An interesting article by Kerlikowske et al. (1) in this issue of the Journal describes how certain biomarkers in ductal carcinoma in situ (DCIS) treated with lumpectomy alone may improve our ability to predict the risk of disease recurrence and progression to invasive breast cancer (IBC). Once DCIS is detected, this therapeutic setting reflects the natural history of any residual disease, and the likelihood of regrowth and progression largely determines the use of adjuvant therapy.

The tumor samples used in this retrospective study were a case-control subset nested within a cohort of nearly 1200 patients who were diagnosed with DCIS between 1983 and 1994 and for whom long-term clinical follow-up data were available. In assembling samples from this cohort, the investigators have created a rare and valuable resource, and they have used it in previous enlightening studies of DCIS published in this Journal (2) and elsewhere (3). Cases of primary DCIS in the study population with available glass slides (n = 502) were comprehensively evaluated for standard histochemistry for expression of several biomarkers. Many of the biomarkers are well known in this setting, including the estrogen receptor (ER), progesterone receptor, p53, human epidermal growth factor receptor 2 (ERBB2, also known as HER2), and Ki67, whereas others are relatively novel, including p16 and cyclooxygenase-2 (COX-2).

All of these factors, and available clinical characteristics, were evaluated individually for their univariate associations (hazard ratio [HR]) with recurrence of DCIS or progression to IBC, with a median follow-up of about 8 years. Larger tumor size, positive surgical margins, and higher nuclear grade were each associated with modestly increased risks for recurrent DCIS (HR = 1.4 to 3.6) and IBC (HR = 1.2 to 1.6), although the latter were not statistically significant. The same histopathologic features were strongly related to recurrences of both DCIS and IBC in a study involving many of the same patients that was published by these investigators 7 years ago (2). The reasons for this apparent loss of predictive ability are unclear, but at least one other study has reported weakened associations between histopathologic features and recurrence with prolonged follow-up (4), suggesting that these features are more predictive of the rate than the fate of tumor progression (5).

Modestly increased risks (HRs = 1.1 to 2.3) for any type of recurrence were also observed with individual unfavorable biomarkers (negative vs positive ER and progesterone receptor; positive vs negative p53, ERBB2, p16, and COX-2), but only a few of these risks were marginally statistically significant. However, certain combinations of these biomarkers, some of which were suggested to have prognostic importance in previous studies (3,6–10), were more strongly associated with recurrence. Interestingly, the combinations that predicted subsequent IBC were different from those that predicted DCIS. In particular, the p16+COX-2+Ki67− vs all others phenotype was statistically significantly associated with subsequent IBC (HR = 2.2), whereas p16+COX-2−Ki67+ and ER+ERBB2−Ki67− vs all others were more common with subsequent DCIS (HRs = 3.2 and 3.6). Among other factors evaluated, detection by palpation vs mammography and age older than 70 years also showed statistically significant associations with recurrent IBC and DCIS, respectively.

Multivariable analyses competing factors with univariate statistical significance confirmed the increased risk of patients whose tumors were p16+COX-2−Ki67+ (HR = 2.2) or detected by palpation (HR = 2.7) for recurrent IBC. Positive vs negative surgical margins, p16+COX-2+Ki67+ protein expression, and ER+ERBB2+Ki67− protein expression remained statistically significant predictors of recurrent DCIS (HRs = 1.3, 3.7, and 5.8, respectively). The investigators developed novel categories of risk based on combinations
of factors with the strongest independent associations. For example, HRs for predicting subsequent IBC ranged from 4.1 (lowest risk category) to 19.6 (high risk), and 3.9 (lowest) to 23.6 (high) for subsequent DCIS at 8 years—which are large differences and potentially useful clinically.

Many studies have evaluated the risk of recurrence in patients with DCIS who were treated by lumpectomy alone (11,12). Nearly all showed unacceptably high rates (30% or more) of subsequent cancer in the same region of the breast, and recurrences that were about equally divided between DCIS and IBC. Both types of recurrences are unwelcome, and everything possible is typically done to prevent them. Thus, many additional studies have evaluated the abilities of various adjuvant therapies to reduce recurrence following lumpectomy (4,13–17). Based on these studies, the standard-of-care for most patients with DCIS today is lumpectomy with as wide and accurately determined surgical margins as possible, followed by radiation therapy and, in some patients with ER-positive DCIS, 5 years of tamoxifen (18,19). Collectively, these strategies have reduced the rate of recurrence to less than 10% (≤5% for IBC) (11,13,16,17) and mortality to less than 2% (20), which are acceptable risks for most patients, especially when the alternative is mastectomy for an essentially benign disease.

Certain results of this study are somewhat mystifying. For example, how can three usually unfavorable biomarkers when combined, for example, ER ERBB2 "Ki67", appear to be biologically good in terms of favoring high risk of subsequent DCIS over IBC? A similar question is raised by p16 COX-2 Ki67, with two unfavorable biomarkers, yet it also favors recurrent DCIS over IBC. A degree of skepticism is warranted because studies involving multiple variables in relatively small cohorts are usually statistically challenged, often difficult to validate, and potentially untrue, which can be even more problematical when combinations of variables are involved. However, let us assume (hope) they are true for the moment. In a simplistic way, recurrences develop from tumor cells left behind and/or some biologically detrimental field effect in adjacent noncancerous breast tissue. In all of these settings, relatively bad biology should favor progression to IBC over DCIS, and relatively good biology should favor DCIS over IBC, which is internally consistent with biology as defined in this study. The apparent inability of traditional histopathologic features to predict subsequent IBC is not overly convincing. It seems reasonable to assume that these features are important (eg, positive surgical margins cannot be good), many previous studies support their importance (12,16,17,21,22), the present study was statistically underpowered, and its design was biased in the sense that histopathologic features were individually compared with combinations of biomarkers.

Overall, this is a thought-provoking study that addresses an important issue. The threats of recurrent DCIS or IBC both elicit substantial and essentially identical efforts to prevent them. The results of this study, if validated, could optimize current therapy in certain settings: For example, adjuvant radiation could be withheld from patients with low-risk DCIS as defined by the study. The investigators were forward-thinking to evaluate whether combinations of older and newer biomarkers improve prognostic power. Combinations of histopathologic features (eg, Van Nuys Prognostic Index) were previously shown to have far more prognostic power than each feature alone (23). It seems reasonable to extend this strategy and investigate whether combinations of histopathologic features and biomarkers are even more powerful, rather than artificially pitting them against each other. Finally, DCIS is rarely treated by lumpectomy alone these days. In addition to independent validation, it will be critical to determine whether the results of this study are influenced by adjuvant radiation and hormonal therapy—so (as noted by the authors), there is still much to learn before translating the results to routine clinical practice.

References


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