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Original article

DCIS and LCIS are confusing and outdated terms. They should be abandoned in favor of ductal intraepithelial neoplasia (DIN) and lobular intraepithelial neoplasia (LIN)

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ABSTRACT

The terms ductal and lobular intraepithelial neoplasia (DIN and LIN) were introduced by Tavossoli 15 years ago, who proposed they should replace, respectively, ductal and lobular carcinoma in situ (DCIS and LCIS). This proposal has been slowly gaining ground. We argue that DCIS and LCIS should now be definitively abandoned. Bringing together 'in situ' and other entities into the simpler and more logical DIN/LIN framework—as has been done with intraepithelial neoplasias of cervix, vagina, vulva, prostate, and pancreas—would eliminate the artificial and illogical distinctions between 'not cancers' (e.g. flat epithelial atypia, atypical ductal hyperplasia—now classified as low grade DIN) and 'cancers' (e.g. DCIS —now considered medium—high grade DIN). Elimination of the term 'carcinoma' from entities that cannot metastasize will reduce confusion among health professionals and patients, and contribute to reducing the risk of overtreatment, as well as reducing adverse psychological reactions in patients.

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Introduction

The term ductal intraepithelial neoplasia (DIN) was introduced by Tavossoli in 1998[1]; lobular intraepithelial neoplasia (LIN) was introduced somewhat later.[2] Tavossoli proposed that these terms should replace, respectively, ductal and lobular carcinoma in situ (DCIS and LCIS), although both DIN and LIN are more extensive and include entities not present within the DCIS and LCIS classifications. This change of name has been slowly gaining ground among pathologists—in our opinion too slowly. Many pathologists see little point in a mere 'change of name'. However, among health professionals involved in the actual treatment of breast diseases, the need to more clearly separate the so-called 'invasive' breast carcinomas from the so-called 'in situ' carcinomas has been apparent for some time. There are several reasons for this. The first is that, unlike 'invasive' breast cancer, neither DIN or LIN metastasize, and women cannot die of these conditions unless they develop into invasive disease.[3,4] Put more forcefully it is illogical to call something 'cancer' which is not cancer. Only a fraction of DIN/LIN cases progress to malignant disease if left untreated. Best estimates are that 14–53% of untreated DCIS/DIN progress to invasive breast cancer over a period of 10 or more years.[5,6] For LIN it has been reported that 20–25% of patients develop invasive breast cancer within 15–20 years of diagnosis.[7] However Tavassoli herself has reported that around 50% LIN of cases develop into invasive disease, although the risk varies with the grade of LIN.[8]

The second reason for a change is that a DCIS diagnosis in particular is challenging and confusing for both health professionals and patients—because of the complexity of the condition[9–14] and because treatment recommendations and the terminology used to communicate the disease contribute to uncertainly.[12] Women with DCIS typically do not fully understand the DCIS diagnosis or its implications[12–15] and this lack of knowledge often gives rise to an unnecessary psychological burden. In fact women with DCIS have been found to experience similar levels of psychological distress to those with invasive breast cancer[11,16] and many are dissatisfied with the information they receive about their diagnosis[17–20]. This confusion is likely to make decisions about treatment more difficult for women.

It is essential that senologists communicate clearly to their patients, explaining that these 'in situ' diagnoses differ from 'invasive' breast cancer. One way of facilitating this communication, and reducing confusion and worry among patients, would be to

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embrace the DIN/LIN terminology, which eliminates the term 'cancer' from conditions which are not cancers. The confusion and worry has become more widespread as the incidence of DIN/LIN have increased in the wake of the initiation and worldwide escalation of screening mammography. It is expected that in the next decade there will be a further increase in the detection of both early breast cancers and DIN/LIN.[4] With earlier diagnosis has come a change in presentation: in the pre-mammography era most DIN were mass producing, visible and high grade; today they are mostly occult and low grade, with consequent reduction in mortality.[21]

In the present paper we summarize the pathological classifications of DIN and LIN in comparison to DCIS and LCIS, and review the controversies surrounding the resistance to the name changes. We then review the confusion surrounding the DCIS and LCIS terminologies among clinicians and patients, and also the psychological effects on women of the DCIS and LCIS diagnoses. We go on to discuss how these conditions should be treated and summarize their biologic characteristics. We conclude by spelling out implications for the current TNM classification and emphasize that DCIS and LCIS should be definitively abandoned in favor of DIN and LIN.

