Editorial

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/or 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 (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 determinants of prognosis associated with only one of these biological features.

Distant metastatic behavior, and (c) the rate of growth (6). It is likely that different measures or reflections of prognosis are associated with only one of these biological features.

The first of these disparate measures of breast cancer prognosis is reflected in tumor volume or size (7, 8), the second is best reflected in breast cancer by the presence of metastases in the axillary lymph nodes, an indicator which is 80% sensitive for the development of distant metastases in the next 10 or more years (9, 10). Finally, the reflection of growth rate may be obtained by histological grading involving mitotic counting or S-phase evaluation by flow cytometry as well as other techniques (11–14). Charlson and Feinstein (15) have indicated the importance of the rate of disease progression as an added predictive parameter to stage of disease at time of detection. Which method of determining growth rate will be most useful and most easily obtained from the several available is not clear (4), but technically, the easiest to obtain, a mitotic count, is an excellent measure of short-term survival (16). Metastatic capacity is best measured by established nodal metastases. It may be measured in the future by markers of cellular adhesion (17). Note that the first two of these major prognostic indicators are readily available and internationally agreed upon measures that are part of the Tumors-Nodes-Metastasis system, which has achieved consensus in its specifics by the American Joint Commission on Cancer (18) and the International Union Against Cancer (19). It is likely that some combination of these relatively proven elements will be added to these in the years to come. However, few additional elements are highly or repeatedly verified (20), and only estrogen and progesterone receptor determinations are needed regularly 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 necessarily accepted in clinical practice.

<table>
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<th>Table I Biologic features of breast cancer</th>
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<td>I. Evolutionary stage</td>
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<td>Tumor mass or size (classic)</td>
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<td>II. Metastatic capacity</td>
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<td>Regional nodal metastases (classic)</td>
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<td>III. Growth rate</td>
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<td>Mitotic count (verified, but methods vary)</td>
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<td>S-phase fraction (recent, verified)</td>
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<td>Other (under development)</td>
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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 oncoproteins 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 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...
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 (19) 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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