Atypical Apocrine Adenosis of the Breast
A Clinicopathologic Study of 37 Patients with 8.7-Year Follow-Up

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BACKGROUND. Apocrine metaplasia is occasionally superimposed on sclerosing adenosis (apocrine adenosis) in breast biopsies, and cytologic atypia is sometimes present (atypical apocrine adenosis). The long term risk of patients developing breast carcinoma subsequent to the diagnosis of this lesion is unknown.

METHODS. Atypical apocrine adenosis was defined as apocrine adenosis with enlarged nucleoli and a greater than threefold variation in nuclear area. Lesions with recognizable cytoarchitectural patterns of intraductal carcinoma were excluded. Surveillance, Epidemiology and End Results (SEER) data were used as the reference population for calculations of relative risk.

RESULTS. Thirty-seven women with atypical apocrine adenosis had a mean follow-up of 8.7 years. Four patients developed invasive ductal carcinoma of the breast (3 ipsilateral, 1 contralateral) after a mean of 5.6 years. The relative risk of developing carcinoma was 5.5 (95% confidence interval [CI], 1.9–16). All patients who developed carcinoma were older than age 60 at the time of breast biopsy showing atypical apocrine adenosis, and carcinoma developed at a mean age of 70 years. In the older than 60 years age group (11 patients), the relative risk of developing carcinoma was 14 (95% CI, 4.1–48).

CONCLUSIONS. Atypical apocrine adenosis confers an increased risk of developing breast carcinoma in women older than age 60, and the risk in younger women is probably low. Some cases of atypical apocrine adenosis may represent in situ apocrine carcinomas that are difficult to diagnose because of the absence of the usual architectural features of intraductal carcinoma. Cancer 1996; 77:2529–37. © 1996 American Cancer Society.

KEYWORDS: breast carcinoma, apocrine metaplasia, atypical hyperplasia, sclerosing adenosis, fibrocystic disease.

Apocrine metaplasia and sclerosing adenosis are benign epithelial alterations in the breast that are regarded as slightly increasing the risk of breast carcinoma, with relative risks in the range of 1.3 to 2.1 times the reference population. Occasionally, apocrine metaplastic changes are superimposed on sclerosing adenosis; this pattern has been referred to as apocrine adenosis. Apocrine adenosis may exhibit cytologic atypia, and may present a confusing histologic appearance that mimics invasive carcinoma. In a recent study of the reproducibility of diagnoses in breast biopsies, 4 of 12 pathologists rendered a diagnosis of invasive carcinoma in a case of apocrine adenosis. It has not been determined whether women with this lesion have an increased long term risk of developing carcinoma. Such patients have been followed for a mean of fewer than 3 years in only 1 report.
Intraductal carcinoma with typical morphologic patterns may occur within sclerosing adenosis or apocrine adenosis, and its behavior is expected to be similar to intraductal carcinomas arising elsewhere. In contrast, the behavior of apocrine adenosis that exhibits atypia but lacks the typical morphologic patterns of intraductal carcinoma is not known. The present study was designed to determine the behavior of atypical apocrine adenosis by observing patients to assess their risk of developing breast carcinoma.

MATERIALS AND METHODS
Lesions of the breast diagnosed as atypical apocrine metaplasia or atypical apocrine metaplasia with sclerosing adenosis were retrieved from the files of the Armed Forces Institute of Pathology (AFIP) from the period 1974–1986. All histologic sections were reviewed. Sclerosing adenosis was defined as suggested by Jensen et al.1 Lesions exhibiting apocrine metaplastic changes within sclerosing adenosis were selected (Figs. 1 and 2). All of these lesions were then classified according to the presence or absence of cytologic atypia within apocrine adenosis. Atypical cytologic features in apocrine-type epithelium have been described,9,12–15 and include prominent nucleoli, multiple nucleoli, variation in nuclear size and shape, and nuclear hyperchromasia. A diagnosis of atypical apocrine adenosis, if it is to have any value, must have specific, defined criteria. Therefore, the diagnostic features require clarification.

