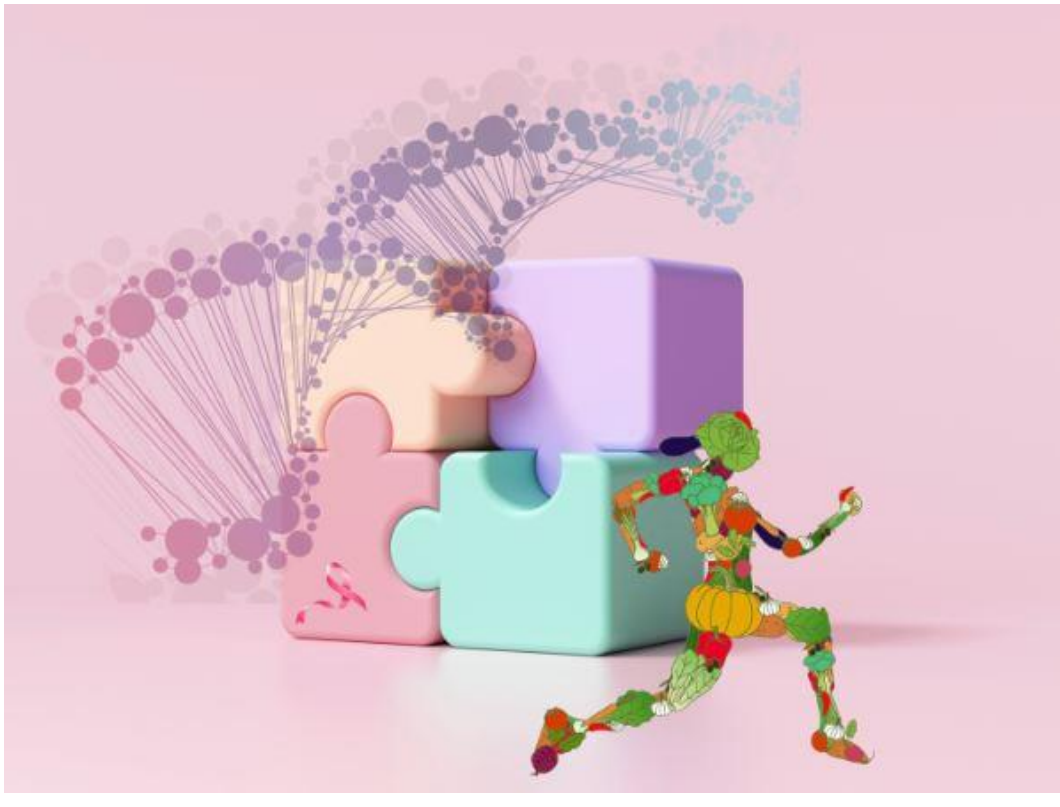
RISK PREDICTION USING GENETIC DATA ADDS VALUE TO BREAST CANCER SCREENING



With increasing interest worldwide in using a risk-based approach to breast cancer screening over the current age-based paradigm, a common question raised by policy makers and the public is “How much value does genetics add?”

In this breast cancer case-only study led by Dr Li Jingmei from the Genome Institute of Singapore, different state-of-the-art breast cancer risk calculators, both genetic and non-genetic, were examined to stratify 7,600 Asian women based on their individual breast cancer risk to see how much genetic risk information can augment traditional stratification tools (i.e. family members diagnosed with breast cancer, Gail model).

Four risk prediction tools were evaluated. Breast cancer patients aged 30 to 75 (n=7,600) were classified into high or low breast cancer risk groups. The following criteria were used to define high risk groups: (1) at least one first degree relative diagnosed with breast cancer (effect of family history), (2) carriership of protein-truncating variants (PTVs) in ATM, BRCA1, BRCA2, CHEK2, PALB2, BARD1, RAD51C, RAD51D or TP53 (effect of rare genetic variants), (3) five-year absolute risk above 1.3% (five-year absolute risk of an average 50 year old woman) estimated by PRS (effect of common genetic variants), and (4) five-year absolute risk above 1.3% estimated by Gail risk model (effect of non-genetic variants).

