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Determination of Risk Factors for DCIS Ductal *in-situ* Carcinoma of Mammary Gland

Aneesh Bang [a≡*] and Shailesh Nagpure [bφ]

[a] Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences, Sawangi (M), Wardha, Maharashtra, India.
[b] Department of Pharmacology, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences, Sawangi (M), Wardha, Maharashtra, India.

Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Mammary gland is altered gland present in skin whose main function in females is that it acts as a lactating gland while in males it is non-functional. When the sample of tissue of mammary gland is observed under microscope it was found that there are 2 major types of tissues which are present. These tissues are epithelial and stromal tissues. The epithelial component of the breast consists of 2 major parts: terminal duct-lobular unit (TDLU) which performs the main secretory function during lactation, and large duct system which performs the function of collection and drainage of secretions; both are interconnected to each other. During the menstrual age of a female patient there are different number of tissues (connective and adipose) is present in the mammary gland these tissues mainly perform as the support system for the mammary gland. Acini, ducts, and lobule are enclosed in intralobular stroma and is mainly formed of connective tissue(loose) myxomatous stroma and some dispersed lymphocyte. The ductal carcinoma is very serious Pathology of breast which is now a major concern in developed country and to a certain extent in developing countries also. There are many major risk factors which are responsible for the same. Some may be of lifestyle based or of genetic based. The treatment for the disease is now possible with advancement in the medical science.

[≡] Dr.;
[φ] MBBS Student;
**Corresponding author: E-mail: banganeesh@gmail.com;*

Purpose for this review article is: Determine the cause affecting factors influencing factors and pathos physiological background of development of DCIS also to describe the gene involved in alteration of cell to enhance tumorous growth and the treatment therapy involved alongside the disease.

Keywords: Mammary gland; lactating gland; menstrual age.

1. INTRODUCTION

The mammary gland, or breast, is the most important component in the pectoral area. The breast is located in the pectoral region's superficial fascia. Upper medial, upper lateral, lower medial, and lower lateral are the four quadrants in which it is split. The axillary tail of Spence is a small extension of the upper lateral quadrant that goes through an aperture in the deep fascia and resides in the axilla [1].

Breast cancer expands mainly through the lymphatic system to its nearest area of lymph nodes, the surgeon places a high value on lymphatic drainage of the breast. The lymph nodes and lymphatics are two different types of lymph nodes. Excluding the nipple present on the mammary gland and the dark coloured area around nipple , the superficial lymphatics drain the skin above the breast. The lymphatics go radially to the lymph nodes in the area (supraclavicular) [2]. The breast parenchyma is drained by the deep lymphatics. The nipple and areola are also drained. The following are some more areas of interest about lymphatic drainage. The axillary nodes are where the majority of the lymphatic fluid is drained from the mammary gland [2,3].

The lymph is drained not only from the inner but also from the outside portion of the breast by the internal mammary nodes. Deep within the areola is a plexus of lymph veins. The subareolar plexus drains into the anterior or pectoral group of lymph nodes, as does the majority of lymph from the breast [2].

These lymphatic fluid at the end drain into the lymph nodes which are present around the mammary gland namely as apical and anternal mammary, they flow from the profound surface of the mammary gland by crossing the muscle of chest the pectoralis major and a fascia that is clavipectoral fascia [4].

To reach the apical nodes and the internal mammary nodes, lymphatics from the profound surface of the breast flow through the pectoralis major muscle and the clavipectoral fascia. After crossing the costal border and piercing the anterior axillary lymph swellings, lymphatics from the inferior and internal compartments of the mammary gland may connect with the part of diagphragm and sub peritoneal lymph retia. Sappey's subareolar plexus: Sappey's subareolar lymph plexus runs through the upper section of the linea alba and into the anterior abdominal wall [2].

When taken in accordance to certain specific medical signs, the natural behavioural pattern and its structural traits, the majority of neoplasms can be classified as benign or malignant.

