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An Insight on types of Breast Cancer

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Abstract

Breast cancer is a complex disease with several different types, each with its own characteristics and behaviors. In this article,an attempt is made to characterize the types of Breast cancers in Human Here's an overview of some common types of breast cancers like Ductal Carcinoma In Situ (DCIS) ,Invasive Ductal Carcinoma (IDC),Invasive Lobular Carcinoma (ILC): Triple-Negative Breast Cancer (TNBC), HER2-Positive Breast Cancer, Hormone Receptor-Positive Breast Cancer, Inflammatory Breast Cancer (IBC) :and Paget's Disease of the Breast. These are just a few examples of the types of breast cancer, and within each type, there can be further variations in terms of tumor behavior, grade, and responsiveness to treatment. Treatment plans are tailored to the specific characteristics of the individual's cancer, including its type and stage. Early detection and advances in treatment have significantly improved outcomes for many individuals with breast cancer.

Key words : Atypical ductal hyperplasia, Carcinoma *in situ* , Ductal carcinoma *in situ*,
Invasive Breast Cancer ,Lobular carcinoma *in situ*

An insight on types of Breast Cancer

Introduction: Cancer is a group of heterogeneous ailments referred as a malignant neoplasm that prompts to uncontrolled cell division. In the long run, a tumor that can metastasize and encroach other parts of the body. They are very complex, and unpredictable, heterogeneous, multidisciplinary malady and its etiology remains largely obscure (Hanahan & Weinberg, 2011,p. 646). Tumors are normally characterized, classified and named according to the tissue of the body from where they start, for instance, lung, bosom, gastric, cervix, cerebrum and so forth and also tissue of starting point, that is carcinoma, sarcoma, glioma, and so on. There are diverse sorts of breast malignancies based on the histopathological groupings with diverse result survival.

Around the world, Breast tumor is the most as often as possibly analyzed life debilitating disease and the main reason for tumor-related deaths among females (MacDonald, et al. 2005, p. 372). It is evaluated that this malady will affect one in eight females in the USA amid their lifetime. Regardless of significant change in tumor diagnosis and treatment approximately 25% of Breast Cancer patients kick the bucket due to their sickness. Despite the fact that breast malignancy is thought to be an ailment of the developed world, a larger part (69%) of a breast cancer deaths happening in developing nations (Mathers, Fat, & Boerma, 2008) and relative less survival in underdeveloped and developing nations (Coleman et al., 2008,p. 730).

Breast cancer can be characterized as 'a development of malignant cells inside of the breast tissue' (Women's Health Queensland Wide 1999a.p. 9). Breast malignancy starts in the mammary gland, the anatomical tissues like Tubule and lobule of the breast. On the premise of origin, it is either Ductal carcinoma or lobular carcinoma. The primary depiction of breast tumor was found on an antiquated Egyptian papyrus in 1600 BC (Silva & Zurrida, 2003, p 13). Right now the malady was confusing, and the "battle" was surrendered effortlessly under the supposition that there was no treatment (Olson, 2002: 10). From that point forward, there have been numerous disclosures and case reports of breast malignancy and, because of medical technological advancements, a more noteworthy comprehension of this disease (Silva & Zurrida 2003 ,p 13). This article addresses the related literature on Ductal carcinoma or lobular carcinoma of breast cancer.

1.1.1 In Situ Breast Cancer (Noninvasive Breast Cancer)

Last century, Ductal carcinoma in situ (DCIS) of the breast is almost a rare disease and but in the past decade it is a most rapidly developing subtype in the breast cancer group due to screening application and imaging techniques. DCIS (ductal carcinoma *in situ*), can be described as a non-invasive, pre-cancerous or intraductal cancer of the breast (Sinn,2013,p.149). It is defined as a proliferation of neoplastic epithelial cells limited to the ductal–lobular system and is an extremely heterogeneous condition in terms of appearance, morphological

features, expression of biomarkers, underlying genetic modifications, and progression of carcinoma. Ductal Carcinoma in Situ (DCIS) is represented by subtle to distinct cytological atypia and an inherent propensity for progression (Lakhani, et al.,2012,p.). It is frequently non-palpable, without symptoms and may be identified as microcalcifications on mammographic screening of breast (Ernster,1997,p.1103).

Characteristics and Classification of ductal carcinoma in situ (DCIS) :

The ductal carcinoma in situ (DCIS) of the breast is categorized into two major groups such as a). Comedo and b). Noncomedo, basing on tumor morphology and histology. The *Comedo type of* ductal carcinoma in situ (DCIS) appears and shows different characteristics from other *in situ* subtypes. The clinical features of ductal carcinoma in situ (DCIS) are diverse and heterogeneous in nature. *Ductal Carcinoma in Situ (*DCIS) developed as a result of architectural disturbances in glandular epithelium of the breast associated with the loss of the hollow lumen and epithelial cell proliferation of epithelial cell in acinar entity which occurs through an inequality between cellular apoptosis and cell proliferation (Debnath ,2002,p. 29) .

