# Women carrying rare breast cancer variants more likely to develop interval breast cancers

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While the presence of common breast cancer mutations was indicative of increased breast cancer risk, the presence of certain rare mutations was indicative of increased risk from interval breast cancers and death.

The study is published in *Cancer Research*, a journal of the American Association for Cancer Research, by Jingmei Li, Ph.D., senior research scientist at the Genome Institute of Singapore

"It is not enough just to know which markers can predict an increase in breast cancer risk," said Li. "We also need to know which biomarkers can identify women with increased risk of aggressive interval cancers that are not usually detected during routine mammography screening."

Interval breast cancers are detected between mammography screenings; these cancers are often aggressive and have a poor prognosis. "About 20 percent of women who partake in routine mammography screening will be diagnosed with interval breast cancer," explained Li. "More sensitive methods to predict and detect these lethal cancers are sorely needed."

Li and colleagues analyzed data from over 5,000 breast cancer patients diagnosed between 2001 and 2008 through the Stockholm-Gotland Regional Breast Cancer quality register. The researchers studied associations with tumor characteristics and survival outcomes for patients with rare protein-truncating variants (PTVs) in 31 cancer predisposition genes, including BRCA1/2. Additionally, the researchers developed a polygenic risk score (PRS) through the weighted sum of all known common breast cancer variants, which was also correlated with tumor characteristics and overall survival.

Because interval cancers are not identified through routine mammography screenings, Li and colleagues analyzed the mode of detection for cancers driven by rare PTVs or common variants. A proportion of interval cancers may include tumors that were missed from routine mammography. Because dense tissue is one of the main reasons for masked tumors, women were stratified into risk categories based on percent breast density (low risk

Of the 5,099 breast cancer patients analyzed, 597 carried PTVs. These patients were younger, had more aggressive tumor phenotypes, and had 1.65 times the risk of death from breast cancer compared to those who did not carry PTVs. After excluding 92 women that carried mutations to BRCA1/2 from this cohort, women with PTVs had 1.76 times the risk of death from breast cancer compared to those without PTVs.

Analysis of 5,077 women who did not carry mutations to BRCA1/2 revealed that a higher PRS was associated with less aggressive tumor characteristics. Notably, no significant survival differences were associated with increases in PRS.

"Polygenic risk score is a good marker for breast cancer prediction," noted Li. "However, there is not enough evidence to show that this score can also predict death from breast cancer."

Among women with low breast density, those who carried PTV mutations were 1.96 times as likely to be diagnosed with interval breast cancers compared to women who did not carry PTV mutations. Further, among women with low breast density, those who carried non-BRCA1/2 PTV mutations still had 1.89 times increased risk compared to women who did not carry PTV mutations. In contrast, women with low breast

density and a higher PRS had a 23 percent decreased risk for developing interval breast cancer.

"Both rare and common variants can predict breast cancer risk," said Li. "Our study shows that different variants are associated with different kinds of breast cancer, and that women carrying rare variants have a higher risk of developing interval breast cancers and have worse overall survival compared to women with common mutations."

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