The diagnosis and management of ductal carcinoma in situ (DCIS) is controversial (1). With widespread mammography screening, diagnosis of DCIS became more prevalent. Some are uncertain whether this has translated into a decrease in invasive cancer and a subsequent decline in breast cancer mortality. Part of the concern has been that frequently the treatments of DCIS are as extensive as for invasive cancer with a similar panoply of risks. A straightforward approach to selecting the optimum therapy—defined here as the minimum needed to avoid recurrence, particularly with an invasive component—is needed. Many solutions have been proposed, but none has gained wide acceptance. For example, the Van Nuys Prognostic Index has been in common use for decades (2). Several randomized clinical trials have compared lumpectomy alone to lumpectomy followed by radiation treatment, but no subset analysis of these results has found a group that does not benefit from radiation with a lower in-breast recurrence risk (3).

In this issue of the Journal, Solin et al. propose a measure, the 12-gene Oncotype DX DCIS Score (DCIS score) to assist clinicians and patients with the task of deciding optimal treatment (4). Genomic Health is currently marketing the assay (http://www.oncotypedx.com/en-US/Breast/HealthcareProfessionalsDCIS). The Oncotype DX score for invasive breast cancer developed by Genomic Health has found widespread acceptance. It also forms the basis for two clinically important ongoing trials. The first, Tailorx, is to determine for women with early-stage, hormonal-positive, node-negative disease and an intermediate score whether adjuvant chemotherapy is needed in addition to hormonal therapy. This trial has closed to accrual and is in follow-up. The other study, spearheaded by Southwest Oncology Group (SWOG) and currently open, RxPonder (Rx for Positive Node, Endocrine Responsive Breast Cancer), will reveal whether chemotherapy benefits patients with node-positive breast cancer who have low to intermediate Oncotype DX recurrence scores.

Solin et al. collaborated with Genomic Health in a rigorous predefined manner to develop the DCIS Score. How well does it work? Should it be adopted? Is it needed for affordable, accountable care? Developmental work used DCIS specimens alone, invasive breast cancer specimens alone, and specimens in which DCIS was adjacent to invasive breast cancer. Initially, the Oncotype DX recurrence assay now in clinical use for invasive cancer was tested, and a wide range of recurrence scores was found, dovetailing with what has been observed about the heterogeneous nature of DCIS. The primary concern was the risk of an in-breast recurrence, scored as an ipsilateral breast event, which included invasive and noninvasive recurrence. The first task was to specifically assess recurrence risk in databases of invasive carcinoma for the 21 individual genes. Seven genes were found to be predictive of recurrence risk. One was progesterone receptor (PR), and a second was a glutathione S-transferase that functions in the detoxification of electrophilic compounds (GSTM1). Five of the genes clustered in a “proliferation group”—Ki67, STK15, Survivin, cyclin B1 (CCNB1), and MYBL2. Interestingly, for invasive cancer the proliferation genes were best categorized with a threshold, whereas for DCIS a continuous score was found to be best. The genetic drivers of progression from DCIS to invasive cancer are poorly understood; the drivers behind proliferation may serve as an avenue for better elucidating this phenomenon. Estrogen receptor (ER) was correlated with hormone therapy benefit, which is logical given that the mechanism of action of tamoxifen is through binding with the ER. A limitation of the Solin et al. study is that 97.2% of the participants in the validation set were ER positive and 29.4% received tamoxifen, so the investigators did not want to use a gene that was predictive of hormonal therapy benefit.

A set of pure intraductal carcinoma, 96 case subjects, from Marin General Hospital, Marin, California, were used for setting specific cutpoints for low, intermediate, and high risk of recurrence. This preset selection of genes and scale formed the DCIS Score that the researchers then validated in a completely

**Notes**

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A Multigene Expression Assay to Predict Local Recurrence Risk for Ductal Carcinoma In Situ

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The incidence of ductal carcinoma in situ (DCIS) has seen a dramatic rise in the United States, particularly over the last three decades. Since the use of screening mammography in the 1980s and with improved technology, DCIS now accounts for 14% to 30% of all diagnosed breast cancers (1,2).

An ipsilateral breast event (IBE) remains the most common first failure event in DCIS management. Mastectomy was once the standard treatment for DCIS, with recurrence rates as low as 1.4% (3,4). Breast-conserving surgery (BCS) has now gained widespread acceptance as an alternative approach, based on the results of four independent set of specimens. This approach is to be commended because the validation set was completely independent of the development sets. The validation set was from the prospective cohort study Eastern Cooperative Oncology Group E5194. The patients accrued in to the study met rigorous selection criteria: 1) low- or intermediate-grade DCIS, tumor size less than or equal to 2.5 cm (cohort 1); or 2) high-grade DCIS, tumor size less than or equal to 1.0 cm (cohort 2). The sample available for validation was comprised of 327 individual patient specimens from the 670 enrolled. Although the authors compare characteristics of the available with the unavailable specimens, a concern of selection bias does enter in at this juncture. Furthermore, the structure of E5194 already provides a strong level of selection bias because patients with larger or more aggressive DCIS had either radiation after lumpectomy or mastectomy. Unfortunately, the authors do not provide any details of the number of individuals assessed before enrollment into E5194. This would be useful, especially to know the number of women ineligible for study because of grade and/or size criteria as opposed to those not interested in participation. The generalizability of the results of the assay is, therefore, still to be determined. The authors do rightly caution against extrapolation outside of the entry criteria of E5194 in their conclusion. However, clinical application frequently speeds ahead of prudence. All pathology specimens that had been centrally reviewed in the original study were re-reviewed by two expert pathologists.

Another limitation of the study is that patients were included who took tamoxifen. Use of tamoxifen was not randomized. The authors control for this by performing adjustments with and without tamoxifen use, but caution is advised.

The 10-year ipsilateral breast event risk was defined as the primary outcome for the continuous DCIS Score. Unfortunately, median follow-up of the cohort was 8.8 years (range = 0.2–13.2 years). The original 10-year recurrence risks were 14.6% for cohort 1 and 19.0% for cohort 2. The DCIS Score for the low-, intermediate-, and high-risk groups were 10.6%, 26.7%, and 25.9% (log rank P = .006), respectively, and for an invasive ipsilateral breast event were 3.7%, 12.3%, and 19.2%, respectively. In multivariable analyses, tumor size and menopausal status remained significant (both P ≤ .02). A comparison with the Van Nuys Prognostic Index in Table 3 shows that there was little discrimination in the E5194 dataset by low or intermediate score, documenting therefore an improvement in ipsilateral breast event risk discrimination for the DCIS score.

The question is will women find this information of use when making a treatment decision in conjunction with their physicians. For some, such as the woman recently featured in the New England Journal of Medicine piece who chose bilateral mastectomies, any risk of recurrence over that from bilateral mastectomies may be perceived as too high (5). However, for others, such as a postmenopausal woman with a low DCIS Score and a small tumor, no further treatment and careful follow-up with appropriate imaging is very reasonable.

The authors are to be commended for their thorough work adhering to a stringent design. The limitation they faced in terms of lack of specimens is one that is well recognized, and efforts from the National Cancer Institute and others to rectify this are important for future scientific advances. The clinical applicability of this assay for all women who present with DCIS remains to be determined. This assay does appear to be a step forward.

References


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