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A mutational signature reveals alterations underlying deficient homologous recombination repair in breast cancer

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Breast cancer cells with defects in the DNA damage repair–genes BRCA1 and BRCA2 have a mutational signature (a pattern of base swaps — e.g., Ts for Gs, Cs for As — throughout a genome) known in cancer genomics as "Signature 3." But not all breast tumor cells exhibiting Signature 3 have BRCA1 or BRCA2 mutations. Therefore, some consider Signature 3 a biomarker for "BRCAness," a sign of a breakdown in BRCA-related DNA repair (a process called homologous recombination, or HR) in general, and not BRCA damage in particular. Following a comprehensive genomic and epigenomic analysis of breast cancer, the authors have identified alterations that were not previously known to be associated with Signature 3. They are also better able to determine whether certain types of genetic variants found in a person are associated with disease, as opposed to simply being innocent bystanders. The defects associated with Signature 3 may make patients more responsive to certain treatments.

Among the breast tumors exhibiting Signature 3, the researchers found that: 1) tumors with germline (inherited) or somatic (acquired) BRCA1 or BRCA2 mutations were overwhelmingly positive for Signature 3. So too were tumors with germline mutations in PALB2, a gene that works in concert with BRCA1 and BRCA2; 2) defects in ATM or CHEK2 (two genes that alert the cell to DNA damage, and which can harbor breast cancer risk-raising germline variants) were not linked to Signature 3.; 3) expression of RAD51C (another BRCA1/2 partner) was epigenetically blocked in several tumors. This latter mechanism was far more common in basal-like breast tumors from younger African-American women in the dataset than in those from white women, as was epigenetic BRCA1 silencing (a known Signature 3 driver). The reverse was true for mutation-based drivers.

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