Previously, many clinical pathologists applied architectural growth patterns of carcinoma for the classification of DCIS. But, several pathologists now classify ductal carcinoma in situ (DCIS) into two major subtypes depending on characteristics such as a) patterns of necrosis, b) nuclear grade, and c) presence or absence of calcification. Those having "*at least one duct in the breast……filled and expanded by large, markedly atypical cells and…abundant central luminal necrosis*" (Fonseca,1997,p. 1015) are treated as comedo type DCIS, where as all other types are categorized as noncomedo type(Fonseca,1997,p. 1015) .

Table 1

Characteristics of Ductal Carcinoma (Swart, 2015)

Feature	**Comedo in Situ Subtype**	**Noncomedo in Situ Subtype**
Nuclear grade	High	Low
Estrogen receptor	Negative	Positive
HER2 overexpression	Present	Absent
Distribution	Continuous	Multifocal
Necrosis	Present	Absent
Local recurrence	High	Low
Prognosis	Worse	Better

Figure 1
Comedo type of Intraductal carcinoma (Swart, 2015)

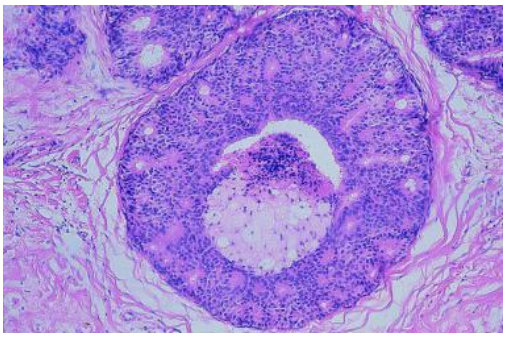


Figure 2
Noncomedo type of Intraductal carcinoma (Swart, 2015)

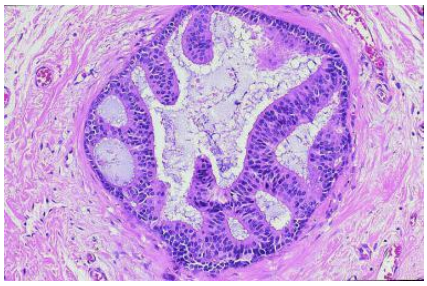


Figure 3

Historical method of classification of Ductal carcinoma in situ (DCIS) (Allred, 2010)

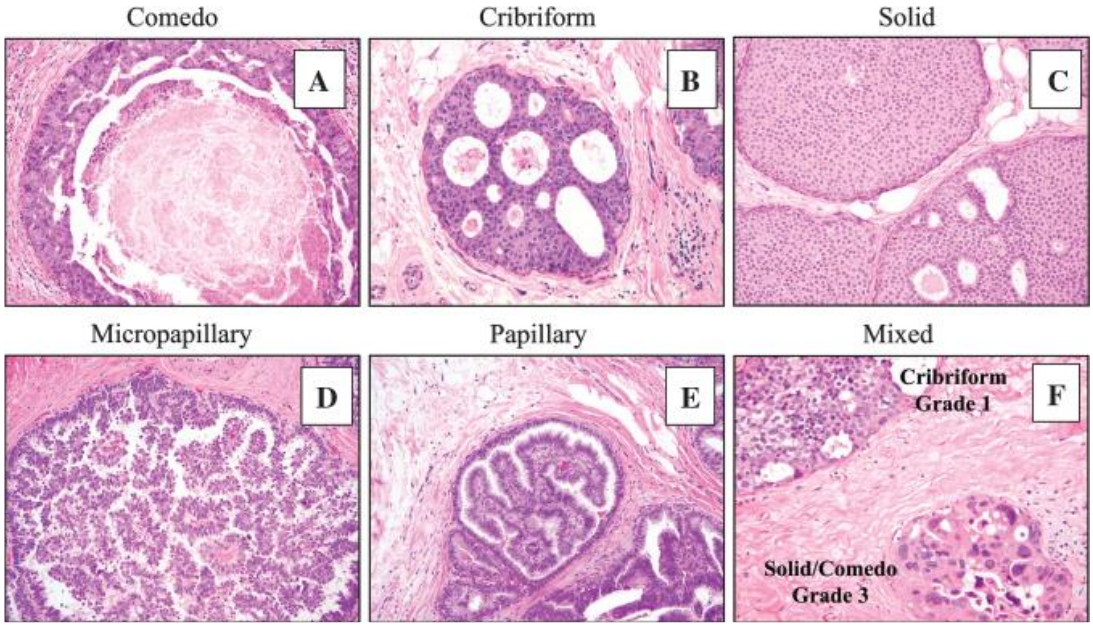


Table 2
DCIS: Classification and grading systems by year (Leonard and Swain, 2004)

