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REVIEW ARTICLE

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Ductal intraepithelial neoplasia of the breast

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Two to three decades ago, a majority of breast carcinomas were invasive at the time of detection. Among the relatively uncommon in situ carcinomas, a majority presented as palpable masses that were predominantly a morphologically high-grade ductal in situ carcinoma (DCIS). The definition of in situ carcinoma emphasized the absence of stromal invasion, indicating that the major diagnostic issue was separation of an invasive from a generally florid, high-grade in situ carcinoma. Simple mastectomy was the accepted treatment for in situ carcinomas, whether ductal or lobular in type.

With the widespread use of screening mammography in the United States, a dramatic change has occurred in the frequency, management, and types of DCIS detected. Contrary to the palpable in situ carcinomas of the yesteryears, the mammographically detected lesions are invisible to the naked eye. The proportion of breast carcinomas diagnosed as DCIS increased from 2.8% in 1973 to 14.4% in 1995 [3]. While close to 90% of premammography DCIS were of the high-grade comedo type, nearly 60% of mammographically detected lesions are non-comedo, and this percentage is increasing. Relative to the premammographic era (prior to the 1980s) when mastectomy was the treatment of choice, a drastic change has occurred in the management of women with DCIS. Of the 28,958 women with DCIS diagnosed in 1995, 37.2% were treated by means of mastectomy, 30.6% had lumpectomy with radiation therapy, 30.4% had lumpectomy without radiation therapy, and another 1.8% received no further therapy following excisional biopsy [3]. The type of therapy for a woman with DCIS is often geographically influenced rather than dictated purely on the basis of morphology, extent, or both. Screening mammography has resulted not only in an increased incidence of DCIS and the proportion of low-grade DCIS but also an increase in the number of younger women with DCIS encountered in our practice as consultant pathologists at the Armed Forces Institute of Pathology (AFIP).

Interestingly, despite the more limited surgical excisions, mortality from "DCIS" has declined. While 3.4% of women with a diagnosis of DCIS diagnosed between 1978 and 1983 (premammographic era) died of breast cancer within 10 years – even though a majority of these women had mastectomy for treatment of their lesion – only 1.9% of women diagnosed with DCIS between 1984 and 1989 died of breast cancer within 10 years, despite the increasing trend toward lumpectomy [3]. Judging from the 10-year follow-up period currently available for these women, it appears as if "DCIS per se is not a life threatening disease" [3]. The deaths that do occur are probably related to an undetected invasive carcinoma present at the time of the initial diagnosis of DCIS, progression of residual, incompletely excised DCIS to invasive carcinoma, or development of a de novo invasive carcinoma elsewhere in the breast [3].

Mammography has also increased detection of a variety of other proliferative lesions within the duct system that can be confused with the non-necrotic variants of in situ ductal carcinoma. As a result, morphologic definitions have had to refocus on defining the lowest threshold for a diagnosis of DCIS or lobular in situ carcinoma (LCIS). These definitions, based mainly on data from premammographic biopsies, resulted in categorization of intraductal proliferations into intraductal hyperplasia (IDH), atypical intraductal hyperplasia (AIDH), and DCIS.

Initially, even cases of florid ordinary IDH were designated as AIDH [20]. As such, AIDH was not found to be associated with an increased risk for subsequent development of invasive carcinoma. Subsequently, IDH

