

# Current management of lesions associated with an increased risk of breast cancer

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**Abstract** | High-risk breast lesions, which comprise benign lesions and *in situ* carcinomas (lobular carcinoma *in situ* and ductal carcinoma *in situ*), are clinically, morphologically, and biologically heterogeneous and are associated with an increased risk of invasive breast cancer development, albeit to varying degrees. Recognition and proactive management of such lesions can help to prevent progression to invasive disease, and might, therefore, reduce breast cancer incidence, morbidity, and mortality. However, this opportunity comes with the possibility of overdiagnosis and overtreatment, necessitating risk-based intervention. Notably, despite the progress in defining the molecular changes associated with carcinogenesis, alterations identifying the individuals with high-risk lesions that will progress to invasive carcinoma remain to be identified. Thus, until reproducible clinicopathological or molecular features predicting an individual's risk of breast cancer are found, management strategies must be defined by population-level risks as determined by models such as the Gail or IBIS models, as well as patient attitudes toward the risks and benefits of interventions. Herein, we review the contemporary approaches to diagnosis and management of high-risk breast lesions. Progress in this area will ultimately be dependent on the ability to individualize risk prediction through better definition of the key drivers in the carcinogenic process.

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## Introduction

High-risk lesions of the breast represent a clinically, morphologically, and biologically heterogeneous group of lesions associated with an elevated risk of breast cancer, albeit to varying levels. In a seminal study, Dupont and Page<sup>1</sup> reviewed over 3,000 benign breast biopsies and categorized lesions as nonproliferative, proliferative without atypia, or atypical hyperplasia; atypical hyperplasias were the only benign lesions associated with a substantially elevated risk of breast cancer development (5.3-fold increased risk).<sup>1</sup> By contrast, nonproliferative disease was associated with no increase in the risk of breast cancer, and proliferative disease without atypia with a small, 1.9-fold increase in risk of this disease.<sup>1</sup> This classification scheme was endorsed by a 1985 consensus conference of the College of American Pathologists, and subsequently updated in 1998.<sup>2</sup>

Since the initial report by Dupont and Page,<sup>1</sup> other investigators have confirmed these findings in large patient cohorts,<sup>3–5</sup> and have extended our knowledge regarding the degree of breast cancer risk associated with atypical breast lesions. Atypical hyperplasias, which include atypical ductal hyperplasia (ADH) and atypical lobular hyperplasia (ALH), are diagnosed more frequently in the current era of mammographic screening than before the widespread introduction of this modality. In the study by Dupont and Page,<sup>1</sup> which evaluated

breast biopsies performed in the pre-mammographic era for palpable lesions, only 3.6% of the biopsy specimens showed atypia. By contrast, atypical hyperplasia is detected in 12–17% of biopsies performed for mammographic microcalcifications.<sup>6</sup> More recently, an additional type of atypical lesion, flat epithelial atypia (FEA), has been described, although the level of breast cancer risk conveyed by this lesion is uncertain at present, as discussed in a later section.

In addition to ADH and ALH, there are two forms of breast carcinoma *in situ* that are recognized to increase the risk of later invasive breast carcinoma development: lobular carcinoma *in situ* (LCIS) and ductal carcinoma *in situ* (DCIS). These lesions differ from the breast atypias in that both were initially considered to be early, favourable forms of carcinoma, rather than merely breast cancer risk factors. DCIS continues to be regarded as a nonobligate precursor lesion to invasive breast cancer, and is managed in a different fashion from LCIS, which is most often considered to be a marker of a generalized increase in breast cancer risk, as are the atypical hyperplasias.

Accurate assessment of the risk of breast cancer development associated with benign lesions, LCIS, and DCIS has become more clinically relevant with the improved availability of advanced imaging technologies to screen women at increased risk of the disease, and with the approval of drugs for breast cancer risk reduction. However, the inability to identify clinicopathological or molecular predictors of which high-risk lesions

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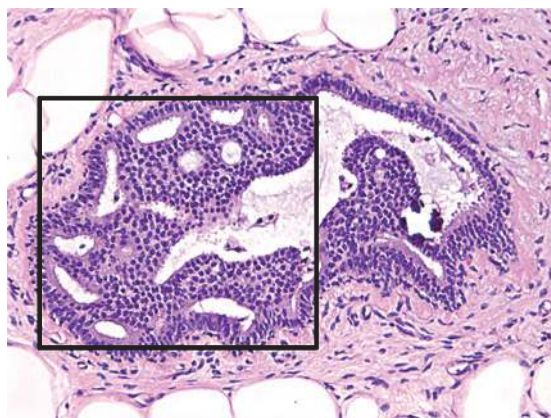
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## Competing interests

The authors declare no competing interests.

**Key points**

- Atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH), lobular carcinoma *in situ* (LCIS), and ductal carcinoma *in situ* (DCIS) are high-risk breast lesions; flat epithelial atypia (FEA) has an uncertain risk level
- ADH or ALH, and LCIS are associated with relative risk of breast cancer development, in either breast, of approximately 4 and 10, respectively
- The degree of risk associated with ALH, ADH, and LCIS is sufficient to justify a discussion of chemoprevention in healthy women, particularly those who are premenopausal at diagnosis
- DCIS is considered a precursor lesion and is routinely treated by surgical excision, sometimes necessitating mastectomy; radiotherapy and/or endocrine therapy are often added, although neither modality reduces breast-cancer-specific mortality
- Clinicopathological features or molecular alterations identifying the individuals with high-risk breast lesions that will progress to invasive breast carcinoma remain to be identified
- Until predictors of invasive carcinoma are found, management strategies must be defined by risk at the population level, rather than individual level, which might result in undertreatment or overtreatment in individual patients



**Figure 1** | Histological appearance of atypical ductal hyperplasia. A portion of this duct contains a proliferation of epithelial cells growing in a fenestrated (cribriform) pattern (see the region within the box). The cells have small, uniform (monomorphic) nuclei. Although the combined cytological and architectural features of this proliferation resemble those seen in low-grade ductal carcinoma *in situ*, it only involves a portion of the duct—in atypical ductal hyperplasia, the atypical cells either partially involve ductal spaces or completely involve ductal spaces over a limited area (<2 mm). Therefore, this proliferation warrants a diagnosis of atypical ductal hyperplasia (haematoxylin and eosin staining; 200× magnification).

will progress to invasive carcinoma remains a key barrier to individualization of risk-management strategies. Current risk-management approaches, out of necessity, are based on population-level risks, resulting in the potential for both overtreatment and undertreatment of individuals. This Review describes the histological diagnosis of high-risk breast lesions, by which we mean the benign breast lesions associated with an increased risk of invasive and *in situ* breast cancer development and breast cancer precursors, outlines their association with breast cancer development, and discusses the current management approaches.