First, the term “prominent nucleoli,” warrants careful definition because its use has been ambiguous. The term “prominent” indicates a feature that stands out. A nucleolus can stand out because it is distinct, with a clear and sharp margin, or it can stand out because it is enlarged. The common type of apocrine metaplasia that occurs frequently in breast biopsies virtually always exhibits small nucleoli that are distinct with sharp margins, and therefore are prominent. This type of nucleolar prominence is a nearly universal feature of apocrine differentiation, whether in benign or malignant lesions, and is therefore of no value for subdividing apocrine lesions. Of much greater importance is nucleolar size. In our experience, and in reports
of apocrine carcinomas, apocrine carcinomas and apocrine atypias frequently exhibit marked nucleolar enlargement. It is this sense of "prominent nucleoli" that is meant in the descriptions of apocrine carcinomas, and it is nucleolar enlargement, not nucleolar prominence per se, that is an atypical feature in apocrine cells.

Second, a quantitative criterion for variation in nuclear size in atypical apocrine lesions has been used by some authors. It is important to note here that nuclear size refers to nuclear area in a 2-dimensional section, and that a 3-fold variation in nuclear size, as suggested by Tavassoli and Norris, corresponds to a 1.73-fold increase in nuclear diameter; i.e., a nucleus that has a diameter of 1.73 times a neighboring nucleus has an area of 3 times this nucleus.

There is no uniformly accepted set of criteria for a designation of atypical apocrine metaplasia or hyperplasia, nor is there a consensus on criteria for the distinction of atypical apocrine lesions from intraductal apocrine carcinoma. During the initial phase of this study, the following criteria for atypical apocrine adenosis were adopted. Four features in the apocrine cells were evaluated: presence of threefold variation in nuclear size (nuclear area), enlarged nucleoli, hyperchromasia, and marked nuclear membrane irregularities. At least two of these four features were required for a designation of atypia. No minimum size requirement was used. During the course of the study, it became apparent that the identification of hyperchromasia and nuclear membrane irregularities was not reproducible in a number of cases, in part because the evaluation of these changes was complicated by fixation artifacts, variation in section thickness and staining intensity, and other factors beyond our control. Therefore, the study inclusion criteria were simplified. Both enlarged nucleoli and threefold variation in nuclear size were required for a diagnosis of atypical apocrine adenosis; again, there was no quantitative requirement. The presence or absence of mitotic figures within the lesion was also noted, but mitotic counts were not performed, and mitotic activity was not included in the diagnostic criteria.

Because we were assessing the risk of atypical apocrine lesions within sclerosing adenosis, cases with atypical apocrine hyperplasia/metaplasia outside of sclerosing adenosis were excluded. Papillary apocrine hyperplasia without atypia outside of sclerosing adenosis did not lead to exclusion. The presence of usual atypical ductal hyperplasia outside of sclerosing adenosis was noted but did not prompt exclusion from the study when atypical apocrine adenosis was present.

The purpose of this study was to evaluate the biologic potential of atypical apocrine lesions that do not form easily classifiable morphologic patterns, and whose biologic potential is not clear. Therefore, cases of apocrine adenosis that contained recognizable patterns of the usual types of apocrine intraductal carcinoma (cribriform or comedo types) were excluded. For cases included in the study, no attempt was made to separate a group of noninvasive apocrine carcinomas beyond the designation of the presence or absence of atypia as defined above.

Follow-up information was obtained by communication with patients, physicians, pathologists, and cancer registries. Almost all patients for whom follow-up was obtained were located through Equifax Government and Special Systems, Information Research Division (McLean, VA). This service locates individuals primarily based on their social security number. Patients who were found to have had breast carcinoma prior to or synchronous with the biopsy showing apocrine adenosis were excluded.
TABLE 1  
Comparison of Study Patients to Patients Lost to Follow-Up

<table>
<thead>
<tr>
<th>Presentation (%)</th>
<th>Study patients</th>
<th>Patients lost to follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. age (yr)</td>
<td>37 50</td>
<td>22 47</td>
</tr>
<tr>
<td>Palpable mass</td>
<td>18 (49)</td>
<td>14 (64)</td>
</tr>
<tr>
<td>Abnormal mammogram</td>
<td>13 (35)</td>
<td>5 (23)</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>6 (16)</td>
<td>13 (35)</td>
</tr>
<tr>
<td>No. &gt; age 60 yr (%)</td>
<td>11 (30)</td>
<td>5 (23)</td>
</tr>
<tr>
<td>Mitotic activity present (%)</td>
<td>15 (41)</td>
<td>12 (55)</td>
</tr>
<tr>
<td>ADH elsewhere in biopsy (%)</td>
<td>3 (8)</td>
<td>1 (5)</td>
</tr>
</tbody>
</table>

ADH: atypical ductal hyperplasia.  
No significant differences were found between study patients and patients lost to follow-up (P > 0.05).  
All patients were diagnosed by biopsy only.

