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Benign and Malignant Proliferative Epithelial Lesions of the Breast; a Review

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INTRODUCTION

THE DISTINCTION between benign and malignant epithelial lesions of the breast is important both in terms of the frequency of the diagnostic problem and its significance to the individual patient. The benign lesions are chiefly the various forms of adenosis and epitheliosis: 'epitheliosis' equates more-or-less with one of the usages of the term 'papillomatosis', but the latter term is unfortunately still used to indicate a number of different clinicopathological entities.

THE RELATIONSHIP OF CYSTIC DISEASE TO CARCINOMA: SOME PROBLEMS IN ASSESSMENT

Much attention has been directed to the question of whether cystic disease and cystic hyperplasia, as a clinical entity but with pathological confirmation, is or is not followed by carcinoma of the breast with a greater than expected frequency. This question is complicated by many factors, including very substantial differences of terminology, as well as a variety of basic problems of differential diagnosis. Worthy of special mention are:

(1) The failure to distinguish clearly between cystic disease and duct ectasia.

(2) The use of the term 'dysplasia' to embrace variations in normal tissue and of involution, benign hyperplasias of diverse types and 'early' forms of *in situ* carcinoma. The term 'papillomatosis' is used both as a synonym of the British term 'epitheliosis' and to describe the presence of multiple ductal papillomas, macroscopic or microscopic. The use of the term 'dysplasia', as used over the last decades, is impossible to justify and it is rightly being abandoned. But, regrettably, 'papillomatosis' is still widely used in different senses, and this loose usage is in danger of perpetuating much of the existing confusion.

(3) Progress in differentiating between 'difficult' benign and malignant proliferative epithelial lesions has been handicapped by a scarcity, until recently, of objective and reproducible criteria which can distinguish clearly, in the vast majority of cases, between benign epitheliosis (one form of so-called papillomatosis) and carcinoma *in situ*. Obviously, if certain types of carcinoma *in situ* are misdiagnosed as benign, a falsely high incidence of carcinoma is likely to be detected in the years following the diagnosis of apparently benign breast disease.

(4) Underdiagnosis of malignancy is not the only problem. Overdiagnosis of malignancy is particularly likely with lesions of benign 'infiltrating epitheliosis', to which reference will be made later. In such cases a diagnosis of invasive carcinoma may be made on tissue containing an essentially benign lesion.

THE EXCESS RISK

The excess risk of breast cancer in cystic disease is at most ×2.5, the figure given by Monson *et al.* [1]: this represents a mortality figure and is not strictly comparable with the morbidity figures of most other workers. Davis *et al.* [2], in one of the most critical older reviews, calculated that the increased risk was exactly ×2. Page *et al.* [3] found an increased risk of only ×1.4: in view of the precision with which this study in general and the pathology in particular are described, due weight must be given to this low figure. Hutchinson *et al.* [4] found an increased risk of ×2.4. There is little escape from the conclusion that the increased incidence is of the order of about ×2. Views that cystic disease carries no increased risk at all are as invalid as those claiming an increased risk of ×3 or more overall.

THE RELATIONSHIP OF THE DIFFERENT COMPONENTS OF CYSTIC HYPERPLASIA TO EXCESS RISK

The components of cystic disease and cystic hyperplasia need to be broken down in order to

establish whether cysts or epithelial hyperplasia are the more important in this context. The excess risk of cancer with pure cystic disease is only ×1.2 according to Page *et al.* [3] and ×1.4 according to Hutchinson *et al.* [4], negligible and very modest increases respectively. The view, championed up to very recently, that cysts *per se* are indicative of a sizeable cancer risk, has been made almost untenable by these data. In the presence of epithelial hyperplasia accompanying cystic disease there is an excess risk of ×1.8 according to Page *et al.* [3] and of 3.3 according to Hutchinson *et al.* [4]. Epithelial hyperplasia is the most significant risk factor for cancer development among the components of cystic hyperplasia: the increased risk is in the range of ×2–3.

HISTOGENETIC RELATIONSHIP OF EPITHELIOSIS AND CARCINOMA

What does this statistical increased risk mean in terms of the histogenetic relationship between epitheliosis and carcinoma? The sequence of events might take the course indicated in Fig. 1.