**High-risk breast lesions**

**Atypical hyperplasias: ADH and ALH**

ADH is defined microscopically in terms of its resemblance to low-grade DCIS, and differs from the latter only with regard to the extent of the proliferation of the abnormal cell population. In particular, in ADH, the atypical cells either partially or completely involve individual ductal spaces such that the total extent of ductal involvement is <2 mm (Figure 1).<sup>7</sup> The atypical cell population in ADH shows high levels of oestrogen receptor (ER) expression, a low proliferative rate, and shares genetic and molecular alterations with those of low-grade DCIS and low-grade ER-positive (luminal type) invasive breast cancers.<sup>7</sup> These features provide strong evidence that ADH is an early lesion in the development pathway of low-grade breast carcinomas.

Several studies have examined the risk of breast cancer development associated with ADH (Table 1),<sup>4,8,9</sup> although the relative risk of breast cancer development was found to be elevated in all studies, that approximately 80% of women remained cancer-free during the follow-up period, which often extended beyond 10 years, is noteworthy. In the study by Degnim and colleagues,<sup>8</sup> the 20-year cumulative risk of invasive or *in situ* breast cancer development was 21% (95% CI 14–28%), and in the study of Page and co-workers,<sup>9</sup> the absolute risk of invasive cancer development was 20% with a median follow-up duration of 17 years.<sup>9</sup>

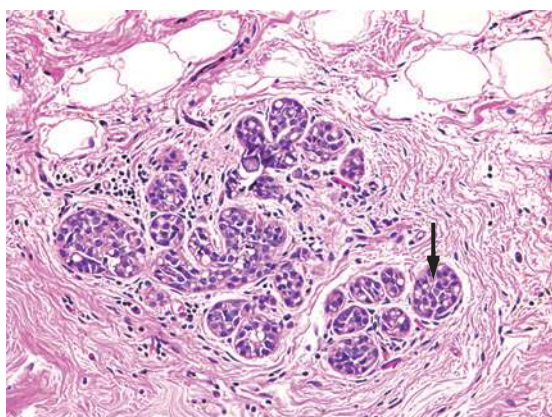
ALH is defined in terms of its morphologic resemblance to LCIS, but differs from the latter with regard to the extent of involvement of the lobular units. In ALH, the atypical cell population distorts and distends less than 50% of the acinar spaces in the involved lobules (Figure 2); any greater involvement is categorized as LCIS.<sup>7</sup> Studies examining the risk of breast cancer after a diagnosis of ALH are also included in Table 1.<sup>4,8–10</sup> As in the case of ADH, the majority of women diagnosed with ALH do not develop breast carcinoma. The magnitude of the risk of breast cancer development is similar between ADH and ALH, with a relative risk of ~4 after a diagnosis of either lesion.<sup>4,8–10</sup>

Because most women with ADH or ALH do not develop invasive breast cancer, there has been great interest in identifying other factors that modify the cancer risk associated with these lesions. Although the initial study by Dupont and Page<sup>1</sup> suggested that a family history of breast cancer increased the relative risk of breast cancer developing in patients with atypia to approximately 10-fold, subsequent studies have not confirmed this finding.<sup>3,5</sup> A 2014 update of data from the Mayo Benign Breast Cohort reported outcomes for 698 women with atypia followed for a mean of 12.5 years;<sup>5</sup> no difference in risk was seen between ADH and ALH, and cancers occurred with a 2:1 ratio in the ipsilateral compared with the contralateral breast.<sup>5</sup> Younger age at diagnosis of atypia, multiple foci of atypia, and less age-related lobular involution were all associated with an increased risk of cancer development in this study.<sup>5</sup> In addition, Collins *et al.*<sup>4</sup> found that premenopausal status at the time of benign biopsy was associated with an increased risk

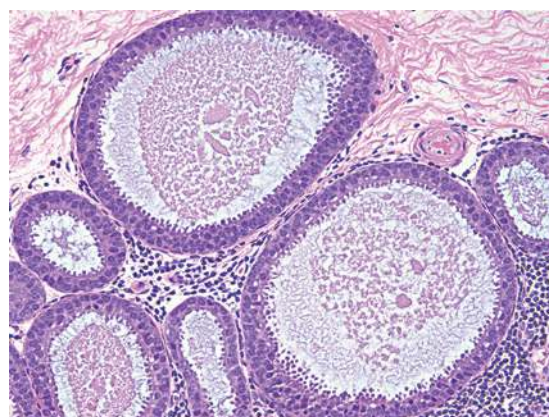
**Table 1** | Relative risk of breast cancer development after a diagnosis of atypical hyperplasia

Study	Number of patients	Median follow-up duration (years)	Outcome measured	Relative risk (95% CI)	
				ADH	ALH
Page <i>et al.</i> (1985) <sup>9</sup>	377	17	Invasive cancer	4.7 (2.5–8.9)	5.89 (3.0–11.0)
Page <i>et al.</i> (2003) <sup>10</sup>	252	NS	Invasive cancer	NA	3.1 (2.3–4.3)
Collins <i>et al.</i> (2007) <sup>4</sup>	395	9.1	Invasive cancer or DCIS	3.1 (2.0–4.8)	5.5 (3.3–9.2)
Degnim <i>et al.</i> (2007) <sup>8</sup>	331	13.7	Invasive cancer or DCIS	3.8 (2.5–5.6)	3.7 (2.5–54.3)

Abbreviations: ADH, atypical ductal hyperplasia; ALH, atypical lobular hyperplasia; CI, confidence interval; DCIS, ductal carcinoma *in situ*; NA, not applicable; NS, not specified.



**Figure 2** | Atypical lobular hyperplasia histology. The acini of this lobule contain a population of small, dysplastic epithelial cells with uniform nuclei. Many of these cells have intracytoplasmic vacuoles (arrow). The involved acinar spaces are not distended or distorted (haematoxylin and eosin staining; 200× magnification).



**Figure 3** | Flat epithelial atypia. The acini of the lobule in this photomicrograph are dilated and lined by one to several layers of cuboidal-to-columnar epithelial cells with monomorphic nuclei (haematoxylin and eosin staining; 200× magnification).