Relative risk was calculated using age-specific incidence rates from 1987–1988 Surveillance, Epidemiology, and End Results (SEER) data for the reference population. The number of expected cancers was calculated for each patient based on age and number of years of follow-up, and then totaled for the entire group. Confidence intervals (CI) were calculated according to Katz's method. Differences in patient age and presenting signs between patients included and excluded from the study were compared using the Student's t test and the chi-square test, respectively.

RESULTS
Fifty-nine biopsies with atypical apocrine adenosis were initially accepted in the study. Clinical follow-up was obtained for 37 patients who form the basis of this report. Differences between study patients and those lost to follow-up are shown in Table 1.

Clinical Presentation
The mean patient age was 50 years (range, 24–69 years). Information on family history of breast carcinoma was not available. Eighteen patients presented with a palpable mass, 13 with an abnormal mammogram, 1 with bleeding from the nipple, and the presentation was unknown in 4 patients. The lesion was an incidental finding in 1 patient in a reduction mammoplasty specimen. All patients were diagnosed by biopsy only; none underwent a mastectomy.

Histologic Findings
Apocrine adenosis was characterized at low power by a lobulocentric distribution of compressed acini with the usual architecture of sclerosing adenosis (Figs. 1 and 2). Apocrine features were usually present throughout the involved lobule(s); however, partial involvement occurred occasionally, particularly in larger lesions (i.e., nodular sclerosing adenosis). Slight

FIGURE 4. High-power view of nonatypical apocrine adenosis showing minimal variation in nuclear size, and small, prominent nucleoli. Compare nucleolar size with that in Figures 5 and 7, which are shown at the same magnification (H & E, x300).
addition to nucleolar enlargement and greater than threelfold variation in nuclear size, marked variation in nucleolar size was often present, and multiple nucleoli were occasionally observed. Three biopsies with atypical apocrine adenosis also had ordinary atypical ductal hyperplasia elsewhere in the biopsy. Mitotic activity was present in 15 cases (Fig. 7).

Cases lost to follow-up were morphologically similar to cases studied, and the frequencies of ordinary atypical ductal hyperplasia and mitotic activity were similar (Table 1).

**Follow-Up**

The 37 patients were observed for a mean of 8.7 years (range, 3–15.9 years). Four patients developed infiltrating duct carcinoma after a mean of 5.6 years (Table 2). One of these four patients had associated ordinary atypical ductal hyperplasia elsewhere in the biopsy. The rate of development of carcinoma was 1.2% per year, and the relative risk was 5.5. Relative risks and analysis of subgroups are shown in Table 3.

Eleven patients were 60 years of age or older at the time of initial biopsy; the rate of development of carcinoma in this age group was 5.5% per year, whereas none of the younger women developed carcinoma. The relative risk in the ≥60 age group was 14.

The 95% confidence limits on the relative risks of all subgroups, except those with lesions without mitoses and those patients younger than age 60, excluded unity (Table 3). Therefore, these subgroups of patients have a significantly elevated risk of developing carcinoma ($P < 0.05$).

Had the 3 patients with ordinary atypical ductal hyperplasia been excluded from the study, the relative risk for all patients would be 4.6 (95% CI, 1.4–15), and the relative risk in patients older than age 60 would be 13 (95% CI, 3.4–50).

**DISCUSSION**

The histologic criteria for atypical apocrine lesions of the breast, including low grade intraductal apocrine carcinoma, are controversial. O’Malley et al. recently described a borderline group of intraductal apocrine lesions. Tavassoli and Norris recently reported a series of intraductal apocrine carcinomas for which they
used their previously evaluated 2 mm criterion for diagnosing noncomedo intraductal carcinomas. Some experts do not accept this criterion. One of the figure legends in Tavassoli and Norris’ study indicates that one of the reviewers disagreed with the diagnosis of the lesion illustrated. Clearly, there is no consensus on the criteria for the distinction of atypical apocrine hyperplasia from intraductal apocrine carcinoma.