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was separated from AIDH based on cytologic features, while AIDH was separated from low-grade DCIS based purely on quantity [22, 29]. Based on this classification system, it was proposed that the relative risk (RR) for subsequent development of invasive carcinoma associated with a diagnosis of IDH and AIDH is 1.9 (mild) and 5.3 (moderate) times that of women with non-proliferative lesions, respectively [2], in comparison with a RR of 11 times for DCIS [21]. A second study compared the absolute risk for subsequent development of invasive carcinoma among 117 women with IDH and 82 with AIDH. The absolute risk for subsequent development of invasive carcinoma among 117 women with IDH was 2.6% compared with an absolute risk of 9.8% for the 82 women with AIDH. Furthermore, the average interval to the subsequent development of invasive carcinoma was over 14.3 years for women with IDH compared with 8.3 years for those with AIDH. Two slightly different criteria proposed by two groups basically promoted application of an arbitrary quantitative criterion to separate morphologically identical lesions into atypical hyperplasia and carcinoma in situ [22, 29]. Since mastectomy was the treatment of choice for DCIS regardless of its quantity or extent, the concept of AIDH was promoted by one group mainly to prevent mastectomy for lesions that were morphologically identical to low-grade DCIS but 2 mm or less in size [29].

Unfortunately, significant inter-observer variability is noted when intraductal proliferations are classified into IDH, AIDH, and DCIS even when experts in breast pathology use the same set of criteria [25, 26]. The discrepancy is even much wider when community and academic surgical pathologists review these lesions [23]. The problem of inter-observer variability in separating AIDH from low-grade DCIS has persisted judging from the large number of such cases sent to us for consultation and despite frequent courses and numerous papers addressing the diagnostic criteria. Multiple studies that claim to have used the criteria of Page et al. for assessment of RR of subsequent development of invasive breast carcinoma among women with AIDH have come up with drastically different RR figures [1, 10, 11, 12, 24]. These figures range from a low of 2.4 (much closer to the RR of 1.9 associated with IDH) to a high of 13, which is even higher than the RR of 8–10 and 11 suggested for DCIS [2, 6], attesting to the futility of this attempt. In effect, the same lesion may be designated as a cancer (DCIS) by one pathologist but a non-cancer (AIDH or IDH) by another. Depending on what it is called, the patient may have re-excision, radiation therapy, and even mastectomy or may simply enter a life-long follow-up regimen. This inter-observer variability would impact cancer statistics and any data and study that includes low-grade DCIS or AIDH, not to mention the psychological impact on patients who may be told they have cancer by one reviewer and hyperplasia by another or vice versa.

The increasing sophistication of detection techniques has resulted in identification of a large number of the various types of intraductal epithelial proliferations other than DCIS. Meanwhile, the difficulty in obtaining reasonable inter-observer agreement on whether a lesion is cancer (albeit in situ) or simply a variant of hyperplasia has persisted. Because of these difficulties and their consequences, we have proposed a shift in paradigm from a division of intraductal proliferations into basically cancer and non-cancer to the consideration that all of these proliferations are intraepithelial neoplasias that constitute risk factors, albeit of variable magnitude, for subsequent development of invasive carcinoma [27, 28]. In a similar context, the term “lobular neoplasia” was first introduced by Haagensen for the spectrum of atypical, loosely cohesive, uniform small epithelial cells proliferating in a solid occlusive fashion within the lobules, with or without a pagetoid extension into the adjacent terminal duct [7]. At AFIP, we immediately accepted Haagensen’s terminology and started using it routinely since the publication of Haagensen’s classic paper in 1978 [7]. Application of the same concept for ductal type proliferations in the breast was not even considered at the time due to the far more heterogeneous nature of the intraductal proliferations. Indeed, the two slightly different criteria proposed for intraductal proliferations in 1985 [22] and 1990 [29] subdivided the ductal-type proliferations into IDH, AIDH, and DCIS. The latter [29], in particular, emphasized cytologic atypia as the feature that separates AIDH from IDH, while it was the presence of cytologic atypia identical to that observed in low-grade DCIS that linked AIDH to low-grade DCIS. Composed of the same cell population, in effect, AIDH was simply a smaller or quantitatively more limited version of low-grade DCIS.

