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The WCC Note™

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BREAST DCIS: PART 1

Breast ductal carcinoma in situ (DCIS) appears to follow two distinct molecular pathways that influence its grade and, therefore, its biobehavior. Common belief holds that most DCIS forms along a stepwise pathologic progression after epithelial atypia and atypical ductal hyperplasia and before, though not obligatorily so, invasive cancer. Genetic point mutations, chromosomal rearrangements, and microenvironmental changes occur gradually and cumulatively to potentially drive the evolution.

In contrast, a recent intriguing discovery published in the January 2011 issue of *Cell* holds that a small percentage of cancers did not adhere to this more orderly genetic accumulation of errors. Rather, they suffered a sudden genetic catastrophe of sorts that might have caused bursts of somatic mutation relatively quickly. (1)

DCIS proves a highly complex pathology, and it has been suggested that the term DCIS be replaced by a classification system of ductal intraepithelial neoplasia, similar to that of cervical or prostate precursor lesions. (2)

Within this ongoing evolving knowledge, breast MRI can help diagnosis DCIS. Its MRI morphology and kinetic appearance provide a potential indicator of these genetic and biobehavioral underpinnings.

This issue of the *WCC Note,* Breast DCIS: Part 1, discusses the epidemiology, pathology, and mammography appearance of DCIS and summarizes some of its recent science. *The WCC Note,* Breast DCIS: Part 2 reviews the MRI findings of DCIS.

EPIDEMIOLOGY

What is the epidemiology of DCIS?

1. The incidence of DCIS was 32.5 per 100,000 women in 2005, having been 1.87 per 100,000 in 1973-1975. By 2004 the incidence had increased for all ages of women, greatest for those older than 50 years. Some, but not all, of the increase can be attributed to greater use of mammography. (3)
2. The largest increase in incidence occurred in non-comedo subtypes of DCIS that are not associated with subsequent invasive carcinoma. (4)
3. Of cancers diagnosed by mammography in the United States, 25% were DCIS. (3, 5)
4. Risk factors include increasing age, family history of breast cancer, high mammographic breast density, and postmenopausal hormone use. (4)
5. DCIS patients aged 40 years and younger display an increased recurrence risk independent of histological and clinical tumor character, with initial treatment (especially involved margins) also predictive. (6)
6. The proportion of untreated DCIS that will progress to invasive cancer is unknown. DCIS carries an excellent 10-year survival rate of 96-98%. (7)

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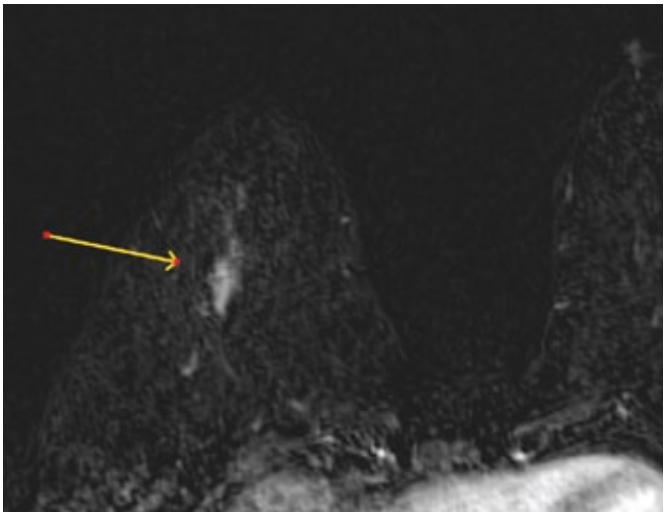
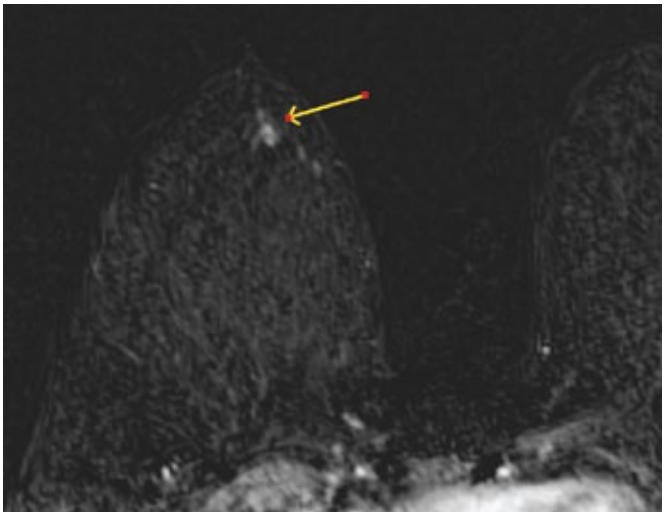


