It is well known that certain types of nonmalignant lesions predispose patients to increased risk of developing breast cancer. Dupont and Page\(^1\) were the first to retrospectively review benign breast biopsies and determine the inherent risk they presented. Over 10,000 specimens were divided into three groups: non-proliferative lesions, proliferative lesions without atypia, and proliferative lesions with atypia. Their findings suggested a 1.9 times greater risk for proliferative lesions without atypia and 5.3 times greater risk for proliferative lesions with atypia.\(^1,2\) Subsequent case-control studies have supported these initial results.\(^2-5\)

In this review, we discuss the categories of high-risk breast lesions and the potential prevention strategies for these patients.
demonstrated in many studies. The relative risk with moderate or florid ductal hyperplasia ranges from 1.5 to 2.0, and the risk is independent of other risk factors such as family history. Even though these patients are at increased risk, the need for chemoprevention and heightened screening has not been supported by studies. Furthermore, surgical excision is not required after core biopsy unless there is a concern for additional disease or a question of concordance between pathology and the clinical picture (e.g., mammogram findings, ultrasound findings, physical examination).

**Intraductal Papillomas**
Due to a marked variation in papillary lesions, a clear strategy toward their management has not been developed. Pathology reports of papillomas may include anything from single, solitary benign papillomas to malignant papillary invasive cancers. To better define these lesions, pathologists have tried to classify lesions according to two characteristics: the number of lesions and the presence or absence of atypia. Papillomas usually present as either a large, solitary, central papilloma (Fig 2) or multiple, peripheral micropapillomas (Fig 3). When atypical hyperplasia (within or surrounding the papilloma) is excluded, a solitary papilloma carries a relative risk of 2.0 to 2.1 compared to 3.0 to 3.5 with micropapillomas. When atypia is associated with the papilloma (Fig 4), this risk increases to a level of 5.1 to 13.1 for solitary papillomas and 4.4 to 7.0 for micropapillomas. Clearly, the presence of atypia and the number of lesions play a role in determining future breast cancer risk. Of note, the presence of papillomas does not predict laterality in cases of future breast cancer. In addition, the risk of finding invasive cancer on an excisional biopsy after finding a papilloma following a core biopsy increases with the presence of atypia and the number of papillomas present.

**Radial Scars**
Radial scars have caused much confusion in the management of breast disease. These lesions are easily confused with invasive cancers on mammography as they form radiating spicules similar to cancer. The only difference is the lack of a central mass and the common

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Fig 1. — Hyperplasia without atypia exhibiting irregularity of cell placement and considerable variation of secondary spaces with regard to shape and size (hematoxylin-eosin, original magnification ×200).

Fig 2. — Intraductal papilloma with focal sclerosis (hematoxylin-eosin, original magnification ×50).

Fig 3. — Multiple peripheral micropapillomas (hematoxylin-eosin, original magnification ×25).

Fig 4. — Papilloma with focal atypical ductal hyperplasia (hematoxylin-eosin, original magnification ×100).
characteristic of a “black star.” Furthermore, on pathologic analysis, differentiation from an invasive cancer is difficult as radial scars demonstrate proliferative changes around a fibroelastic core (Fig 5) that can mimic a well-differentiated invasive ductal carcinoma. It has been suggested that the entire lesion be excised to make the correct pathologic diagnosis. However, it appears that an 11-gauge vacuum core biopsy may be adequate to sample radial scars. In a comparison between 11- and 14-gauge biopsy techniques, there were no missed cancers in the 11-gauge group but a 5% missed cancer rate in the 14-gauge biopsy.

The Vanderbilt group has recently published a retrospective cohort study of 880 cases of radial scar with an average follow-up of 20 years. In this study, 7% of patients went on to develop breast cancer, a relative risk of 1.82 at 10 years compared with controls. Interestingly, this increased risk was seen only in those lesions with coexistent proliferative disease (92% of total number of lesions), while the small percentage without proliferative disease was identical to controls. There may be an association with tubular cancer and radial scars since tubular neoplasms have often been identified with radial scars.

Sclerosing Adenosis

Another biopsy finding that can be confused with invasive cancer is sclerosing adenosis (Fig 6). One study reported that 4 out of 12 pathologists misdiagnosed sclerosing adenosis as invasive cancer. Sclerosing adenosis can be defined as tumor-like lobulocentric proliferation of both epithelium and myoepithelium, in contrast to invasive carcinomas, which lack myoepithelial growth. Sclerosing adenosis is usually identified on mammographic findings of microcalcifications. As in radial scars, there may be a central radiolucent area rather than the opaque center found with cancer.