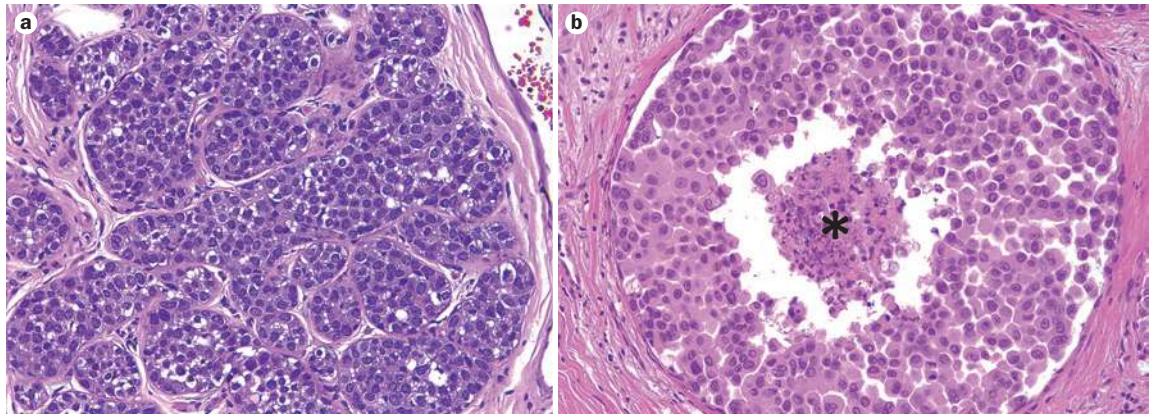
of breast cancer for women with ALH, but not ADH. In the Mayo study, the cumulative incidence of breast cancer at 25 years was 29%, with cancers developing within 5 years of the biopsy demonstrating atypia more likely to be ipsilateral than cancers arising beyond this time point (80% versus 62%;  $P=0.04$ ).<sup>5</sup>

Models incorporating multiple breast cancer risk factors, including atypia, have been developed. The Gail model was originally developed to estimate the risk of breast cancer in women participating in annual mammographic screening programmes based on hormonal risk factors, such as age at menarche, menopause, and first birth; the number of first-degree relatives with breast cancer; the number of breast biopsies; and the presence of atypia on biopsy.<sup>11</sup> This model has also been modified (Gail model 2) to predict age-specific probabilities of only invasive breast cancer development.<sup>12</sup> Using data from the National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1 trial,<sup>12</sup> the Gail model 2 predicted that 159 invasive cancers would occur among the study cohort, and 155 were observed, indicating its utility in predicting risk in a population. However, the ability of the Gail model to predict which individuals will develop cancer is limited. Indeed, when studied at the individual level in the Nurses' Health Study,<sup>13</sup> only 3.3% of the women who developed breast cancer had a Gail model 2 risk score above the age-risk thresholds used to predict breast cancer cases in the NSABP P-1 trial. The IBIS or Tyrer-Cuzick model

incorporates additional hormonal variables and greatly extended family history information compared with the Gail models, but has been shown to substantially overestimate breast cancer risk in women with atypical hyperplasia.<sup>14</sup> Thus, although these models are useful to provide a general numerical estimate of risk for a group of women with risk profiles similar to an individual woman with atypia, they have not solved the problem of individualized risk prediction. For this reason, great interest surrounds the identification of molecular biomarkers that predict the risk of cancer development in women with atypia, but efforts, to date, have been unsuccessful.<sup>15</sup> In aggregate, studies indicate that although ADH and ALH differ in their microscopic appearance, their clinical implications are very similar—an increased bilateral risk of breast cancer development that persists over time.

### Flat epithelial atypia

In contrast to ADH and ALH, which have been recognized as risk factors for breast cancer development since the 1980s, FEA is a relatively new term established in 2003 by the WHO Working Group on the Pathology and Genetics of Tumours of the Breast and Female Genital Organs.<sup>16</sup> FEA is an alteration of the breast lobules characterized by replacement of the native luminal epithelial cells with one to several layers of a single epithelial cell type showing low-grade cytological atypia (Figure 3), akin to that seen in the abnormal cells of ADH and low-grade DCIS.



**Figure 4** | LCIS histology. **a** | Classic-type LCIS histology. The acini of this lobule are distended and distorted by a proliferation of small cells with uniform nuclei. Cellular dyshesion, characterized by the lack of well-defined intercellular borders and the presence of spaces between many of the epithelial cells, is evident in some of the acini (haematoxylin and eosin staining; 200× magnification). **b** | Pleomorphic LCIS histology. This form of LCIS is characterized by distension of the acinar spaces due to a proliferation of dyshesive cells with considerably more variability in nuclear size and shape than those of classic LCIS. The asterisk indicates a central (comedo) area of necrosis is evident (haematoxylin and eosin staining; 200× magnification). Abbreviation: LCIS, lobular carcinoma *in situ*.

FEA lesions have a tendency to calcify and are seen in 3.8–10% of breast biopsies performed for mammographic microcalcifications.<sup>17,18</sup> FEA is commonly seen in association with ADH, ALH, and low-grade DCIS. Furthermore, the cells comprising FEA lesions share morphological, immunophenotypic, molecular, and genetic alterations with the cells of ADH, low-grade DCIS, and low-grade invasive cancers, as well as with the cells of ALH and LCIS, providing evidence that FEA represents a precursor to these more-advanced lesions.<sup>7</sup> However, although the natural history of FEA occurring in isolation is less well understood than that of ADH or ALH, the available studies suggest that the risk of breast cancer development is lower than is seen with these other types of atypia. For example, in a prospective study of 145 patients with pure FEA (95 with subsequent excisional biopsy), no carcinomas had developed after a mean follow-up period of 5 years.<sup>19</sup> Moreover, a recent study from the Mayo Benign Breast Cohort found that FEA did not further increase the breast cancer risk among women with atypical hyperplasia and that the risk associated with FEA was similar to that of patients with proliferative lesions without atypia.<sup>20</sup> Therefore, current evidence suggests that FEA should not be considered equivalent to ADH and ALH with regard to cancer risk assessment or patient management.

#### Lobular carcinoma *in situ*

The term LCIS was first used by Foote and Stewart<sup>21</sup> in 1941 to describe a lesion thought to be a precursor to invasive breast carcinoma, and based on this belief, total mastectomy was the recommended treatment. Subsequent studies demonstrating that the risk of invasive cancer development, approximately 1% per year, was lower than would be expected with a true precursor lesion, and that this risk was present in both breasts even when LCIS was unilateral, led to the view that LCIS should be considered only as a risk factor for breast

cancer development.<sup>22,23</sup> Haagensen *et al.*<sup>22</sup> suggested changing the name of this entity to ‘lobular neoplasia’, and to include ALH in this category to reflect the continuum of risk among these lesions. Enthusiasm for renaming this lesion lobular intraepithelial neoplasia (LIN) persists among some groups today.<sup>24</sup> However, differences in the degree of risk of breast cancer development between ALH and LCIS argue against the clinical utility of this combined term in our opinion. More recently, observations that ALH and LCIS are clonal and commonly contain the same genetic alterations found in adjacent invasive lobular carcinomas<sup>25,26</sup> have renewed interest in the theory that LCIS is a precursor lesion in addition to being a marker of increased risk.