Author and reference	Histological variable (s)	DCIS categories
Lagios et al., *(1990)*	a) Nuclear grade, b) Architecture, and c) Necrosis	a) High grade, b) Intermediate grade, and c) Low grade
Ottensen et al., *(1992)*	a) Histological growth pattern, b) Lesion size c) Nuclear size, d) Comedonecrosis, e) Subhistologic type	a) Microfocal, b) Diffuse, and c) Tumor forming
Bellamy et al., *(1993)*	a) Histologic pattern, b) Nuclear grade, c) Necrosis, d) Involved duct counts	a) Comedo, b) Solid, c) Cribriform, d) Micropapillary, and e) All with nuclear grade
Poller et al., *(*1994*)* (Nottingham)	a) Architecture	b) Comedo, c) DCIS with necrosis (nonpure comedo), and d) DCIS without necrosis
Holland et al., *(*1994*)*	a) Cytonuclear differentiation, b) Architectural, c) Differentiation (cell polarization)	a) Poorly differentiated, b) Intermediately differentiated, and c) Well-differentiated
European Breast Screening Groups *(*1997*)*	a) Cytonuclear differentiation	a) Poorly differentiated, b) Intermediately differentiated, and c) Well-differentiated
Page et al., *(*1982, 1995*)*	a) Nuclear grade, b) Architecture, c) Necrosis	a) High grade, b) Intermediate grade, c) Low grade
Silverstein *(*1995*)* (Van	a) Nuclear grade,	a) Group 1 (non–high grade without

Nuys)	b) Comedo-type necrosis	necrosis), b) Group 2 (non–high grade with necrosis), and c) Group 3 (high grade)
Consensus Committee *(*1997*)*	a) Nuclear grade, b) Necrosis, c) Polarization, d) Architectural pattern	a) High grade, b) Intermediate grade, and c) Low grade
Tavassoli *(*1998*)* (AFIP)	a) Idh/adh, b) Grade (atypia, necrosis)	a) Din 1a, -b, -c; b) Din2; , and c) Din3
Warnberg et al., *(2002)*	a) Histologic grade, b) Necrosis, c) Lymphoid infiltration, d) Mitosis, e) C-erb-2, f) P53, g) Progesterone receptor, and h) Bcl-2	A) Phenotype A, and B) Phenotype B

Several research investigators assume the theory of linear progression of DCIS from low to high grade, and the other theory the mutation of low grade to high grade of ductal carcinoma in situ **(**DCIS) (Vassiliki L.T. et al, 2006,p.305). It hypothesized that heat shock protein (hsp) 27 and similar to hsp27 proteins play an essential role in DCIS progression (O'Neill,. et al., 2004, p.183). Ductal Carcinoma In Situ **(**DCIS) can be investigated mainly through techniques such as mammography, stereotactic needle biopsy and magnetic resonance imaging (MRI).

Paget's disease of the breast, also known as Paget's disease of the nipple, is a rare form of breast cancer that affects the skin of the nipple and areola. It typically presents as redness, scaling, flaking, or crusting of the nipple and surrounding area, which may resemble eczema or dermatitis. Paget's disease of the breast is often associated with underlying ductal carcinoma in situ (DCIS) or invasive breast cancer within the breast tissue.

1.1.1.2 Lobular Carcinoma in Situ (LCIS).

In Lobular Carcinoma in Situ (LCIS), abnormal growth of cells stays inside the lobule and does not spread to encompassing tissues. Individuals with LCIS have a tendency to have more than one lobule affected. Regardless of the way fact that its name incorporates the expression "carcinoma," Lobular Carcinoma in Situ (LCIS), is not the true breast malignancy. Rather, it is a sign that an individual is at greater risk of breast cancer in later life. Thus, some oncologists lean toward the expression "lobular neoplasia" rather than "lobular carcinoma." However, the first clear explanation utilizing the term LCIS was by Foote and Stewart in 1941 (Foote & Stewart,1941,p.491). LCIS has been widely described in the literature, however, regardless of this long time span, issues and confusion encompassing the most suitable terminology and classification for these malignancies. Foote and Stewart (1941) have chosen the term to focus the morphological likenesses between the cells of LCIS and those of invasive lobular carcinoma (ILC). They theorized that LCIS, in a way much the same as DCIS may display an established pathway to an advancement of invasive malignancy. Haagensen et al (1978, p.737) introduced a comprehensive term, lobular neoplasia (LN) to cover both atypical lobular hyperplasia (ALH) and Lobular Carcinoma in Situ (LCIS). The present World Health Organization (WHO) book does join this term one next to the other with the ALH/LCIS phrasing. The lobular neoplasia (LN) can referred as as '*a proliferation of generally small and often loosely cohesive cells originating in the terminal duct lobular unit, with or without pagetoid involvement of terminal ducts (*Tavassoli, et al.,2003.p.). The following table presents the characteristics of classic and Special Lobular Carcinoma in Situ

At present, histological characteristics enable in classification of LCIS malignancies. The three primary histological sub-groups of LCIS are classical (CLCIS), flowery (FLCIS) and pleomorphic (PLCIS) and these classes can be found to coincide. Histologically, CLCIS is portrayed by a monomorphic populace of little round cells with a ring of clear cytoplasm (Simpson,2003,p.25.).