The accuracy of core biopsy in the diagnosis of sclerosing adenosis appears adequate. In one study, 8% of core biopsies demonstrating sclerosing adenosis had associated cancer (mostly intraductal cancer) with 86% accuracy (6 out of 7 patients) using 11- and 14-gauge biopsy devices. For the one false-negative patient, mammography demonstrated a suspicious, spiculated...
mass. At our institute, we generally do not excise these lesions identified on core biopsy. However, it is important to have a high level of suspicion for additional disease. With regard to breast cancer risk, sclerosing adenosis carries a 1.5 to 3.7 times relative risk of developing invasive cancer.\textsuperscript{29,30} This relative risk might increase to 5.5, translating to a 1.2% risk per year of cancer, if atypia is associated with the sclerosing adenosis.\textsuperscript{28}

**Fibroadenomas**

The risk of cancer in patients with fibroadenomas has been reviewed in multiple studies. Although initial work by Dupont et al\textsuperscript{31} pointed to a slight increase in risk, they have since concluded that when family history and adjacent proliferative changes are factored out, the relative risk approaches 1.\textsuperscript{32} Furthermore, atypia found within fibroadenomas did not seem to increase the risk for cancer as only 1 patient out of 13 went on to develop cancer.\textsuperscript{32}

**Proliferative Lesions With Atypia**

The relative risk of atypical hyperplasia on developing future breast cancers was initially described to be between 3.9 and 13.0.\textsuperscript{1,3-5} The National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1 study went on to report nearly a 57% increase in invasive cancer compared to patients without atypical hyperplasia (10.11 events per 1,000 patients vs 6.44 events per 1,000 patients) with a mean follow-up of 47.7 months.\textsuperscript{33} This increase in risk appears to be related to patient age as the incidence of breast cancer in the tamoxifen arm was greater in the Study of Tamoxifen and Raloxifene (STAR) trial, which evaluated postmenopausal women (1.43 per 1,000 patients in the NSABP P-1 study vs 5.21 per 1,000 patients in the STAR trial).\textsuperscript{34} However, these associations did not differentiate between atypical ductal hyperplasia (ADH, Fig 7A) and atypical lobular hyperplasia (ALH, Fig 7B). Upon subdividing this group, it appears that ALH carries a slightly higher risk of subsequent cancer, especially in the premenopausal patient.\textsuperscript{35,36} The Vanderbilt group initially published relative risks of 4.7 for ADH and 5.8 for ALH.\textsuperscript{37} Subsequent publications produced similar results in finding odds ratios of 2.4 to 2.8 for ADH and 5.3 to 5.5 for ALH.\textsuperscript{35,36} Interestingly, an updated study by Page et al\textsuperscript{38} modified the relative risk for ALH to be 3.1. Some have hypothesized that this difference might be due to the percentage of premenopausal patients in each study.\textsuperscript{35} As far as laterality is concerned, atypical hyperplasia implies increased risk for cancer in either breast. ALH displays a slightly greater prediction toward the future development of ipsilateral breast cancers (58% to 69%), and the ipsilateral breast is affected in 50% to 56% of ADH patients.\textsuperscript{35-37,39}

Clinically, all patients with a core biopsy identifying atypical hyperplasia, either ADH or ALH, need to have an excisional biopsy. Cancer has been found in 14% to 31% of biopsy specimens.\textsuperscript{30,35} Examination of additional tissue is important, especially with ALH, as the pathologic analysis of the same specimen is variable between pathologists and ALH does not have mammographic or clinical manifestations.\textsuperscript{30,34} Margins of excision do not appear to be important as long as malignancy has been properly ruled out.\textsuperscript{35}

**Lobular Carcinoma In Situ**

First described in 1941, lobular carcinoma in situ (LCIS) contains foci of neoplastic cells similar to invasive lobular carcinoma with the exception of an intact basement membrane (Fig 8A). Initially, compared to ductal carcinoma in situ (DCIS), LCIS was thought to be a similar precursor lesion and mastectomy was recommended.\textsuperscript{40} However, further study on this entity indicated that LCIS acts more as a marker of increased risk rather than an actual precursor lesion because LCIS did not...
predict laterality of invasive cancer. The relative risk of subsequent invasive cancer in patients with LCIS has been reported to be 8.0 in the first 15 years following a biopsy of LCIS. The NSABP P-1 trial demonstrated an increased incidence of invasive cancers with a history of LCIS compared to patients without a history of LCIS: 12.99 events per 1,000 patients vs 6.41 events per 1,000 patients, respectively. As in patients with atypical hyperplasia, patient age appears to increase the risk of breast cancer in patients on tamoxifen (5.69 per 1,000 patients in the NSABP P-1 study vs 9.83 per 1,000 patients in the STAR trial). With regard to the type of invasive cancer, the majority of lesions are invasive ductal (49%), but invasive lobular occurs at a higher frequency (23%) than in the general population (6%).