Figure A



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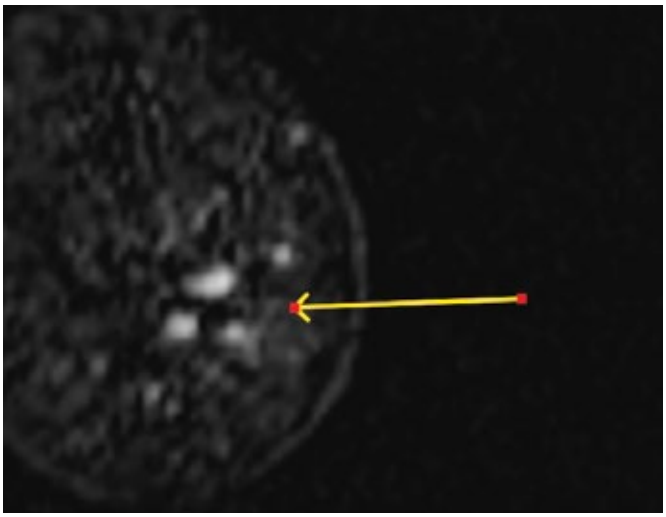

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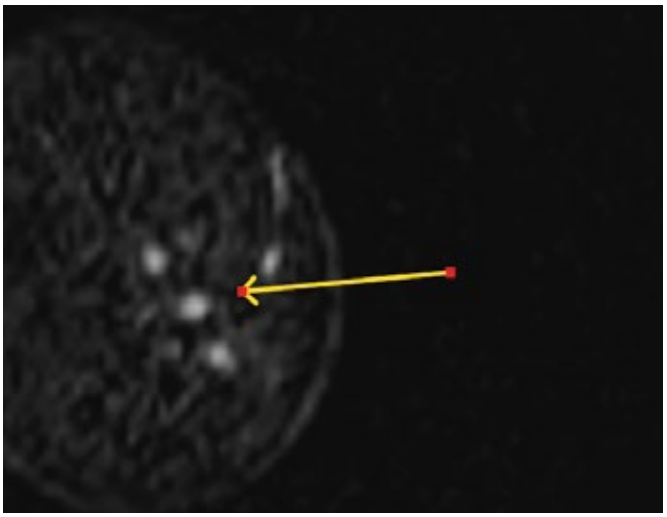

Figure D

ABOVE:

- ***History: right breast thickening and areolar retraction***
- ***Post contrast subtracted axial image (Figure A) shows 6-o'clock, radially oriented irregular enhancement with wash out kinetic curve, 18 x 13 mm. Enhancing radially oriented duct coursed 22 mm anterior from this lesion, toward the anterior breast.***
- ***Post contrast subtracted axial image (Figures B) shows retroareolar central to inner breast enhancing nodule. The area had grouped nodules, largest 6-mm, 4-mm, and 4-mm nodular foci, one of which is shown on the axial image (Figures B); and the group shown on the coronal images (Figures C and D).***
- ***Pathology: Three areas biopsied. DCIS intermediate and high grade; DCIS low to intermediate grade; Atypical ductal hyperplasia.***

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PATHOLOGY

Description of DCIS pathology

1. DCIS represents the most common noninvasive breast lesion. It is defined as the proliferation of malignant ductal epithelial cells without penetration of the basement membrane. (5)
2. The location of many DCIS lesions involves the terminal duct-lobular unit. (8)
3. All breast cancers begin as carcinoma in situ, but only a subset progress to invasive disease. It may be factors such as contralateral cancer, biologically new ipsilateral cancer, or the degree of resistance of the normal stroma to invasion, rather than residual disease, that proves more important in determining survival. (9)
4. The major differentiation between DCIS and invasive cancer is the presence of intact basement membrane and myoepithelial cell layer. (10)
5. The most aggressive form of DCIS shows high-grade cellular and nuclear features called comedo-type and frequently has necrosis and microcalcification. Other architectural types are cribiform (appearing to have small holes or open spaces); papillary (showing fingerlike projections); micropapillary (displaying smaller fingerlike projections); and solid types. Many cases of DCIS show at least two different architectural types. The average size of DCIS is about 10 to 15 mm, and about one-half are high grade. “Noncomedo” is the most common subtype. (7)
6. While the traditional classification is based on architectural pattern, the architecture subtype is independent of necrosis presence and histologic grade. Other classification systems proposed for DCIS rely predominantly on cytologic features and whether necrosis exists. These show reproducibility and prognostic importance. (11)
7. The Van Nuys system is the simplest and most reproducible classification system. Lesions are labeled according to nuclear grade and whether necrosis exists. (11)