Having been the principal investigator for one of those studies, our main aim in using the term AIDH was to prevent mastectomy for those minuscule lesions that were defined arbitrarily as 2 mm or less in maximum dimension, even though qualitatively they were identical to low-grade DCIS [29]. Subsequently, Rosai proposed the designation of mammary intraepithelial neoplasia when he noted significant inter-observer variability in the interpretation of borderline mammary intraductal proliferations [25]. Due to the heterogeneity of the morphologic phenotypes of ductal intraepithelial proliferations, acceptance of the concept of ductal intraepithelial neoplasia (DIN) was more difficult without further exploration and information.

With increasing support from molecular studies [8, 15, 16], we recently suggested the designation of DIN and offered a translational table for conversion of the currently used terminology [27, 28]. In effect, we have restricted the term “carcinoma” to lesions that have invaded the stroma. Neoplasia is defined simply as a proliferation that serves no physiologic function. In the DIN system (Table 1), basically high-grade DCIS has become grade 3 DIN (Fig. 1). Furthermore, grade two DCIS becomes grade 2 DIN (Fig. 2), grade 1 DCIS and AIDH are grouped together as DIN1c (Fig. 3). Finally, flat epithelial atypia without intraluminal proliferation is designated as DIN1b (Fig. 4), while IDH is designated DIN1a

Table 1 Current ductal intraepithelial neoplasia (DIN). Special types include non-comedo apocrine and clear cell phenotypes. References: [27, 28]. *IDH* intraductal hyperplasia; *AIDH* atypical intraductal hyperplasia; *DCIS* ductal carcinoma in situ; *crib* cribriform; *micropap* micropapillary

Proposed DIN classification		Current designation	Pleomorphic nuclear atypia	Necrosis	Re-excision, if margin is +
DIN1a		IDH	– or +	No	No
DIN1b		AIDH, flat monomorphous type	–[a]	–	?/No
DIN1c[b]	≤2 mm	AIDH			Yes
	>2 mm	DCIS, grade 1 (crib/micropap)	–[a]	–	Yes
DIN2[b]		DCIS, grade 2	–	+	Yes
		(Crib/micropap + necrosis or atypia)	+ (+)	+	
		Special types, specify			
DIN3[b]		DCIS, grade 3	+++	+++	Yes
		(Anaplastic DCIS, +/– necrosis)	+++	–	

[a] No significant pleomorphic nuclear atypia is present, although at least a minor degree of atypia is assumed in all DCIS (and AIDH) proliferations

[b] Specify precisely in millimeters

Table 2 Initial ductal intraepithelial neoplasia (DIN) proposal. References: [27, 28]. *IDH* intraductal hyperplasia; *AIDH* atypical intraductal hyperplasia; *DCIS* ductal carcinoma in situ; *crib* cribriform; *micropap* micropapillary

Proposed DIN classification	Current designation	Pleomorphic nuclear atypia	Necrosis	Re-excision, if margin is +
DIN1a	IDH	–	– or +	No
DIN1b	AIDH, flat monomorphous AIDH	–[a]	–	No
DIN1c	AIDH, extensive[b] DCIS, grade 1 (crib/micropap)	–[a]	–	Yes
DIN2	DCIS, grade 2	–	+	Yes
	(Crib/micropap + necrosis or atypia)	+ (+)	+	
DIN3	DCIS, Grade 3	+++	+++	Yes
	(Anaplastic DCIS, +/– necrosis)	+++	–	

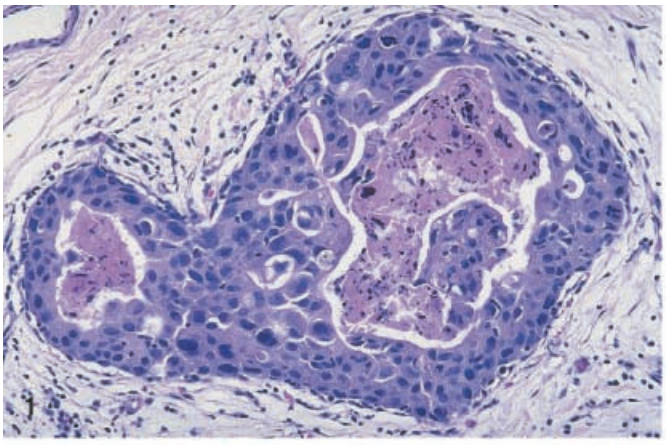
[a] No significant pleomorphic nuclear atypia is present, although at least a minor degree of atypia is assumed in all DCIS (and AIDH) proliferations.