Classic LCIS is diagnosed microscopically when more than half of the acinar spaces in a lobule are distended and distorted by a dyshesive proliferation of cells with small, uniform nuclei (Figure 4a). The cells comprising LCIS show strong ER expression, have a low proliferation rate, and are characterized by chromosomal loss at chromosome 16q22.1, the site of the *CDH1* gene encoding E-cadherin (also known as cadherin-1).<sup>7</sup> This chromosomal aberration is often accompanied by other genetic events (mutations, promoter methylation) that inactivate the *CDH1* gene and result in loss of E-cadherin protein expression;<sup>7</sup> similar genetic alterations are seen in ALH.<sup>7</sup>

A more-recently described pleomorphic variant of LCIS (PLCIS) is characterized by cells that exhibit marked nuclear pleomorphism (equivalent to that seen in high-grade DCIS), often with a central area of necrosis in the involved acinar spaces (Figure 4b). These lesions share genetic and molecular alterations with classic LCIS, including loss of E-cadherin expression, but exhibit a biomarker profile more akin to high-grade DCIS than to classic LCIS. For example, classic LCIS is almost always ER-positive and progesterone receptor (PR)-positive, and HER2-negative with a low Ki-67 proliferation rate. By contrast, PLCIS and high-grade

**Table 2** | Relative risk of invasive breast cancer after a diagnosis of LCIS

Study	Number of patients	Follow-up duration (years)	Patients who developed invasive cancer (%)	Relative risk
Haagensen <i>et al.</i> (1978) <sup>22</sup>	287	16.3	18	6.9
Rosen <i>et al.</i> (1978) <sup>23</sup>	99	24.0	34.5*	9.0
Salvadori <i>et al.</i> (1991) <sup>34</sup>	80	5.0	6.3	10.3
Otteson <i>et al.</i> (1993) <sup>35</sup>	69	5.0	11.6	11.0
Chuba <i>et al.</i> (2005) <sup>30</sup>	4,853 <sup>†</sup>	10.0	7.1	NR
Coopey <i>et al.</i> (2012) <sup>33</sup>	296	10.0	23.7	NR

\*Percentage calculated for 85 patients with follow-up data. †Includes patients who had unilateral mastectomy at LCIS diagnosis. Abbreviations: LCIS, lobular carcinoma *in situ*; NR, not reported.

DCIS can be ER-negative and/or PR-negative, over-express HER2, and have intermediate-to-high Ki-67 proliferation rates.<sup>7</sup> Although the histological features and biomarker profile of PLCIS raise concern that these lesions might have a different clinical behaviour than classic LCIS, adequate outcome studies addressing this issue are currently lacking.<sup>7</sup> Furthermore, these studies will be difficult to perform because cases in which PLCIS occurs in the absence of invasive cancer are rare. Although the exact incidence of PLCIS is uncertain, a multi-institutional review of cases from three university pathology departments over a 12-year period identified only 31 cases with no concurrent or past history of invasive cancer that met the WHO criteria for PLCIS.<sup>27</sup>

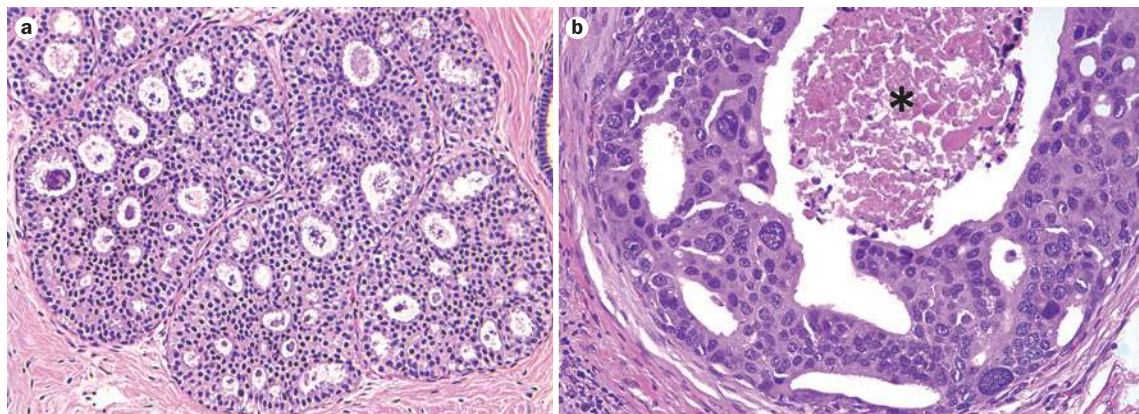
LCIS lacks clinical manifestations; hence, classic LCIS is an incidental finding in 0.5–3.8% of benign breast biopsies.<sup>22,28</sup> However, the pleomorphic variant of LCIS can present with mammographic microcalcifications. LCIS is often multifocal and is present bilaterally in approximately one-third of patients with LCIS.<sup>29</sup> A common misconception is that invasive cancers developing after a diagnosis of LCIS are usually invasive lobular carcinomas. In fact, a population-based study from the Surveillance, Epidemiology, and End Results (SEER) registry,<sup>30</sup> which included 4,853 women with LCIS, reported that of the 350 invasive cancers that developed in this population, only 26% were invasive lobular or mixed ductal and lobular carcinoma, with the remaining majority being some form of invasive ductal carcinoma. Thus, although invasive lobular carcinoma seems to be more common in women with an antecedent history of LCIS than in the general population of women with breast cancer, most cancers that develop after a diagnosis of LCIS are of ductal histology.<sup>30,31</sup> In the SEER study,<sup>30</sup> as in many earlier studies,<sup>22,23</sup> the risk of subsequent cancer development among women with LCIS was equal in both breasts and persisted over time, with a 10-year risk of invasive cancer development of 7.1 ± 0.1%. In 2013, King and colleagues<sup>32</sup> published data from 776 women diagnosed with LCIS at a single institution since 1999; in this cohort, the annual risk of cancer development was constant at 1–2% per year in years 1–6 after diagnosis.<sup>32</sup> This degree of risk was similar to that seen in a group of 296 patients diagnosed between 1987 and 2010, in which the estimated 5-year and 10-year risks

of invasive breast cancer development were 10.5% and 23.7%, respectively.<sup>33</sup> Thus, contemporary studies indicate similar levels of invasive breast cancer development in patients with LCIS to those reported by Haagensen *et al.*<sup>22</sup> and Rosen *et al.*<sup>23</sup> in the 1970s (Table 2).<sup>30,33–35</sup> As a whole, current evidence suggests that LCIS is both an indicator of an increased risk of breast cancer development and a nonobligate precursor lesion. To date, efforts to identify features of LCIS that are predictive of the subsequent development of breast cancer have not been successful, and further study in this area is needed.

### Ductal carcinoma *in situ*

The term DCIS encompasses a histologically heterogeneous group of lesions that vary with regard to their architectural pattern, cytological features, biomarker profile, and molecular and genetic alterations. The term ductal intraepithelial neoplasia (DIN)—paralleling the previously discussed LIN—has been proposed to describe these diverse lesions as well as ADH; however, owing to the marked difference in breast cancer risk between ADH and DCIS, and the completely different management strategies they necessitate (as discussed in the following sections), this term has never been widely accepted, and we do not use it. Currently, no universal agreement on a pathological classification system for DCIS has been reached, but most modern systems are based on nuclear grade alone (low [Figure 5a], intermediate, high) or nuclear grade in combination with comedo necrosis (that is, central necrosis of the cells within the ducts; Figure 5b).

