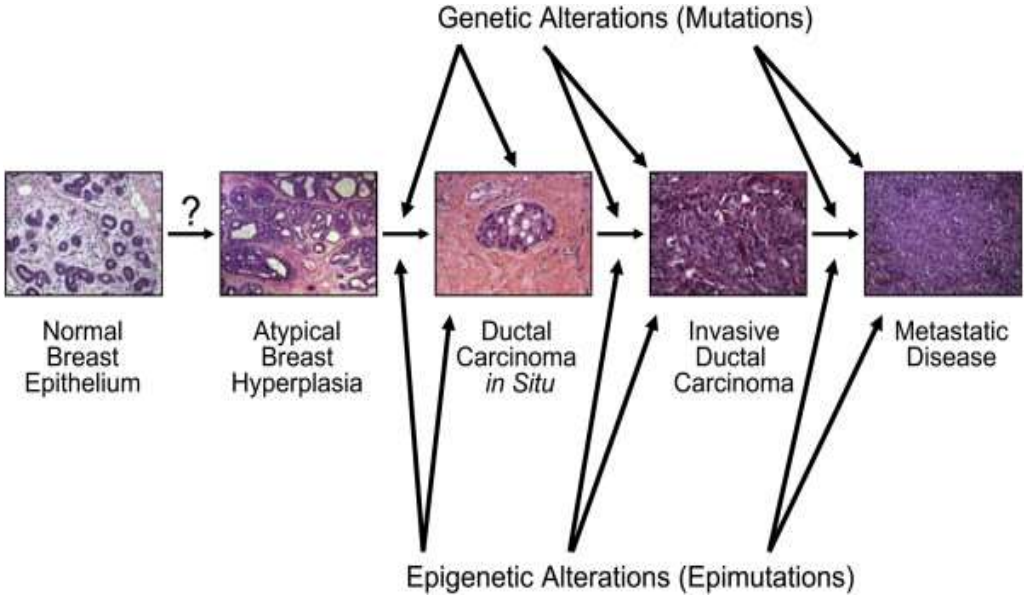

Figure 3- Breast cancer tumor tissue in different stages (21)

3-4-1- Hormonal receptors

Estrogen and progesterone receptors, which are present in some breast cancers, are nuclear hormone receptors that, when the appropriate hormones bind to them, promote DNA replication and cell division. Therefore, drugs that block these receptors may be useful in treating tumors with these receptors. About two-thirds of postmenopausal patients with cancer have an estrogen receptor positive (ER+) tumor. The incidence of ER+ tumors is lower among premenopausal patients. (23)

Another cellular receptor is human epidermal growth factor receptor 2 (HER2, also called HER2/neu or ErbB2). Its presence is associated with a poorer prognosis in any given stage of cancer. HER2 receptors are overexpressed in about 20% of breast cancer patients. Drugs that block these receptors are part of the standard treatment for these patients. (24)

Histopathological analysis of breast tumors plays an essential role in the diagnosis of breast cancer. For example, invasive ductal carcinoma (IDC) or invasive lobular carcinoma (ILC) and histologic grade (summary score of epithelial tube formation, mitotic count, and nuclear pleomorphism) have been reported to guide clinical management. Microscopic assessment of tumor-infiltrating lymphocytes can predict improved response to chemotherapy and prognosis in erb-b2 receptor tyrosine kinase (HER2) positive breast cancer. Beyond these features, breast tumors show a set of other morphological features such as necrosis, whose clinical significance is not well defined.

Breast cancer is a heterogeneous disease at both morphological and molecular levels. The molecular "intrinsic" subtypes of PAM50, duct A, duct B, HER2-associated, basal-like, and normal-like, have distinct biological characteristics, epidemiological risk factors, treatment response, and prognoses, and are associated with specific morphologic features. The normal-like subtype is highly variable and is not recursively defined. Morphological and molecular data complete the description of breast cancer phenotypes. For example, basal tumors do not show high histologic grade, necrosis, tumor-

infiltrating lymphocytes, and fibrotic foci and are generally IDC, while HER2-associated tumors show high histologic grade and may It contains features of apocrine and ductal carcinoma in situ. (25,26)