[b] Extensive AIDH equals partial involvement by cribriform or micropapillary in >20 duct cross sections or similar involvement distributed over 1.5 cm

(Fig. 5). One important advantage of the DIN terminology is that it incorporates into the system a variety of flat lesions that simply show replacement of the native epithelial cell layer by a single layer of mildly (monomorphous) to severely atypical (polymorphous) cells with or without necrosis. These flat lesions are often missed because of the absence of intraluminal hyperplasia.

Initially, separation of AIDH and low-grade DCIS was retained to help with the adjustment to the DIN system from the IDH, AIDH, DCIS classification (Table 2). With the increasing application and understanding of the DIN classification, coupled with the molecular findings supporting the similarities between AIDH and low-grade DCIS, the system was further simplified. This was accomplished by combining AIDH with low-grade DCIS (DIN1c) and requiring quantification of the extent/size of the lesions as a totally separate parameter. The quantity is included in parenthesis next to the diagnosis. Although cytologically identical to low-grade DCIS and unequivocally proven to be very similar to adjacent well-differentiated in situ or invasive carcinomas at the molecular level [14], the flat (monomorphous) epithelial atypia remains in the DIN1b category until we learn more about its clinical implications. In the simplified current version (Table 1), once the cytologic features of low-grade DCIS are identified either partially or completely involving a duct, it is designated as DIN1c whether it is 1, 2, or 10 mm. The size or extent (quantity) of the lesion is added in parenthesis next to the diagnosis. Quantification is absolutely necessary to direct management of the patient. Regardless of its quantity, the presence of DIN1c at the margin or within 2 mm of the margin requires re-excision in my opinion. Its presence in a core biopsy would require an excisional biopsy as well. This is the best way to ascertain complete excision and precise determination of the actual size/extent of the lesion.