As to current management recommendations, a subsequent excisional biopsy is recommended after a core biopsy finding of LCIS because LCIS usually does not cause changes in either imaging or physical examination and additional disease must be ruled out. Intraductal or invasive cancer can be located in 10% to 35% of excisional biopsies following a core biopsy of LCIS. Once other abnormalities have been ruled out, the recommended course of action includes close observation with or without chemoprevention.

The role of bilateral prophylactic mastectomy is debatable as only 16% of patients who elect to observe LCIS will eventually develop cancer. More recently, questions have resurfaced as to whether LCIS is a precursor lesion. In a review of the SEER data from 1988 to 2001, Li et al noted a higher rate of ipsilateral tumors in patients with prior LCIS (ipsilateral incidence of 7.3/1,000 person-years vs contralateral incidence of 5.2/1,000 person-years). Interestingly, the rate with LCIS occurred at a higher rate than DCIS (ipsilateral incidence of 5.4/1,000 person-years vs contralateral incidence of 4.5/1,000 person-years). The authors hypothesize the difference may be due to the different management strategy for each lesion: surgery for DCIS and observation/chemoprevention for LCIS. Furthermore, Fisher et al noted an increased incidence of ipsilateral breast cancer after excisional biopsy demonstrating LCIS (14.4% vs 7.8%), and 96% of the ipsilateral tumors occurred at the site of initial LCIS.

One variant of LCIS worth mentioning is newly termed pleomorphic LCIS. This form of LCIS shows high-grade cytological and architectural features associated with both DCIS and LCIS. These lesions typically lack staining for E-cadherin (Fig 8B), and additional findings such as comedo necrosis (Fig 8C) might be seen. Due to a lack of extensive follow-up, current recommendations are to treat these patients more like patients with DCIS than with LCIS. They require excision to negative margins with consideration towards postoperative radiation.

Prevention Trials

Tamoxifen

The most extensive evaluation of chemoprevention agents has been with tamoxifen. Tamoxifen, a selective estrogen receptor modulator (SERM), inhibits the bind-
ing of estrogen to estrogen receptors and also acts as an agonist on bone, the uterus, and liver. The data from multiple, randomized studies have supported the use of tamoxifen for prevention of breast cancer in high-risk individuals. The largest of these studies, the Breast Cancer Prevention Trial (NSABP P-1), compared tamoxifen to placebo in over 13,000 women with a Gail model score ≥1.66%. The study was halted early due to a 49% reduction of invasive breast cancer. More specifically, tamoxifen reduced the risk of breast cancer in LCIS patients by 56% and in atypical hyperplasia patients by 86%. It is interesting that tamoxifen preferentially decreased the incidence of estrogen receptor (ER)-positive tumors, a common finding of atypical hyperplasia and LCIS. In addition, there was a 50% reduction in the incidence of noninvasive cancers in the tamoxifen arm. Adverse outcomes due to tamoxifen, such as increased risk of endometrial cancer and thromboembolic events, were reported (risk ratio of 2.53 for endometrial cancer and 3.01 for pulmonary embolism).

A smaller reduction was noted in the International Breast Cancer Intervention Study (IBIS-I) in which a 32% risk reduction was noted after 50 months in patients with a greater than twofold relative risk of breast cancer. Two additional European studies, the Royal Marsden Hospital study and the Italian study, have failed to demonstrate a statistical benefit toward tamoxifen, but many believe that differences in patient selection, poor compliance, and insufficient power account for the differences. A further meta-analysis of these four trials produced a 38% reduction in the incidence of breast cancer and decreased ER-positive tumors by 48%.