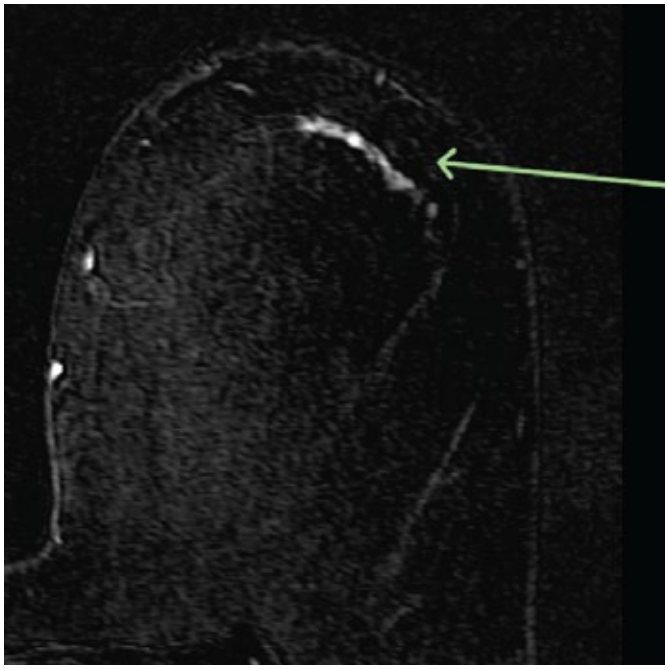

Figure E

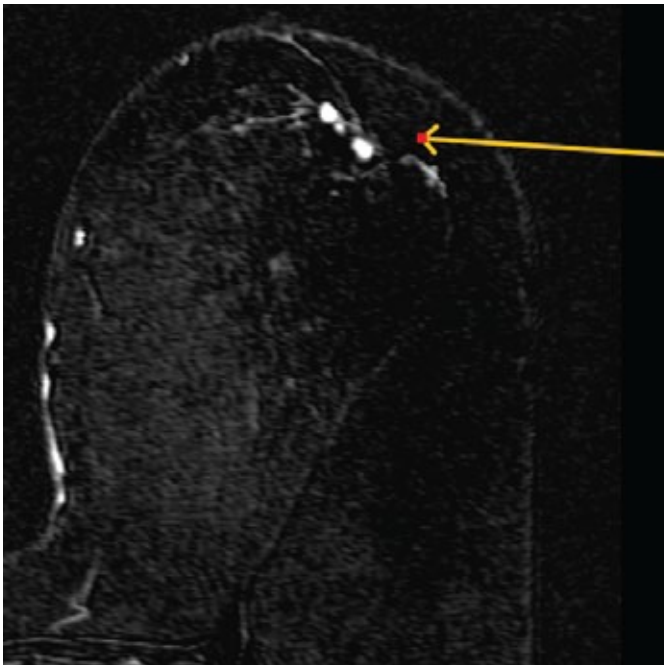

Figure F

Above:

- ***History: new microcalcifications***
- ***Post contrast axial subtracted images (Figures E and F) show grouped foci***
- ***Pathology: DCIS, high grade, 18 x 15 mm containing 5 mm invasive carcinoma.***

DCIS & MAMMO

What features does DCIS display on mammography?