Once a localized DIN1c of up to 2 mm (AIDH) is completely excised with an approximate 2-mm margin, either no further therapy or tamoxifen therapy may be all that the patient would require. This approach may eventually be extended to the management of completely excised, margin clear (>2 mm from margin) DIN1c lesions that are up to 5 mm in size/extent. Our proposals are based on reviewing a tremendous number and a wide range of variations possible among ductal intraepithelial proliferations. Over 1000 DIN lesions are reviewed annually in the Gynecology and Breast Pathology Department of AFIP.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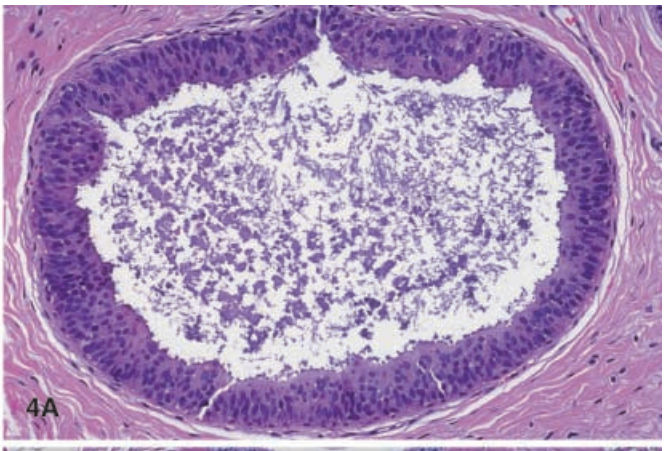
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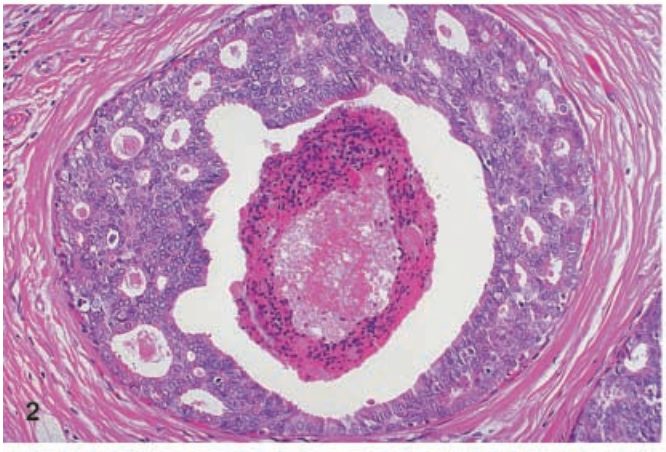
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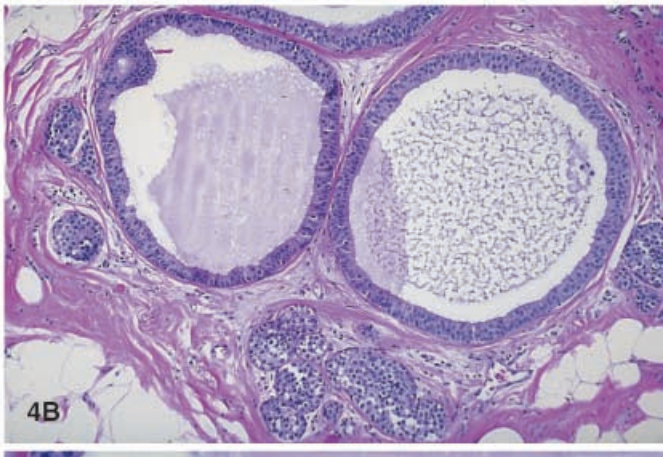
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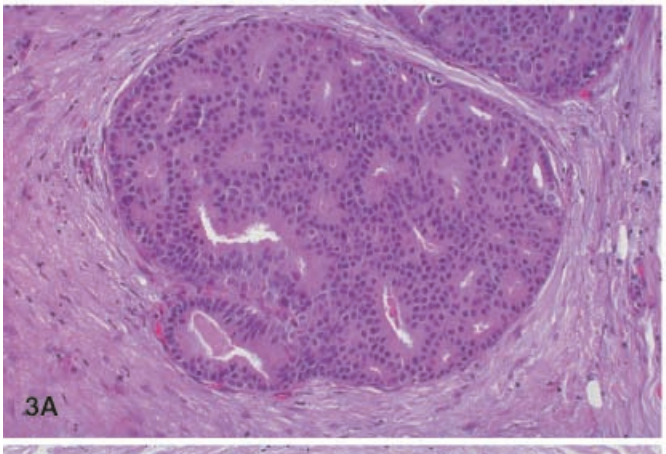
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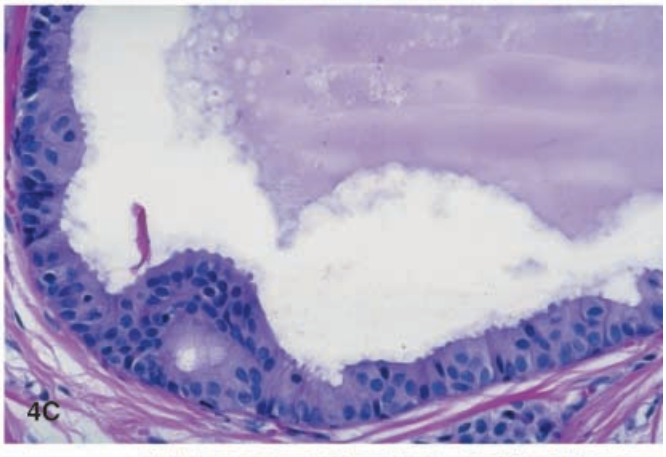
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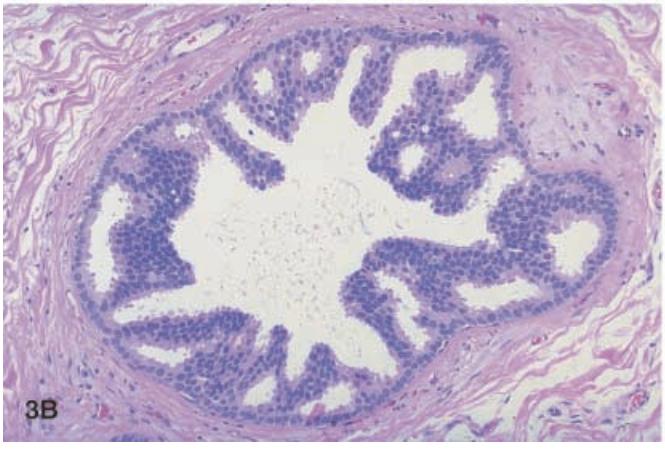
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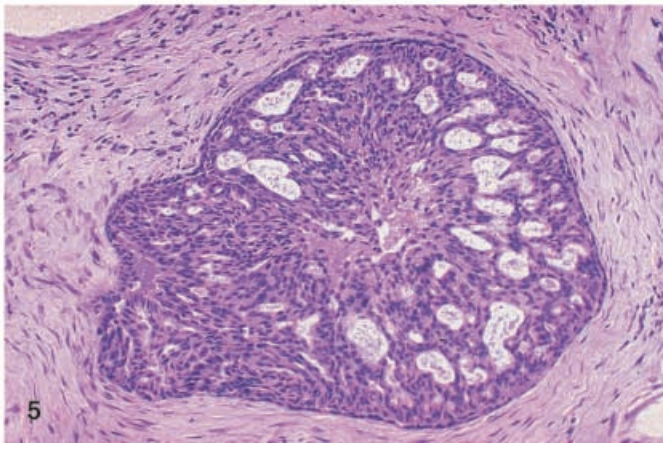
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Basically, we have accepted that AIDH is a smaller version or a more limited quantity of low-grade DCIS. By providing the size of the lesion, we allow for management that might vary based on lesion size since smaller lesions may not and often do not have the same clinical implications as larger ones. There is no need to use different terms merely because of differences in lesion size. It is well accepted that a small invasive breast carcinoma does not behave the same as a larger invasive carcinoma. Nonetheless, a 3-mm invasive breast carcinoma without axillary node metastases is given the same designation as a 2.5-cm invasive carcinoma with axillary node metastases.

