Research provides insight into genetic link to potential treatment response among BRCA1/2 breast cancer patients

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New findings from researchers in the Perelman School of Medicine at the University of Pennsylvania provide clues about immune response of

tumors in patients with BRCA 1/2-related breast cancers. The research, published in the journal *Clinical Cancer Research*, could shape treatment strategies and clinical trial design for these patients, who make up about two percent of newly diagnosed cases of breast cancer.

"This study helps to highlight the immune characteristics of BRCA1/2 breast cancers and to identify the molecular features that may predict immunogenicity," said the study's senior author Katherine L. Nathanson, MD, Pearl Basser Professor for BRCA-Related Research at the Abramson Cancer Center of the University of Pennsylvania. "These data provide a strong building block for our work in uncovering the biological mechanisms that may inform treatment response for patients with BRCA1/2-related breast cancers. Each time we uncover new information that could help tailor the most effective treatments for each patient, we see it as a positive step forward."

Checkpoint inhibitors are a popular immune therapy cancer treatment for some types of cancers and currently are being studied in clinical trials to test the efficacy in treating BRCA1/2 breast cancers.

Researchers sought to determine whether specific genomic markers could provide clues about the immune environment in BRCA1/2 mutation-associated breast cancers. To do so, the team analyzed genomic data from the Cancer Genome Atlas (TCGA) to compare breast cancers with (89) and without (770) either germline (inherited) or somatic (acquired) BRCA1/2 mutations. They also studied 35 breast cancers with germline BRCA1/2 mutations from Penn patients using whole exome sequencing (WES) and immunohistochemistry. It has been hypothesized that breast cancers with somatic or germline BRCA1/2 mutations may be more responsive to checkpoint blockade due to their relatively higher mutational burden. Nevertheless, in this study, researchers found that a higher frequency of mutations was associated with lower immune infiltration of tumors, suggesting that BRCA1/2 mutation status may not

be directly predictive of response to checkpoint blockade.

The team found that higher levels of genomic instability, as measured by homologous recombination deficiency (HRD), were associated with lower immunogenicity and tumor infiltration by T cells. These results were unexpected and go against conventional clinical wisdom. "One aspect of the study that was particularly interesting was that it builds upon our prior studies. Previously we found that tumors in germline BRCA1/2 mutation carriers that did not lose the wild type allele were likely to be less sensitive to DNA damaging agents, and our new data suggests they may be more sensitive to checkpoint blockade," Nathanson said.

"We had assumed that all BRCA1/2 cancers with the highest HRD scores were most likely have the strongest immune response," said study author Susan Domchek, MD, the Basser Professor in Oncology and executive director of the Basser Center for BRCA at the Abramson Cancer Center at the University of Pennsylvania. "But with this data, we now know that these assumptions were incorrect."

Although this study is one of the largest BRCA1/2 breast tumor analyses to date, authors suggest a larger sample size would help to further understand how the molecular features of BRCA1 and BRCA2 mutation associated breast cancers are linked to immune response.

More information: Adam A Kraya et al. Genomic signatures predict the immunogenicity of BRCA-deficient breast cancer, *Clinical Cancer Research* (2019). DOI: 10.1158/1078-0432.CCR-18-0468

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