DIN and LIN classifications

The DIN and LIN classifications are illustrated in Tables 1 and 2, respectively, with the traditional DCIS and LCIS classifications given alongside. DIN1A is the new name for the entity flat epithelial atypia, not considered DCIS. Flat epithelial atypias are lesions of breast terminal duct lobular units (TDLU)—site of origin of most ductal and lobular lesions—in which variably dilated acini are lined by one to several layers of usually columnar epithelial cells displaying low grade cytologic atypia. Limited clinical data suggest that the risk of both local recurrence and progression of these lesions to invasive cancer is extremely low.[22]

DIN1B corresponds to the well-known entity atypical ductal hyperplasia (ADH)—a proliferative ductal lesion that shows some but not all the features of low or intermediate grade DCIS. In fact it is difficult to distinguish ADH from low grade DCIS, and this is a major reason why the DCIS/ADH classification is unsatisfactory.[2] Since these two entities are so similar, bringing them together as DIN1B and DIN1C appears logical, although the problem of distinguishing them pathologically still remains. DIN2 corresponds to grade 2 DCIS and DIN3 to grade 3 DCIS.[23]

LIN is characterized by proliferation of loosely cohesive small uniform cells (type A), which distend the TDLU, without surpassing the basal membrane. Sometimes there is pagetoid spread into adjacent ducts. However cells may deviate from this type A appearance by being of larger size and having more prominent nucleoli (type B). The native epithelial cells in the terminal duct lobular units may be completely replaced or just displaced by these neoplastic cells. The degree and filling of distension of the lobules, together with the characteristics of displacing cells, determine the LIN grade. Thus, LIN1 (atypical lobular hyperplasia) is characterized by small round cells that may fill, but do not distend, the lobular lumens and partially or completely replace the normal epithelium of the lobule. LIN2 is characterized by more abundant proliferation of small uniform cells that fill and distend lobules, although lobular outlines remain distinct. In LIN3, the lobules are almost entirely replaced by small cells so that they appear distended and confluent without intervening stroma. In other cases LIN3 is characterized by the presence of large atypical (pleomorphic) cells or signet ring cells.[24]

Table 1
Classification of DIN in comparison with traditional classification.

DIN classification	Traditional classification
Ductal intraepithelial neoplasia grade 1a (DIN1A)	Flat epithelial atypia
Ductal intraepithelial neoplasia grade 1b (DIN1B)	Atypical ductal hyperplasia (ADH)
Ductal intraepithelial neoplasia grade 1c (DIN1C)	Low grade DCIS (DCIS G1) cribriform or micropapillary
Ductal intraepithelial neoplasia grade 2 (DIN2)	Intermediate grade DCIS (DCIS G2) cribriform or micropapillary with necrosis or atypia or other types)
Ductal intraepithelial neoplasia, grade 3, DIN3	High grade (DCIS G3) with or without necrosis

Table 2
Classification of LIN in comparison with traditional classification.

LIN classification	Traditional classification
LIN1	Atypical lobular hyperplasia
LIN2	Classic type LCIS
LIN3	High grade or pleomorphic LCIS

Several classifications of non-invasive breast neoplasms have been proposed, but none has been accepted as standard (mainly because the prognostic significance of the entities defined in all classifications remains unclear). This lack of standardization is problematic when comparing results from studies that use different classifications. Molecular markers hold the promise of improving standardization, but so far most studies have been conducted on small sample numbers.[6] We accept that even the DIN/LIN classifications have disadvantages as well as advantages but feel that the latter outweigh the former. In particular the 'intraepithelial neoplasia' terminology unifies and simplifies the terminology of both ductal and lobular lesions, avoids the term "carcinoma" for lesions that are not invasive and have variable potential to develop into invasive lesions. One disadvantage of the DIN grades is that they suggest the possibility progression from low to high grade and there is only limited biological support for this. For example, one study described the presence of direct transitions between flat epithelial atypia (DIN1A) and low grade DCIS (DIN1C) suggesting that DIN1A may be a stage on a low grade pathway to breast cancer.[25]

Perceptions of 'carcinoma in situ' among physicians and patients

Kennedy et al.[26] assessed perceptions and experiences of DCIS among 296 UK health professionals (mostly surgeons, pathologists and radiologists) involved in the treatment of the condition. They found that respondents had diverse perceptions of the clinical significance of the condition, considered that explaining DCIS to patients was challenging, and used highly variable terminology in their explanations. Although DCIS was generally viewed as a low or medium risk condition, only a small majority of each professional group considered that DCIS was not breast cancer. The authors concluded that their study highlighted substantial diversity in the perceptions and communication of DCIS among health professionals that could have repercussions for the provision of appropriate care, support and information to patients.