In contrast to ADH, ALH, and LCIS—which are considered to increase the risk of breast cancer development in either breast—DCIS is regarded as a precursor lesion. As such, the risk of subsequent breast cancer development is greatest in the index (ipsilateral) breast, at or near the site of the prior DCIS. In the pre-mammographic era, DCIS presented clinically as a palpable mass, nipple discharge, or Paget disease of the nipple, and was an uncommon finding, accounting for only 3.8% of all breast cancers diagnosed in the USA in 1983.<sup>36</sup> By contrast, mammographic screening has resulted in a dramatic increase in the detection of this lesion; in 2013, DCIS was estimated to account for 20–25% of new breast cancer diagnoses,<sup>37</sup> largely due to its identification as mammographic microcalcifications. This marked increase in the diagnosis—and, therefore, treatment—of DCIS, coupled with only a modest decrease in breast cancer mortality during the same time period, has led to the suggestion that DCIS is not an obligate precursor of invasive carcinoma and is often overtreated. Very limited information on the natural history of DCIS is available to support or refute these claims, mostly because surgical removal of the lesions precludes evaluation of their evolution. Most studies examining the behaviour of ‘untreated’ DCIS consist of cases initially diagnosed as benign and reclassified as DCIS on pathology review.<sup>38–41</sup> Thus, these studies represent one end of the spectrum of DCIS: usually small, low-grade lesions with behaviours that might not be representative of all



**Figure 5** | DCIS histology. **a** | This specimen represents a low nuclear grade DCIS. Ductal spaces are filled with a fenestrated (cribriform) proliferation of small epithelial cells with uniform nuclei. **b** | This image shows a high nuclear grade DCIS. This ductal space contains a proliferation of large epithelial cells with pleomorphic—variably sized and shaped—nuclei. The asterisk indicates an area of central (comedo) necrosis is evident (haematoxylin and eosin staining; 200× magnification). Abbreviation: DCIS, ductal carcinoma *in situ*.

types of DCIS.<sup>38–41</sup> Results of these studies are summarized in Table 3. Importantly, although these studies are probably skewed toward less-aggressive forms of DCIS, the risk of subsequent invasive breast cancer development they demonstrate is substantial. Moreover, most of the cancers in these studies occurred in the same breast as the initial DCIS diagnosis, and usually in the same breast quadrant.<sup>38–41</sup> These findings indicate that DCIS, indeed, represents a true precursor of invasive breast cancer.

Additional insight into the behaviour of small DCIS lesions treated with complete excision alone comes from a multicentre intergroup trial open to patients with low-grade or intermediate-grade DCIS >0.3 cm and ≤2.5 cm in size ( $n = 565$ ), or high-grade DCIS >0.3 cm and ≤1.0 cm in size ( $n = 105$ ).<sup>42</sup> All lesions were excised to margins of at least 3 mm and all patients had negative postexcision mammograms.<sup>42</sup> With a median follow-up period of 6.3 years, the 7-year rates of local recurrence were 10.5% and 18.0% for the low-to-intermediate-grade and high-grade DCIS groups, respectively, with invasive carcinoma comprising 53% of recurrences in the low-to-intermediate-grade group and 35% in the high-grade group.<sup>42</sup> In a subset of 327 patients, 10-year rates of invasive cancer recurrence were 3.7%, 12.3%, and 19.2% in the low-grade, intermediate-grade, and high-grade groups, respectively.<sup>43</sup> In addition, risk factors for the development of DCIS mirror those for invasive cancer, supporting the idea that they are part of the same process.<sup>44</sup> Moreover, these studies indicate that the risk of the recurrence of DCIS and progression to invasive carcinoma in women with DCIS treated with excision alone is substantial, regardless of size or grade of the DCIS lesion.

The distinction between ADH and low-grade DCIS of limited extent can be difficult. A single-institution study comparing the outcomes of 143 patients diagnosed with so-called 'borderline lesions' to those of 2,328 patients with DCIS reported a 5-year rate of development of DCIS or invasive cancer of 7.7% for borderline

lesions and 7.2% for DCIS ( $P = 0.80$ ).<sup>45</sup> By contrast, in a smaller study of patients with 'borderline lesions', 37 out of 38 patients had no recurrence after surgical excision alone with a mean follow-up period of 54 months.<sup>46</sup> Thus, this issue requires further study before lesions not clearly classified as DCIS are managed with aggressive strategies, such as mastectomy or radiotherapy.

Clearly, the identification of risk factors predictive of the development of invasive carcinoma would be of major benefit in selecting the most-appropriate management strategy from those available for women with DCIS (discussed in the following sections). A number of factors predictive of the risk of recurrence after treatment with excision or excision and radiotherapy have been recognized in therapeutic trials, including younger age at diagnosis,<sup>47,48</sup> and clinical rather than mammographic presentation.<sup>49</sup> Furthermore, high nuclear grade and comedo necrosis are predictive of a shorter interval to recurrence, but are not predictive of higher recurrence rates in studies with extended follow up.<sup>50</sup> However, clinicopathological features that enable selection of the patients who will have tumour recurrence with invasive carcinoma rather than DCIS remain elusive. Studies of genetic alterations that might predict the development of invasive carcinoma have found that DCIS and invasive carcinoma have similar gene-expression patterns,<sup>51</sup> gene copy-number aberrations,<sup>52</sup> and similar levels of promoter hypermethylation.<sup>53</sup> Attention has also been focused on the role of the microenvironment in the progression from DCIS to invasive carcinoma, and some evidence indicates that the normal myoepithelium might exert tumour suppressive effects on the DCIS lesion, with loss of this suppression resulting in invasion.<sup>54</sup> Other evidence indicates that genetic heterogeneity and clonal evolution could result in the development of an invasive phenotype in DCIS lesions.<sup>55</sup> Of note, it seems that many of the molecular events associated with carcinogenesis are also evident even in atypical hyperplasia lesions; thus, the key drivers of the development of invasive carcinoma remain to be identified.

**Table 3** | Risk of invasive breast cancer after DCIS\* treated by biopsy alone

Study	Number of patients	Mean interval to carcinoma (years)	Proportion of patients who subsequently developed invasive breast cancer (%)
Rosen <i>et al.</i> (1980) <sup>41</sup>	15	9.7	53
Eusebi <i>et al.</i> (1994) <sup>39</sup>	80	NR	14
Page <i>et al.</i> (1995) <sup>40</sup>	28	6.1	32
Collins <i>et al.</i> (2005) <sup>38</sup>	13	9	46

\*Unrecognized, that is, initially diagnosed as benign and found to be DCIS on pathology audit review. Abbreviations: DCIS, ductal carcinoma *in situ*; NR, not reported.