Risk prediction using genetic data identifies high risk women missed by using only non-genetic data

In total, 53% (n=4,041) were identified as high risk by one or more of the risk stratification tools. While there is a certain degree of overlap in the high risk individuals identified by the four tools, each of the four tools only identified 1,247 (positive family history: 16%), 385 (PTV carriership: 5%), 2,774 (five-year absolute risk ≥1.3% by PRS: 36%) and 1,592 (Gail model: 21%) of unique (only identified by that tool) breast cancer patients considered as high risk respectively. The correlation between individual breast cancer absolute risk estimates predicted by PRS (genetic) and Gail model (non-genetic), two tools which identified the largest proportions of high risk individuals, was low (r=0.27).

The findings show that germline genetic tools which are currently not used widely in many countries for breast cancer risk stratification in the general population can identify substantially more persons at risk. The genetic risk stratification models, PTV carriership and PRS, identified 2,183 (54% of 4,041) high risk individuals who were not identified by the Gail model or family history. The overlap between high risk individuals identified by high penetrant breast cancer predisposition genes and common variants identified by genome-wide association studies was low. Among 385 PTV carriers, 110 (28%) were considered high risk by PRS.

Genetic risk predictors can identify high risk women who are not yet at the age eligible for mammography screening

The (non-genetic) Gail model did not perform as well for younger women. For women below the standard mammography screening entry age of 50 years (age 30 to 50 years; n=3,227), the breast cancer risk stratification tools studied identified 40% (n=1,276) of the breast cancer patients to be high risk. Risk stratification by positive family history, PTV carriership, and five-year absolute risk ≥1.3% by PRS or Gail model identified 470 (15%), 213 (7%), 769 (24%) and 325 (10%) unique breast cancer patients who were considered at high risk of breast cancer, respectively. PRS and PTVs together identified 745 (59% of 1,276) high risk individuals who were not identified by the Gail model or family history.

Regional collaboration to improve breast cancer health in Asia

Breast cancer patients in the study were recruited from the Singapore Breast Cancer Cohort study, which includes six participating hospitals that diagnose approximately 70% of breast cancer cases in Singapore. Breast cancer patients recruited by Malaysian collaborators were also included in this study.

Empower and engage women for better breast health

“In view of public health policies, the findings support the incorporation of genetic tools for breast cancer risk stratification. Given that screening uptake and adherence is alarmingly low even when cost is not a barrier to entry, we believe that increasing women’s personal stakes in taking control of their own health may be the way forward. Individual risk profiles gathered from genetic information may help women make informed decisions and motivate them to attend screening.”

Dr Li Jingmei, Group Leader,
Laboratory of Women's Health & Genetics, GIS

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The study team is leading a new BREAst screening Tailored for HEr (BREATHE) project which uses existing breast cancer risk calculations that take into account information from genes and self-reported questionnaires. BREATHE is supported by the JurongHealth Fund, PRECISION Health Research, Singapore (PRECISE) and A*STAR. This pilot study identifies women who are at a higher risk of developing the condition than the general population. Women who are expected to have a higher risk of breast cancer are directed to study sites' specialists and provided breast health recommendations in addition to the current screening standards. The BREATHE project aims to raise breast cancer awareness, education, and screening adherence in the long run.

The study was published in *BMC Medicine* (article DOI: 10.1186/s12916-022-02334-z) on 26 April 2022.

“This paper highlights the importance of using a multipronged approach to identify women of increased risk of breast cancer. As a clinician, using both genetic and non-genetic factors is essential in our practice of prevention.”

Associate Professor Mikael Hartman
Practising clinician and Principal Investigator
of the Singapore Breast Cancer Cohort study

“A personalised screening strategy that comprehensively considers different aspects of breast cancer risk is a sustainable way to reduce healthcare spending in the long run.”

Dr Ho Peh Joo, Senior Research Fellow
Laboratory of Women's Health & Genetics, GIS

“Working on a cohort study that lasts for 10 years is an arduous journey. With great passion and dedication to breast cancer research, we have collected risk factors and genetic information for more than 10,000 breast cancer patients. We strive to deliver effective research in personalised medicine with the hope to make a real difference in the lives of patients.”

Ms Yeoh Yen Shing, Research Associate
Saw Swee Hock School of Public Health, NUS