

# Papillary Apocrine Change of the Breast: Associations with Atypical Hyperplasia and Risk of Breast Cancer<sup>1</sup>

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## Abstract

**Micropapillary patterns of apocrine change in human female breasts are common histological findings. They have been identified as cancer associated and implicated as an indicator of cancer risk in a predictive manner.**

This study has stratified papillary apocrine change (PAC) into categories of increasing complexity using a combination of cytological and histological pattern rules. Cases (2,876) were identified in a review of 10,357 benign breast biopsies. Of 5966 women, 1613 had PAC and were followed for a median of 20 years after biopsy for the development of invasive carcinoma of the breast. There was a slight association with cancer risk elevation, but most of this disappeared when women with concurrent, specifically identified patterns of atypical hyperplasia (AH) were excluded from the groups with PAC. The resultant relative risk was only 1.2 after women with AH were excluded. Only 1% of the reviewed biopsies demonstrated highly complex patterns of PAC, and 20% of these had coexistent lesions of AH. Women with highly complex patterns of PAC without AH did experience a relative risk of 2.4 (95% confidence interval = 0.77–7.04) but without statistical significance. More than one-half of all PAC patterns occurred without concurrent foci of lesions of proliferative disease that are associated with a slight elevation of breast cancer risk (at least 1.5 times); when present without proliferative disease, there was no suggestion of later breast cancer risk for PAC.

## Introduction

Alteration of human mammary epithelium to the histological appearance seen in apocrine sweat glands is quite common. It is a cytological alteration associated with most breast cysts. These apocrine-appearing cells are present frequently in papillary clumps of cells extending into the central lumen. This common appearance has been termed PAC<sup>3</sup> (1, 2).

In an initial study by our group, PAC was accepted as a single entity without stratification by complexity and was found to have a slight association with increased breast cancer risk over the age of 45 years, but this was not true in younger women (1). The current paper presents our experience in a much larger series of patients (3, 4) in whom PAC was stratified by degree of complexity, and associations with risk of subsequent invasive breast cancer were ascertained. Concurrent associations with AH defined separately and specifically (3, 4) in nonapocrine foci were also evaluated.

The criteria for follow-up were the same as those given in Dupont and Page (3) except that the lack of proliferative breast disease was not a reason for exclusion for patients from any study hospital. Follow-up was obtained on 5966 (89%) of eligible patients.

## Patients and Methods

**Study Design.** The study cases and conduct of study are as reported previously (3); briefly stated: all breast biopsies performed at Vanderbilt University Hospital between July 1959 and December 1968 and at St. Thomas and Baptist Hospitals between 1952 and 1968 were reviewed. Of these biopsies, 10,366 were diagnosed originally as benign and selected for histological examination. Slides with PAC by our histological criteria were identified. The criteria for follow-up were the same as those given in Dupont and Page (3) except that the lack of PD was no longer a reason for exclusion of patients from any study hospital. Follow-up was obtained on 5966 (89%) of eligible patients. Prevalence information in this paper is included from the whole group of histologically reviewed cases, whereas current risk statements were derived from the follow-up group of 5966 women. FH was defined as present when a first-degree relative (mother, daughter, or sister) had a history of breast carcinoma.

The histological definitions of the three types of PAC are as follows. They have been constructed in order to be as simple as possible to foster agreement in diagnostic assignment, and all categories require classic apocrine cytology (5, 6). The simple form of PAC is diagnosed when the epithelium lining an apocrine cyst is focally three or more cells thick, and the resulting "mounds" of cells show no tendency to touch one another within the lumen of the space in which they reside. These clumps or hummocks of cells were broader more regularly at the base than at the tip (Fig. 1A). In the moderate or complex form of PAC, papillae similar to those seen in the simple form were taller and somewhat broader at the base, but otherwise they were more attenuated and showed a tendency to come close to or touch each other within the lumen (Fig. 1B). Highly complex papillary

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<sup>3</sup> The abbreviations used are: PAC, papillary apocrine change; RR, relative risk; AH,

atypical hyperplasia; CI, confidence interval; FH, family history; DCIS, ductal carcinoma *in situ*; PD, proliferative disease; ADH, atypical ductal hyperplasia.