Cells inside of the tumor are freely adherent, lining the lumen of the acini and distending the TDLU, yet they maintain the structural engineering of the lobules with an intact basement membrane and myoepithelial cell layer [Moumen,2011,p.763].Mitotic index and necrosis, and in addition to calcifications, are not regular in CLCIS. Pagetoid spread, in which neoplastic cells reach out along the mammary duct, is regularly observed. There are two classes of CLCIS, sort An and sort B (King , et al, 2014,p.487]. Type A CLCIS is for the most part low grade, with little nuclei and subtle nucleoli. Type B CLCIS is made out of cells with bigger nuclei and little nucleoli. CLCIS has a tendency to be positive for estrogen receptor (ER) and progesterone receptor (PR), and negative for HER2. FLCIS is a relatively more uncommon sore, histologically described by a huge development of the included TDLUs, frequently connected with necrosis and calcifications. Morphologically, it takes after strong type DCIS. The injury is every now and again connected with ILC, supporting FLCIS as a forerunner of ILC [Bagaria, et al., 20011,p.1845]. FLCIS indicates more genetic instability than CLCIS, including a higher division of genomic changes and breakpoints [Shin, et al., 2013,p.1998].

PLCIS is a subtype of LCIS that is ordinarily connected with pleomorphic ILC, and that has a tendency to be high grade (Simpson,2003,p.25.).As opposed to CLCIS and FLCIS, the nuclei and nucleoli in PLCIS are bigger, and cells have more cytoplasm. Calcifications and comedo type necrosis are more regular in PLCIS than in CLCIS. PLCIS can be separated into apocrine or nonapocrine PLCIS, in view of the vicinity or unlucky deficiency, individually, of eosinophilic granules in the cytoplasm, intracytoplasmic vacuoles and vesicular chromatin (King ,et al, 2014,p.487].)

Table 3

Lobular Carcinoma in Situ (LCIS)(Chen et al., 2009,p.1683).

	classic	Special
Cell dyshension	present	present
Cell shape	round	Round to oval
Nuclear atypia	low	Low to severe
Cytoplasm	scant	Scant to abundant
Intracytoplasmic vacuoles	Present	Present
Intracytoplasmic mucin	Rare	Common
nucleoli	Rare	Common
Necrosis	Absent	Present
mitoses	Absent	Present
calcification	incidental	Common
E-caderin	negative	Negative

The lobular neoplasia (LN) incorporates a group of individual with specific histological characteristics. The most widely recognized sort, classic type LCIS, is made out of acini loaded with a monomorphic populace of little, round, polygonal or cuboidal cells, with a dainty edge of clear cytoplasm and a high atomic to-cytoplasmic proportion (Foote,1941,p.493; Schnitt, 1999,p.209). These cells nuclei are uniform in shape and evenly scattered. A unique cytological element is the occurrence of intracytoplasmic lumina or fuchsia bodies in the cells. The cells are freely strong and frequently divided, spaced, fill and enlarge the acini; on the other hand, general lobular construction design is maintained (Schnitt, 1999,p.210). Glandular lumina are not seen and while mitoses, calcification, and necrosis are remarkable. Pagetoid spread, where the neoplastic cells reach out along nearby pipes between in place overlying epithelium and basic basement layer is additionally as often as possible seen. Similar genomic hybridization (CGH) examination is a strategy where ""test"" DNA is contrasted and typical DNA on metaphase chromosome spreads to know DNA structural number changes. PC supported investigation enable to identify and distinguish chromosome loci that vary from normal. Comparative genomic hybridization (CGH) investigation of Lobular Carcinoma in Situ (LCIS), and Atypical lobular hyperplasia

(ALH) has shown deletion of genetic material from chromosomes 16p, 16q, 17p, and 22q and addition of genetic material from 6q at a comparative high recurrence in both lesions. Deletions at 1q, 16q, and 17p are likewise seen in ILCs (Buerger,et al., 1999,p.521; Nishizaki, 1997; p.513). E-cadherin is a tumor suppressor gene present on 16q22.1 that is included in cell–cell adhesiveness and in the regulation of cell cycle through the catenin/Wnt pathway ((Jiang and Mansel, 2000,p.151). E-cadherin shows positive staining and play A role in the pathogenesis of lobular malignancies and assumed that it has precursor role in LCIS (Vos, et al. , 1997, p.1131).