Sachey et al.[27] investigated patient perceptions. The used questionnaires to explore long-term health related quality of life (HRQOL), body image, and emotional reactions in 162 women with DCIS treated by various surgical methods (47 had mastectomy and immediate breast reconstruction, 51 had breast-conserving surgery, and 64 had breast-conserving surgery plus radiotherapy). They found that the women had very satisfactory long-term HRQOL. However, body image was negatively affected by mastectomy and breast reconstruction and it was concluded that these

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women needed more preoperative information about the changes in body image they could expect after surgery.

A cross-sectional survey of 144 Australian women diagnosed with DCIS[28] investigated knowledge, satisfaction with information, decisional conflict, and psychological morbidity. Misunderstanding, confusion and a desire for more information were pervasive among the women: About half were worried that their condition might metastasize and half again had uncertainty about decisions in relation to their condition; 12% were anxious, and 2% were depressed. Worry about dying was significantly greater among those who did not know that DCIS could not metastasize; while confusion about metastatic potential was associated with dissatisfaction with information received. The study concluded that good communication about how DCIS differs from 'invasive' breast cancer was essential to alleviating worry and confusion. A focus group study by De Morgan et al.[29] produced more alarming conclusions, finding that women with DCIS were confused about whether or not they had cancer, a confusion compounded by the term 'carcinoma' and by the recommendation of treatments such as mastectomy. The confusion was not alleviated by appropriate information, and most women reported dissatisfaction with the information they received about DCIS. Overall the study found that a DCIS diagnosis had a significant psychological impact. It is noteworthy that because of the problems associated with communicating a DCIS diagnosis, De Morgan's group felt it necessary to develop a specific aid for communicating the DCIS diagnosis.

Clearly the uncertainly about the natural history of DCIS (see below) complicates decision-making for both patients and doctors. Furthermore, studies indicate that doctors fear communicating uncertainly to patients not only because it will increase patient anxiety, but also because it may undermine patient trust, or that patients will perceive the doctor as inadequate.[30–33] These attitudes should be considered alongside the experience of an articulate woman with DCIS: "My discussions with doctors were … an exercise in frustration. I was … [told in the same meeting] … that I [had] cancer and I [did not] have cancer… the cryptic, garbled, and sometimes alarmist information that I got from my doctors was not good enough to make decisions about treatments or to make peace with myself."[34]

Diagnosis and treatment

LIN almost never produces clinical signs and is not diagnosed by instrumental examination. It is discovered in biopsies (usually core biopsy) or incidentally, typically after plastic reduction. There is considerable controversy regarding the management of LIN, irrespective of the circumstances in which it is diagnosed. When found on a core biopsy there is the possibility that malignancy is also present. Thus, a recent study which retrospectively assessed a large series of core biopsies diagnosed as LCIS or atypical lobular hyperplasia, found that, of the 71% of cases that underwent surgical excision, 13% had malignancy.[35] The policy at out Institute regarding LIN on core biopsy is that if there is clinical or instrumental suspicion of malignancy, surgical excision should be performed. Other authors tend to 'watch carefully'.[36]

In the situation where LIN (only) is found at a surgical margin, radicalization is not usually performed and radiotherapy is not recommended (unless there is concomitant malignancy or DIN). In fact, the presence of LIN at surgical margins is frequently not even noted in pathology reports. However these 'minimal' approaches to LIN are complicated by uncertainty regarding the biological significance of the disease. Although LIN is considered to be a risk factor—not a precursor—of breast malignancy, LIN and lobular carcinoma may have molecular biological features in common and some data suggest genetic progression of LIN to lobular carcinoma.