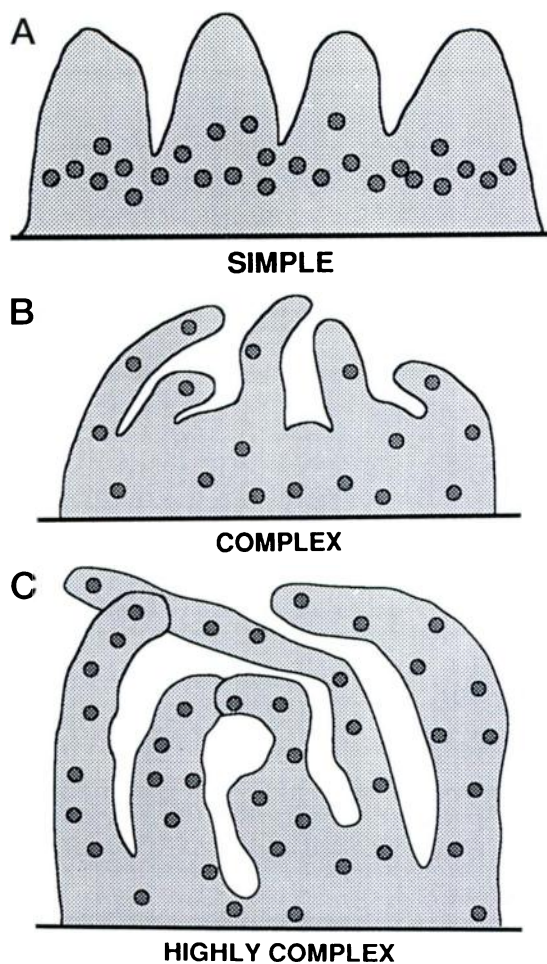


Fig. 1. A, simple PAC with small hummocks of characteristic cells of apocrine cytology. B, complex PAC with prolongation of the arches into the lumen and tending to touch each other once. C, highly complex PAC with arches extending far into the central space and tending to cross or touch each other at least twice.

change was diagnosed when the papillae were greatly elongated, tended to be only two or three cells in width, and extended well within the lumen (Fig. 1C). In these last presentations, narrow arcades of apocrine cells frequently appeared intertwined with other papillations having separated tethers.

The last category was quite uncommon. Nuclear features were those seen regularly in usual or common presentations of apocrine change with frequent prominent nucleoli. However, nuclei were quite similar one to another and frequently vesicular. The nuclei, although large, were not greatly so. In some examples, occasional nuclei showed enlargement, but this did not reach >10% of the cells (6). Patterns of apocrine change with complex cribriform architecture that are properly considered ADH or DCIS (6) are rare and were excluded from the PAC category.

RRs for breast cancer were calculated with respect to women from the Third National Cancer Survey (Atlanta, GA) and are adjusted for age at time of biopsy and length of follow-up (3).

	All biopsies with PAC	% of biopsies with AH <sup>a</sup>
Simple	20.3% (n = 2,102)	5.1
Complex	6.5% (n = 673)	9.2
Highly complex	1.0% (n = 101)	20.8
All biopsies	100% (n = 10,357)	3.6

<sup>a</sup> Atypical hyperplasia, lobular, or ductal patterns.

	All patients with PAC (95% CI)	All patients with PAC but without AH [95% CI]
Simple	1.39 <sup>b</sup> (1.1–1.8) (n = 1,169)	1.29 (0.96–1.7) (n = 1,111)
Complex	1.30 (0.77–2.24) (n = 384)	0.90 (0.47–1.7) (n = 355)
Highly complex	3.14 <sup>c</sup> (1.3–7.6) (n = 60)	2.0 (0.77–7.4) (n = 45)

<sup>a</sup> Compared to analogous women from the Third National Cancer Survey.

<sup>b</sup>  $P = 0.02$ .

<sup>c</sup>  $P = 0.007$ .

## Results

Follow-up was obtained on 5966 women who had undergone biopsy revealing benign breast tissue. This represents 89% of women who were eligible for follow-up. The median follow-up interval was 20 years. The prevalence of PAC is presented in Table 1. The simple form is common, whereas the highly complex form is rare. An obvious positive association of increasingly complex patterns of PAC with AH is also presented in Table 1.

Table 2 presents cancer risk associations of PAC with and without AH. Statistical significance was reached for only two categories, simple PAC ( $P = 0.02$ ) and highly complex PAC ( $P = 0.007$ ). When women with coexistent AH were removed from these groups, statistical significance was lost. The associated lesions of AH were not evenly distributed throughout the three forms of PAC. In simple PAC there were equal numbers of ADH and atypical lobular hyperplasia, whereas in highly complex PAC only one biopsy had atypical lobular hyperplasia. Complex PAC was intermediate with twice as many examples of coexistent ADH (21 examples) as atypical lobular hyperplasia (10 examples). There were three biopsies in each of the lesser complexity categories with both ADH and atypical lobular hyperplasia, with none of the identifying women developing cancer on follow-up. Overall, the RRs in each category of complexity were similar, and did not approach statistical significance after removal of associated lesions reaching full criteria of AH. Similarly, when analysis of cancer risk relative to concurrent patterns of non-atypical PD and AH (collectively known as PD) was performed, PAC was not associated with an increased risk of breast cancer of any meaningful size (10%) or

