

# The Relationship of Cyst Type to Risk Factors for Breast Cancer and the Subsequent Development of Breast Cancer in Patients with Breast Cystic Disease

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**Abstract**—*The frequency of epithelial hyperplasia and papillary apocrine change in patients with palpable breast cysts lined by either apocrine or flattened epithelium has been compared. Hyperplasia of any degree, severe hyperplasia with or without atypia and papillary apocrine change were all seen significantly more frequently in patients with clinically palpable apocrine cysts. Twelve patients were identified with breast cancer with a history of cyst aspiration, in whom all cysts aspirated could be classified as apocrine or flattened on the basis of cytology or electrolyte composition of cyst fluid. Eleven patients had single or multiple apocrine cysts and one had a single flattened cyst. This represents a significantly increased preponderance of apocrine cysts as compared with that normally seen in patients with cystic disease. The mastectomy specimens of those 11 patients with a history of apocrine cyst aspiration more frequently contained hyperplastic changes and non-invasive carcinoma than age- and menopausal-matched controls who did not have a history of cystic disease. This study suggests that patients who develop cysts lined by apocrine epithelium may be at a greater risk of subsequent breast cancer than those with flattened epithelial cysts.*

## INTRODUCTION

SOME 7% of all women in the Western World develop a palpable breast cyst [1], and it has been reported that these women are at increased risk of breast cancer [1-3]. Pathological studies performed in patients with cystic disease have shown that the subsequent incidence of breast cancer is greatest in those women with epithelial hyperplasia associated with cysts [2-8]. The majority of women with cystic disease are not biopsied but treated by simple aspiration, and it remains uncertain which of these women are at greatest risk.

From studies of the composition of aspirated cyst fluids it has been possible to identify two populations of breast cysts on the basis of electrolyte content [9, 10]. The composition

appears to be directly related to whether the cyst is lined by apocrine or flattened epithelium [11]. The aim of the present study was first to compare the frequency and degree of hyperplasia in groups of patients with the two types of cysts and second to classify those cysts aspirated from patients who subsequently developed breast cancer.

## MATERIALS AND METHODS

During the 1960s it was the practice in Edinburgh to biopsy all palpable breast lumps, even if they were considered cystic. From the years 1966 and 1967 all patients who were clinically thought to have a palpable breast cyst were identified and the histology from each patient was reviewed. The nature of the lining epithelium of two groups of cysts was noted: (i) cysts bigger than 3 mm, which have been defined previously as macrocysts [1]; and (ii) cysts bigger than 1 cm, which would make them clinically palpable. Any pathological change in each of these groups of

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biopsy specimen was recorded. Particular attention was paid to the presence of foci of apocrine change, papillary apocrine change and any hyperplasia. Hyperplasia, when present was assessed on a five-point scale using similar criteria to those of Wellings *et al.* [12]: grade I, normal; II, minimal or moderate hyperplasia; III, severe hyperplasia; IV, hyperplasia with atypia; and V, carcinoma *in situ*.

From a review of patients with breast cancer, 12 were identified who had a history of cyst aspiration and where all cysts aspirated could be classified either on the basis of cytology (five patients) or electrolyte composition (seven patients) as apocrine (apocrine cells on cytology or  $\text{Na}^+/\text{K}^+$  ratio in cyst fluid  $<3$ ) or flattened epithelium (simple epithelial cells on cytology or  $\text{Na}^+/\text{K}^+$  ratio in cyst fluid  $\geq 3$ ). It has been previously shown that lining epithelium and electrolyte composition of cysts are directly related [11].

The mastectomy specimens of these 12 patients were reviewed, as were 12 age- and menopausal status-matched controls who did not have a history of cyst aspiration. The presence of cysts, apocrine change, hyperplasia and carcinoma *in situ* was recorded.

