Commentary

The *p53* Tumor Suppressor Gene in Ductal Carcinoma *in Situ* of the Breast

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The advances in molecular characterization of *p53* in invasive breast cancer have far eclipsed our knowledge of the possible role this tumor suppressor gene may play in earliest stages of breast cancer. Thus, the promise of studying the relationship of *p53* in noninvasive precursors of invasive breast cancer is obvious. The tumor suppressor gene *p53* serves a multifunctional role as a transcriptional regulator, genomic stabilizer, inhibitor of cell cycle progression, facilitator of apoptosis, and also perhaps an inhibitor of angiogenesis. Most studies assessing the possible biological and clinical roles of *p53* in human breast cancer have used immunohistochemistry to assess protein expression and overexpression. Lukas et al in this issue of *The American Journal of Pathology* have provided us with the most extensive molecular characterization of *p53* in ductal carcinoma *in situ* of the breast yet available.¹ Most of the previous molecular studies of ductal carcinoma *in situ* (DCIS) have been restricted to exons 4–9, and these authors have sequenced all coding exons of *p53* after screening by SSCP. While confirming that the great majority of mutations that lead to decreased expression of *p53* are in the exons 4 to 9,^{2–4} they have found some changes associated with other exons that have increased expression of *p53*, a new finding. Indeed, it is possible that increased expression of functional *p53* would be beneficial during the progression of carcinoma.

The finding of Lukas et al¹ of the consistency of *p53* mutations, when present, in the *in situ* and invasive components of breast cancers when both occur together is important. There has never been much doubt about the linkage of *in situ* to invasive carcinoma and the progenitor relationship of *in situ* to invasive disease,^{5–8} but precise genetic proof is reassuring. More importantly, this molecular approach sets the groundwork for studies that will determine those features of invasiveness and metastatic capacity that reside in the invasive component and not the *in situ* carcinoma. Lukas et al¹ document one case in which the *p53* mutations are different between the *in situ* and invasive components.

Prior efforts on *p53* have been largely consistent with those of Lukas et al,¹ but provide one caveat concerning their conclusion that *p53* mutations may be higher in DCIS than previously recorded. Indeed there has been evidence that *p53* mutations are rare (at most) in low grade DCIS.^{3,4} Lukas et al provide no evidence of the rate of *p53* mutations in low grade DCIS because they have only two cases of grade I DCIS, and neither of those had mutations. A vital piece of information related to behavior of DCIS is its size. Although Lukas et al do not provide the size of their DCIS lesions, we can assume that, if the tissue were large enough to be contributed to a frozen repository, the examples of DCIS were probably several centimeters in extent. Although this approach is critical for the painstaking genetic discovery of Lukas et al, it may not be possible to describe the same alterations in the small, lower grade DCIS often detected only by mammography. Therefore, this is a selected series of relatively large and high grade DCIS cases. We cannot conclude that such a selected series represents the full range of lesions within the broad sweep of the rubric of DCIS. One of many elements of the heterogeneity of DCIS^{9,10} may be mentioned: the low grade lesions are frequently estrogen receptor-positive, whereas the high grade lesions are regularly estrogen receptor-negative,⁵ with obviously different implications for prevention strategies. The epidemiological studies upon which we rely to indicate the local risk of invasive breast cancer in women followed after biopsy alone^{6,7,11} have involved only the low grade DCIS cases, which essentially are not included in this study by Lukas et al.

The possible prognostic and predictive value of *p53* has been studied extensively in invasive breast cancer.¹² Loss of the protective effects of its tumor suppressor function would seem to indicate a more aggressive phenotype and a worse clinical outcome, and, indeed, the preponderance of studies confirm this, with the risk of recurrence and death increasing by 50% or more if *p53* is abnormal. Lack of unanimity of results is undoubtedly

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due to many factors that limit the certainty of a direct link of *p53* changes to prognosis; however, the complexity and random nature of genomic change present in cancer cells may also contribute to the lack of unanimity. Because many anticancer agents may exert a therapeutic effect through genomic damage and subsequent triggering of apoptosis, and because *p53* can respond to genomic damage and facilitate apoptosis, it can be hypothesized that an intact *p53* would predict sensitivity to therapy. Present data in breast cancer, however, do not clearly indicate that this is the case.¹²

These data relating cancer behavior to *p53* status encourage the further exploration of links between molecular events and phenotypic diversity of breast cancer in its invasive and pre-invasive stages.^{9,10} Pairing the genetic diversity of DCIS with known phenotypic and natural historical variants, including size, length of preinvasive stage, and determinants of invasion and metastasis, will be a challenging task with the promise of controlling and eradicating breast cancer. Certainly the increasing incidence of DCIS¹¹ and its known linkage to progression to invasive and killing disease are reasons to support continuing studies of DCIS itself.

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