Table 3 Associations of histopathology with age at biopsy

Age	PAC			All biopsies: PAC and non-PAC (%)
	Simple (%)	Complex (%)	Highly complex (%)	
<35	15	20	30	27
35-44	49	47	35	41
45-54	28	24	22	23
>54	7	9	13	9
Total	100	100	100	100
n	2,102	673	101	10,357

not increased at all. Specifically, of the 672 cases of simple PAC at biopsy, the subsequent RR of invasive breast cancer was 1.10 with a P value of 0.6 and a 95% CI of 0.75 to 1.61. When both forms of complex PAC were combined (for reasons of small numbers) and considered apart from concurrent appearance with PD (10 examples of highly complex PAC and 160 examples of complex PAC), the RR of later cancer development was 0.89. On the other hand, it is evident that most cases of Highly complex PAC (50 of 60) were associated with PD.

Cysts were present (over 3 mm in size) in just over 99% of the cases of PAC. The cancer risks of women with PAC were not demonstrably altered by age at detection. This conclusion is indicated by the age distributions of lesion types which are remarkably similar (Table 3) to each other and to overall age distribution of all women in the study. When age groups were stratified into decades, an increasing prevalence of PAC into the fifth decade is evident with a subsequent mild decline (Fig. 2).

No associations with a FH of breast cancer were evident. There was no increased incidence of any type of PAC with FH, and there was no increased risk of breast cancer over that of FH alone when FH and PAC were present in the same women. The overall RR for women with FH without PAC was 2.29 (95% CI = 1.68-3.12); when the 213 women with PAC and FH were analyzed, the overall RR was virtually the same: 1.97 (95% CI = 1.17-3.32). No further positive association or synergy of FH and PAC was found when the several strata of PAC were analyzed separately. Specifically, for the 60 women with complete follow-up and highly complex apocrine change, 11 had a positive FH, and none of these eleven developed breast cancer.

## Discussion

Apocrine alteration of mammary epithelium has occasioned a great deal of interest over the last several decades. There is a continuing body of evidence that cysts characterized by this type of epithelium have a greater incidence of recurrence after initial fluid aspiration, as well as a suggestion that cysts and apocrine change may be associated with the elevation of breast cancer risk (7-10). Therefore, it is appropriate to evaluate variations and possible stratifications of groups of women with apocrine change to see if any excess cancer risk is associated with this change in general or with defined subsets of this change.

This paper has evaluated the common types of apocrine change that are most frequently found in cysts of either small or large size. Our initial review of PAC did not recognize subdivisions and involved a different and much smaller cohort of approximately 1000 women from Vanderbilt Hospital only (1). The current study was designed to better understand the variations in the presentation of PAC and to evaluate these varia-

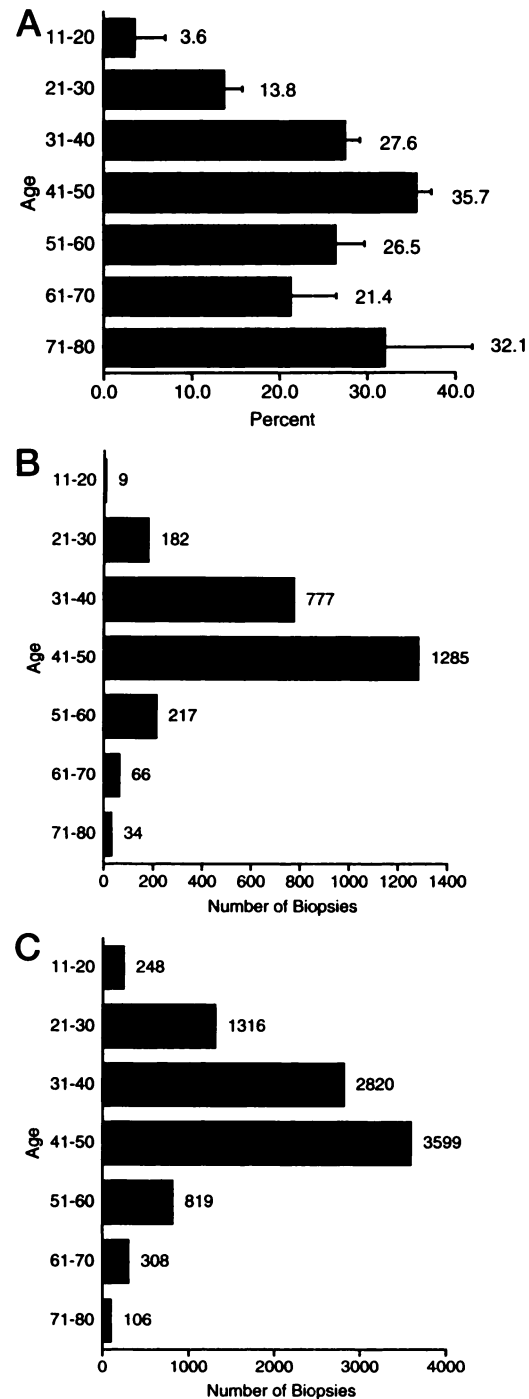


Fig. 2. A, incidence of PAC as a percentage of biopsies done in individual decades. Bars, 95% CIs. B, number of biopsies with PAC in each decade of patient age reflecting relative lack of information at young and older ages. C, number of all benign breast biopsies in the cohort.