If that not the case, there are some certain specific conditions which do not follow this criteria a very minute percentage of cancerous cells exhibit some characteristics that signal benign growth while others indicate more alarming behaviour [5].

DCIS is basically presence of abnormal cells in the lactating duct in breast. When a patient under goes mammogram to investigate BREAST LUMP then at such times DCIS can be seen or can be identified. It is not an extreme emergency case but it certainly requires an utmost care. Patient however comes with some signs such as ‘’a mass or lump is felt on breast ‘’ or also with bloody nipple discharge.

The cancerous cells which invade the nearby or the cells which are located far away from the origin of cancer can also increase by expanding, and some cancer cells which can be well recognized from the normal cells such as follicular carcinoma thyroid, can be partially encapsulated. However, the properties of the cancerous cells by which they invade and then infiltrate and destroy the nearby tissues of these cells , as well as goes far away areas or metastasis, distinguish them from benign tumours [5]. Tumors generally penetrate by the path of least resistance, yet most malignancies eventually lose their ability to recognise anatomical limits. Cancers frequently spread through the gaps present between the two

tissues, lymphatics, blood arteries, and the gaps between the two or more neurons in the Central Nervous Systems, and can even enter the cavity of the bone by the small hole present in the bone known as nutional foramina. Tumors that infiltrate thin-walled vessels are more common [5].

2. DCIS CAN BE DIAGNOSED BY VARIOUS WAYS

These are the following ways:-

[1]Breast Imaging:-

DCIS is most commonly identified via a mammography, which is a type of breast cancer screening. Further, recommend breast imaging if your mammogram indicates abnormal areas such as bright specks (microcalcifications) in a cluster with abnormal shapes or sizes.

[2]Removing Breast Tissue Sample For Testing:-

A hollow needle is used to take tissue samples from the suspected area during a core needle biopsy, which is usually guided by ultrasound or X-ray. The tissue samples are transported to a laboratory to be examined.

Based on histology and molecular subtyping, breast cancer is categorised into subtypes. Clinicopathological choices is basically depend upon individual immunohistochemistry levels of oestrogen receptor (ER), progesterone receptor (PgR), human epidermal growth factor receptor (HER2), and Ki-67 expression. Individualised therapy is indicated for each subtype of BC, which includes luminal A, luminal B (HER2), luminal B (HER2+), HER2+ (non-luminal), and triple-negative (TN) [6]. A relationship between histological classification and molecular subtypes has been discovered in recent studies.

Either DCIS lesions are treated with a mastectomy or a breast-conserving surgery coupled with radiation [7]. The majority of DCIS lesions, on the other hand, stay dormant. Many individuals may overtreat this condition due to difficulty distinguishing innocuous lesions from potentially aggressive ones. A global, comprehensive, and multidisciplinary collaboration is essential to combat overtreatment and reform clinical practise.

3. DEFINITION AND HISTOPATHO-LOGICAL FEATURES

The histological grade ranged from one to three. In-situ carcinomas were described as tumour cells that grew in situ, and clogged hair like appearance-like necrosis was defined as cancerous substantial encircled by feasible carcinoma cells in the vessel or ductal-based spread in hostile motivations [6]. TILs were characterised as lymph cell infiltrating the cancerous Stroma, and they were termed positive if they were found in almost half of the stroma. Apocrine characteristics were defined as eosinophilic granular cytoplasm in 10% of the tumours, indicating apocrine metaplasia. A profuse bundle of fibres or the process by which cells eats or kills each other by encircling an in situ or in situ-based cancer was characterised as healing counting around stages by or unused to TILs. The arrangement and worsening tree (CART) classical was used to assess histomorphological traits in each group simultaneously. Both models were investigated using 30 asymmetric combinations of histomorphological features. The impacts of the irregular histostructural traits on individually collection were then tested using multinomial logistic regression. To characterise the morphological and immunological response patterns, the likelihood of being a member of each group was assessed.