### Management of high-risk breast lesions Is excision of all high-risk lesions required?

In current clinical practice, the majority of initial diagnoses of breast lesions are made based on image-guided core needle biopsy specimens. A diagnosis of ADH on core biopsy is an indication for surgical excision and the rationale for this approach is clear, as the distinction between ADH and DCIS is, in part, quantitative. Studies examining surgical excision after a core-biopsy-based diagnosis of ADH report DCIS or invasive carcinoma in 10–20% of cases, even with the use of large-gauge vacuum-assisted biopsy devices.<sup>56</sup> Conversely, DCIS lesions are routinely excised for therapeutic purposes following their detection by core biopsy, and 25.9% of 7,350 cases of DCIS diagnosed at core biopsy, reported in a meta-analysis of 52 studies,<sup>57</sup> were found to have invasive carcinoma at excision.

Whether or not patients with ALH and LCIS on core biopsy specimens require surgical excision is a matter of controversy. Differentiating between these lesions and DCIS or invasive cancer is not dependent upon the size of the lesion (as is the case for ADH and DCIS). However, early studies that demonstrated upgrade rates to DCIS or invasive carcinoma as high as 50% in patients diagnosed with lobular neoplasia at core biopsy led many to advocate routine excision of all of these lesions.<sup>58</sup> Many of these early studies did not routinely excise all lobular neoplasias, selecting only higher-risk cases for surgery, whereas others failed to account for radiological–pathological discordance, which mandates surgical excision regardless of the pathological diagnosis.<sup>58</sup> Several recent studies suggest that when a core-biopsy-based diagnosis of lobular neoplasia is made and no other lesions requiring excision (ADH, papilloma, radial scar) are present and radiological–pathological concordance is present, upgrade rates are less than 5%.<sup>59–63</sup> Furthermore, most of the more-serious lesions identified in such cases are DCIS or small, low-grade invasive cancers.<sup>59–63</sup> For these reasons, we no longer advocate routine excision of ALH or LCIS when the radiological and pathological diagnoses are concordant and no other lesions requiring excision are present.

The need for surgical excision of pure FEA is even less well documented. FEA frequently occurs in association with ADH and/or DCIS, which necessitates excision. Reported upgrade rates after a core-biopsy-based diagnosis of FEA alone are low in many recent series, ranging from 0–3.2%.<sup>19,64–66</sup> These low upgrade rates suggest that observation of FEA is a reasonable strategy in the absence of other indications for excision.

Importantly, the presence of ADH, ALH, or LCIS at the resection margins when surgical excision is undertaken is not an indication for additional surgery, as the goal of resection is to exclude the presence of carcinoma. In patients with invasive carcinoma, the presence of these high-risk lesions at the margin of resection is not associated with an increased risk of local recurrence,<sup>67,68</sup> supporting the safety of this practice.

### Current options for ADH, ALH and LCIS

For women with ADH, ALH, and LCIS, active surveillance, chemoprevention, and, less commonly, bilateral prophylactic mastectomy, are all management options. Women with DCIS have traditionally been treated as if they had cancer: mastectomy, excision and radiotherapy, or excision alone can be used; and endocrine therapy may be added to any of these surgical approaches (see following section).

#### Active surveillance

Screening mammography is the mainstay of active surveillance. A study comparing the accuracy of screening mammography in women matched for age group, breast density, family history, screen year, and screening site found no difference in sensitivity of mammography for breast cancer detection among women with ADH, ALH, or LCIS compared with a control group lacking a history of these lesions, although specificity was lower in the high-risk group.<sup>69</sup> Evidence that MRI screening reduces the rate of interval cancers in women at increased risk of breast cancer due to *BRCA1* and *BRCA2* mutations has stimulated interest in the use of this approach among other women at high risk of breast cancer. King *et al.*<sup>32</sup> examined outcomes of patients with LCIS followed with ( $n = 455$ ) and without MRI screening ( $n = 321$ ) based on physician and patient preference, in addition to annual mammography; after a median follow-up period of 58 months, 104 cancers had developed, with no significant differences in nodal status or invasive tumour size (0.8 cm versus 0.5 cm,  $P = 0.09$ ) noted between groups.<sup>32</sup> DCIS was numerically more frequent in the MRI group compared with the mammography only cohort (41% versus 26%), but this difference did not reach statistical significance.<sup>32</sup> Only 50% of the cancers in the MRI group were initially detected by MRI, and benign breast biopsies were more frequent in patients having MRI than in those screened by mammography alone (36% versus 13%;  $P < 0.0001$ ).<sup>32</sup> The lack of benefit of MRI in this study emphasizes the fact that *BRCA*-related cancers have a unique biology and that the surveillance strategies of proven benefit in *BRCA*-mutation carriers might not translate to other high-risk groups. Although American Cancer Society screening guidelines recommend the use of MRI in women with a 20–25% lifetime risk of breast cancer development,<sup>70</sup> this recommendation is largely based on studies in women at genetic risk, and the guidelines indicate that there is insufficient evidence to recommend for or against MRI screening in women with atypia or *in situ* carcinoma. Differences in both the level of breast cancer risk, time to cancer development,

and the phenotype of cancers between women at genetic risk and those deemed to be at risk on the basis of ADH, ALH, and LCIS emphasize the need for prospective studies of MRI screening in women with histological high-risk lesions to clarify this issue.

Evidence suggests that screening with whole-breast ultrasonography in addition to mammography increases cancer detection by 3–4 cases per 1,000 screens in women with dense breasts, but at the cost of a marked decrease in specificity compared with mammographic screening alone.<sup>71</sup> Specific evidence of the benefit or lack thereof of whole-breast ultrasonography or newer imaging technologies, such as contrast-enhanced digital mammography or tomosynthesis, in women identified to be at risk of breast cancer on the basis of atypia or LCIS is currently lacking. The importance of physical examination as a component of screening in high-risk populations is often forgotten. In the study by King and colleagues,<sup>32</sup> 13 of the 104 cancers reported were detected by physical exam. Hence, good evidence supports the current National Comprehensive Cancer Network (NCCN) guidelines for active surveillance of women with ADH, ALH, and LCIS, in which clinical breast examination every 6–12 months and annual mammography are recommended.<sup>72</sup>

The potential of lifestyle interventions, including increasing physical activity, maintaining an ideal body weight, and lowering the use of alcohol as risk-reduction strategies, in high-risk women has attracted great interest. However, whether modification of these factors later in life, particularly in women with atypia or LCIS, could have an impact on the risk of breast cancer development remains unknown.

