The Epidemiology of Tumor Markers in Breast Cancer
Management: Prognostic Markers

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A rose by any other name may still be a rose, but this truism is always tenuous when employed in the opposite direction. Thus, a marker or indicator of a rose may not guarantee the full visual, tactile and odoriferous qualities of a rose. The qualitative and quantitative degree of "rosiness" needs to be evaluated on an individual basis for each of the qualities of roses (e.g., thorn, color, resistance to disease, etc.).

This analogy may be strained but is nonetheless largely appropriate to many current lines of inquiry into the epidemiological, clinical, and mechanistic aspects of human breast cancer. Indeed, even these three aspects of oncology are further stratified by considerations of tumorigenesis and tumor evolution.

Note that this discussion is confined to prognostic concerns, not screening, diagnosis, or detection of subclinical recurrent disease. My focus is primarily on assessment of technology (new or old) as an aid to clinical management decisions (1, 2).

The question is: Does an associated phenomenon or marker act as a surrogate for a tumor or, even when the association is validated, does it merely indicate an increased likelihood of some associated neoplastic event. Many problems in understanding arise from a difficulty in separating interesting associations of putative markers from determinant information of proven practical utility on which clinical decisions may be based. Thus, it is ever more important to evaluate the evidence on which a single indicator has its claims for relevance. In the clinical setting this evaluation demands repeated verification in clinical settings applicable to the specific one at hand (3, 4). The confusion is evident because markers are cited often as indicating the fully developed product which they usually do not. And what is "fully developed" anyway—a lesion that will cause death, or merely one that threatens unless we intervene? And is "threaten" an absolute, qualitative concept of doom and gloom? No, it is quantitative and stochastic. It is both helpful to complete treatment plans beyond the measures already noted.

One further addition or stratum in the characterization of cancers is a growing recognition of tumors analogous to inflammatory carcinomas as being particularly benefited by more intensive chemotherapeutic regimens (21). These highly malignant tumors are recognized by large size, inflammatory clinical appearance, frequent and extensive lymphatic involvement, and usually high histological grade.

Of great interest has been the advent of new indicators of outcome after diagnosis of invasive breast cancer. The reason for this has been the hope that such genetic or biochemical markers would solve the practical problem of whether to employ chemotherapy. We have passed rapidly (in 2–3 years) from a time of widespread and unquestioning acceptance of suggested indicators to a time when demanding requirements of validation are mandated before acceptance (3, 4, 22). The pressure for this acceptance was probably the result of the initial response to a clinical alert on breast cancer in the late 1980s (23). With widespread belief that all types of breast cancer benefited from chemotherapy, sadly including some patients with carcinoma in situ initially (23), physicians realized that some patients did not need...
therapy and looked for aid in decision making. We have quickly evolved a general consensus (24) that stage information gives excellent basis for decision making in many situations, supplemented by other information, such as hormone receptors, histological typing and grading, and S-phase from flow cytometry. In general, it is felt that any other measures, including oncogene markers (25), should await careful verification and be considered as under development (Table 1).

There is a continuing evolution of acceptance of subtyping. These are small groups of breast cancers, recognized by a clustering of features that signify an excellent prognosis (e.g., tubular) (26, 27) or a dismal prognosis (e.g., inflammatory-like) (28) without therapy. There is also a developing understanding that some indicators will be treatment specific and not general prognostic indicators (20). Thus, there is support from recent studies that the erb2 oncogene marker indicates the likelihood of tumor response to chemotherapy (29). There seems little doubt that predictive roles will be found for many markers currently associated with prognosis. However, the growing recognition of heterogeneity and complexity of breast cancer has produced wide acceptance that there is no simple fix. Few of the "biomarkers" introduced recently into clinical practice are terribly useful. Some laboratories are listing various "markers" in an evaluation of individual breast cancers as "good or evil" and reporting such information in a menu format, such as "eleven good, five bad." This information is unvalidated because the multiple parameters probably could never be tested adequately in all possible combinations. For example, we recently reviewed a breast biopsy from which tissue had been sent to a distant laboratory to have almost 20 markers evaluated with the final report of "one poor prognostic indicator present." These reports are regularly made without reference to size, nodal status, etc., allowing for clinical bias for treatment to override a reasoned, combined analysis. In this specific example, the case was fibroadenoma with a pattern of atypical epithelial hyperplasia within it. This is an unfair example because it had been sent in the misguided belief that a diagnostic problem of possible carcinoma in situ could be resolved by prognostic markers developed for invasive carcinoma. However, the point is made that a series of separate factors without knowledge of interactions or incremental additions of predictive certainty is of little use. Obviously, we continue to be bound to histopathologic data for the fundamental diagnosis.

