Mammographic Parenchymal Patterns: Value as a Predictor of Hormone Dependency and Survival in Breast Cancer

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The relation between the parenchymal pattern of the breasts as demonstrated on a mammogram and the estrogen-receptor status of the primary tumor in 337 patients with operable invasive breast cancer has been studied. These factors have also been correlated with the response to endocrine therapy in 92 patients who subsequently developed secondary disease. It has been shown that patients with a DY pattern are more likely to develop tumors that are estrogen-receptor (ER) positive ($p = 0.01$). Patients with secondary disease who have a DY pattern are more likely to respond to endocrine therapy ($p = 0.001$). The DY pattern has been shown to be at least as good an indicator of the probability of response to endocrine therapy as the estrogen-receptor status, and a combination of the two factors better than either taken singly. In a series of 141 postmenopausal women, the DY pattern, as determined at the time of mastectomy, was associated with significantly improved survival ($p = 0.001$). Mammographic parenchymal pattern could form the basis for selecting patients for endocrine therapy where no estrogen-receptor assay is available.

The various forms of benign mammary dysplasia are demonstrated mammographically as different parenchymal patterns. Wolfe [1, 2] first drew attention to a relation between mammographic parenchymal patterns and the risk of the development of breast cancer in 1976. Since then, Wolfe's estimate of the degree of risk associated with the different patterns has been challenged [3–8]; however, although some authors recommend minor variations for some purposes [8], the basic classification has now become widely accepted. The value of including mammographic parenchymal patterns in epidemiologic studies has been repeatedly demonstrated [3, 5, 8, 9], and the teaching of mammographic interpretation while considering parenchymal pattern is now widely accepted. However, it has been considered that the parenchymal pattern has little relevance when dealing with individual patient management. It is apparent from the epidemiologic studies referred to above that the development of a particular parenchymal pattern in an individual is at least partly dependent on the hormonal environment. Preliminary results of a study of the relation between these hormone-dependent changes in the breast and the development of hormone-dependent breast cancer were summarized by Roebuck [8] (fig. 1.) We present our further findings in the study of parenchymal patterns and hormone-dependent breast cancer and show how the identification of the parenchymal pattern may be of value in individual patient management.

Materials and Methods

From a series of 550 patients with primary, operable, invasive breast cancer, 337 had both preoperative mammography and samples of the primary tumor taken for estrogen-receptor estimation. The mammographic parenchymal pattern was determined by consideration of the contralateral, uninvolved breast following a subsidiary study reported below, which showed patterns to be bilaterally symmetric. Thus, difficulties in interpretation due to distortion

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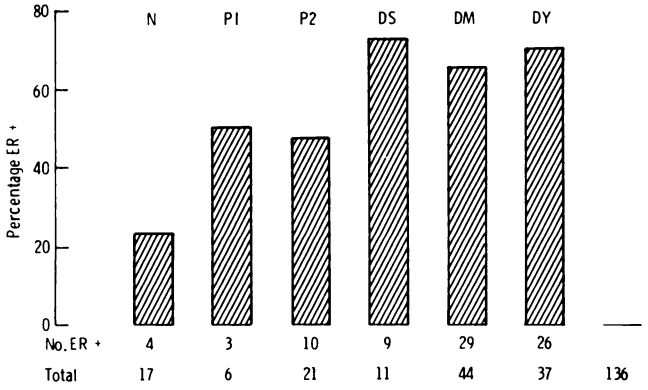

Fig. 1.—Parenchymal pattern related to estrogen receptor status. Distribution of mammographic patterns in patients with estrogen-receptor-positive (ER+) breast cancers. Numbers of estrogen-receptor-positive tumors and total number in each group are given below histogram. (After [8].)

resulting from the presence of the carcinoma or any local reaction in the breast tissue to the presence of the tumor were avoided. The mammographic parenchymal pattern was classified as DY, P, or N according to the Wolfe classification.

The appearance of the DY pattern varies with the degree of dysplastic activity [8]. In the active phase, it is recognized as poorly defined, blotchy areas of density with a tendency for the formation of band shadows. With involution of glandular tissue and the reduction of dysplastic activity, the resultant fibrosis results in a characteristic honeycomblike appearance with lobulation of the mammary fat (fig. 2A). The P patterns, in contrast, are recognized by prominent duct shadows giving characteristically rather beaded, linear opacities converging toward the nipple (fig. 2B). In the absence of either of these two features, the parenchymal pattern consists of tissue of fatty density criss-crossed by blood vessels and the ligaments of Astley Cooper. This type of appearance is classified as N (fig. 2C).

In the majority of cases, the distinction among these patterns is clear, but in some cases both DY and P shadowing are seen superimposed. We have classified these cases according to the predominant type of shadowing.