The  $\chi^2$  test was used to compare the frequency of pathological changes in the biopsies of patients who had cysts lined by either apocrine or flattened epithelium, and also to compare the ratio of women who had apocrine or flattened cysts in the group with breast cancer with that from a consecutive series of 100 patients treated in this department [13]. McNemar's test was used to compare the frequency of pathological changes in the pairs of matched mastectomy specimens.

## RESULTS

One hundred and thirty-six patients underwent biopsy for single or multiple breast cysts during 1966 and 1967 in the Royal Infirmary, Edinburgh. In six of the biopsies no macrocyst ( $>3$  mm) was identified and in 14 biopsies the epithelium lining the macrocyst had become detached and was not present on the sections examined. Thus

biopsies from 116 patients contained macrocysts suitable for analysis, of which 80 contained macrocysts lined only by apocrine epithelium, 30 contained macrocysts lined only by flattened epithelium and six had cysts lined by both types of epithelium. The 80 patients with apocrine cysts had a total of 183 macrocysts and the 30 with flattened cysts a total of 38. Thus on average there were 2.3 macrocysts per patient in the group with apocrine cysts, significantly more than the 1.3 macrocysts per patient in the group with flattened cysts ( $P < 0.01$ ). Eighty-six of these 116 biopsies contained cysts which were bigger than 1 cm and which would therefore have been clinically palpable and suitably treated by aspiration; 50 biopsies contained only apocrine cysts, 30 only flattened cysts and six mixtures of the two types. There was a mean of 2.2 cysts  $>1$  cm in the apocrine group and 1.2 cysts  $>1$  cm in the flattened group, the difference being significant ( $P < 0.01$ ).

A summary of the pathological changes in the biopsy specimens from the 110 patients who had either all apocrine or all flattened macrocysts and of the 80 with palpable apocrine or flattened cysts  $>1$  cm are present in Tables 1 and 2. Separate foci of apocrine change, papillary apocrine change and epithelial hyperplasia were all significantly more common in patients with apocrine cysts. Hyperplasia of a severe degree (grade III) or with atypia (grade IV) were only seen in patients with palpable apocrine cysts.

The 12 patients who subsequently developed breast cancer had a total of 33 cysts aspirated. Three of these had only a single cyst, five had two cysts aspirated, one had three, two developed four cysts and one had nine cysts. Eleven patients had single or multiple apocrine cysts and one patient had a single flattened cyst. No patient had mixtures of the two types of cyst. This ratio of 11 apocrine:1 flattened is significantly different from that of approximately 1:1 in a consecutive series of 100 patients treated by aspiration previously reported by us ( $P < 0.01$ ) [13]. It is also different from the 50:30 ratio of patients with palpable cysts in the histological study ( $P < 0.05$ ).

Table 1. Comparison of the frequency of pathological changes in the surrounding breast tissue in the groups of patients who, on biopsy, were shown to have macrocysts all lined by either apocrine or flattened epithelium

Cyst epithelium	No. of patients	No. and % of patients in each group with:			
		foci of apocrine change	papillary apocrine change	hyperplasia grade II—IV	hyperplasia grade III—IV
Apocrine	80	68* (85%)	49* (61%)	50* (63%)	9† (11%)
Flattened	30	12 (40%)	8 (27%)	8 (27%)	0 (0%)

Significantly greater frequency in apocrine group: \* $P < 0.005$ ; † $P < 0.05$ .

Table 2. Comparison of the frequency of pathological changes in the surrounding breast tissue in the groups of patients who, on biopsy, were shown to have cysts >1 cm (palpable), all lined by either apocrine or flattened epithelium

Cyst epithelium	No. of patients	No. and % of patients in each group with:			
		foci of apocrine change	papillary apocrine change	hyperplasia grade II-IV	hyperplasia grade III-IV
Apocrine	50	44* (88%)	32* (64%)	39* (78%)	9† (18%)
Flattened	30	12 (40%)	8 (27%)	8 (27%)	0 (0%)

Significantly greater frequency in apocrine group: \* $P < 0.01$ ; † $P < 0.02$ .