2.1.2 Invasive Breast Cancer (Infiltrating Breast Cancer)

2.1.2.1 Invasive Ductal Carcinoma (IDC)

Invasive ductal carcinoma (IDC): Invasive ductal carcinoma (IDC), is also known as penetrating ductal carcinoma, or Invasive carcinoma of no special type (NST), or invasive ductal carcinoma or ductal NOS, and not otherwise specified (NOS) is the most well-known kind of breast malignancy(Sinn, & Kreipe, 2013,p.149).. Around 80% of all bosom malignancies are invasive ductal carcinomas. *Invasive* implies that the malignancy has "invaded" or spread to the encompassing breast tissues. Ductal implies that the tumor started in the milk channels, which are the "ducts" that convey milk from the milk-delivering lobules to the areola. Carcinoma alludes to any disease that starts in the skin or different tissues that cover inner organs —, for example, breast tissue. All together, "Invasive ductal carcinoma" indicate to a tumor that has broken through the milk conduit and started to attack the tissues of the breast. After some time, *Invasive* ductal carcinoma can invade to the lymph nodes and possibly to different regions of the body (Breastcancer.org,2015).

There are a few types of Invasive ductal carcinoma that occur less regularly than others. In these tumors, the cells can look and carry on fairly uniquely in contrast to Invasive ductal carcinoma cells more often than not do. Some Less Common Subtypes of Invasive Ductal Carcinoma are a) Tubular Ductal Carcinoma : b) Medullary Ductal Carcinoma : c) Mucinous Ductal Carcinoma :d) Papillary Ductal Carcinoma; and **e)** Cribriform Carcinoma(Breastcancer.org,2015).

a) Tubular Ductal Carcinoma: It is a subtype of invasive ductal carcinoma and generally small (around 1 cm or less). Tubular Ductal Carcinomas are made of tubules." These tumors have a tendency to be low-grade implying that their malignant cells look to some degree like ordinary, healthy cells and have a tendency to multiply slowly. The name is derived from how the malignant cell looks under the magnifying lens; like many tiny tubules. Tubular carcinoma of the bosom is less inclined to spread outside the breast than different types of breast malignancy. It's additionally less demanding to treat. Studies have observed that the normal age for diagnosis of tubular carcinoma ranges from the mid-40s to late 60s (Breastcancer.org,2015).

b) Medullary Ductal Carcinoma : This type of malignancy is uncommon, and just three to five percent of breast diseases are analyzed as medullary ductal carcinoma. The tumor more often than not appears on a mammogram, and it doesn't generally feel like a protuberance; rather it can feel like a spongy tissue like a change in the breast.This type of cancer is rare, and only three to five percent of breast cancers are diagnosed as medullary ductal carcinoma. The tumor usually shows up on a mammogram and it does not always feel like a lump; rather it can feel like a spongy, soft, fleshy mass change in breast tissue. Medullary carcinoma can happen at any age; however, it, for the most part, affects ladies in their late 40s and mid 50s. Medullary carcinoma is more regular in women who have a BRCA1 mutation. Research studies have demonstrated that medullary carcinoma is likewise more regular in Japan than in the United States. Medullary carcinoma cells are normally high-grade in their appearance and low-grade in their cellular behavior. As such, they look like severe, abnormal tumor cells, yet they don't behave like them. Medullary carcinoma doesn't develop more rapidly and normally doesn't spread outside the bosom to the lymph nodes. Therefore, normally it is easy to treat than different forms of breast tumor (Breastcancer.org,2015).

c) Mucinous Ductal Carcinoma : It is also known as colloid carcinoma and an uncommon type of invasive ductal carcinoma. This happens when tumor cells inside the breast produce mucous, which contains breast malignant cells. The abnormal cells and mucous join to form a Carcinoma. The mucinous ductal carcinoma conveys a superior prognosis than more normal types of Invasive ductal carcinoma (IDC)s. In mucinous carcinoma, on the other hand, the bodily fluid the mucus turns into a fundamental part of the tumor and encompasses the breast malignancy cells. The mucinous carcinoma has a tendency to affect women after they've experienced menopause. A few studies have found that the standard age at analysis is 60 or more. Mucinous carcinoma is more averse to spread to the lymph nodes than different types of bosom growth. It's likewise simpler to treat (Breastcancer.org,2015).

d) Papillary Ductal Carcinoma – This tumor looks like very small finger-like projections under the magnifying instrument. It is just in uncommon cases that this sort of malignancy gets to be invasive. Normal among ladies age 50 and more, this type of tumor is treated like DCIS, in spite of being an invasive malignancy. Regularly it is Grade 2, or moderate grade on a size of 1 to 3 — with Grade 1 portraying tumor cells that look and carry on fairly like normal breast cells, and Grade 3 depicting exceptionally strange, rapidly developing malignant cells (Breastcancer.org,2015).