Estrogen-receptor analysis was performed at the Tenovus Institute, Cardiff, by the dextran-coated charcoal method. Tumors were considered to be estrogen-receptor positive if values greater than 5 fmol/mg cytosol protein were obtained.

During the period of follow-up (3–10 years), 92 patients have had symptomatic locoregional or distant recurrence treated by first-line endocrine therapy, consisting either of oophorectomy, in premenopausal women, or tamoxifen (20 mg twice a day), in postmenopausal women. Response to therapy has been assessed according to Universal Institute for Cancer criteria, incorporating the British Breast Group recommendation of a 6-month regression interval, and has been externally assessed without the knowledge of the estrogen-receptor assay or the background mammographic pattern. This assessment was undertaken as part of a separate study relating estrogen-receptor status to response [10].

The Bilaterality of Parenchymal Patterns

In studies of parenchymal patterns and breast cancer, difficulties may arise if the preoperative mammograms of some patients are not available, and in others the background pattern may be considerably distorted (or even obscured) by the primary lesion. The mammograms of 300 patients in whom there was no evidence of cancer were studied. Three patients with severe infection were excluded, and the 594 oblique projections from the remaining 297 patients were mixed in a random fashion. The films were classified by two observers according to the expanded modification of Wolfe's classification proposed by Roebuck [8]. These two observers had previously been shown to have a degree of concordance of 89% in the interpretation of parenchymal patterns [8].

The individual films of each patient were then paired and the classifications of the two sides were compared. The results are shown in table 1. Absolute bilateral symmetry was found by both observers in 68% of cases, and by one or the other observer in 85%. In no case did either observer classify a patient as having predominantly D or P shadowing on one side and having the other pattern contralaterally. The differences arose in classification of the degree of D shadowing (e.g., one side being classified as severe, the other moderate) and in the assessment of the extent of involvement by P shadowing.

It was concluded, therefore, that the factor(s) that determine the predominant type of parenchymal pattern in an individual affect(s) both breasts in a similar fashion and that the degree of parenchymal pattern that develops is symmetric in the vast majority of cases.

Results

Mammographic Pattern and Tumor Estrogen-Receptor Status

The distribution of estrogen-receptor status in the tumors of patients with breasts of different mammographic patterns is shown in table 2. There is an increased incidence of estrogen-receptor-positive tumors in patients with DY pattern breasts, which is significant ($p = 0.01$). This relation holds true for both pre- and postmenopausal patients.

Response of Secondary Disease to Endocrine Therapy

In the 92 patients assessed for response to endocrine treatment by secondary disease, the overall response rate was 23%. Of the patients in whom estrogen-receptor status of the primary tumor was available, the response rate for estrogen-receptor-positive tumors was 34%, and for estrogen-receptor-negative tumors, 14%.

The incidence of response to primary endocrine therapy according to the mammographic pattern is shown in table 3. The response rate among patients with DY pattern breasts was 38%, and among patients with P or N pattern breasts, 5% ($p = 0.001$). This relation holds true for both pre- and postmenopausal women (table 4).

When patients are further categorized according to both the mammographic pattern of the breasts and estrogen-receptor status, even greater discrimination is achieved (table 5), ranging from a 48% response rate in the 27 patients with a DY pattern whose tumors were estrogen-receptor-positive, to a response rate of 0 in the 22 patients with a P or N pattern whose tumors were estrogen-receptor-negative.

Mortality

Within the overall group of patients studied, there were 141 postmenopausal women with a minimum follow-up period of