It is important to note that DIN does not necessarily imply a continuous progression from one grade to the next. Even based on purely morphologic features, there is not good evidence to support progression from lower-grade DIN1a (IDH) to the higher-grade lesions (DIN 3 or high-grade DCIS) through intermediate grades of DIN1c or DIN2 (low- or intermediate-grade DCIS, respectively). While any of these lesions has the potential to progress to an invasive carcinoma, none necessarily reflects an obligate precursor of invasive carcinoma with the highly probable exception of DIN 3 (high-grade DCIS). There is not even sufficient evidence that low-grade DCIS would always progress to high-grade DCIS. There is not enough information concerning DIN2 (intermediate-grade DCIS) on this issue. A proportion of these intraepithelial neoplasias, the precise quantity of which has not been established, does appear to progress from a lower grade to higher grades based on the finding of various stages in the same biopsy and identification of shared molecular features among the high- and low-grade lesions. Progression is most readily recognizable in the case of flat DIN1b advancing to DIN1c through development of epithelial tufts and bridges, and DIN1c advancing to DIN2 through development of either focal intraluminal necrosis or focal moderate nuclear pleomorphism. When high- and low-grade DIN are present in different ducts within the same biopsy, it is possible and more likely that they reflect two completely separate and unrelated clones. When low- and high-grade cells are present in the same duct with transition through intermediate grade cells, however, the likelihood of progression must be considered. Nonetheless, such progression probably occurs in a relatively small proportion of cases. Most low-grade intraepithelial lesions remain low grade on recurrence and develop into a low-grade invasive carcinoma when they invade, while the high-grade lesions remain high grade [13].