Adenosis
Epitheliosis
Atypical Epitheliosis
Carcinoma in situ

Fig. 1. A possible pathway of progression of epithelial proliferation in the human breast.

Epitheliosis perhaps blends with 'atypical epitheliosis', and this in turn might merge imperceptibly with carcinoma *in situ*. This type of progression is held explicitly or implicitly by many workers to be a common sequence of events. The alternative view is that while all hyperplasias might share a very similar early ancestry, divergence between benign and malignant lesions usually takes place at a very early stage in their development (Fig. 2). The issue is whether epitheliosis and carcinoma form a continuous spectrum or whether they are very largely distinct in morphological, as well as behavioural, terms.

Davis *et al.* [2] found that only one of 16 patients with 'solid epithelial hyperplasia' developed cancer following excision biopsy after a mean follow-up period of 14 yr. MacGillivray [5] found

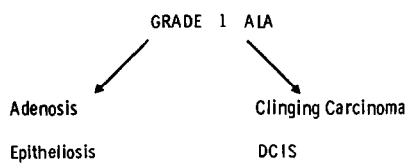

Fig. 2. Early divergence of atypical lobule type A along benign and malignant paths—the commoner situation.

that none of 30 patients with epitheliosis (which included 10 with 'severe epitheliosis') treated by local excision subsequently developed cancer. The average follow-up period was 7 yr. A follow-up study of 20 yr or more is needed in future work, and this will of necessity entail retrospective prospective studies for the most part.

From a structural standpoint, the author has been singularly unimpressed by the evidence which would purport to indicate an unbroken spectrum linking epitheliosis and carcinoma. Such evidence as exists in the literature fails to stand up to critical scrutiny. Having searched my personal material for such evidence for many years, with the preconception that it existed, and very largely failed to find it, the conclusion seemed inescapable that my preconception was a misconception, nurtured by years of traditional teaching. Histogenetically, epitheliosis arises by the heaping up of cells, often largely of indeterminate character, within preformed units. Typically epitheliosis has irregularly shaped spaces, a syncytial growth pattern, eccentric proliferation, spindle-cell bridging and, above all, the streaming of cells and their nuclei in parallel array. The structural patterns and cytological features of carcinoma very rarely show transitions from or blend with epitheliosis.

RADIAL SCAR/SCLEROELASTOTIC LESION/BENIGN INFILTRATING EPITHELIOSIS

One of the major advances in breast pathology of the last decade has been the identification of the lesion called 'sclerosing papillary proliferation' by Fenoglio and Lattes [6]. It is known by a variety of different names, including 'radial scar', 'sclerosing adenosis with pseudo-infiltration', 'scleroelastotic lesion', 'benign sclerosing ductal proliferation', 'non-encapsulated sclerosing lesion' and other variations on a theme. No one term is ideal because all omit some important attribute. All those listed, as well as a few others, have something to commend them. I have called this lesion 'benign infiltrating epitheliosis' because this term seems to encapsulate best the essence of the lesion; in particular it emphasizes the features of it which are most likely to trap even experienced pathologists into a mistaken diagnosis of invasive carcinoma.

Stegner [7] discusses this lesion extensively and tabulates the differential diagnosis between it and tubular carcinoma.

This lesion, by whatever name, is important because clinically, radiologically, grossly and microscopically it can closely simulate a cancer. It is the benign lesion most frequently mistaken for invasive carcinoma even today. Microscopically,

it possesses the essential attributes of epitheliosis, usually associated with fibroelastosis, together with infiltration of the stroma by the benign hyperplastic tissue. The stroma is infiltrated by streams of hyperplastic cells similar to those seen in ordinary epitheliosis, except that they have escaped from the confines of pre-existing normal epithelial structures. The tissue invades perineural spaces, nerve bundles and even vein walls, and yet it is biologically benign. In any of these sites dual differentiation into myoepithelial and epithelial cells, indicated by staining for actin and milk fat globule membrane antigen respectively, testifies to the benign nature of the infiltrative process. The concept that 'infiltration' in breast disease is not synonymous with malignancy is an important one, now known to apply to other organs also [8]. The fear sometimes expressed that surgeons might be confused by this concept has proved unjustified and no doubt underestimates the intelligence and adaptability of our colleagues.