The frequency of pathological changes in the mastectomy specimens of the 12 patients with a past history of cyst aspiration and 12 matched controls is presented in Table 3. It can be seen that cysts greater than 1 cm in size were seen only in the mastectomy specimens of those patients with a past history of aspiration of apocrine cysts. Apocrine change, papillary apocrine change, hyperplasia and carcinoma *in situ* were also seen more frequently in this group.

### DISCUSSION

Controversy exists as to whether patients with cystic disease are at increased risk of breast cancer, although it is generally accepted that individuals with severe hyperplasia, epithelial atypia and papillary apocrine change are at a significantly higher risk [1-8]. Two populations of breast cysts lined by either apocrine or flattened epithelium have been described [11] and this study has clearly shown that histological risk factors for breast cancer are significantly more common in patients with clinically palpable apocrine cysts.

A number of other observations support this finding. First, in populations with a high risk of breast cancer, apocrine change is a more common finding in the breast than in populations with a low risk [14]. This may indicate that the proportion of patients with cystic disease who have apocrine cysts may vary in different parts of the world and may relate to the breast cancer risk of that area. Second, it has been reported that

women with palpable breast cysts who have histological evidence of apocrine change within the breast are more than 11 times more likely to develop breast cancer than those women with cysts without evidence of apocrine change [15]. Third, it has previously been noted that there is an association between apocrine change and epithelial hyperplasia [12, 14-17].

Having established that histological risk factors for breast cancer were more frequent in the biopsies of patients with apocrine cysts, it is of interest that this study has shown that cysts aspirated from patients who later developed breast cancer were more likely to be apocrine. Furthermore, those patients with apocrine cysts were more likely than matched controls to have within their breasts epithelial hyperplastic changes and non invasive carcinoma. It has been suggested that women who have cysts aspirated at different times develop breast cancer more often than those who have cysts on only one occasion [1]. We have previously shown that women with apocrine cysts are more likely to develop subsequent cysts [13, 18]. This, and the finding of a greater frequency of hyperplasia in the apocrine cyst group, add support to the concept that patients with apocrine cysts are more at risk of breast cancer.

The observation that individual patients with multiple cysts tend to develop cysts lined by only apocrine or only flattened epithelium has been previously reported [13, 18] and is confirmed in

Table 3. Comparison of the frequency of pathological changes in the mastectomy specimens of 12 patients with a prior history of cyst aspiration and 12 matched controls

Breasts	No. of patients	Cysts >3 mm	Cysts >1 cm	Apocrine change	Papillary apocrine change	Hyperplasia III + IV	Carcinoma <i>in situ</i>
PH* of apocrine cysts	11	11†	9†	11†	11†	11†	8†
PH of flattened cysts	1	1	0	0	0	0	0
Matched controls	12	3	0	2	1	2	2

\*PH = past history.

†Significantly greater frequency of these pathological changes in mastectomy specimens of patients with apocrine cysts;  $P < 0.01$  by McNemar's test.

this study. This suggests that there may be a factor, possibly genetic [19] or hormonal, which determines whether patients develop cysts lined by apocrine or flattened epithelium. This same factor, therefore, may also influence the subsequent risk of breast cancer [14].

The findings in this study relating cyst type in patients treated by simple aspiration and breast cancer cannot be directly compared with those of any other studies. This is because all previous reports relate to histopathological studies of biopsy material. As the majority of patients with cystic disease are not biopsied but treated by simple aspiration, the results of these studies are of limited relevance to clinical management. We

have previously shown that the electrolyte composition of cyst fluid is closely related to the nature of the epithelium lining the cyst [11]. As the behaviour of the two cyst types differ in relation to both natural history [13, 18] and subsequent breast cancer risk, analysis of the composition of cyst fluid may be of value in the management of patients with cystic breast disease.

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