4. RISK FACTORS FOR DCIS

In a big residents-created research of females, relations among many, well-being, existence, and multiplicative variables and the prevalence of ductal adenocarcinoma in situ of the mammary gland were investigated. Phase, household past of cancer of mammary gland, ages among the first start of menstrual cycle and primary living biological, and standing of the time in which the menstrual flow in females stops, all of which are identified to be allied with IBC, were similarly related with danger of emerging DCIS in this study population, whereas additional issues inspected in earlier educations remained non [8].

Post-menopausal women with Class 1 Obesity and above (BMI >30) were studied and concluded that such females were more prone to such condition that is DCIS than other females. Reduction of epithelial tissue due to involvement of the mammary gland during perimenopause and the physiologic condition in which females menstrual cycle stops has shown a decreased

risk of DCIS later in life. However there is improved danger of DCIS independent of menopausal grade in women with first degree relative with positive family history [8].

The connection of physical activity with DCIS has not shown any proper results in studies however females with higher total physical activity have shown reduced chances of developing DCIS which can be due to a lower association of body weight and adiposity due to a satisfactory effect seen on the mechanisms for metabolism and inflammation thus the connection can be studied [8].

A high stature is not associated with DCIS, but is associated with various types of cancer, including mammary gland in females via many many studies that were done for this purpose [8]. Genetic factors along with environmental factors in early life also seem to play a role in development of cancer in adulthood [9].

A inverse association between BMI and DCIS is observed in postmenopausal females and a more chance of having DUCTAL CARCINOMA IN SITU in overweight persons having high body mass index (BMI ≥ 30 kg/m^2) post-menopausal women.

Increased lean mass after menopause is linked to greater levels of inflammatory markers, which are thought to have a role in the development of DUCTAL CARCINOMA IN SITU of mammary glands in females [8].

Hormone replacement therapy is seen with a greater chanches of risk in certain studies, while others have shown no link. There was no link between oral contraceptive use and the risk of DCIS. Time since the last use of an oral contraceptive was likewise not linked to an increased risk.

Benign breast disease have been not been found to have increased risk of DCIS.

Other factors, including smoking, alcohol, and diabetes, they are not included in risk factors based on studies [8].

Overall, the findings of the research imply that multiple factors are said to be included to a major risk factor for DCIS and IBC, and that these may play a role in breast tumour development earlier in life. These studies indicate a that DCIS may be a precursor to invasive breast cancer [8].

After a DCIS diagnosis, women's quality of life was generally equivalent to that of women of similar age who had never had DCIS. Our findings indicate that DCIS survivors, especially those diagnosed at a younger age, may benefit from mental health assistance [10].

5. RADIOLOGY DESCRIPTION

- Mammography is most commonly used diagnostic modality as it is highly sensitive and microcalcifications are found in most of the patients suffering from DCIS.
- Ductal Carcinoma in-situ presents with microcalcifications mostly in radiologic finding. DCIS presenting as a mass or cellular distortion without calcification is seen very rarely.
- Pleomorphic calcifications are frequently associated with high grade DCIS, whereas fine or granular calcifications are commonly associated with low grade DCIS. Calcifications may be beneficial in diagnosing DCIS prognosis. It's common to notice a clustered or linear distribution.
- Limited utility in diagnosing DCIS is observed by Ultrasound technique.
- MRI is thought to be a good tool for detecting DCIS without calcifications, multifocal DCIS, and determining the disease's extent.

Future study should focus on identifying women with a multiple occurrence of this disease for whom radiation should be a standard part by which the mammary gland is spared, and those with a less aggressive lesion, for whom a watchful waiting approach can be used after surgery [5].

6. TREATING OF DCIS

Clinical and histological variables, as well as molecular biomarkers, could be used to properly stratify DCIS patients based on risk.

In the management of ductal carcinoma in situ of the breast, current therapeutic trends and the need for new prediction tools are discussed [11].

When treating pure DCIS, surgical removal of the lymph nodes present in the axillary part of body is not necessary, but it is recommended when a very small invasion is present.

