

# Ductal carcinoma in situ (DCIS) of the breast: prognostic models and predictive molecular markers

## Editorial

Ductal carcinoma in situ (DCIS) of the breast is the most common type of noninvasive breast cancer lesions. Considered as a direct precursor for invasive breast cancer,<sup>1,2</sup> local recurrence is the major concern in patients diagnosed with DCIS, as its invasive component has been associated with high rates of distant disease and even mortality.<sup>3,4</sup>

Screening programs in advanced health systems<sup>1</sup> resulted in increased incidence of DCIS detected either by mammography or through biopsies.<sup>5,6</sup> Surgical biopsy delivers important information about the extent of a lesion, its margins, multifocality or multicentricity, along with histopathological grading and immunohistochemical information (estrogen and progesterone receptor status, HER2 status and the proliferative potential of the lesion, often by using Ki-67 index). The detailed findings of DCIS may usually help the clinician to make a decision about the need of an additional surgery, adjuvant radiotherapy or tamoxifen chemoprevention.<sup>7</sup> Van Nuys prognostic index is a well established framework that in the initial version (1996) combined three predictors of local recurrence: tumor size, margin width, and pathological classification.<sup>8,9</sup>

After a short period of time, the updated University of Southern California/Van Nuys prognostic index also incorporated patients' age at an inverse pattern. DCIS patients with intermediate scores can be considered for treatment with excision only, whereas patients with high scores of (10 or higher) should be considered for further treatment (whole-breast irradiation, mastectomy, tamoxifen).<sup>10,11</sup> Multi-gene assays has recently been established in the DCIS prognostic characterization.<sup>12</sup>

Further improvement of both risk stratification and treatment recommendation for women with DCIS, current research has aimed to identify biological markers of local recurrence, which may potentially differentiate women with DCIS in high and low risk populations.<sup>13</sup> Conflicting results have been published, as some studies supporting that biological markers are associated with recurrence rates,<sup>14,15</sup> whereas other studies did not.<sup>16</sup> A very important study, in a multivariate model, Kerlikowske et al.,<sup>17</sup> suggested that DCIS lesions that were p16(+)/COX-2(+)/Ki-67(+) or those detected by palpation were significantly associated with subsequent invasive cancer.<sup>17</sup> The role of high grade in the prognosis of DCIS recurrence is also in agreement with the University of Southern California/Van Nuys prognostic index framework.<sup>8-10</sup>

Recurrence rates of a DCIS have also been examined at the meta-analytical level, with various results. Wang et al.,<sup>18</sup> synthesized 44 eligible articles and highlighted as risk factors for ipsilateral recurrence of DCIS comedonecrosis, focality, margin status, method of detection, tumor grade and tumor size. The most recent meta-analysis, published in 2015 by Zhang et al.,<sup>19</sup> confirmed the significant associations with DCIS recurrence and positive margin, the non-screening (symptomatic) detection method, but did not support a significant association with high or intermediate nuclear grade, comedonecrosis, large tumor size, multifocality, estrogen receptor-status, progesterone

Volume 1 Issue 3 - 2015

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**Received:** December 04, 2015 | **Published:** December 07, 2015

receptor-status, or HER2/neu-positivity, leaving the issue open to discussion. Markedly, Wang et al.,<sup>18</sup> underlined the scarcity of data regarding the role of Ki-67 in DCIS recurrence<sup>18</sup> whereas Zhang et al.<sup>19</sup> did not address Ki-67 in this context.<sup>19</sup>

Regarding underlying mechanisms, Ki-67 is a marker of cellular proliferation; it is present during the active phases of the cell cycle, but not during the resting phase G0.<sup>20</sup> Increased cellular proliferation may therefore signal the potential for a future recurrence. Molecular predictors for DCIS recurrence is challenging because the expression levels are often correlated. Therefore the evaluation of multiple markers simultaneously in a multivariate model seems mandatory, so as to disentangle the various, mutually superimposed, prognostic effects. Moreover, the adoption of cut-off point values for molecular markers may also affect results at a certain degree. Future studies for in-depth knowledge of the biology components and additional molecular markers could reveal additional predictive elements on this field.

## Acknowledgements

None.

## Conflict of interest

The author declares no conflict of interest.

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