#### Chemoprevention

The observation that women with invasive breast cancer who received adjuvant tamoxifen had a substantial reduction in the incidence of contralateral cancers<sup>73</sup> led to studies of tamoxifen therapy for chemoprevention in women at increased risk of breast cancer development. The NSABP P-1 trial<sup>74</sup> randomly assigned women aged  $\geq 60$  years regardless of the presence of breast cancer risk factors and younger women with a 5-year risk of breast cancer development of 1.66% or greater to receive tamoxifen (20 mg daily) or placebo for 5 years. Prior biopsies showing atypical proliferative breast lesions was one of the factors that put women into the high-risk category.<sup>74</sup> At 7 years of follow up, tamoxifen treatment reduced the relative risk of invasive breast cancer to 0.57, and the relative risk of noninvasive breast cancer to 0.63.<sup>74</sup> Women at risk due to atypical hyperplasia experienced a 75% reduction in breast cancer development, and those at risk due to LCIS experienced a 46% reduction; the reduction in risk of cancer development was attributable entirely to a decreased incidence of ER-positive breast cancers. Although a 32% reduction in the frequency of osteoporotic fractures was also observed, the relative risks of endometrial cancer (both adenocarcinoma [0.71 cases versus 2.2 cases per 1,000 patients] and sarcoma [0 cases versus 0.17 cases per 1,000 patients]), stroke, pulmonary embolism, deep-vein thrombosis, and

cataracts—but not of ischaemic heart disease or overall mortality—were increased. In addition, an overview analysis of four randomized trials of tamoxifen chemoprevention demonstrated that this approach was associated with a 38% reduction in breast cancer incidence.<sup>75</sup> However, with longer follow-up study in three of the four trials, a greater magnitude of benefit for tamoxifen was observed, with a reduction in the number needed to treat to prevent one cancer, from 95 women at 5 years to 60 women at 10 years.<sup>76</sup> The long-term benefit of tamoxifen for breast cancer risk reduction was examined in the IBIS-1 trial,<sup>77</sup> a study that randomized 7,154 women at increased risk of breast cancer development to tamoxifen or placebo for 5 years. After a median follow-up duration of 16 years, 7% of women randomized to tamoxifen developed invasive or *in situ* breast cancer compared with 9.8% in the placebo group (HR 0.71, 95% CI 0.60–0.83;  $P < 0.0001$ ).<sup>77</sup> Although tamoxifen was only administered for 5 years, the degree of reduction in the risk of breast cancer development did not differ in years 0–10 of the study and after 10 years,<sup>77</sup> emphasizing that the risk reduction persists after completion of a 5-year course of treatment. However, no survival benefit was noted, and a trend toward increased all-cause mortality in the tamoxifen-treated group will require further study.<sup>77</sup>

The toxicities of tamoxifen, particularly endometrial carcinoma, have limited the use of this agent for prevention of breast cancer. The search for a hormonal prevention strategy with a more acceptable toxicity profile than tamoxifen treatment led to additional studies. The NSABP P-2 trial<sup>78</sup> compared raloxifene—a selective ER modulator (SERM) used for the management of osteoporosis—with tamoxifen in healthy postmenopausal women at increased risk of breast cancer development. This study demonstrated that raloxifene retained about three-quarters of the efficacy of tamoxifen in the prevention of invasive and noninvasive breast cancer, with somewhat reduced toxicity.<sup>78</sup> In particular, the relative risk of endometrial carcinoma was 0.55 (95% CI 0.36–0.83) compared with tamoxifen.<sup>78</sup> Nevertheless, similarly to tamoxifen, the use of raloxifene for primary prevention of breast cancer development in the general community has been limited.

Aromatase inhibitors are effective hormonal agents in the adjuvant setting for the treatment of breast cancer, and have also been observed to reduce the incidence of contralateral breast cancers;<sup>79</sup> however, these agents are not SERMs, and have a different mechanism of action and are associated with different adverse effects. The IBIS-II<sup>80</sup> and MAP-3<sup>81</sup> trials examined the use of the aromatase inhibitors anastrozole and exemestane, respectively, for chemoprevention in postmenopausal women at increased risk of breast cancer. The use of these drugs was associated with a 53% reduction in breast cancer risk in both studies.<sup>80,81</sup>

In practice, the use of chemoprevention strategies has been shown to reduce breast cancer incidence among women with atypical hyperplasia and LCIS at 10 years from 21.3% to 7.5% ( $P < 0.001$ ).<sup>33</sup> A risk–benefit analysis of tamoxifen and raloxifene for postmenopausal women



of European and African-American ethnicity of varying ages, with and without a uterus, has been created and is useful for counselling patients.<sup>82</sup> Current guidelines recommend discussion of tamoxifen chemoprevention with premenopausal women at high risk of breast cancer, and discussion of tamoxifen, raloxifene, and exemestane with postmenopausal women at high risk of this disease.<sup>83</sup>

#### *Bilateral prophylactic mastectomy*

Bilateral prophylactic mastectomy is the most-effective method of breast cancer risk reduction, but comes at the cost of a major surgical procedure and loss of breast sensation, which is unacceptable to many women. In the absence of other risk factors, bilateral prophylactic mastectomy is not usually recommended for atypia or LCIS, and in a contemporary cohort of women with LCIS treated at the Memorial Sloan Kettering Cancer Center, only 5% chose to undergo this procedure.<sup>84</sup> It is important to recognize that even the best bilateral prophylactic mastectomy surgery leaves behind microscopic breast tissue that can undergo malignant transformation, but studies suggest a 95% reduction in the risk of breast cancer for women treated with this procedure in community practices.<sup>85</sup> How the recent trend to perform nipple sparing mastectomy, which necessitates leaving behind breast tissue to retain the nipple blood supply, might alter the degree of risk reduction after bilateral prophylactic mastectomy in high-risk populations is uncertain at present. In the absence of other risk factors, bilateral prophylactic mastectomy is an unnecessarily radical approach to breast cancer risk reduction for women with atypia or LCIS.

#### **Clinical management of DCIS**

##### *Surgery with or without adjuvant radiotherapy*

Current management options for DCIS include total mastectomy, breast-conserving surgery plus radiation therapy, or breast-conserving surgery alone. As discussed, the inability to reliably exclude the presence of invasive carcinoma after a core-biopsy diagnosis of DCIS means that observation without excision is not standard practice, except in patients with severe co-morbidities. Management options for DCIS are reviewed in detail elsewhere.<sup>86,87</sup> Briefly, the selection of breast-conserving surgery versus mastectomy is determined by the extent of the DCIS lesion and patient preference. Despite being detected mammographically in the majority of cases, many DCIS lesions are microscopically extensive and cannot be excised to clear margins with a cosmetically acceptable result. Four prospective randomized trials that evaluated the benefit of radiotherapy after breast-conserving surgery for women with DCIS have been analysed in a meta-analysis,<sup>88</sup> among 3,729 women followed for a median of 8.9 years in these studies, the addition of radiotherapy halved the risk of ipsilateral disease recurrence (either DCIS or invasive breast cancer), with a 10-year absolute risk reduction of 15.2% (12.9% risk with radiotherapy versus 28.1% risk with breast-conserving surgery only).<sup>88</sup> Approximately 50% of the recurrences were invasive cancers, and the benefit of radiation

therapy was seen in all patient subgroups.<sup>88</sup> On the basis of this substantial reduction in disease recurrence, and the inability to define subsets of women who do not benefit from radiotherapy, the authors concur with current NCCN guideline recommendations<sup>86</sup> for the use of radiotherapy in the majority of women with DCIS. In fact, a multigene assay to predict the risk of local recurrence in women with DCIS has been developed,<sup>43</sup> but has not been shown to predict the benefit of radiotherapy in groups at varying risk of recurrence, limiting its current clinical utility.