1. On mammography, DCIS most commonly appears as microcalcifications, though these occur more often in intermediate or high grade lesions; low-grade DCIS without necrosis are less likely to display microcalcifications. (11)
2. Calcification in DCIS probably results from necrosis due to hypoxia in the central DCIS lesions. Blood flow to DCIS occurs via diffusion from extraductal vessels; no new vessel growth occurs within the ducts. Therefore, if the ducts are packed with DCIS, the diffusion distance may be too great, resulting in hypoxia and calcified necrosis. (12)
3. The mammographic manifestations of DCIS (11) are:
    i. Microcalcifications (50-75%)
        a. Fine pleomorphic or fine linear-branching can reflect high-grade DCIS and have associated necrosis.
        b. Round calcifications can correlate with low-grade DCIS.
        c. High grade DCIS can have more extensive calcification.
    ii. Dominant mass (10%)
    iii. Architectural distortion (7-13%)
4. The shapes of microcalcification particles most associated with DCIS are amorphous, fine and coarse pleomorphic, and fine linear, with distributions that are linear or segmental. (13)
5. A study from the United Kingdom reviewed 2564 cases of DCIS who had mammographic and pathologic data. The study found that in patients undergoing breast-conserving surgery, preoperative mammography underestimated the extent of disease in 30%, resulting in further surgery. (14)
6. Women with mammographically dense breasts who had DCIS may be at higher risk of subsequent breast cancer, especially in the contralateral breast, according to a study of 935 DCIS patients. (15)
7. Issues relating to mammographic detection of DCIS include (12):
    i. Calcifications not infrequently develop only in part of the DCIS; a large part of the tumor may be mammographically occult.
    ii. It is estimated that from 10 to 25% of DCIS lesions diagnosed with mammography will never progress to invasion.
    iii. There is reason to assume that mammography does not depict DCIS in a substantial number of women, and despite annual screening, the majority of intraductal stages go undiagnosed.
8. A 2005 review of 909 mammograms with DCIS showed (16):
    i. Microcalcification in 75%
    ii. Soft-tissue abnormalities in 27%, with association with calcification in 14%
    iii. The soft tissue abnormalities were:
        a. Masses with well-defined margin in 14%
        b. Obscured, indistinct masses with ill-defined or spiculated margin in 2%
        c. Architectural distortion and focal asymmetry in 12%
    iv. Palpable masses in 12%
    v. Nipple discharge in 12%

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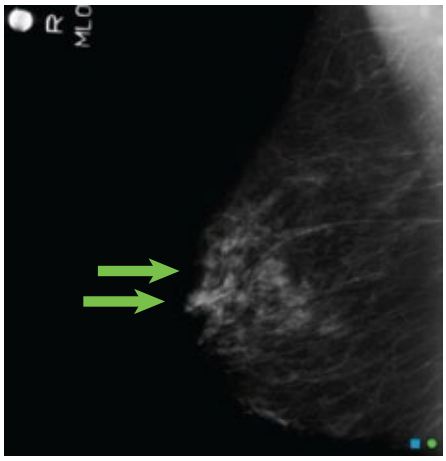

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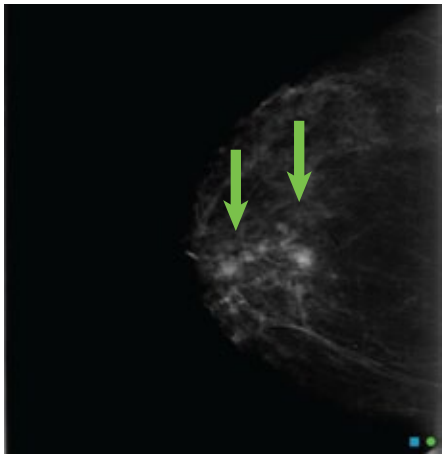

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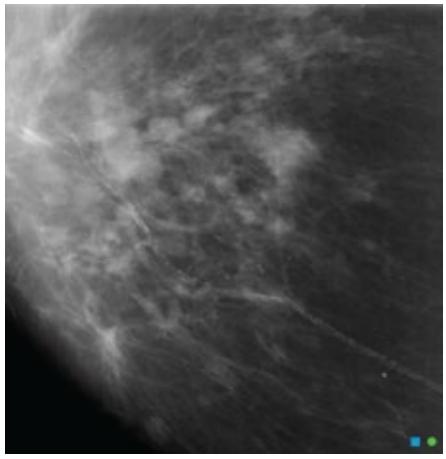