LIN is frequently over-treated by mastectomy. Even prophylactic contralateral mastectomy is recommended in some cases.[37] We suggest that further treatment for LIN should depend on factors such as family history or genetic risk. It might be worth considering pharmaco-preventive agents before recommending prophylactic surgery in genetically pre-disposed patients.

In contrast to LIN, DIN is usually detected as microcalcifications at mammography or more rarely by ultrasound. Magnetic resonance imaging (MRI) is not used for the routine diagnosis of DIN as the false-positive rate is high, but MRI may be useful for identifying diffusely distributed DIN lesions.[38] The treatment for DIN is somewhat less controversial than for LIN. Clinical trials[39–42] demonstrate that conservative breast surgery, flanked by hormonotherapy in receptor-positive patients, is effective; and that radiotherapy (RT) reduces the risk of recurrence, but does not increase overall survival. The 2011 San Gallen consensus conference recommended RT after complete excision of DIN, but accepted that RT may not be necessary in elderly patients and those with low grade low risk DIN.[43] There are few data on the use of partial breast irradiation in DIN.[44]

The Van Nuys Prognostic Index (VNPI) has been proposed to predict the risk of invasive recurrence in DIN. Lesions with low VNPI scores may be suitable for excision without RT, while high scores may require mastectomy.[45] However it is unclear whether the three factors used to define the VNPI score (histological type, width of surgical margin and lesion size) are the most important in determining outcome. In particular, age and family history may be more important influences on risk of recurrence, so individualized assessment may be preferable to VNPI. Clearly it would be useful have biomarkers able to reliably predict outcomes for this condition and select the most appropriate treatment.

Oncoplastic surgery has enlarged the indications for conservative treatment, permitting wider resections and good cosmetic results. As regards mastectomy, the only indications are for multicentric or extensive DIN, or when the breast is too small to permit conservative treatment with an acceptable cosmetic result: in that latter case immediate reconstruction is mandatory.[46]

As regards axillary dissection, this should never be performed for DIN since by definition DIN cannot metastasize. Similarly, sentinel node biopsy is not usually required for DIN, although may be indicated for very large lesions and in patients scheduled for mastectomy, when the presence of malignant disease is suspected. In the rare cases of a DIN patient having a positive sentinel node, axillary dissection should not be performed unless subsequent pathological investigation identifies 'invasive' disease in the specimen.[47]

Biomarkers

At the very least DIN and LIN are markers of increased risk of developing breast malignancy. And in both conditions, the higher the grade the greater the probability of malignant recurrence. It would be very useful therefore if biomarkers able to divide these neoplasias into forms at high and low risk of development to malignant disease were available, so that treatments could be tailored accordingly. Such markers would improve the classification of these entities as well as our understanding of their relation to malignant disease.

The main biomarkers investigated in DIN/LIN are those commonly studied for their ability to predict treatment response and prognosis in malignant breast disease. Not only hormonal receptors and HER2, but also markers of cell proliferation, cell cycle regulation, extracellular molecules, and factors involved in extracellular matrix degradation and angiogenesis have been investigated.[6] Overall results from the such studies indicate many parallels

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between LIN/DIN and malignant breast disease.[6] However the value of these markers in DIN prognosis is controversial.[48]

Conclusions

The DIN/LIN classification of intraepithelial neoplasias of the breast is neither perfect nor definitive. However we hope we have shown that abandoning the DCIS/LCIS terminology, and bringing together 'in situ' and other entities into the simpler and more logical DIN/LIN framework as has been done for intraepithelial neoplasias of cervix, vagina, vulva, prostate, and pancreas[2] has a number of important advantages. Firstly it eliminates the artificial and illogical distinctions between, on the one hand, flat epithelial atypia and ADH (not cancers) and DCIS ('cancer'); and also between atypical lobular hyperplasia (not cancer) and LCIS ('cancer'). Furthermore, elimination of the term 'carcinoma' will reduce confusion among health professionals and patients, hopefully reducing the risk of overtreatment, and—not less important—reducing adverse and psychological reactions among patients.

Finally we note that the DIN/LIN classifications have consequences for the current TNM classification. As these neoplasias do not metastasize, the categories N and M do not apply and DIN and LIN should therefore be excluded from the TNM, so the pTis categories would be eliminated.[49]

Conflict of interest statement

The Authors attest that they have herein disclosed any and financial or other relationships which could be construed as a conflict of interests.

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