It is impossible to satisfactorily complete any discussion of prognosis in breast cancer because of its extreme complexity. This complexity extends from guidelines necessary for general practice to areas at the leading edge of research where new correlates of breast cancer biology are being discovered. This discussion has highlighted current clinical utility. However, it is hoped that many of these new discoveries will lead to mechanistic aspects which may allow us to control the behavior of some breast cancers. The association of the p53 tumor suppressor gene (30, 31) with aspects of cell growth and control of apoptosis indicates that it may be of use with regard to promise of gene therapy and related therapeutic control through growth factors. However, its direct use as a prognostic indicator is not yet clarified. This is true of the great majority of the "new" prognostic factors as indicated in Table 1. Certainly for general practice and the day-to-day decision making with regard to breast cancer therapy, the new markers have little place, except in some specific areas where personal experience may develop local guidelines. It is of note here that many continue to use the marker cathepsin D. However, it has been measured in several different ways and most often has been found to be unassociated with prognosis (32). Cathepsin D is present in both macrophages and epithelial cells. The presence of this proteolytic enzyme in the carcinomas may be a reflection of necrosis or dense cellularity, which are well known prognostic factors in their own right. It is this complex interaction of the many prognostic factors associated with clinical outcome which makes guidelines and evaluation difficult. The heterogeneity of breast cancer is the unavoidable major biological and practical feature of breast cancer. I believe that the future of breast cancer research is in accepting this heterogeneity and evaluating multiple subtypes and interactions of different indicators.

With this extreme complexity in mind, we have not even discussed serum markers. Markers of cancer in serum present a completely different viewpoint and area for evaluation, which is surely even more complex. In this issue there is a discussion of the presence of elements of the oncogenes erb-B2 and myc present in the serum in 36 women with breast cancer (33). It is obviously an extremely small study but enticing with regard to the possibility of identifying some small groups of patients with specific outcome interactions. It is disappointing that the seven cases of in situ carcinoma were not further specified. It is likely that those positive cases were of the comedo variety. Breuer et al. (33) also extend the use of tumor markers to suggest use in early diagnosis rather than early detection of recurrence (6). Serum markers are not usually considered as contenders for early diagnosis of breast cancer (34). There are a two other serum markers of breast cancer that are of some interest. One of these is related to the frequently evaluated tumor-associated glycoprotein antigens of the cell surface. A new approach to this area has been discussed and worked on recently by Ceriani et al. (35). Also, one serum marker that does not seem to have attained general clinical use certainly would seem to be as useful as a carcinoembryonic antigen in the possibly early detection of recurrences of cancer. The protein that is designated gross cystic disease fluid protein-15 is present in 50–60% of breast cancers, and when those cancers recur with metastases, the material may be present in the serum. There has not been a great amount of further research on this since its early discussion by Mazoujian et al. (36).

Rather than approaching indicators individually, one could accept the classic ones, and add the new (Table 1) individually to see if the addition increased the power of prediction. This incremental approach of taking the strongest currently validated indicators of prognosis and systematically attempting to add others to see if they will improve the predictive model or index has been done by only a few groups in the world. Both the Institute Gustave-Roussy in Paris (37) and the group in Nottingham, England (38, 39) continue to use nodal status, size, and histological grade

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predominantly, having tested other parameters and found they add little to the model in proportional hazards statistical studies. They have defined one "excellent prognosis" group of patients whose survival is not statistically significantly different from that of the general population, and another group that is about 80% likely to die within 5 years (Fig. 1). These measures have been verified several times by each group and may be taken further to indicate that there are fundamentally different types of breast cancer. Improvements in this index are more likely to separate some of the patients from the intermediate predictive zone rather than to make the predictions regarding excellent and poor prognosis patients any more precise (4, 40). Actually, some of the special histological types (although they constitute only 20–30% of breast cancers) are themselves predictors of both growth and metastatic capacity. For example, the pure medullary carcinoma (41) is certainly an example of a very fast growing tumor with rare metastatic capacity. On the other hand, the pure and classic varieties of invasive lobular carcinoma usually have metastatic capacity, but are very slow in their clinical evolution, predicting clinical failure more frequently beyond 10 years (42, 43).

Thus, one must focus constantly on whether markers of prognosis are verified for the precise clinical setting being evaluated (2). Markers or associates of prognosis may elucidate the role of a marker in breast cancer, but may not necessarily have practical use.

The important accomplishment of international agreement between the International Union Against Cancer and the American Joint Commission on Cancer on a complex system of staging noted above involves only the basic features of size and nodal status because the additional classic histological features do not have adequate guidelines for general acceptance. We should take this as a cue that broad agreement may be attained, although with difficulty in even the most seemingly basic categories of size and nodal status. We hope to extend that agreement to the modality most basic to the characterization and diagnosis of breast cancer beyond size and nodal status, namely, histopathology. This transfer of information to an international consensus should proceed simultaneously with the enthusiastic testing of the new biological markers. These are two quite disparate aspects of test development, the interface between basic science and clinical relevance (testing), and the widespread clinical acceptance of reliable tests (application). The linkage between the two has always required wisdom and patience. If we understand this linkage to be complex and indirect, we will be more tolerant of the necessary delays. It took over 50 years for histopathology to be widely accepted as a replacement for gross evaluation of surgical specimens (44). We can hope now to do better than that. Our goal should be to have schema that guide clinical decisions and not just a catalogue of phenomena. This goal mandates the continual evaluation (45) of the utility derived from any classification or putative indicators of prognosis.

References
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