Figure I

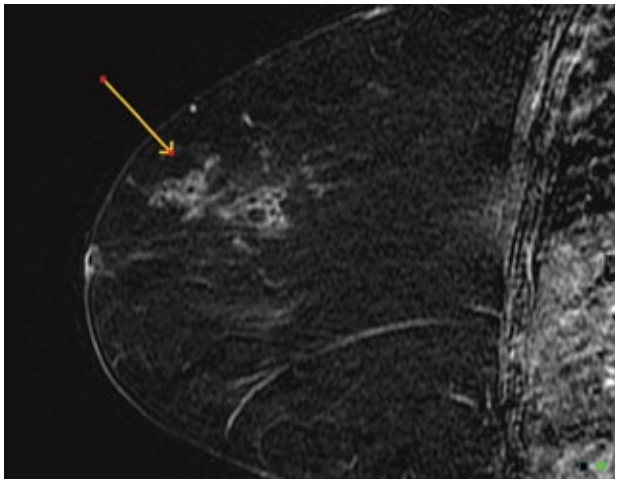

Figure J

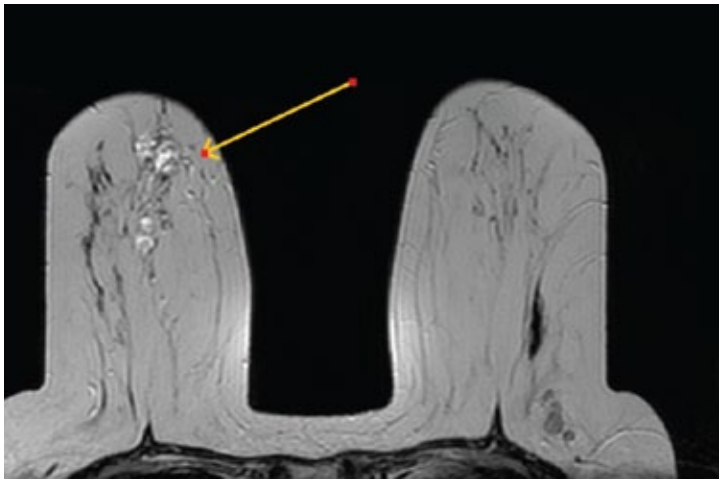

Figure K

ABOVE:

- ***Screening mammogram right MLO view (Figure G) shows upper inner asymmetry***
- ***Screening mammogram right CC view (Figure H) and magnification view (Figure I) show the asymmetry***
- ***Post contrast sagittal MR image with subtraction (Figure J) shows multiple complex cystic areas with enhancing walls. The tram track enhancing complex cystic lesions correlated with mammogram and ultrasound findings.***
- ***Axial T2 weighted MR image of the right breast (Figure K) shows the radially oriented clumped complex cystic areas.***

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- ***Ultrasound (Figure L) shows complex cystic lesion with internal solid projection.***
- ***Ultrasound (Figure M) shows right cluster of solid/complex cystic lesions that were evident at the 11-12 o'clock location***
- ***Pathology: DCIS, low grade. Predominantly cribiform type.***

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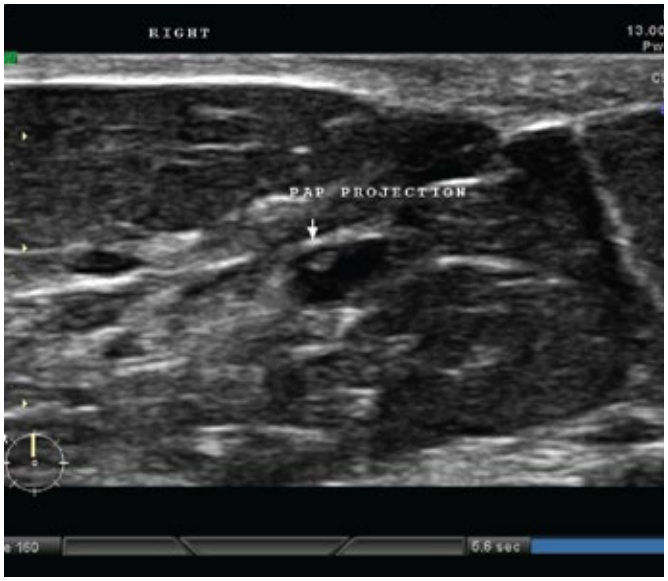

