Study shows genetic effects of pre-surgical chemo in breast cancer

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Results from one of the first studies to determine the effects of pre-surgical, or neoadjuvant, chemotherapy on the breast cancer genome offer up two key insights. One is a before treatment finding that can help

predict which patients would most benefit from pre-surgical chemo, and the other an after treatment finding which sheds light on how cancer cells survive chemotherapy. Findings appear in *Clinical Cancer Research*.

SWOG Cancer Research Network made the work possible. Ten years ago, a SWOG team launched S0800, an innovative trial that compared two 20-week chemotherapy treatments before surgery for patients with HER2-negative, locally advanced, or inflammatory breast cancers. For the study, tumor tissue samples were taken before and after chemotherapy and stored in SWOG's biospecimen bank, a resource open to scientists around the world.

SWOG investigators Lajos Pusztai, MD, and Ryan Powles, Ph.D., both at Yale Cancer Center when the study was conducted, used those banked samples to conduct their study. They submitted the samples to whole exome sequencing, a laboratory technique that catalogues a genome's protein-coding regions, a small fraction of the human genome known as the exome.

For their study, Pusztai and Powles analyzed 29 pre-treatment biopsies from S0800 to identify DNA mutational patterns, then look at post-treatment chemotherapy response to see if any patterns emerged. They found that patients whose breast cancer was completely eradicated by chemo had a higher proportion of DNA mutational "signature 3," a pattern that indicates defects in DNA repair and could be caused by damage to genes like BRCA.

"This is a clue," said Powles, a former Ph.D. student in the Pusztai lab at Yale and now a research investigator at Bristol-Myers Squibb. "Doctors can look at the results of genetic testing to see which of their breast cancer patients might respond best to neoadjuvant chemotherapy, and which patients may need a different, or additional, course of treatment."

For their post-treatment analysis, Pusztai and Powles were only able to analyze nine of the 29 pre- and post-chemo samples. That's because the treatment killed so many tumor cells that most samples were too small to examine. However, the nine remaining samples were well-suited to study chemotherapy resistance. The SWOG team found no single gene or gene mutation present in tumor tissue that survived chemo. Rather, these tumor cells featured mutations that belonged to two biological pathways—E2F Targets and G2M Checkpoint. These pathways are sets of genes that act together to regulate cell growth, a process that can cause cancer if it goes awry.

"What is important about this paper is that it demonstrates that while each cancer acquires mutations in different genes, the affected genes are not random," said Pusztai, chair of SWOG's breast cancer research committee and director of breast cancer translational research at Yale Cancer Center. "Cancer cells that survived chemotherapy all had alterations in cell growth regulation at various levels. So, while the genes may be different, they do the same work."

More information: Ryan L. Powles et al, Analysis of pre- and post-treatment tissues from the SWOG S0800 trial reveals an effect of neoadjuvant chemotherapy on the breast cancer genome, *Clinical Cancer Research* (2020). DOI: 10.1158/1078-0432.CCR-19-2405

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