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Personalised Breast Cancer Screening vs One-size-fits-all Approach

INTRODUCTION

Breast cancer is the most common cancer and the leading cause of cancer-related deaths in women worldwide. In 2020, 2.3 million women were diagnosed with breast cancer, with 685,000 deaths registered globally. As of the end of 2020, there were 7.8 million women alive who were diagnosed with breast cancer in the past 5 years, making it the world's most prevalent cancer.[1]

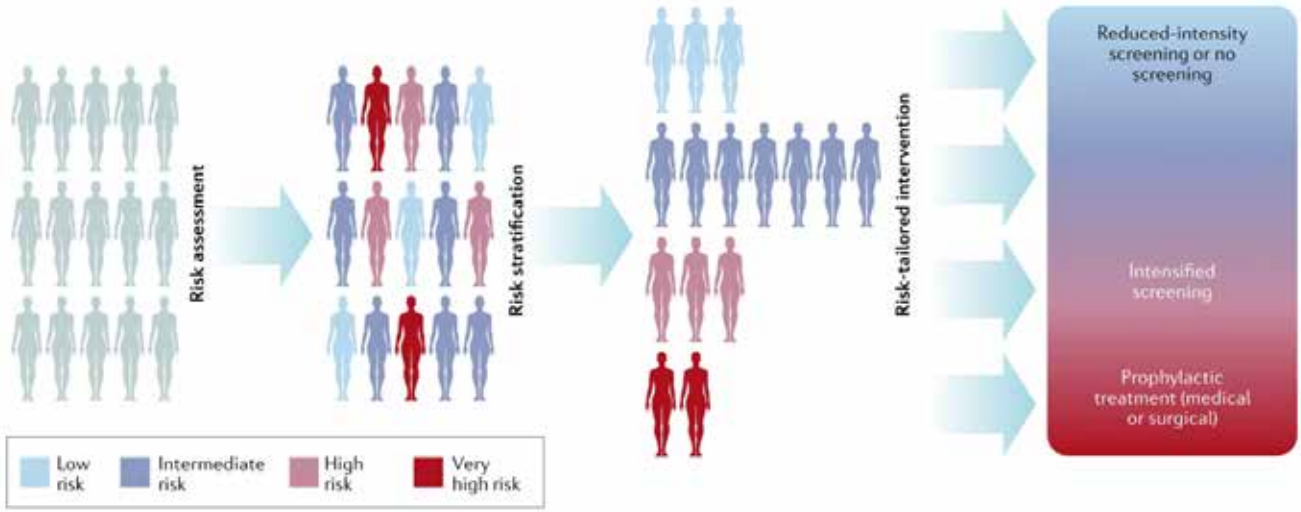
There was little change in breast cancer mortality from the 1930s through to the 1970s when surgery alone was the primary mode of treatment. Improvements in survival began in the 1990s when countries established breast cancer early detection programs together with comprehensive treatment programs including effective medical therapies.[1]

NATIONAL BREAST SCREENING PROGRAMMES

The aim of a National Breast Screening Programme, widely implemented in many healthcare systems, is to reduce breast cancer mortality through the expedited diagnosis of smaller, clinically occult breast cancers. In a meta-analysis of 11 randomised trials, the relative risk of breast cancer mortality for women invited to screening compared with controls was 0.80 (95% CI 0.73–0.89), which is equivalent to a relative risk reduction of 20%.[2]

The Malta National Breast Screening program currently invites women between 50 and 69 years of age for a full field digital 2D mammogram (FFDM) once every two years. During 2022, 11,645 mammograms were performed. Each mammogram is double read by two breast radiologists blindly. If the mammogram is reported as normal by both readers, the patient will be invited for her next mammogram after two years. If only one of the two readers reports a positive finding, the mammogram will be further read by a third reader who then decides whether to recall the patient for further investigations or not. If both readers report a positive finding, the woman is recalled for further investigations such as digital breast tomosynthesis (DBT)/3D mammogram, ultrasound (US), and magnetic resonance imaging (MRI). In some cases, a core biopsy is also performed.

Figure 1. A schematic outlining a personalized approach to early detection and prevention of breast cancer.



