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Perspectives and Commentaries

Are Breast Cysts a Premalignant Marker?

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(A COMMENT ON: Dixon JM, Lumsden AB, Miller WR. The relationship of cyst type to risk factors for breast cancer and the subsequent development of breast cancer in patients with breast cystic disease. *Eur J Cancer Clin Oncol* 1985, **21**, 1047–1050.)

WE ARE departing from an era in which all identifiable benign breast conditions, including those defined by subjective perceptions of discomfort and nodularity, were routinely diagnosed as a single disease entity. The performance of a surgical biopsy on the breast is often accepted as a sufficiently precise starting point on which to base a study of breast conditions. However, the indications for breast biopsy are no more specific as regards etiology and pathogenesis than were diarrhoea and abdominal pain as regards intestinal disease. We are now entering a time when more specific determinants or definitions of breast disease will allow more precision in the understanding of pain, nodularity and premalignant significance.

The study of Dixon *et al.* [1] is an example of a new approach to categorization of breast conditions with an eye towards precision of prognosis and understanding of pathogenesis. This group has combined expertise in surgery, biochemistry and pathology to divide breast cysts into apocrine and flat types. Although the terminology of this classification comes from histologic appearance of the cyst wall, electrolyte and estrogen conjugate composition of the cyst fluid correlates with histology and a sodium/potassium ratio may be used to classify the cyst examined [2]. Although routine clinical chemical procedures used on serum may not be applicable to this determination because of the viscidity of many such fluids, the determination of sodium and potassium may still be easily accomplished. This Edinburgh group has also shown that the natural history of breast cysts differs between the two types, with the incidence of recurrences and multiplicity being greater in the apocrine cyst group [3–9]. The current presentation broadens the usefulness of this classification by suggesting that the apocrine cyst is a marker for increased cancer risk. This will remain a suggestion until stronger corroborating studies are done. The authors have performed a retrospective study that shows a link between apocrine type of cysts and hyperplastic lesions. They also found that of the 12 breast cancer patients with a previous history of cyst aspiration, 11 had apocrine cysts at time of their initial aspiration.

There are, unfortunately, some methodologic problems with this study. Dixon *et al.* [1] found that 11 of 80 patients (14%) with apocrine cysts developed breast cancer as opposed to 1 of 30 patients (3.3%) with flattened cysts. Although this difference in observed cancer incidence is large, it is not statistically significant due to the small numbers of cancer outcomes ($P = 0.22$ from Yates' corrected chi-squared statistic). This P value can be reduced to 0.14 by combining the six women with mixed cyst type with the 30 women with flattened cysts. However, this result is also not significant, and it is unlikely that it would be altered by using the (more powerful) log-rank statistic. Thus, the cohort data presented in this paper does not provide convincing evidence of enhanced cancer risk in patients with apocrine cysts, even though there is a 4-fold increase in the observed cancer incidence in the apocrine group over the flattened group. In their paper, Dixon *et al.* contrast the 11 : 1 ratio of apocrine to flattened cysts in their cancer patients to a 1 : 1 ratio in a consecutive series of 100 patients treated by aspiration. The P value associated with the difference between these ratios is approx. 0.01. However, to use this information as evidence that women with apocrine cysts are more likely to develop breast cancer, we must accept the 100 aspirated patients

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as a suitable control group for the 12 breast cancer patients. If these control women are comparable with the cancer patients in every way except for their cancer and cyst status, then the standard case-control argument can be used to infer an association between cyst type and cancer outcome. Unfortunately, however, the aspirated and cancer patients differ in a number of important ways other than these two factors. The cancer patients originally presented for biopsy during the sixties. In contrast, the aspirated patients presented almost two decades later for a much less invasive procedure. The clinical management of breast symptoms has changed dramatically during this time, and it is most likely that women biopsied in the sixties differ from women aspirated in the eighties in many important ways that may be related to both cyst type and cancer risk. For example, if the time to presentation was longer for the biopsied women than for the aspirated women, and if flattened cysts tend to evolve into apocrine cysts, then the difference in cyst type between the patient groups may be due to the natural history of these lesions as opposed to differences in cancer risk between these patient groups. Thus, the results presented by Dixon *et al.* concerning cancer risk associated with apocrine cysts are not yet convincing.

Previous studies seeking to demonstrate the relationship between cyst formation and cancer risk have given somewhat conflicting information, particularly in view of the fact that women undergoing biopsy have an increased risk of subsequent carcinoma development. Haagensen *et al.* in 1981 did show an increased risk for cancer in women with palpable cysts. However, this risk varied between different groups studied. Our own work has not shown a great increase of subsequent carcinoma risk for women with cysts who do not have a family history of breast cancer [10]. Subdividing these women into those whose largest cyst is at least 1 cm, and those with cysts between 3 mm and 1 cm does not substantially change these results. However, the demonstration in our studies that hyperplastic lesions were the major determinants of cancer risk reopened the possibility that the apocrine type cysts, not separately designated in these studies, may be specifically associated with hyperplastic lesions as shown quite convincingly in the Dixon *et al.* (1) paper.

Other questions remain to be pursued, particularly the relationship between the two types of cysts. Why are the flattened cysts larger in size on the average? Specifically all of these cysts are over 1 cm in largest size. Is it possible that this is the late stage of a single type of cyst development in which the active element is no longer present? And what, specifically, is the relationship in time between the two cysts types? Although it may seem readily evident, it should be emphasized that these studies are somewhat preliminary and need further corroboration before there is sufficient certainty that the magnitude of risk elevation is large enough to affect clinical practice.

How will precision of cancer risk assessment help us, even if it is facilitated by analysis of easily-obtained cyst fluid? We will probably never completely remove risk from a significant segment of the population. However, the reliable determination of increased cancer risk will at least identify women who will benefit most (in the aggregate) from heightened programs of surveillance for early cancer detection. We feel that the greatest current promise from simple and reliable prediction of high cancer risk will be the enabling of studies of preventive strategies. Thus, following groups of women with a high future incidence of breast cancer will allow sufficient statistical power to determine the effects of interventions aimed at retarding or blocking tumor promotion.

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