Unlike some who may prefer a two-grade system (low- and high-grade), I strongly believe that an intermediate grade is necessary. We place all unusual variants of DCIS that lack high-grade nuclear features with or without necrosis into the intermediate category of DIN2 and specify the subtype (i.e., non-comedo apocrine, clear-cell, spindle-cell, etc.). More frequently, DIN2 consists of cribriform or micropapillary DCIS with either mild to moderate nuclear atypia, necrosis, or a small amount of both. It may be true that the present clinical studies on DCIS have failed to note significant distinctions in outcome between low-grade and intermediate or intermediate and high-grade lesions depending on how these cases have been classified and the number of cases in each category. Since the approach to management of these tumors is basically similar (excision with or without radiotherapy), we may not see any differences in the outcome. This does not imply that they would not respond differently once the optimal treatment for those subtypes is recognized. For example, apocrine DCIS generally lacks estrogen receptors and progesterone receptors, but it does have androgen receptor immunoexpression [30]. It is incredible that this important information is not being further explored in the management of women with apocrine lesions. If clinicians continue to ignore such information and require a simplistic approach to management based on low- or high-nuclear grade, then a lot of potentially significant information would become irrelevant.

The advantages of the DIN classification are as follows:

1. It diminishes the impact of having two drastically different designations of cancer and non-cancer applied to the same lesion by different observers.
2. It incorporates the flat epithelial atypias (so-called monomorphous “clinging carcinoma”) that have been proven to have molecular alterations similar to those of cells in low-grade DCIS and tubular carcinoma in the classification system as DIN1b, while the high-grade polymorphous flat lesions are categorized as DIN3. These lesions are often totally overlooked because they lack intraluminal hyperplasia.
3. It allows for management approaches that may vary based on the size of either the low- or higher-grade lesions.

◀ **Fig. 1** Ductal intraepithelial neoplasia, grade 3 (DIN3=grade 3 ductal in situ carcinoma). High-grade nuclei, with or without necrosis, are the hallmark of high-grade DIN

Fig. 2 Ductal intraepithelial neoplasia, grade 2 (DIN2=grade 2 ductal in situ carcinoma). The most common DIN2 is characterized by a cribriform proliferation of uniform, low nuclear-grade cells with intraluminal necrosis.

Fig. 3 **A** Ductal intraepithelial neoplasia 1c (DIN1c), cribriform type. **A** Cribriform proliferation of uniform, low nuclear-grade cells is the most common phenotype of DIN1c. This lesion involved multiple adjacent ducts measuring 7 mm in extent (low grade DCIS). **B** DIN1c, <1 mm [atypical intraductal hyperplasia (AIDH)]

Fig. 4 DIN1b (flat epithelial atypia). **A** The native epithelial cell layer is replaced by a flat proliferation of stratified spindle cells. **B**, **C** A rare focus of epithelial tufting, arcading, or mounding is acceptable in this category

Fig. 5 DIN1a [intraductal hyperplasia (IDH)]. Despite the abundant epithelial proliferation, the lack of morphologically apparent (cytologic) atypia of the type characterized by uniform cells with round to ovoid nuclei and subtle increased nuclear/cytoplasmic ratio qualifies this lesion as the lowest level risk for subsequent development of invasive carcinoma

4. It diminishes the anxiety and emotional stress associated with a diagnosis of cancer for the patient and her family, while allowing for an individualized approach to managing the disease.
5. It eliminates the term cancer and the likelihood of mastectomy – a possibility that persists due to geographic variations in practice standards even for small low-grade DCIS.
6. Modifications can be made easily as we learn more about distinctive subgroups within the system.