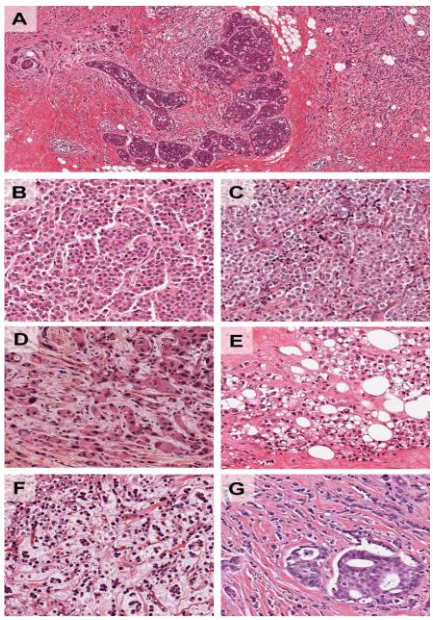
e) Cribriform Carcinoma of the Breast :In this type of invasive cribriform carcinoma, the malignant cells attack the stroma of breast tissue, in nest like arrangements between the ducts and lobules of breast. Inside of the breast tumor, there are distinctive gaps in the middle of the malignant cells, making it look like Swiss cheddar. Invasive cribriform carcinoma is generally low grade, implying that its cells look and

carry on to some degree like ordinary, breast cells. In around 5-6% of invasive bosom malignancies, some segment of the tumor can be considered cribriform (Breastcancer.org,2015).

2.1.2.2 Invasive Lobular Carcinoma (ILC)

Invasive lobular carcinomas (ILCs) are the second most common subtype of invasive bosom malignancy after Invasive ductal disease (IDC), representing 5 to 15 % of new bosom growth analyze [Lee, et al, 2010,p.34]. Since the first depiction of ILC by Foote and Stewart in 1946 [Foote & Stewart , 1946,p.74], there have been a few histopathologic variations of ILC reported, which may represent the variation in the reported occurrence of ILC crosswise over studies [Orvieto,2014,p.183] The previous two decades have seen an increase in the frequency of ILC. Despite the fact that this expanded rate is likely multifactorial, a standout amongst the most very much portrayed danger elements connected with the discovery of Invasive lobular carcinomas (ILCs) is the utilization of postmenopausal hormone substitution treatment

Figure 5:Invasive lobular carcinoma and its variants characteristics ((Reed et al., 2015,p.2)



(A) Low power view of a terminal duct lobular unit colonised by lobular carcinoma in situ. Classic invasive lobular carcinoma is seen diffusely infiltrating the whole specimen as single cells and single files of cells. The characteristic targetoid growth pattern is evident on the left-hand side (see also Figure 2). (B-G) Morphological variants of the classic type:

(B) alveolar type, with globular aggregates of approximately 20 cells;

(C) solid type with discohesive tumour cells growing in solid sheets;

(D) a pleomorphic variant - note the pink, foamy cytoplasm typical of an apocrine phenotype and irregular nuclei;

(E) pleomorphic invasive lobular carcinoma with prominent signet ring cells;

(F) invasive lobular carcinoma showing mucinous/histiocytoid morphology;

(G) mixed ductal-lobular carcinoma.

The growth pattern in invasive lobular carcinoma (ILC) includes the infiltration of single cells or single records of cells through the stroma, with little aggravation of ordinary tissue structural design. The attacking malignant cells are as often as possible organized in a concentric (targetoid) design around typical conduits or structures . (Reed et al., 2015,p.2)..

There are an array of morphologically variants that exhibit either cytological or e structural variety of the main components of classic ILC. Pleomorphic lobular carcinoma (PLC) holds the characteristic developmental pattern example of classic ILC but as in its in situ partner (PLCIS), there is clear cell atypia and atomic pleomorphism in respect to classic LN and ILC. PLC might likewise have an expanded mitotic rate, be made out of signet ring cells (Figure x) and/or exhibit apocrine or histiocytoid discrimination (Reed et al., 2015,p.2).. The strong and alveolar variations are both portrayed by classic ILC cells (small, regular sized and lacking union) that are organized in sheets (solid type) or in aggregation less than 20 cells (alveolar sort, Figure x) as opposed to in single cord of cells (Reed et al., 2015,p.2).. Solid ILC might likewise be all the more as often as possible pleomorphic and mitotically dynamic in respect to classic ILC. classic ILC may be amalgamated with one or a with other morphological variations or with tumor cells of a tubular development design (tubulo-lobular carcinoma). Besides, around 5% of all invasive bosom tumors display features elements of both ductal and lobular differentiation.The discohesive character of ILC is the consequence of the dysregulation of cell-cell bond properties, essentially determined by the focused on disturbance of the cell attachment atom E-cadherin(Reed et al., 2015,p.2).