tions in regard to their possible risk potential. The first consideration in subdividing or subtyping this change into reproducible categories is to define readily identifiable features. Basically, the resulting three categories recognize increasing complexity of cellular architecture and increasing number of

cells found above the basement membrane. The simplest form of PAC may be more frequent than a single layer of apocrine cells in a pure form. The most complex patterns are those that start to describe intersecting narrow arcades similar to patterns recognized in some examples of noncomedo ductal carcinoma *in situ*. However, in general it has been our practice to deny a diagnosis of AH or ductal carcinoma *in situ* if the nuclear cytological pattern present is that seen in usual apocrine change (6). Definition of these two extreme patterns left quite a few cases in the middle category defined as more similar to the simple papillations but having sufficient extension of the papillae to touch in the center of expanded spaces (Fig. 1B).

In our cohort of over 10,000 benign breast biopsies, the increasingly complex apocrine alterations were found in decreasing frequency as seen in Table 1. Note also that there is a slight but definitely favored association of the more complex examples with the co-occurrence of AH in the same biopsy. To determine predictive breast cancer risk without the possible influence of AH, cases of PAC with and without co-occurrence of AH were segregated as shown in Table 2. Note that although there is a suggestion of increased risk for the most complex patterns of PAC, it is not greatly different from that associated with common patterns of hyperplasia (1.6–1.9 times; Refs. 3, 12) unless also associated with patterns of AH.

We also analyzed the association of PAC with the other elements of PD of the breast, that is histological diagnoses associated with a slight (1.5–2.0 times) elevation of breast cancer risk: moderate and florid hyperplasias, sclerosing adenosis, and papillomas (3). When concurrent lesions of PD are excluded, the women with PAC have no increased risk of breast cancer. As with AH, it appears that there is an association between highly complex PAC and all forms of PD because only 10 of the 60 women with highly complex PAC did not also have PD with or without atypia in the same biopsy.

The very close association of apocrine cytology with cyst formation is acknowledged. Indeed, 99% of our cases of PAC were associated with cysts or microcysts (3). Thus, we have not directly answered the question of the risk association of cysts with cancer risk (7–9, 11–16). However, this study demonstrates that the cancer risk association of an epithelial alteration often seen in cysts (PAC) is weak, even when present in complicated form. The elevated breast cancer risk in women with more complex patterns of PAC appeared to be almost entirely due to a concurrent association with AH, and any risk elevation lost statistical significance when women with concurrently associated lesions of AH or PD were not included in the analysis (Table 2).

One of the major goals of our large follow-up study (3) was to clarify the suggestion of increasing cancer risk among women with PAC who were also over the age of 45 years at entry biopsy (1). This current and much more extensive evidence does not support any age stratification, which could result in indicating a role in breast cancer risk for PAC. The age distribution for PAC is similar to the overall study (Table 3). The greatest prevalence of PAC exists in the ages surrounding the premenopausal years (Fig. 2).

We conclude that complex patterns and arcades of apocrine-type cells in the breast are not of clinical concern with regard to concurrent or future breast cancer risk. Their presence might encourage a more intense search for concurrent AH if

that is considered of clinical interest. Most importantly, they are often present without concurrent elements of PD, which identifies increased risk of breast cancer of at least 50%. When only cases of PAC without concurrent patterns of PD are considered, the risk of later cancer is not increased over expected risk levels in the United States (Table 2). It is relevant to emphasize that patterns within the highly complex category of PAC are close to the patterns noted in McDivitt *et al.* (17) as indicating carcinoma *in situ* of ductal pattern. This is little problem in differential diagnosis when, as is usually the case, the alteration of PAC is <2 mm in extent. When the lesion is >4–8 mm in size or has >25% of nuclei with alternate patterns, some form of atypia or low-grade DCIS may be diagnosed as presented in O'Malley *et al.* (6). In the current study, lesions represented as apocrine DCIS in O'Malley *et al.* (6) are not considered. We believe that relatively concise rules foster interobserver agreement in this area (apocrine cytology plus histological patterns seen in Fig. 1), but there is no practical reason to separate simple PAC from complex PAC. Also, the occurrence of highly complex PAC is of practical importance only in avoiding over-diagnosing a borderline lesion, which it is not.

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