After treatment of DCIS with mastectomy, breast-conserving surgery followed by radiotherapy, or breast-conserving surgery alone, the rate of breast-cancer-specific mortality is extremely low. Retrospective studies of mastectomy in patient with DCIS report breast-cancer-specific survival rates at 10 years of greater than 98%.<sup>89,90</sup> In the meta-analysis of trials of breast-conserving surgery plus radiotherapy versus breast-conserving surgery only, the 10-year cumulative risk of breast cancer mortality was 4.1% for those receiving radiation therapy and 3.7% in the observation arm.<sup>88</sup> The very low risk of breast-cancer-related death in patients diagnosed with DCIS has led to concerns that the use of mastectomy, breast-conserving surgery plus radiotherapy, or even surgery at all constitutes 'overtreatment'.<sup>91</sup> However, invasive recurrence after DCIS is associated with an increased risk of breast cancer mortality,<sup>49</sup> and recurrence is psychologically traumatic to patients. Furthermore, evidence indicates that a recent trend towards increased use of mastectomy for the management of DCIS reflects patient, rather than surgeon, preference.<sup>92</sup> In addition to the risk of ipsilateral breast cancer events, women with DCIS have an elevated risk of contralateral breast cancer development compared with women in the general population, with approximately 10% developing a contralateral breast cancer within 15 years of a DCIS diagnosis.<sup>49</sup>

##### *Endocrine therapy in DCIS*

Most DCIS lesions are ER-positive; in a subset analysis of patients enrolled in the NSABP B-24 trial, ER expression was present in 79%.<sup>93</sup> A study of 352 patients comparing screen-detected DCIS to symptomatic DCIS reported ER positivity in 86% versus 68% of cases ( $P < 0.001$ ).<sup>94</sup> Owing to the high frequency of ER positivity in DCIS, several trials evaluating the use of tamoxifen in patients with DCIS have been published. For example, the aforementioned NSABP B-24 trial<sup>95</sup> found a significant benefit from the addition of tamoxifen (20 mg daily) after breast-conserving surgery and radiotherapy in women with DCIS; after a median 6.2 years of follow up, a 37% reduction in all breast cancer events was observed with tamoxifen in a group of women whose ER status was unknown.<sup>95</sup> The retrospective subset analysis<sup>93</sup> in the 40% of patients with tissue available for determination of ER status found, with long-term follow-up data (14.5 years), that tamoxifen use reduced the occurrence of breast cancer events (ipsilateral and contralateral, and invasive and noninvasive) from 31% to 20% (HR 0.58,  $P = 0.0015$ ) in the ER-positive patients. No significant

benefit was observed in patients with ER-negative DCIS,<sup>93</sup> and as in the NSABP P-1 trial,<sup>74</sup> tamoxifen use had no impact on overall mortality.<sup>74,93</sup> The adverse effects of the drug were consistent with prior experience.<sup>93</sup> The UK/Australia/New Zealand (UK/ANZ) trial<sup>96</sup> examined the benefit of tamoxifen with and without adjuvant radiotherapy in patients with DCIS. A significant reduction in the overall breast cancer event rate from 24.6% to 18.1% was seen at 12.7 years with tamoxifen treatment ( $P = 0.002$ ). A Cochrane review<sup>97</sup> examining both of these studies estimated that 15 patients with DCIS need to be treated with tamoxifen to prevent one invasive or *in situ* cancer.

All of the data regarding tamoxifen therapy in women with DCIS relate to regimens lasting 5 years. More-recent reports that longer durations of tamoxifen treatment improve the outcome of women with invasive cancer<sup>98,99</sup> are of unknown relevance to patients with DCIS, but might motivate further studies specifically in this population. In addition, studies comparing tamoxifen and aromatase-inhibitor therapy in postmenopausal women with DCIS are underway or have completed accrual,<sup>100–102</sup> and offer the potential for additional risk-reduction strategies. Because endocrine therapy has not been associated with an overall mortality benefit, it must be considered only as an option for women with DCIS, rather than a mandatory part of treatment. Premenopausal women treated with breast-conserving surgery who have two breasts at risk for future cancer development—or in the case of the index breast with DCIS, future local recurrence—have the most favourable risk–benefit ratio with tamoxifen therapy.

### Conclusions

ADH, ALH, LCIS, and DCIS all indicate an increased risk of invasive breast cancer development. The relative risk of invasive cancer after a diagnosis of ADH or ALH is approximately 4, and increases to 10 in women

with LCIS. The lack of untreated cohorts of women with DCIS make calculation of the relative risk associated with such lesions more challenging, but based on cases treated with excision only, the risk exceeds that seen with LCIS. In contrast to the other high-risk lesions, which are associated with an increased risk of cancer development in both breasts, the risk in women with DCIS is primarily in the index breast, and management strategies are similar to those used for invasive cancer.

Although great progress has been made in defining the molecular changes associated with carcinogenesis, alterations identifying the women with high-risk breast lesions who will develop invasive carcinoma remain to be identified. Reproducible clinicopathological features to stratify those who will and will not develop invasive cancer are also lacking. Until such predictors are identified, management strategies must be defined by population-level risk rather than individual-level risk.

Risk-reduction strategies for atypia and LCIS range from active surveillance to prophylactic mastectomy. The application of these approaches is largely driven by patient attitudes toward risks and benefits of various interventions for conditions associated with a low risk of breast-cancer-related death. However, the substantial and persistent elevation in breast cancer risk in these women is sufficient to justify a discussion of chemoprevention with those in good health, particularly premenopausal women in whom the risk–benefit ratio of tamoxifen therapy is most favourable. For DCIS, surgical excision, sometimes necessitating mastectomy, is routine, and radiotherapy should be given to most women who undergo breast-conserving surgery. Endocrine therapy can be added to reduce the risk of bilateral breast cancer events. Progress in breast cancer risk reduction in patients with high-risk breast lesions will ultimately be dependent on the ability to individualize risk prediction through better definition of the key drivers of the carcinogenic process.

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#### Author contributions

All authors contributed substantially to all stages of the preparation of this manuscript.