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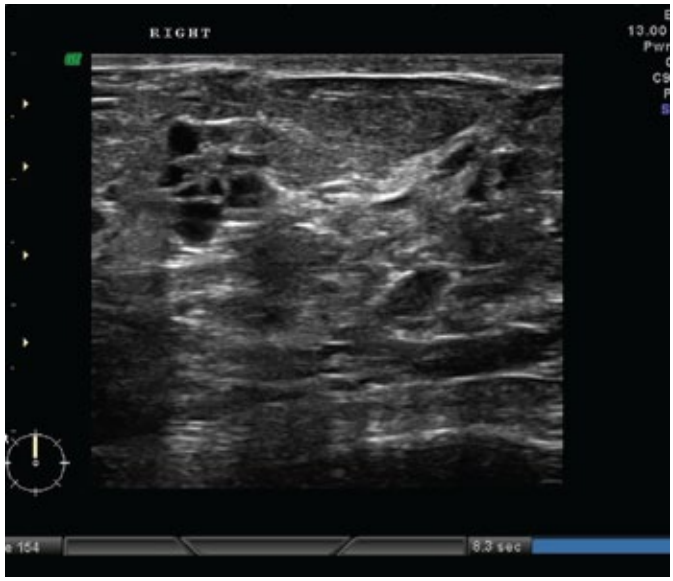

Figure M

RECENT DEVELOPMENTS

What are some recent scientific developments about DCIS?

A great emphasis in recent investigations aims to understand the genetics of DCIS, with the goal of classifying these lesions to predict their biobehavior. A hope is to identify the very low-risk DCIS cohort who could then avoid over-treatment, while recognizing which settings pose higher risk. The following summarizes some of this recent science:

1. When considering DCIS genetics, it is helpful to review what is known first about the genetics of invasive ductal carcinoma (IDCA). Molecular subtyping of invasive breast cancer has identified four subtypes of invasive breast cancer, and they display distinct clinical behavior. Since findings support DCIS as non-obligate precursor to IDCA, it may be possible to classify DCIS based on its molecular subtypes.
    i. Invasive breast cancer shows intrinsic gene signatures that identify subtypes.
        a. The subgroups of IDCA show prognostic significance. A goal has been to identify an immunohistochemical profile that can be used as a surrogate of genetic analysis.
        b. A five-marker panel shows promise in being able to categorize IDCA into molecular subtype.
        c. These subtypes are: estrogen receptor, progesterone receptor, Her2, CK5/6, and EGFR.
        d. However, the clinical behavior of a lesion is more complex than that reflected in the biomarker panel, and additional markers exist, such as P-cadherin. The microenvironment may also influence the behavior.
        e. The goal of a recent study aimed to analyze 16 biomarkers relevant in IDCA and evaluate them in cases of pure DCIS. Each molecular subtype found for IDCA was identified in DCIS, but the frequency differed. For example, triple negative and basal-like phenotype was very uncommon in DCIS. (17)

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2. A recent eloquent review of breast cancer molecular pathology summarized the following (18):
    i. The model of breast cancer progression for ductal lesions is thought to involve progression from flat epithelial atypia, atypical ductal hyperplasia, and DCIS as non-obligate precursors of invasive and metastatic ductal carcinoma.
    ii. The genetics of breast cancer appear to take two distinct molecular genetic pathways that strongly associate with tumor grade.
    iii. Both the epithelial component of the tumor and the tumor's microenvironment undergo molecular alterations at the gene expression level before local tumor invasion.
    iv. The epithelial compartment experiences no major additional genetic expression alterations between preinvasive and invasive breast cancer.
    v. The tumor microenvironment sustains marked epigenetic and genetic expression changes while transitioning from preinvasive to invasive disease.
3. The 2009 NIH State-of-the-Science Conference on the diagnosis and management of DCIS concluded that the disease is highly complex and has many unanswered questions – including the natural history of untreated disease. It was the group's opinion that due to the noninvasive nature and favorable prognosis of DCIS, removing the term "carcinoma" from its descriptor should be strongly considered. The panel noted that outcomes in treated patients are excellent, and focus should turn to accurate identification of patient subsets. These should be based on risk stratification methods, understanding the clinical, pathological, and biological features of the disease. (7,19)

CONCLUSION

***Conclusion:* Current investigations seek to clarify the subsets of DCIS in attempt to tailor optimal treatment. Reviewing the epidemiology, genetics, and pathology of DCIS helps understand the mammographic and MRI appearance of this complex pathology.**

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