The intent of the DIN system is not to improve inter-observer agreement but, rather, to diminish the (clinical) impact of drastically different designations (cancer and non-cancer) used for the same lesion. Since both AIDH and low-grade DCIS have now been incorporated into DIN1c, this classification most probably will also improve inter-observer agreement since it has eliminated a major source of inter-observer variability.

Given the observed trend toward decreasing mortality from DCIS and continuous advances in imaging technology, it is quite likely that mortality from DCIS will be even further reduced from its already low rate of 1.9% at 10 years [3]. It is, therefore, important to replace the ominous designation of cancer by a term that is scientifically appropriate and allows for management of the lesion according to its severity and extent. DIN fulfills these requirements.

The focus should be removed from efforts at separating AIDH from low-grade DCIS and placed on an optimal surgical approach for as complete an excision of DCIS as possible. Incomplete excision or residual disease is probably a major reason for recurrence (observed in 5–25% of patients) and eventual progression of DCIS. The residual disease may be simply in the form of flat epithelial atypia (DIN1b) that lacks intraluminal hyperplasia, an alteration that is currently often overlooked whether present at the margin or elsewhere in the biopsy. Determination of why DCIS recurs could help us determine how it should be treated. Based on the finding of similar molecular alterations [loss of heterozygosity (LOH)] in the primary and recurrent DCIS with acquisition of additional molecular changes in the recurrent DCIS, a recent study from our lab concluded that, with occasional exceptions, recurrent DCIS is generally due to residual disease that progresses [9]. In a similar study, but using comparative genomic hybridization (CGH), it was confirmed that recurrent DCIS is clonally related to the primary lesion in most cases [31]. By no means should this be taken as implying that residual disease is the only reason for recurrence, because one cannot fully exclude the possibility of de novo disease developing in response to the same factors that induced the initial DCIS lesion. While the number of cases in both studies was small, we feel that efforts should focus on approaches that would ascertain complete excision of the disease, taking into consideration the route of progression of the disease from the terminal duct lobular unit (TDLU) toward the nipple.

A superb approach to excision and subsequent tissue processing suggested in separate studies by Ohtake et al. [17, 18] and Ohuchi et al. [19] should be explored and widely disseminated. Some have suggested removing a 1-cm margin from around the entire region of “DCIS”. A DCIS that has already filled a TDLU can progress within the duct system in the form of an intraepithelial neoplasm only by extension toward the larger ducts and eventually toward the nipple. Therefore, the ascertainment of the absence of disease along this route of progression should be of greatest concern. The optimal management of DCIS should consider its route of natural progression, focus on the means of arriving at an accurate estimation of the extent of disease, and require orientation of the excised sample in a way that would facilitate determination of the distribution of the lesion within the sample. Interdisciplinary communication on this issue should be increased.

Technologic advances could basically eradicate some of our current dilemmas in detection, diagnosis, and management of DCIS. Radiation therapy has significantly reduced the chances of local recurrence following lumpectomy [4]. It also appears that Tamoxifen therapy may contribute to reducing the likelihood of local recurrence [5]. In fact, Tamoxifen may be all that is necessary for the of management of smaller DIN1c lesions. As part of a better future, we could possibly envision “ductectomy” as the future “gold standard” in treatment of intraepithelial neoplasias. Ablation of the DIN-containing portion, segment, or the entire duct system after age 40 years could not only eliminate the DIN but would prevent any subsequent invasive carcinoma. While moving toward that goal, the widespread utilization of the DIN classification system could significantly diminish the level of anxiety experienced by:

1. Pathologists trying to decide whether a lesion is DCIS (cancer) or AIDH (non-cancer)
2. Surgeons whose decision to re-excise on the basis of a diagnosis of DCIS could be questioned when the patient’s biopsy is re-examined at another center and diagnosed as AIDH
3. Increasingly younger women who are diagnosed as having in situ cancer on their breast biopsies

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