Dissecting the contribution that mutated p53 (also known as TP53) makes to the progression of breast cancer is made difficult by the multiple functions of this tumor suppressor gene and by the study material itself. Most of our data come from the study of well-established, invasive carcinoma; if not already metastatic, these tumors certainly have that capacity.

Although there have been attempts to establish a sequence of epithelial proliferative events that lead to invasive cancer, the only proven precursor to this disease is ductal carcinoma in situ (DCIS) (1). The study of the natural history of DCIS has been difficult because the diagnosis was linked to definitive therapy, mastectomy. From the few available studies of DCIS treated by excision to negative margins alone, we know that recurrence is more common (2) and progression to invasion is virtually limited to high-grade DCIS (3,4).

Earlier attempts at addressing the molecular progression of breast cancer focused on DCIS that either was adjacent to an invasive cancer or was large enough to allow tissue to be frozen away for future study (5). Progress in delineating the role that p53 may play in the earliest stage of breast carcinoma required technical advances in microdissection of small foci in routinely processed, archival tissue. In this issue of the Journal, Done et al. (6) report on the use of microdissection techniques to select areas of breast DCIS for p53 mutational analysis, adding to their previous important studies of this gene in breast cancer (7).

The critical contribution of their current study is the careful selection of case patients, with analysis occurring within clinically relevant categories of DCIS, based on grade and size. In a recent commentary (8) of another series (5) of large examples of DCIS that were predominantly high grade, we underscored the importance of case selection reflective of the disease that is so commonly diagnosed. Done et al. have now provided us with just such a series.

In previous work, this group (9) showed that, in the presence of invasive cancer that harbored p53 mutations, a broader spectrum of adjacent DCIS also contained mutations. In contrast, the current study (6) limited to the DCIS alone did not detect p53 mutations in the 49 DCIS samples of low grade (low Van Nuys Prognostic Index); mutations were restricted to samples with an intermediate and high prognostic index (approximately 4% and 41%, respectively), results similar to those of O’Malley et al. (10). Many earlier studies have been deficient in examples of this large group of non-high-grade DCIS. Because there were no cases with concurrent invasive carcinoma, there was no possibility of contamination of results by an invasive component growing in an existing ductal structure. This is especially important in the study of the potential progression of a preinvasive lesion.

Although the actual extent of the lesions is not given, Done et al. (6) have provided the Van Nuys Prognostic Index, in which size of the lesion is one of the incorporated parameters, along with nuclear grade and marginal status. It is interesting that only 18 lesions had a low nuclear grade, while 49 lesions had a low prognostic index, suggesting that 31 were of intermediate grade but of limited extent. In this series, among sample with p53 mutations, the nuclear grade paralleled the Van Nuys Prognostic Index. The Van Nuys Prognostic Index was devised to address the likelihood of local recurrence after biopsy of DCIS alone (4). One of the parameters of the index is margin status, certainly an important aspect; it is probably the most decisive aspect for the surgical management of DCIS but is of less importance in understanding the biology of the disease. In future studies, we encourage the inclusion of nuclear grade in the analysis of results.

In the current study, Done et al. (6) screened 94 samples of DCIS for p53 immunohistochemical expression to select samples for further mutational analysis. Based on their previous study (7) that showed comparable results of staining intensity with missense mutation, the authors chose samples with the greatest immunohistochemical expression of p53 protein (n = 11) for microdissection and mutational analysis. The authors limited their mutational analysis to exons 4 through 10 of the p53 gene, a reasonable choice because studies in the other exons have been unrevealing (5). The percentage of cells positive by immunohistochemistry as well as the extent of disease did not influence the likelihood of finding a mutation. For eight lesions in which p53 was mutated, the DCIS ranged from small (2.8 mm) up to 10.5 mm. The number of ducts involved also varied, with p53 mutation found in as few as four ducts involved by DCIS or in 100 or more involved ducts.

This report indicates that p53 should be included in gene expression array studies directed at identifying expression patterns associated with breast cancer, invasive or DCIS (11,12). Given adequate probes, expression profiling provides useful insight into the multiple pathways coupled to proper p53 function that, if mutated, might contribute to the invasive potential in DCIS.

The study by Done et al. (6) will add to the understanding of the biology of the different forms of DCIS. Histologically, different forms of DCIS are recognized not only from patient to patient (13), but also within individual patients (14). For example, one of the examples presented by Done et al. showed a single duct with maximal-intensity p53 expression, which had a higher nuclear grade than the surrounding areas of DCIS that did not express p53 immunohistochemically.

Despite the imprecise nature of the Van Nuys Prognostic Index as a reflection of biologic potential of these DCIS lesions,
it is clear that only the lesions with a high score (both high grade and larger size) show missense mutations. This study by Done et al. (6) lends biologic support to the important concept that DCIS is not a single disease and treatment should be based on clinically relevant subsets.

REFERENCES