DUCTAL CARCINOMA *IN SITU*

There are four generally recognized types of ductal carcinoma *in situ* (DCIS): comedo, solid, cribriform and papillary. To these has been added a fifth: clinging carcinoma [9]. Ductal carcinoma signifies a type of carcinoma rather than a specific site of origin. Since the work of Wellings *et al.* [10], it has become clear that ductal carcinoma mostly originates in the TDLU (terminal duct lobular units). A large number of small units becomes converted into a small number of larger units by a process of distension of acini and their 'unfolding'. This process gave rise in the past to the erroneous impression that ductal carcinoma originates in larger ducts.

Comedo carcinoma, most solid and most cribriform carcinomas *in situ* are easily recognized by experienced pathologists. Myoepithelial cells at the periphery of the containing structures may atrophy and disappear, or may persist and represent non-neoplastic pre-existing myoepithelial cells surrounding carcinoma *in situ*. In contrast with benign disease, myoepithelial cell differentiation does not take place in the interior of the neoplastic cell mass, for it is not an integral part of the neoplastic process.

'Early' and especially 'incidentally' discovered DCIS offers a unique opportunity of studying the histogenesis of DCIS. With comedo, solid and cribriform carcinomas there is very little evidence to suggest origin within areas of epitheliosis, but admittedly in the more obvious, larger and 'later' lesions such evidence, had it existed originally, may have been lost. In 'clinging' carcinoma it is most apparent that malignant change affects the epithelial cell layer of ductules and acini which are not affected by previous benign hyperplasia. Epithelial cells are enlarged, nuclei are enlarged with an increased nuclear–cytoplasmic ratio, hyperchromasia and alterations of nuclear chromatin are observed, nucleoli are enlarged and there are aberrant mitoses and varying degrees of loss of cell polarity. In 'early' bridging carcinoma structural alterations are present in addition sometimes to the cytological atypia of malignancy. Epithelial loops form arches and colonnades at the periphery of the involved structures. Particularly characteristic is a viaduct-like structure supported on robust pillars with transversely oriented nuclei. As with clinging carcinoma, these bridging *in situ* carcinomas rarely show any evidence of transition from areas of epitheliosis—they arise *de novo*.

In patients in whom these 'incidentally' discovered carcinomas have been missed initially and no further treatment given, some have returned, usually many years later, with invasive carcinoma in the same breast and at the same site as the original excision for apparently benign disease. This demonstrates that these carcinomas at the microscopic level have a potential for aggressiveness, but it gives no indication of the magnitude of this potential.

BIOLOGICAL SIGNIFICANCE OF 'SMALL' DCIS

The biological significance of small foci of DCIS, only locally excised, has just begun to be explored. Not all patients will develop cancer: 27 and 28% did so in the respective series of Rosen *et al.* [11] and Page *et al.* [12] (Fig. 3). These are high incidences, but not as high as one might have expected if this type of DCIS had a very high incidence of multifocality combined with a very high tendency to become invasive. Whether mastectomy is justified in all such patients is debatable. A conservative policy with regular and indefinite follow-up, as practised by some for lobular neoplasia (LCIS), is probably a legitimate

Rosen et al	8/30	:	27%	Inv Ca	average 9.7 years
Page et al	7/25	:	28%	Inv Ca	average 6.1 years
Lagios et al	3/20	:	15%		average 5.2 years FU for whole series

Fig. 3. 'Missed' DCIS treated by biopsy only. A third series (Lagios et al.*) of lesions mostly detected radiographically compares favourably: why?*

therapeutic option. Lagios *et al.* [13] treated a group of 20 patients with chiefly mammographically detected DCIS with a mean size of 8 mm by conservative surgery (tylectomy). In a relatively short follow-up study, averaging 5.2 yr for all patients, only 15% developed recurrent tumour, and two of the three patients with recurrence developed *in situ* carcinoma only. This prospective study differs in many respects from the other two quoted above. Further data of this type are necessary before the biological behaviour of DCIS of various types, detected in different ways, can be accurately assessed. It will probably be a good few years yet before this becomes possible.

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