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Quantifying heterogeneity in breast cancer

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A variety of mutations may give rise to breast cancer, but scientists generally assume that it starts off with just a few. That's because later-stage breast cancers tend to have more mutations—they are more heterogeneous—than early stage cancers. Now, new findings by scientists at Fox Chase Cancer Center demonstrate heterogeneity is prevalent even within legions of ductal carcinoma in situ (DCIS), the most common, earliest stage non-invasive breast cancer (stage 0). The results, to be presented at the AACR Annual Meeting 2013 on Tuesday, April 9, suggest that a multiple-target approach to diagnosis and therapy may be needed to fight breast cancer from the very start.

"The pathologists recognize this intra-patient heterogeneity exists," says study author Xiaowei Chen, PhD, assistant professor at Fox Chase, "but it is a challenge in the clinical setting" because pathologists have to decide on a case-by-case basis how many DCIS legions to review in order to get a complete picture of each patient's disease. "In the clinical setting, they basically only evaluate one nodule, one part of the tumor," says Chen, and so may miss heterogeneity in other legions.

During the study, Chen's team randomly selected ten DCIS legions from thirty-eight breast cancer cases in which patients were concurrently diagnosed with DCIS and invasive ductal carcinoma (IDC). They then scored the heterogeneity of each patient's DCIS legions using standard immunohistochemistry (IHC) techniques. More than 70% of cases had heterogeneous expression in at least two of the six IHC markers for breast cancer. Chen explains these results account for why tamoxifen, for example, which targets only one mechanism of cancer's growth, may

not be sufficient for some patients: "Treating a cancer with one drug can shrink the tumor," says Chen, "but after a couple of months it may come back" because another subtype of cancer cells, already present, take over. Chen admits examining every legion of every patient is not practical. But quantifying how common heterogeneity is among DCIS legions raises awareness for clinicians and researchers alike.

"Within the research community, we'll need more carefully designed experiments" to avoid relying on tissue microarrays, says Chen, a standard technique used in preparing tumor samples for analysis. Growing evidence shows the technique contributes to conflicting results about heterogeneity when compared to the type of thorough legion analysis done as part of this study.

It will take more research to determine whether DCIS homogeneity contributes to IDC development because patients in this study were concurrently diagnosed with both types of cancer. Still, Chen notes that those patients exhibiting more DCIS heterogeneity were more likely to have lymph nodal involvement, an indicator of cancers' spread.

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