Cancer Prevention Research

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RESEARCH ARTICLES

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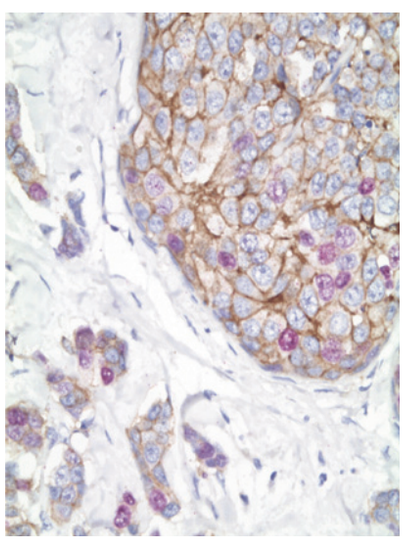
ABOUT THE COVER

Breast ductal in situ carcinoma (DCIS) accounts for approximately 20% of all breast neoplasms, but its treatment is still controversial. Large randomized phase III trials are difficult to conduct, and new efficient clinical trial models are needed to accelerate drug discovery, particularly for HER2-positive DCIS. The oral antidiabetic drug metformin has been associated with lower breast cancer risk in epidemiological studies and has shown antitumor activity in HER2-positive preclinical models. In this randomized trial, proliferation of intraepithelial lesions surrounding breast cancer was assessed in 200 patients who received metformin or placebo for 28 days prior to surgery. Upon surgery, specimens of cancer-adjacent, unaffected tissue were screened for intraepithelial lesions and characterized by immunohistochemistry. Overall, metformin did not affect proliferation in premalignant disorders. However, proliferation of HER2-positive DCIS lesions was significantly lower in women allocated to metformin relative to placebo, especially when ER was coexpressed, providing the background for an adjuvant trial incorporating metformin in HER2-positive DCIS. The micrograph shown on the cover (40× magnification) is stained for HER2 (membranous, brown) and Ki-67 (nuclear, violet) in a representative case of a grade 2 DCIS (upper left hand side) adjacent to a grade 3 ductal invasive carcinoma (lower right hand side). The DCIS component shows intense, circumferential membranous staining for HER2 in most cells, 14% of which coexpress Ki-67. The invasive tumor shows incomplete, faint HER2 and high Ki-67 staining. See the article by DeCensi *et al.* (beginning on page 888) for more information.



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