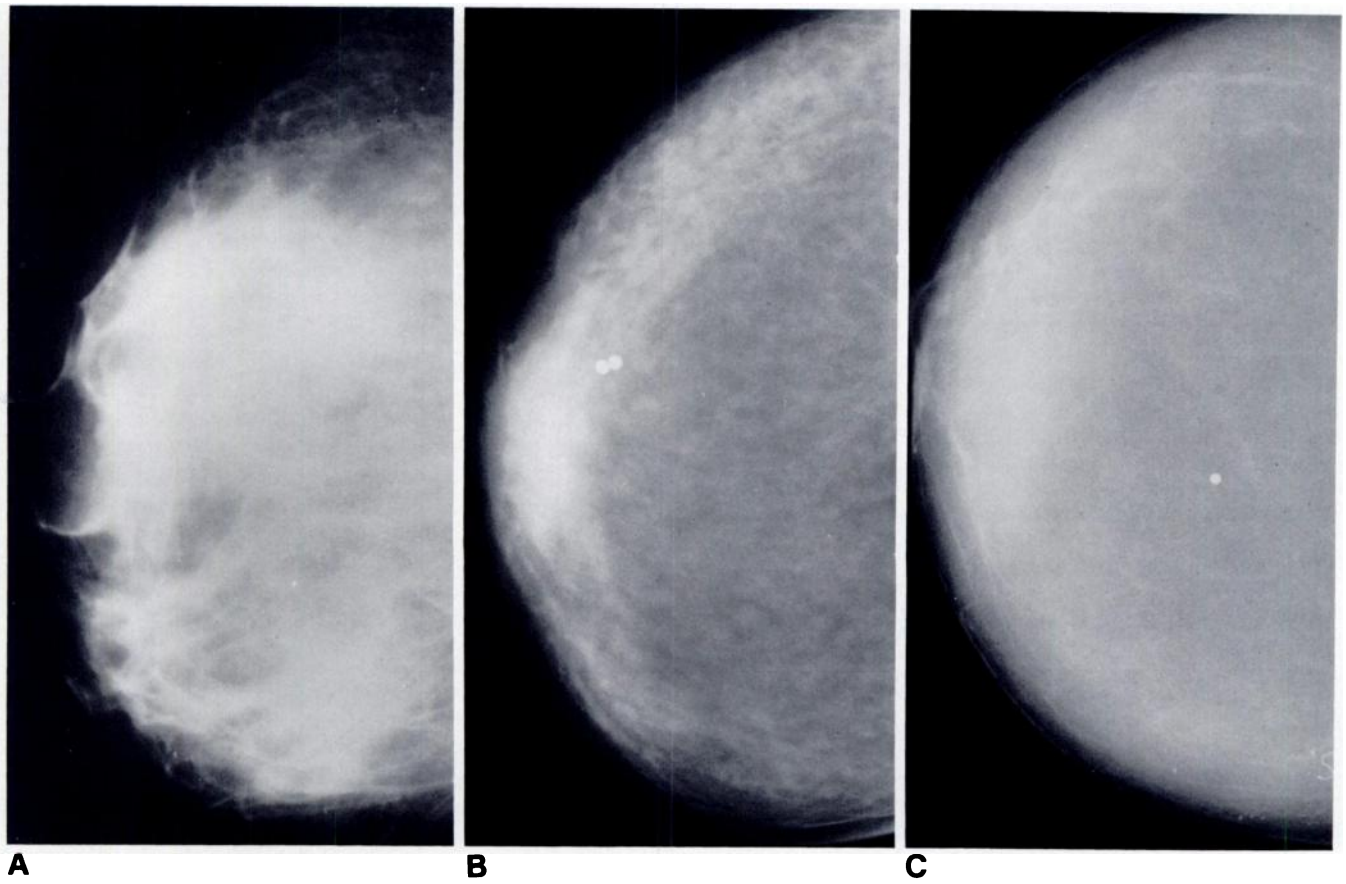

Fig. 2.—**A**, DY (dysplastic) parenchymal pattern. **B**, P (prominent duct shadow) parenchymal pattern. **C**, N (normal) parenchymal pattern.

TABLE 1: **Bilaterality of Parenchymal Patterns: A Study of 297 Cases by Two Observers**

Pattern	Observer A	Observer B	Both Observers
Symmetric	210 (71)	226 (76)	201 (68)
Asymmetric:			
D: 1° of difference	45 (15)	39 (13)	36 (12)
D: 2° of difference	15 (5)	9 (3)	7 (2)
P1/P2	1 (7)	17 (6)	15 (5)
IND/DY	3 (1)	6 (2)	1 (0.3)
P/D	0	0	0
Total	297	297	260*

Note.—For *either* observer A or B, symmetric pattern was seen in 252 (85%). D shadowing is classified as severe, moderate, or slight (Nottingham expansion of Wolfe classification). One degree of difference between the two sides occurs when one side is classified as severe and the other moderate, or one side moderate and the other slight. Two degrees of difference between the two sides occurs when one side is classified as severe and the other slight. Numbers in parentheses are percentages.

* In 37 cases, one observer recorded 2° of difference (asymmetry) and the other, 1°.

TABLE 2: **Mammographic Pattern and Tumor Estrogen-Receptor Status**

Estrogen-Receptor Status	Mammographic Pattern	
	DY	P or N
Positive (no.)	129	69
Negative (no.)	69	70
Positive (%)	65	50
Of these:		
Premenopausal (no.)	59	45
Postmenopausal (no.)	70	51

Note.—$\chi^2 = 8.108$, $p = 0.01$.