5-3- Stages of breast cancer

According to the American Joint Committee on Cancer, the stages of breast cancer can be divided into the TNM system: T: the size of the breast tumor, N: the extent of tumor spread to nearby lymph nodes, and M: the extent of the tumor. Metastasis to other organs of the body is the first stage of breast cancer called stage zero or carcinoma in situ. In the first stage, the tumor is small and has not spread outside the patient's breast. Stage II cancer is less than 2 cm in diameter and may also be seen in some lymph nodes under the armpit. In the third stage, the tumor found in the breast may be of any size, but the armpit cancer will not be equivalent to the second stage. In addition, the cancer has spread to the chest wall or the skin of the breast and has caused indentation, inflammation or change in the color of the skin of the breast. Finally, in stage IV breast cancer, the cancer has spread to distant parts such as the brain, lungs, or bones. (26)

6-3- Metastasis in breast cancer

One of the signs of cancer, which is responsible for about 90% of cancer deaths, is metastasis. Metastasis describes the spread of cancer cells from their original tumor to nearby tissues or other organs. Therefore, the importance of understanding the mechanism of the metastatic process and the factors that increase metastasis, along with the pathways involved in this process, is widely recognized (27, 28).

Breast cancer is the second most malignant cancer in the United States, and most patients do not die because of the primary tumor, but from tumor metastasis to distant places. Of all breast cancer patients, 10 to 15% have an aggressive disease that leads to the spread of the tumor to other organs within 3 years after the initial tumor.

Breast cancer is classified as a heterogeneous disease, so it has a different nature of metastasis, which makes it difficult to treat. Normally, primary breast cancer cells metastasize to various distant organs such as lungs, liver, and bones through blood vessels or lymph nodes (30).

In general, the spread of breast cancer cells includes the process of metastasis common in many solid tumors as follows.

Separation of breast cancer cells from the extracellular matrix (ECM) and initiation of local invasion and migration: Metastasis begins with the disruption of cell attachment to the ECM through cell adhesion proteins such as integrin and leads to the separation of cancer cells from adjacent cells. Cells with this increased invasive ability attack the surrounding tissue with the help of secreted proteolytic enzymes to destroy the ECM and create an invasion pathway (31,32).

Blood circulation: tumor cells spread to other organs through the blood or lymphatic circulation.

Adhesion and extravasation in the metastases: Tumor cells undergo a cell cycle arrest before being removed in the metastases and stick to the capillary walls in the target organs (33).

Metastatic tumor formation: cancer cells with tumorigenic potential multiply and form small tumors. Since metastasis is a complex and multi-step process, metastatic cells need different characteristics to overcome obstacles and most importantly, the ability to survive in isolated conditions, invade and generate new tumors. Disturbance in any of these stages stops the process of cancer metastasis. In addition, to survive, cancer cells must resist an immune response that kills cancer cells and bypasses apoptotic signals. If the tumor cells can complete these steps, they produce secondary metastases. (34, 44, 45, 35)

3-6-1- Mechanisms involved in the metastatic potential of breast cancer cells

According to the presented cancer characteristics, the cancer cell's ability to invade and metastasize is an important factor in determining the aggressive characteristics of the disease and is a promising molecular target for drug discovery(Figure 4). (46,36,37)

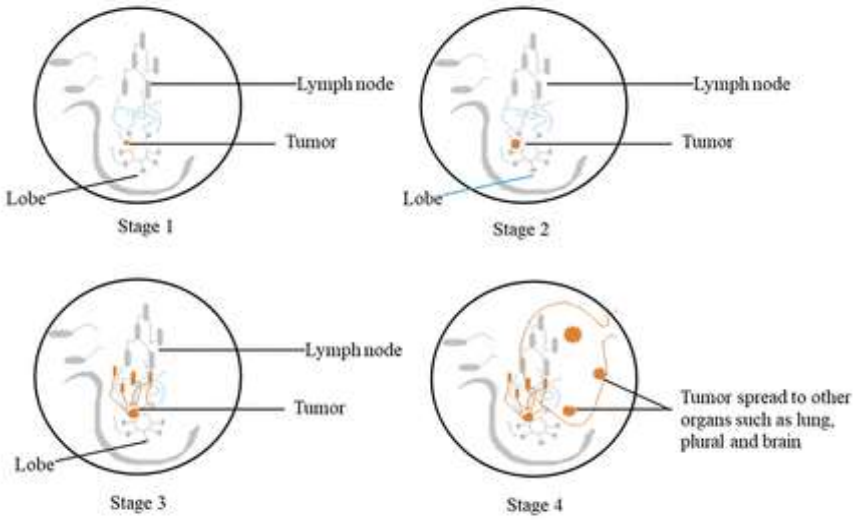

Figure 4- Stages of metastasis in breast cancer (38)

