

# Drug resistance is a powerful menace in certain breast and ovarian cancers. Now scientists are figuring out why

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Just as bacteria, viruses and fungi develop strategies to outsmart antimicrobial medications, cancer cells can become resistant to

chemotherapy. And among tumors, those associated with triple negative breast cancer and ovarian tumors can develop a powerful form of resistance.

In an intriguing line of research, a multi-center team of U.S. researchers has found that epigenetic signatures in breast and ovarian cancers may ultimately guide physicians' treatment decisions for a subset of patients whose cancers are notoriously capable of thwarting chemo.

By pinpointing which molecular signatures correlate with optimum treatment response, oncologists can be better informed when designing treatment regimens for cancers with reputations for aggressive drug resistance.

Reporting in *Science Translational Medicine*, cancer biologists at Jackson Laboratory for Genomic Medicine in Farmington, Connecticut, spell out why triple negative breast cancer—TNBC—and ovarian carcinoma are especially difficult to treat. For one thing, loss of BRCA1 or BRCA2 [gene activity](#) is common in TNBC and ovarian cancer the scientists underscored, and has a potent bearing on prognosis. However, the type of alteration involving the genes can result in different responses to treatment, the researchers said.

Collaborating with medical investigators at Fred Hutchinson Cancer Center at the University of Washington in Seattle and researchers at the City of Hope Comprehensive Cancer Center in Duarte, California, scientists examined how various flaws involving the genes affected responses to platinum-based chemotherapy.

They explored situations involving TNBC and ovarian cancer where there were BRCA losses, gene alterations as well as the biological phenomenon known as promotor methylation of BRCA. Gene promoter methylation is a common epigenetic event, occurring early in the process

of tumorigenesis. Methylation is a simple biochemical process involving the transfer of atoms: one carbon and three hydrogens atoms—CH<sub>3</sub>—are transferred from one molecule to another. Methylation, scientists have found, has potential as a diagnostic and prognostic biomarker.

"Triple-negative breast cancer and ovarian carcinomas with BRCA1 promoter methylation—BRCA1meth—respond more poorly to alkylating agents compared to those bearing mutations in BRCA1 and BRCA2—BRCAmut," writes Francesca Menghi, an associate research scientist at Jackson Laboratory, and the study's first author.

Platinum-based chemo is an alkylating agent and some women with TNBC or ovarian cancer fare poorly when treated with this form of chemotherapy. "This is a conundrum," Menghi added, noting that she and her team "dissected this problem through detailed genomic analyses of triple negative breast cancer and ovarian carcinoma cohorts, and experimentation with patient-derived xenografts and genetically engineered cell lines. BRCA1meth uniformly associates with poor outcomes," she emphasized.

TNBC is a form of breast cancer in which three key receptors are missing on tumor cells: Estrogen and progesterone receptors are missing, as is the human epidermal growth factor receptor-2, known commonly as HER-2. Hence the term, triple negative. These receptors are the targets of medications that are used to successfully treat other breast cancer subtypes, boosting patients' survival. An estimated 15% to 20% of all female breast cancers in the United States are triple negative, according to the patient advocacy organization, Susan G. Komen For The Cure, based in Dallas, Texas.

For reasons not yet fully explained, [triple-negative breast cancer](#) occurs most frequently among young women, often under age 40, particularly those who are Black or Hispanic. People with mutations in either of their

BRCA genes also are at elevated risk, and those with BRCA<sub>meth</sub> are at particular risk for poor outcomes, Menghi and her colleagues found in a multi-pronged study.

Scientists had long known that triple negative breast and [ovarian cancers](#) with mutations in the BRCA1 and BRCA2 genes can be sensitive to platinum-based chemotherapies. However, cancers with epigenetic promoter methylation in BRCA1 tend to respond less favorably to platinum-centered treatments for reasons that had remained stubbornly unclear. Menghi and colleagues wanted to know why and designed a series of elegant experiments aimed at teasing out the answers.

They studied humanized mouse models, cell lines, and [genetic data](#) from 42 patients with TNBC who received [platinum-based chemotherapy](#). The researchers compared how epigenetic and genetic changes in BRCA—promoter methylation or genetic loss of BRCA1—affected how the patients and mice responded to platinum-based chemo. Although both subtypes led to similar downstream genetic signatures, BRCA1 promoter methylation vigorously endowed tumors with platinum-therapy resistance and was linked to worse outcomes.

"We found that despite identical downstream genomic mutational signatures associated with BRCA1<sub>meth</sub> and BRCA<sub>mut</sub> states, BRCA1<sub>meth</sub> uniformly associates with poor outcomes," Menghi and colleagues reported in *Science Translational Medicine*.

"Exposure of BRCA1<sub>meth</sub> triple negative breast cancers to platinum chemotherapy, either as clinical treatment of a patient or as experimental in vivo exposure of preclinical patient derived xenografts, resulted in allelic loss of BRCA1 methylation and increased BRCA1 expression and platinum resistance," the scientists asserted.

The team concluded that their data answer some key concerns about

BRCAMut and BRCAMeth: BRCAMut cancers, the team says, is a genetically "fixed" deficiency state. The other subtype of is a totally different story. BRCA1meth cancers are highly adaptive to genotoxin exposure, and because of promoter methylation, become resistant to therapy.

"We further found a specific augmented immune transcriptional signal associated with enhanced response to platinum chemotherapy but only in patients with BRCA-proficient cancers," Menghi concluded, noting the research opens a new window of understanding into TNBC and ovarian carcinoma. "The ability to de-escalate a toxic combination in a subset of patients with TNBC and [[ovarian cancer](#)] potentially identified by our decision tree would have a meaningful impact on cancer survivors."

**More information:** Francesca Menghi et al, Genomic and epigenomic BRCA alterations predict adaptive resistance and response to platinum-based therapy in patients with triple-negative breast and ovarian carcinomas, *Science Translational Medicine* (2022). [DOI: 10.1126/scitranslmed.abn1926](#)

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