Tamoxifen lowered the risk of invasive and non-invasive breast cancer in both breasts.

Selected patients who were initially treated with lumpectomy alone may be eligible for breast-conservation therapy if they recur, as long as they follow the same tight tumour margin clearance requirements as the primary lesion; radiation therapy should be given after local excision.

- Optimal management of ductal carcinoma in situ of the breast

Although the current study found no differences in HER2 status that would alter recurrent disease supervision, there is always a chance that the cancer of mammary gland may repeat itself in the patient, this is a new primary neoplastic malignancy, so features such as long interval of time in which the patient is free from the disease, unusual radiological features, and clinical finding of baseline cancer of mammary gland should be considered because there is always a chance that the cancer may repeat itself in the patient [1].

Ductal carcinoma in situ: a brief review of treatment variation and impacts on patients and society [12].

Adverse effects of hormonal therapy is seen and is not clearly understandable results ,the tamoxifen therapy is avoided in post-menopausal women.

The surgical process in which the part of mammary gland that is infected is only removed and not the whole breast or in other word the unaffected part is left ,is the standard therapy in which there is resection of tumor free margins [13].

There are two main goals in the treatment that is given to the female patient suffering from DCIS;-

To avoid the chance of developing cancer of mammary gland tumours, in the same infected part of mammary gland or the unaffected part of the gland.

To lower the chance of the cancer of mammary gland may repeat itself in the patient of the DCIS lesion in local region whereas Tamoxifen lowers the risk formation of primary tumor on opposite side of the Breast [13].

In early-stages of invasive breast cancer of postmenopausal women aromatase inhibitors as adjuvant therapy can be used and there is no significant difference in efficacy of a Anastrozole and Tamoxifen [14].

From some detailed studies it is concluded that Disease progression of DCIS can be altered by Antiestrogen therapy[15,16] .

7. HER2 VACCINES

Recent research on the diagnostic value of tumour infiltrating lymphocytes supports the claim that immunogenic tumours are better repressed by the host, and that methods to boost tumour cell immunogenicity might be beneficial [17-20].

HER2 peptide-pulsed dendritic cell (DC1) vaccination that sensitises both CD4+ and CD8+ T cells and produces a significant anti-HER2 immune response [14].

Ductal Carcinoma In Situ of various molecular characteristics may progress to aggressive cancer of mammary gland as a result of various genetic or epigenetic hits [1].

When compared to normal tissues, FGF2 expression was reduced in Breast cancer. FGF2 has a significant inhibitory effect on cells in vitro, there is always a possibility of involvement of the MAPK cascade and the cellular cycle G1/S phases transition [15,1]. In primary breast cancers, GAS1 is downregulated. Hedgehog (Hh) signalling has been proposed as a key factor in cancer progression. There was a gradual rise in Hh expression and Hh pathway activation. Sonic hedgehog (SHH), which is one of the majar three proteinoid molecules, is binded by GAS1 protein, which may decrease Hh signalling [21,22]. Although there was a GAS1-SHH interaction, it was not at all significant. The SFRP1 gene is a suppressor of the WNT signalling pathway, which is abnormally active in breast cancer. SFRP1 has statistically significant interactions with WNT pathway genes, and enrichment analysis revealed that the canonical WNT receptor signalling pathway is negatively regulated [1]. In primary breast cancer, SFRP1 was downregulated as compairing between the normal or ideal tissues as well as the aggressive tissues [1]. FGF2, GAS1, and SFRP1 are down regulators of cell cycle G1/S transition, Hh transmission, and the WNT pathway as well, and hence may have a role in DCIS progression [15,1].

8. CONCLUSION

The downregulation of these genes promotes the evolution of DCIS. Unfortunately, it becomes

unable to separate our models but can be divided into two different grades that is higher and lower grade DCIS, nor investigation of samples based on cancerous molecular sub types could be done.

Seperating the groups cam lead to various conditions which are are of quite importance in the further evolution of DUCTAL CARCINOMA IN SITU of mammary gland.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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