4- Diagnosis of breast cancer

For rapid and accurate screening of breast cancer, many diagnostic methods based on imaging and molecular biotechnology have been developed. Summarizing and evaluating these methods is necessary to provide valuable information for clinical diagnosis. (39,40,41,4749)

4-1- Diagnosis by imaging

The use of imaging techniques clearly shows the morphology and location of tumor tissues and proves a lot of clinical information that is valuable for doctors (48,43). However, imaging techniques may harm patients when using contrast agents and high-energy beams. These imaging techniques mainly include mammography, ultrasound, magnetic resonance imaging, positron emission computed tomography, computed tomography, and single photon emission computed tomography. (50)

4-2- Mammography

Mammography is the preferred strategy for breast cancer screening and diagnosis and helps doctors to obtain clinic information of affected patients. Evidence shows that the death rate of patients can be reduced by 30 to 40% with early screening. (51)

4-3- Ultrasonography

Ultrasonography is used to observe the morphology and condition of tumor tissues and can accurately determine the location of lesions. The history of the development of ultrasonography is as follows: the initial gray-scale ultrasonography only showed whether there was a tumor at the diagnosis site, but it was difficult to distinguish between benign and malignant tumors because its resolution was low. Two-dimensional ultrasonography only receives some flat images of the tumor and doctors' judgment is affected. Therefore, 3D ultrasonography technology has been developed for 3D imaging of tumor morphology and blood vessel distribution, which is shown during the diagnosis of patients. Color doppler ultrasonography is one of many three-dimensional ultrasonography and can clearly reflect the state of the tumor and blood flow information and provide more valuable clinical information to doctors to diagnose benign and malignant tumors. (52)

4-4- Magnetic resonance imaging

Magnetic resonance imaging (MRI) allows early diagnosis of familial breast cancer regardless of age, breast density or risk status. (53) There are differences in the water dispersion coefficient of different tissues. Magnetic Resonance Diffusion Weighted (MRDW) is a technique that can show the transparent movement of water molecules in the body. Therefore, MRDW has become a method for diagnosing breast cancer patients. Malignant tumors have limited water diffusion effects compared to benign tumors, so researchers can distinguish between benign and malignant breast tumors by using MRDW to measure apparent diffusion coefficient (ADC) values. (54,55)

4-5-Molecular biotechnology tests

Molecular biotechnology tests can detect tumors before imaging methods. However, they cannot replace imaging techniques and become auxiliary methods for breast cancer diagnosis. The aim of molecular biotechnology is to analyze specific biomarkers such as nucleic acid, proteins, cells and tissues of patients. These examinations can help doctors obtain a lot of clinical information at the molecular level. Currently, these examination techniques mainly include nucleic acid hybridization system, quantitative fluorescence PCR system, protein hybridization system, flow cytometer, needle biopsy and immunohistochemistry (IHC). (56)

The Real Time PCR technique is divided into two methods based on the molecule used for detection:

1-Non-specific detection using dyes bound to DNA

Here, dyes bound to DNA are used as fluorescent reporters to observe the PCR reaction. This fluorescent increases in successive cycles due to doubling. By recording the fluorescent amount emitted in the cycle, the reaction can be observed during the exponential phase.

If a graph is drawn between the logarithm of the starting value of the reaction and the fluorescent increase of the reporter, a linear relationship will be observed. Cyber Green is often used along with double-stranded DNA as a special reporter dye. This dye binds to a small gap in the double-stranded helix of DNA. In solution, unbound dyes show very little fluorescence, and fluorescence increases markedly when the dye binds to double-stranded DNA.

SYBR Green remains stable under PCR conditions. An optimal level of temperature regulates the induction and propagation of wavelengths. As mentioned earlier, ethidium bromide can also be used for diagnosis, but it is rarely used due to its carcinogenicity.

2-Specific detection using target identifiers

Another technique is to use the reporter probe or Taqman, which creates a fluorescent signal by connecting to the PCR products, and its use is more common. This technique is known as Taq Man´ 5 nuclease assay. The probe used in this process is called reporter because it indicates the presence of the desired product. The probe connection point is to the template strand and close to the main PCR primers and below it.

