Breast cancer progression from earliest lesions to clinically relevant carcinoma revealed by deep whole genome sequencing

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With improvements in preventive screening methodology, diagnosis of breast cancer is increasingly due to detection of relatively early carcinomas. In a small subset of cases more tissue than just the carcinoma is obtained for histological examination, which then leads to the identification of precancerous lesions that are distinct from, but concurrent with, the diagnostic carcinoma. Such concurrent lesions of varying degrees of severity serve as surrogates for cancer progression.

We deep-sequenced (50x whole genome coverage and more) such concurrent precancerous lesions, as well as normal breast tissue and the diagnostic carcinomas, from several patients. We then identified somatic mutations that serve as markers for cancer progression. In contrast to highly advanced cancers that are the focus of much of current cancer genome sequencing, these early lesions, and the carcinomas as well, harbor a striking paucity of somatic mutations. Those mutations that are present serve as lineage markers to establish the evolution of the cancer from normal breast tissue to precancerous lesions to carcinoma. We illustrate how high-fidelity somatic mutation detection of SNVs and structural variants facilitate studies of early lesions that do not yet exhibit a high frequency of mutations. Our studies begin to shed light on the earliest genomic events that occur in founder cells of eventual breast cancer.

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