3.1.2.3 Inflammatory Breast Cancer (IBC)

Inflammatory breast cancer:

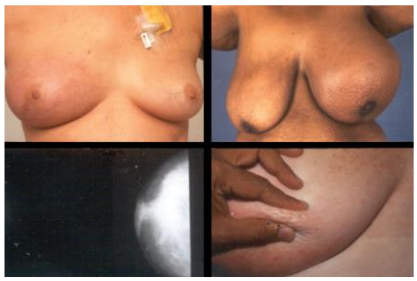
During 1924, Lee and Tannenbaum (Lee and Tannenbaum, 1924), first used the term Inflammatory breast cancer (IBC) to describe the uncommon, lethal, and aggressive type of breast cancer in young women. It is named as inflammatory, as it is presented with symptoms that are similar to inflammation. It is described as a rare form of breast cancer due to its clinical manifestation in the skin of breast and inflammation. Normally, inflammatory breast cancer was observed at a younger age, and at a risk of the metastatic condition, and have diminished longevity than women affected with non-inflammatory breast cancer.

Historically, Taylor and Meltzer (1938, *p*.33) presented a standard characterization of inflammatory breast cancer in a research paper as "*The redness, which may vary from a faint blush to a flaming red, spreads diffusely over the breast, which becomes hot, pitted, and edematous, presenting an 'orange-skin' appearance. Meanwhile, cancer spreads rapidly throughout the entire breast in the form of a diffuse, ill-defined induration.*

The breast may swell to two or three times its original volume within a few weeks (Taylor and Meltzer 1938, *p*.33). Taylor and Meltzer (1938, p .35) proposed the two main clinical types of Inflammatory breast cancer such as primary Inflammatory breast cancer or "*de novo* IBC" and secondary Inflammatory breast cancer (Taylor and Meltzer (1938, p.35), to discriminate between Inflammatory breast cancer and locally progressive breast cancer. The primary Inflammatory breast cancer is described as the new progression of IBC in a normal breast, while the secondary Inflammatory breast cancer illustrates the inflammatory recurrence of non-IBC breast cancer (Taylor and Meltzer, 1938,p.35).

Figure 6

Inflammatory breast cancer (Giordano, and Hortobagyi , 2003,p.285)



During 1956, the first diagnostic criteria for Inflammatory breast cancer were reported by Haagensen (Haagensen, 1956,p.142). According to this diagnostic criteria, American Joint Committee on Cancer (AJCC) described the Inflammatory breast cancer as '*a clinicopathological entity characterised by diffuse erythema and oedema of the breast, often without an underlying palpable mass'* (AJCC, 2002,p.228).

Primarily, inflammatory breast cancer has no distinct histological characteristics and by itself is not an identified morphological subtype of invasive breast cancer (Infiltrating Breast Cancer). According to contemporary World Health Organization definition (Lakhani et al, 2012,p. 10) the diagnosis should be established basing on the clinical findings and also it focuses on the clinical report of effect of involvement of dermal lymphatic and embolization. The basic invasive breast cancer is frequently a high level of grade and of no exceptional type. There is an indication that tumors correlated with an inflammatory appearance are remarkably *angiogenic, lymphangiogenic and vasculogenic* (Vermeulen et al., 2010,p. 2749).

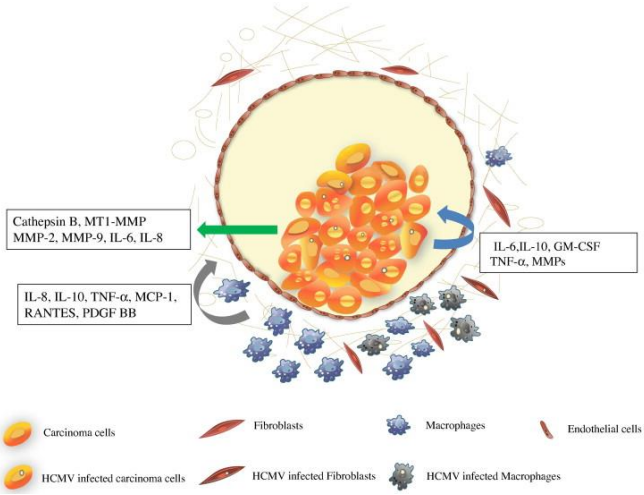
The mammographic image characteristics of inflammatory breast cancer are different from other breast cancer tumors as less than half will display discrete mass (Ueno et al., 1997, p. 322 ; Kushwaha et al., 2000,p. 535). The other atypical features like thickening of skin and trabecula, and axillary adenopathy are observed in maximum affected individuals (Kushwaha et al., 2000,p. 538). Inflammatory breast cancer is not correlated with a specific histological subtype and may appear in infiltrating ductal or lobular, small cell, medullary, and large cell cancers (Jaiyesim, 1992,p.1014).