This method is less prone to errors resulting from incorrect connections such as primer dimers. In this case, each probe molecule consists of one oligonucleotide and two labels. The fluorescent dye is attached to the end of the 5 oligonucleotide

strand and the quencher compound is attached to the other end of the strand. This compound is responsible for inhibiting the fluorescent signal and it does this by absorbing energy from the fluorescent dye. This phenomenon is called (FRET).
In the normal state, the fluorescence signal is not created; Because the oligonucleotide is designed in such a way that its two ends are complementary to each other and the fluorescent dye and the quencher compound are placed next to each other. The hybridization between the oligonucleotide and the PCR product disrupts the connection between the two oligonucleotides and this creates a fluorescent signal.
During PCR, Taq polymerase reaches the probe with exonuclease property and decomposes it into 5, and with this, the dye and quencher compound are released in the environment. The more products produced, the more probes bind to their complementary sequence in these products. The more probes are connected, the more fluorescent signal is generated as the dye is released from the quencher. As a result, there is a relationship between the fluorescent signals created in Real-time PCR and the value of the template sequence.

4-5-1- Development of new specific biomarkers in breast cancer diagnosis
Circulating tumor cells enter the blood circulation from primary tumor tissues and their number in the peripheral blood is about 1 to 102 per milliliter. The ability to use the CytoSorter system to identify circulating tumor cells and evaluate the diagnostic value of circulating tumor cells has already been investigated (57). The results showed that circulating tumor cells can distinguish breast cancer patients from patients with benign breast diseases or healthy volunteers as a diagnostic aid for early cancer diagnosis and cancer staging.
Circulating tumor DNA (ctDNA) is a fragment of tumor genomic DNA that contains features of gene alterations consistent with the primary solid tumor. Therefore, ctDNA is very useful in identifying DNA from tumor cells or normal cells, because the amount of ctDNA in peripheral blood is very low. Therefore, quantitative and qualitative detection methods for ctDNA are mainly based on PCR and next-generation sequencing (NGS). (58,59)

4-5-2- Exosomes in breast cancer diagnosis
Exosomes are extracellular phospholipid vesicles enclosed in a membrane with a variety of tumor antigens, which can be used in cancer diagnosis and treatment due to their high secretion on the surface of cancer cells. Exosomes have stable chemical properties and their size is 30 to 150 nm. (60)

4-5-3- RNAs in breast cancer diagnosis
Circular RNAs (circRNAs) were recently discovered as a circular subset of endogenous RNAs with the ability to regulate gene expression by microRNA. The researchers found that a total of 715 circRNAs were significantly overexpressed and 440 were significantly downregulated in breast cancer lesions compared to healthy tissue samples among 1155 differentially expressed circRNAs. In 2019, Yan et al. introduced hsa_circ_0072309 as a novel prognostic biomarker, which is a downregulated miR-492. Dysregulation of this circRNA increases the proliferation, migration and invasion of breast cancer cells and therefore has a potential role in breast cancer. (61)

4-5-3-1- Non-coding RNAs
In the past years, new technologies such as next-generation deep sequencing have shown that most of the genome is transcribed into RNA. However, only 1-2% of the human genome is for proteins that encode RNA into RNAs that have coding potential and RNAs without coding potential that are called non-coding RNAs (ncRNAs). Although mRNAs have been widely studied before, ncRNAs constitute the majority of RNAs. (64)
ncRNAs are divided into two subclasses according to a relatively wide size threshold. ncRNAs smaller than 200 nucleotides (nt) are called small or short non-coding RNAs, while ncRNAs longer than 200 nucleotides are called long non-coding RNAs (LncRNAs). These two groups are relatively heterogeneous. Small ncRNAs can range from a few to 200 nucleotides, while LncRNAs are up to several kilobases in size. MicroRNAs (miRNAs) with a size of 20 nucleotides are the most known group of small ncRNAs and have already been extensively studied. Their main action is to negatively regulate gene expression by binding to the target mRNA and inducing its destruction or inhibiting its translation. (65)
Compared to miRNAs, the mechanistic properties of LncRNAs are relatively weak. This is partly due to the fact that LncRNAs can regulate gene expression at multiple levels in the cell through complex molecular mechanisms. In addition, unlike miRNAs, LncRNAs are relatively weak in nucleotide sequence and can be found in a wide range of species, including plants, prokaryotes, yeast, and viruses. This limits the availability of cell and animal models to investigate LncRNA functions. LncRNAs that differ from each other in terms of nucleotide composition can still show the same three-dimensional structure and therefore the same molecular function. (66)
Increasing evidence points towards LncRNAs as regulators of almost every cellular process and it seems that the expression of these non-coding molecules is highly regulated in physiological conditions as well as in several human diseases including cancer. (65)
From a more general perspective, the classification and annotation of putative LncRNAs should be deeply evaluated to exclude RNAs that are actually protein-coding. In fact, it has recently been reported that despite their classification as non-coding molecules, some LncRNAs can encode micropeptides. A skeletal muscle-specific RNA, hypothesized to be an LncRNA, encoded a functional micropeptide, suggesting that any newly investigated LncRNA should be validated as a non-coding transcript before drawing conclusions about its regulatory role. (67,59)