**Raloxifene**

Raloxifene, a second-generation SERM, is similar to tamoxifen in its effects on breast, bone, and liver. However, raloxifene is not an estrogen agonist on the uterus. The initial study, the Multiple Outcomes of Raloxifene Evaluation (MORE), primarily evaluated osteoporosis...
with a secondary endpoint of breast cancer incidence. A 76% decrease in breast cancer incidence was noted in the raloxifene group compared to placebo over 4 years. The Continuing Outcomes Relevant to Evista (CORE) trial further evaluated raloxifene after 4 additional years of use, for a total of 8 years. A 66% reduction was noted in the raloxifene arm of the study. The results of these trials led to the NSABP STAR P-2 trial where 5 years of raloxifene was compared head-to-head with 5 years of tamoxifen in high-risk, postmenopausal individuals. Raloxifene could not be administered to premenopausal women secondary to increased incidence of ovarian cyst. In approximately 20,000 randomized patients, there were no statistical differences in invasive breast cancer incidence between the two groups ($P = .83$). Compared with tamoxifen, the raloxifene arm had fewer in the number of uterine cancers ($P = .07$), thromboembolic events ($P = .01$), and cataracts ($P = .002$). These results support the use of raloxifene as an alternative to tamoxifen. It is important to note that the incidence of noninvasive cancer was lower in the tamoxifen arm although this was not statistically significant ($P = .052$).

**Aromatase Inhibitors**

Aromatase inhibitors have played a limited role in chemoprevention due to their use being restricted to postmenopausal women. Aromatase inhibitors act through inhibiting the aromatase enzyme, thereby blocking systemic production of estrogen. In premenopausal women, the majority of estrogen is produced by the ovaries. Therefore, aromatase inhibitors would be ineffective unless the premenopausal woman was made postmenopausal via surgery, radiation, or luteinizing hormone-releasing hormone (LHRH) agonists.

Studies of aromatase inhibitors have mainly focused on the adjuvant treatment to hormone receptor-positive breast cancer in the postmenopausal patient. Three randomized trials have demonstrated superior disease-free survival rates with various aromatase inhibitors over tamoxifen in the adjuvant setting. Interestingly, these studies have demonstrated a greater reduction in contralateral cancers compared to tamoxifen (38% to 58% reduction compared to tamoxifen). Furthermore, patients had an improved safety profile compared to tamoxifen with decreased incidence of uterine cancer and thromboembolic events.

With such dramatic results in the adjuvant setting, one would hypothesize similar results as a chemopreventive agent in the postmenopausal woman. Results are awaited from current randomized trials such as the National Cancer Institutes of Canada Clinical Trials Group MAP3 (ExCel) trial evaluating exemestane in prevention of cancer in postmenopausal women at increased risk of developing breast cancer, the International Breast Cancer Intervention Study-II (IBIS-II) trial, and the Aromasin Prevention Study (ApreS). The IBIS-II trial compares anastrozole to placebo in high-risk women. The ExCel study will compare exemestane to placebo in patients with a Gail score of $\geq 1.66$, and the ApreS will do the same comparison in BRCA carriers.

Some authors have put forward the possibility of using aromatase inhibitors in premenopausal women. By targeting estrogen production within the breast or by using a lower dose of an aromatase inhibitor, the systemic effects of aromatase inhibitors for the premenopausal patient and the subsequent ovarian stimulation might be avoided. Future studies might be able to develop an option for this patient subset.

**Other Agents**

Multiple other agents have been studied for their potential chemopreventive effects in breast cancer. An agent such as aspirin or ibuprofen, which blocks prostaglandin synthesis, would theoretically decrease aromatase gene stimulation. Two retrospective studies have shown a 20% to 28% risk reduction with aspirin. Early studies reported that agents such as ornithine decarboxylase inhibitors and retinoids interfered with carcinogenesis, but benefit was not shown in prospective trials. Statin medications have demonstrated risk reduction of breast cancer in preliminary evaluation. In a Canadian study, there was a 28% risk reduction when statin users were compared to bile-acid binding resin users, suggesting an alternative mechanism to interfere with breast cancer development.

**Conclusions**

Benign lesions of the breast can confuse both the clinician and patient. Fig 9 represents an algorithm of the strategy employed at our institute. Much of the decision making falls onto clinical judgment as many lesions are confusing and because every patient is different (eg, family history, level of fear in patient, comorbidities). Clearly, the “busy breast” puts a patient at increased risk for breast cancer. The role of the clinician is to rule out an adjacent malignancy and develop a proper prevention/screening strategy. As research continues, additional chemoprevention medications will be identified, and the significance of benign, high-risk lesions will be better understood. As genetic testing on these lesions continues, the possibility of a gene test to stratify risk should become available for premalignant lesions.

**References**