No attempt was made in this study to separate apocrine atypias from intraductal apocrine carcinomas. Within the compressed epithelial structures of sclerosing adenosis, atypical proliferative epithelial lesions do not always develop the usual architectural features of intraductal apocrine carcinoma (cribriform or comedo patterns) that would facilitate their diagnosis. Readily recognized patterns of apocrine intraductal carcinoma within sclerosing adenosis were excluded from this study to assess the biologic potential of the more problematic apocrine lesions.

Carter and Rosen studied 51 patients with atypical apocrine metaplasia in sclerosing adenosis (apocrine adenosis). They described a spectrum of atypical changes in these lesions that is similar to our observations. They did not state how many of their cases had more than a mild degree of atypia. Their mean follow-up period was 35 months, and none of the patients developed carcinoma. If our follow-up had been limited to 3 years, we also would not have observed any carcinomas, because all 4 carcinomas in the present study developed 4 years or longer after the initial biopsy.

In the present series, the mean follow-up was almost 9 years. In addition, we have precisely defined our criteria for atypia. Our findings indicate that women with atypical apocrine adenosis have a risk of developing invasive breast carcinoma of approximately 1.2% per year, and that both breasts are at risk. This description of risk is very similar to that of lobular neoplasia (lobular carcinoma in situ), which is approximately 1% per year. Importantly, all 4 women who developed carcinoma were older than age 60 at the time of the biopsy showing apocrine adenosis, and developed invasive carcinoma at a mean age of 70 years. Thus, younger women with atypical apocrine adenosis may be at little or no risk, whereas women older than age 60 appear to be at substantially increased risk of developing invasive breast carcinoma.

The relative risk of 14 in women older than age 60 is notably higher than that conferred by other proliferative breast lesions. For nonatypical proliferative lesions, the relative risk of developing invasive breast carcinoma is approximately 1.3–2.1 and for atypical hyperplasia, 2.6–5.3. Atypical hyperplasia in women with a positive family history of breast carcinoma confers a relative risk of approximately 8–11. Carcinoma in situ of ductal or lobular type is also associated with an 11-fold increased risk. The overall risk of 5.5 found in the present study is thus similar to that for other types of atypical hyperplasia. The relative risk of 14 in patients older than age 60 is comparable with that associated with carcinoma in situ. However, this high relative risk cannot be directly compared with the previously reported risk estimates because the latter have not been broken down by patient age in most reports.

There are several viable explanations, which are not mutually exclusive, of the nature of atypical apocrine adenosis. First, this may be a true atypia of apocrine-type epithelium, and may be a risk factor for carcinoma, as are other mammary epithelial atypias. Second, these lesions may be in situ apocrine carcinomas within sclerosing adenosis; the ipsilateral carcinomas might then represent invasive recurrences of these in situ carcinomas. Third, these lesions could represent lobular neoplasia within sclerosing adenosis. Although the usual morphology of lobular neo-
TABLE 2
Characteristics of the Patients Who Developed Carcinoma

<table>
<thead>
<tr>
<th>Age at initial biopsy (yr)</th>
<th>Presentation</th>
<th>Age at diagnosis of carcinoma</th>
<th>Interval (yr)</th>
<th>Laterality of carcinoma</th>
<th>Histology of carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>61</td>
<td>Palpable mass</td>
<td>69</td>
<td>8.3</td>
<td>Ipsilateral</td>
<td>Invasive duct, minor apocrine features</td>
</tr>
<tr>
<td>66</td>
<td>Abnormal mammogram</td>
<td>72</td>
<td>5.8</td>
<td>Contralateral</td>
<td>Invasive duct, minor apocrine features</td>
</tr>
<tr>
<td>64</td>
<td>Palpable mass</td>
<td>68</td>
<td>4</td>
<td>Ipsilateral</td>
<td>Invasive apocrine</td>
</tr>
<tr>
<td>68</td>
<td>Abnormal mammogram</td>
<td>72</td>
<td>4.4</td>
<td>Ipsilateral</td>
<td>Invasive duct</td>
</tr>
</tbody>
</table>