Recently, evidence has shown that the expression of ncRNAs is not limited to classical mechanisms. A type of genome editing causes the creation of circular RNAs (circRNA). CircRNAs are made of a covalently closed loop and therefore lack a 5' cap and 3' tail. Such RNAs are not only well conserved, but also relatively stable and often tissue specific. (60)
The emerging links between non-coding RNAs and diseases have opened a new field of therapeutic and diagnostic opportunities. Many miRNAs are already successfully used as biomarkers or therapeutic targets for many different diseases. There is also evidence that the same is true for LncRNAs and circRNAs. (67)

5-conclusion:
Breast cancer, which is caused by the accumulation of genetic and epigenetic mutations, is one of the most important causes of cancer mortality. Conventional diagnosis and treatment of breast cancer is based on estimating the prognosis using anatomical features of the cancer (TNM system) and clinical findings, but studies have shown that the response of individuals to these treatments varies and some patients continue to experience recurrence after treatment. . This problem indicates that molecular changes occur before any phenotypic, clinical and pathological changes, and molecular evaluations along with clinical and pathological findings will be fruitful. Therefore, genomic and molecular studies and the role of targeted therapies based on the individual genome have become more colorful. Nowadays, progress in personalized medicine is possible to a large extent by using the specific molecular profile of each person through human genetic research. In the field of personalized medicine, the ultimate goal of these studies is to provide a set of markers that can be used to assess the risk of developing disease during the lifetime of each individual in the presence of various environmental variables. This modern science has made it possible to take a big step in the field of treating people with breast cancer by identifying specific markers and specific treatment goals and through specific and targeted treatments using monoclonal antibodies and special molecules such as trastuzumab and tamoxifen. Therefore, primary prevention is recommended in the form of lifestyle changes, avoiding risk factors, and extensive education and information, especially through mass media such as: radio, television, and newspapers, in order to raise people's awareness of breast cancer screening methods; Also, secondary prevention includes: early detection of cancer or pre-cancerous lesions, with effective and efficient screening methods, currently mammography is the most effective method in detecting breast cancer, it can play an important role in reducing the incidence and mortality of breast cancer. slow This cancer is a highly heterogeneous disease that is divided into several types such as (Lobular carcinoma in situ) LCIS, (Ductal carcinoma in situ) DCIS, and invasive carcinoma. BRCA1 and BRCA2 genes are associated with high risk and are associated with hereditary breast cancer. Mutations in the CHEK2 gene also lead to the majority of familial cancers. Predisposing alleles of other genes are also rare causes of breast cancer. More than 1,000 mutations have been reported in BRCA1 and BRCA2, and today molecular tests are used to find mutations in these two genes. Mutations in BRCA1 and BRCA cause genome instability, which itself leads to changes in other key genes, including tumor suppressor genes or oncogenes. There is hope that in the near future, it will be possible to design treatment plans for each person. One of the new candidates for diagnostic and prognostic markers and therapeutic targets are miRNAs as gene expression regulators. Finding the role of miRNAs in the development and progression of human malignancies has made it possible to improve current strategies in the field of diagnosis and treatment of cancer patients. Identifying new miRNAs, specifying their target mRNA and determining their functional effects will improve our knowledge about the role of these markers in the development of cancer, especially breast cancer, and will provide new possibilities for therapeutic interventions.

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