TABLE 3: **Response to Endocrine Treatment According to Mammographic Pattern and Estrogen-Receptor Status**

	Responders (%)	Total
Mammographic pattern:		
DY	19 (38)	50*
P or N	2 (5)	42*
Estrogen-receptor status:		
Positive	15 (34)	44†
Negative	6 (14)	42†

* $\chi^2 = 14.3153$, $p = 0.001$.
† $\chi^2 = 4.566$, $p = 0.02$.

5 years after mastectomy, of whom 41 had died. Of these 41 patients, there were 16 with a DY parenchymal pattern, and 25 with a P or N type background. This difference is highly significant ($p = 0.001$). Survival probability curves for the two groups calculated from the mortality data are shown in figure 3.

TABLE 4: **Mammographic Pattern and Response to Endocrine Treatment According to Menopausal Status**

Mammographic Pattern	% Responders	
	Premenopausal	Postmenopausal
DY	27	46
P or N	0	6

TABLE 5: **Mammographic Pattern Combined with Estrogen Receptor (ER) Status and Response to Endocrine Treatment**

Mammographic Pattern	Responders (%)	Total
DY:		
ER positive	13 (48)	27*
ER negative	6 (32)	19†
P or N:		
ER positive	2 (12)	17*
ER negative	0	22†

* $p = 0.0119$, Fisher's exact test.
† $p = 0.006$, Fisher's exact test.

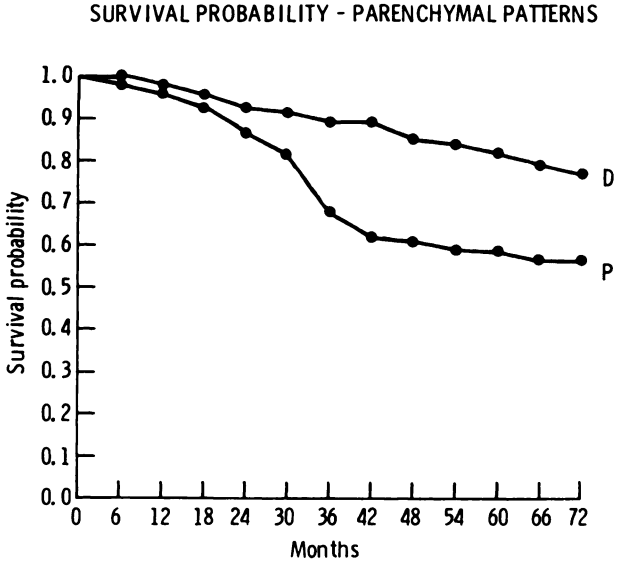

Fig. 3.—Survival probability according to parenchymal pattern of patients as determined at time of mastectomy (postmenopausal patients).

Discussion

Some breast cancers are known to be under the influence of circulating sex steroid hormones, as judged by their response to endocrine ablation or the administration of blocking agents. The relation between the mammographic parenchymal pattern of the breasts and their hormone environment led us to investigate whether there was a relation between these background patterns and the development of hormone-sensitive breast cancer. The finding that there is a relation between the estrogen-receptor status of the tumor and the parenchymal pattern of the breast from which it arises has provided evidence that such a relation exists.

The only true test of the hormone dependency of a breast cancer is its response to endocrine manipulation. The relation between parenchymal pattern and response to therapy is very striking indeed and cannot be explained solely on the basis of the differing incidence of estrogen-receptor-positive tumors in these groups. If this were the case, one would expect a response rate among tumors occurring in P or N pattern breasts (half of which are estrogen-receptor-positive) to be 15%–20%; however, the observed value is only 4%. Furthermore we have observed a response rate of 32% among estrogen-receptor-negative tumors arising in DY pattern breasts.

The mortality data presented parallel the variation between the two groups in the response to endocrine therapy. When expressed in survival probability terms, it illustrates the better prognosis of individuals with a DY parenchymal pattern.

The findings reported here, if confirmed, will have considerable practical value in individual patient management. Estrogen-receptor status is known to be a predictor of response to endocrine therapy [5], and it seems that mammographic parenchymal background pattern is as good. It could form the basis for selecting patients for endocrine therapy where no estrogen-receptor assay is available. The DY pattern would be of value in identifying patients in whom there is a reasonable chance of a response to hormone therapy. Conversely, the identification of a P or N parenchymal pattern in a patient would suggest that hormone therapy may well fail.

It seems that a greater degree of accuracy in prediction of the response to hormone therapy may be achieved by using a combination of estrogen-receptor status and mammographic pattern, rather than either of these factors singly. The most interesting implication of these findings is that there is some common factor, probably in the hormonal environment, that results in the development of DY shadowing in the breast as seen on mammography and the development of hormone-dependent breast cancer. It would seem, therefore, that the hormone sensitivity of a breast cancer is at least in part dependent on the environment in which it arises.

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