TABLE 3
Relative Risk of Developing Carcinoma by Subgroups

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>No. observed carcinomas</th>
<th>No. expected carcinomas</th>
<th>Relative risk (observed/expected)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>37</td>
<td>4</td>
<td>0.723</td>
<td>5.5</td>
<td>1.9-16</td>
</tr>
<tr>
<td>Age &lt;60</td>
<td>26</td>
<td>0</td>
<td>0.436</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>Age ≥60</td>
<td>11</td>
<td>4</td>
<td>0.287</td>
<td>14</td>
<td>4.1-48</td>
</tr>
<tr>
<td>With mitoses</td>
<td>15</td>
<td>2</td>
<td>0.228</td>
<td>8.8</td>
<td>2-38</td>
</tr>
<tr>
<td>Without mitoses</td>
<td>22</td>
<td>2</td>
<td>0.494</td>
<td>4</td>
<td>0-17</td>
</tr>
<tr>
<td>Age ≥60 with mitoses</td>
<td>4</td>
<td>2</td>
<td>0.119</td>
<td>17</td>
<td>2.4-121</td>
</tr>
<tr>
<td>Age ≥60 without mitoses</td>
<td>7</td>
<td>2</td>
<td>0.169</td>
<td>12</td>
<td>2.3-62</td>
</tr>
</tbody>
</table>

CI: confidence interval.

plasia within sclerosing adenosis is well described and unlike this lesion, lobular neoplasia and invasive lobular carcinoma occasionally have prominent apocrine features (Fig. 8), and, as noted above, the behavior of atypical apocrine adenosis is reminiscent of that of lobular neoplasia. Finally, and most likely, atypical apocrine adenosis reflects some combination of these three possibilities.

We did not have enough information regarding the precise location of the carcinomas to determine whether they were located near the prior biopsy site, and therefore might represent invasive recurrences of in situ apocrine carcinomas. The relatively short mean interval to invasive carcinoma (5.6 years), the fact that 3 of the 4 carcinomas were ipsilateral to the initial biopsy, and the presence of apocrine features in some of the invasive carcinomas would support the belief that some of our cases of atypical apocrine adenosis are actually in situ apocrine carcinomas.

The lack of a control group of women with apocrine adenosis without atypia is a limitation of our study. We were unable to obtain follow-up on a sufficient number of women with nonatypical apocrine adenosis to make any meaningful comparisons. Well over 100 patients with long term follow-up would have been necessary for such an internal control group to have any reasonable degree of statistical power. Our available resources did not permit accrual or follow-up of this large number of patients. Nonetheless, the SEER database is a valuable alternative to an internal control group. This allowed us to calculate a relative risk compared with the general population, but did not permit a comparison with women with nonatypical apocrine adenosis.

We have shown that the elevated risk associated with atypical apocrine adenosis is statistically significant, particularly in the age group older than 60 years. The hormonal milieu differs between premenopausal and postmenopausal women, the biology of premenopausal and postmenopausal breast carcinoma differs, and advanced age is one of the most important risk factors for breast cancer. Therefore, the influence of patient age on the risk of breast carcinoma with atypical apocrine adenosis is not surprising. However, it is possible that the relative risk of 14 is an overestimate of the risk of atypical apocrine adenosis in the general population because of the consultative nature of AFIP material. This may have skewed our study group inasmuch as the most severely atypical lesions tend to be submitted for consultation.

Other potential sources of bias relate to the relatively small number of patients studied, and the number of patients lost to follow-up. It can be argued that the significant number of patients lost to follow-up...
Figure 8. An illustration of lobular neoplasia with apocrine features (not from the present study). The neoplastic lobular cells exhibit pagetoid spread with undermining and flattening of the overlying epithelial layer. Apocrine features in the atypical lobular proliferation include prominent nucleoli and abundant granular cytoplasm that was eosinophilic (H & E, x300).

(22 of 59) may have elevated our risk estimates because of the possibility that a patient who develops carcinoma is more easily located. This bias did not influence our results because our follow-up methods ultimately relied almost exclusively on the availability of an accurate social security number to locate patients. Virtually all patients for whom we had an accurate social security number were located, and very few others were found. This is essentially the only factor that played a significant role in which patients were located and which were not.

It is possible that some experts would classify some of our cases of atypical apocrine adenosis as intraductal apocrine carcinoma (within sclerosing adenosis). However, in light of the difficulty in assessing architectural features within sclerosing adenosis when the usual patterns of intraductal atypia or carcinoma are absent, and the lack of a consensus on criteria for the diagnosis of intraductal apocrine carcinoma, we believe our approach is reasonable at present. We recommend careful clinical follow-up of all women with this lesion and thorough histologic sampling of all biopsy material to exclude carcinoma. In women older than age 60, complete excision with documented negative surgical margins would seem prudent, because some of these lesions may represent in situ carcinomas.

REFERENCES