# Researchers discover inherited genetic mutations can predict interval breast cancer

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An investigation conducted by researchers at Karolinska Institutet has led to a discovery in breast cancer diagnostics and treatments that could reshape screening programs and clinical approaches. The study,

published in *JAMA Oncology*, unravels the impact of rare genetic variants on interval breast cancers, providing new insights into tailored screening strategies.

Interval cancers, a type of breast cancer diagnosed between routine screenings, have long posed challenges due to their aggressive nature and poorer patient outcomes compared with screen-detected cancers. However, until now, the role of genetic variants in these breast cancer types has been largely unexplored.

The study, involving 4,121 breast cancer patients and 5,631 controls, meticulously examined 34 breast cancer susceptibility genes. The primary focus was to discern the influence of carrying deleterious variants on differentiating between interval cancers and screen-detected cancers, taking mammographic density into consideration.

The investigation provided two clinical take-home messages. Firstly, researchers found that protein-truncating variants (genetic mutations that shorten the protein-coding sequence) of the five major genes for breast cancer (ATM, BRCA1, BRCA2, CHEK2, and PALB2) increased the probability of being diagnosed with interval cancer. Notably, this elevated risk was predominantly attributed to variants in BRCA1/2 and PALB2.

"Women with a family history of breast cancer, in combination with genetic variants in any of these five genes, were four times more likely to develop interval cancer compared with screen-detected breast cancer, suggesting that further large-scale sequencing efforts are necessary to uncover the full genetic contribution of the observed interaction," says first author Juan Rodriguez, post-doctoral researcher at the Department of Medical Epidemiology and Biostatistics.

Secondly, if a patient received a diagnosis of interval cancer, carriers of

deleterious variants in any of these five genes had significantly worse survival compared with women not carrying any of them.

According to the researchers, this is the first report looking into the genetic differences between screen-detected and interval cancers using the five major genes for breast cancer. The results suggest that screen-detected and interval cancers are indeed distinct in both underlying genetics and biology, thus providing valuable information for identifying women who are at very high risk for developing aggressive breast cancer.

"These results show novel and important insights into the genomic differences between interval and screen-detected breast cancer," stated Juan Rodriguez. "Our work clarifies the picture of what type of breast cancer is likely to evade detection in population-based screening programs, with potential applicability in clinical care and in future optimizations of screening programs aimed at lowering mortality."

"Enriching the capacity to detect breast cancer at an earlier stage will ultimately lead to better treatment outcomes, an improved quality of life for affected women, and a reduction in the financial burden on the health care system," says the study's last author, Professor Kamila Czene at the same department.

**More information:** Juan Rodriguez et al, Investigation of Genetic Alterations Associated With Interval Breast Cancer, *JAMA Oncology* (2024). DOI: 10.1001/jamaoncol.2023.6287

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