Combined RB and PTEN loss identifies DCIS primed for invasive breast cancer

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The combined loss of two tumor suppressor genes, retinoblastoma (RB) and phosphatase and tensin homolog (PTEN) was shown to be strongly associated with progression of DCIS to invasive breast cancer, according to a study published November 28 in the *Journal of the National Cancer Institute*.

Ductal carcinoma in situ (DCIS) is a breast cancer precursor lesion for which there are no established markers defining risk of progression to invasive breast cancer. As a result, the majority of women are treated uniformly with surgery and radiation therapy potentially with additional hormonal therapy. However, only a subset of DCIS patients are at risk for developing potentially life-threatening invasive breast cancer requiring such treatment. Thus, defining these patients is a high priority for improving patient care by more effectively directing treatment of DCIS.

Dr. Agnieszka Witkiewicz, Department of Pathology at the University of Texas, Southwestern, and colleagues, assessed RB and PTEN expression in the tissue from over 200 DCIS patients who were treated by surgical resection. They analyzed the association of the loss of each tumor suppressor with DCIS recurrence and progression to invasive breast cancer and conducted functional studies of the two tumor suppressors in cell line models.

About one-third of the women in the study had either recurrence of DCIS or progression to invasive disease and RB loss was statistically

significantly associated with recurrent DCIS. Although PTEN loss was not independently associated with clinical outcome, in combination with RB loss, PTEN deficiency defined DCIS cases that were at substantially increased risk for recurrence and progression. Women with DCIS lacking both RB and PTEN were over 5 times as likely to develop invasive breast cancer. Cellular studies demonstrated that each gene plays a distinct role in facilitating aberrant proliferation and invasive properties that contribute to disease progression.

Dr. Erik Knudsen, an author on the study, concluded that "RB and PTEN together have prognostic utility that could be used to define those DCIS cases that need to be treated aggressively." The authors note, however, that these findings are from only one cohort treated solely by surgery and therefore must be replicated in other cohorts and with additional therapeutic interventions such as radiation. Dr. Witkiewicz believes that, "Such planned studies will be particularly informative for providing a means to spare women from unnecessary radiation exposure and improve the care of women with DCIS." Dr. Knudsen also says, "Interventions exploiting tumor suppressor loss could be utilized to more effectively treat high-risk DCIS". The authors believe that such work will lead to a personalized/rational approach to the treatment of DCIS replacing the current "one size fits all" treatment.

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