The distinctive pathologic feature is a dermal lymphatic invasion by a tumor that can result in the blockage of the lymphatic drainage leading to erythematic and edema symptoms. The examination of inflammatory carcinoma is based on the clinical signs and symptoms. The absence of dermal lymphatic invasion does not eliminate diagnosis. Patients affected with inflammatory breast cancer symptoms should be treated intensively, even though patients do not show the pathologic conditions of invasion of dermal lymphatic tissue. The essential prognostic factor is the lymph node involvement in females with inflammatory breast cancer (Palangie et al., 1994,p.922). Considerable erythema, the absence of receptors for estrogen, and the occurrence of *p53* gene mutations are linked with low results in patients with inflammatory breast carcinoma (Palangie et al., 1994,p.923; , Chevallier et al., 1987,p.899). As many women affected with inflammatory tumor do not have distinct masses, tumor size is not useful in clinical examination of non-inflammatory cancer.

The inflammatory breast carcinoma has specific biological features that discriminate it from other non-inflammatory carcinoma. The inflammatory breast tumors are more frequent in high S-phase fraction, and are high-grade, in aneuploid condition, and absence of hormone receptor expression (Paradiso et al., 1989,p.1922 ;Aziz et al., 2001,p. 398). Paradiso and co-workers (1989) reported that forty-four percent of inflammatory breast cancers were positive for estrogen receptor and thirty percent were positive for progesterone receptor , when compared with the individuals affected with non-inflammatory breast cancer, sixty four percent cases were positive for estrogen-receptor and fifty-one percent cases were positive for progesterone receptor respectively (Paradiso et al., 1989,p.1924).

Figure 7

Tumor emboli of inflammatory breast cancer (IBC) (Mohamed et al, 2014,p.531)



The biology of inflammatory breast cancer is very complex; recent studies revealed that cellular and molecular factors such as cytokines, enzymes like proteases, and viral diseases play a key role in the progression of inflammatory breast cancer. Figure 2 displays the Tumor emboli of IBC, depicting carcinoma cells (green arrow) secrete proteases and cytokines that facilitate extracellular matrix degradation, invasion, and motility. TAM (gray arrow) secrete molecules such as cytokines, chemokines, and growth components that activate immunosuppression (Mohamed et al., 2014,p.532).

Furthermore, inflammatory breast cancers are more likely to exhibit *p53* gene mutations. Aziz and co-workers (2001) have made a comparative research study on prognostic markers in inflammatory breast cancer ,and reported the over expression of p53 gene inflammatory breast cancers (Aziz et al., 2001). The p53 gene function may be modified by two specific procedure such as direct mutation and cytoplasmic sequestration of the protein in inflammatory breast cancer (Moll, Riou and Levine, 1992,p. 7262). Aziz et al., (2001) and Prost et al., (2001) described that there is no difference in the rates of c-*erbB-2* over expression between inflammatory breast cancer and non-inflammatory carcinomas breast cancer.Aziz (2001) also observed that there is, no difference in the frequency of expression of EGFR and cathepsin D between inflammatory breast cancer and non-inflammatory carcinomas breast cancer ((Aziz et al., 2001,p.400).

McCarthy and co-workers (2002) have studied 67 tumor specimens of the inflammatory breast and reported that there is high microvessel density in inflammatory breast (McCarthy et al.,2002,p.3858) . Merajver and co-workers (2000) have reported that there is high levels of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) in inflammatory breast cancer cells (Kleer et al.,2000,p.423). They assumed that the high levels of vascular endothelial growth factor (VEGF) might be a cause for tumor neovascularization and the lymphatic process in inflammatory breast cancer (Kleer et al.,2000,p.424). In Inflammatory breast cancers cells, the E-cadherin is involved in cell–cell adhesion and also in lymphovascular invasion (Tomlinson et al., 2001,p.5232]. Kleer and others (2000) have observed that 100% expression of E-cadherin in inflammatory Carcinomas while 68% expression of E-cadherin in non-inflammatory breast tumors (Kleer et al.,2000,p.424). There is an enhanced increase in survival fitness of Inflammatory breast cancer-affected individuals with medication with chemotherapy, mastectomy of breasts, and radiation therapy.

HER2-positive breast cancer is a subtype of breast cancer that tests positive for the human epidermal growth factor receptor 2 (HER2) protein. HER2 is a protein that promotes the growth of cancer cells when it is overexpressed or amplified. This overexpression of HER2 can lead to aggressive tumor growth and poorer prognosis if not properly treated. HER2-positive breast cancer tends to be more aggressive than HER2-negative

breast cancer. However, the prognosis has significantly improved with the development of targeted therapies specifically designed to inhibit HER2 signaling.

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