Women entering a personalized early detection programme would initially be assessed using a validated tool to determine their estimated risk of breast cancer. Subsequently, the women would be stratified into appropriate risk groups such that they can receive tailored interventions. *Source: Pashayan N, Antoniou AC, Ivanus U et al. Personalized early detection and prevention of breast cancer: ENVISION consensus statement. Nat Rev Clin 2020:687–705.*

Apart from high-risk scenarios such as the presence of highly penetrant genetic mutations, breast screening programs typically comprise mammography or tomosynthesis strategies defined by age alone.[3] But what about other breast cancer risk factors individual women may possess? How can they be assessed and integrated in breast cancer screening programme strategies? How can we shift from a one-size-fits-all approach to personalised risk-stratified screening?

PERSONALISED RISK-STRATIFIED SCREENING

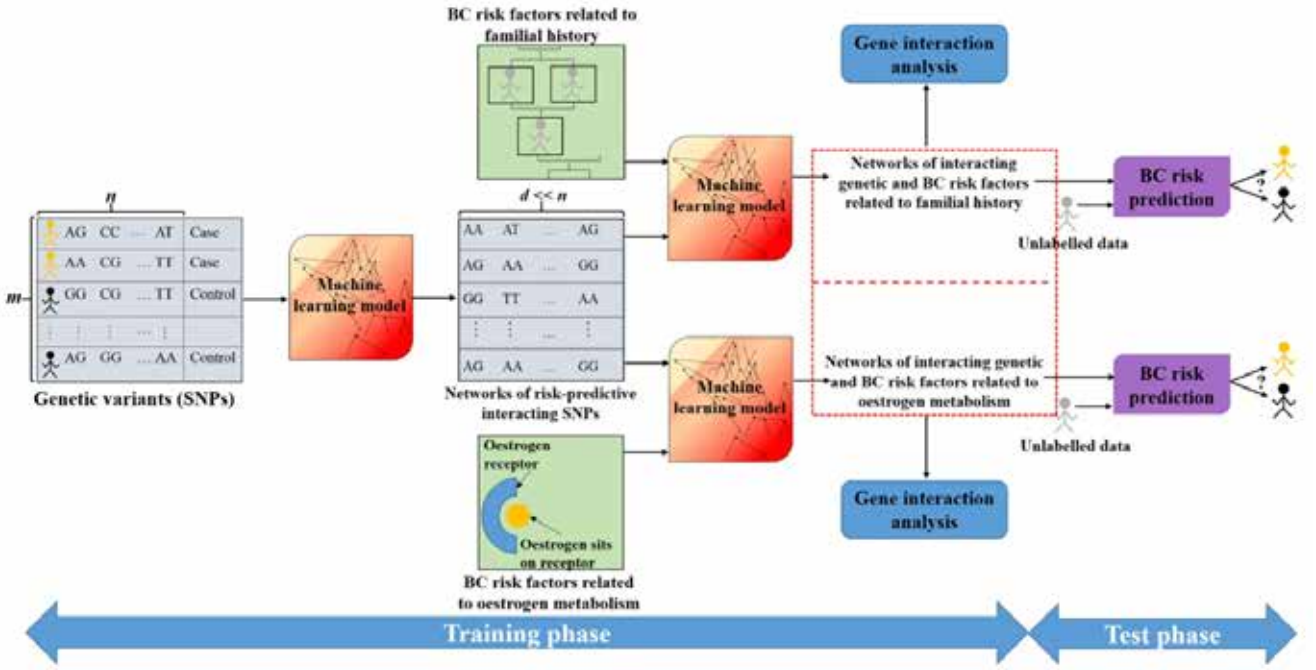
Personalised screening requires an accurate measure of an individual's risk of developing breast cancer. Age, reproductive history, breast density, family history of breast or ovarian cancer, previous benign breast disease, hormonal and lifestyle factors, and a combination of common genetic variants such as single-nucleotide polymorphisms (SNPs) and mutations in the BRCA or other susceptibility genes can be amalgamated to predict breast cancer risk.[4]

This individualised risk assessment would then determine an individualized screening strategy which would include establishing the age of screening initiation and cessation, the screening frequency, the type of screening exam, consideration of preventive treatments for high-risk women, or even decisions regarding the non-screening of low-risk women (Figure 1). In modelling studies, personalised risk-based approaches to the early detection of breast cancer appear to be more efficient and have a better balance of benefits and harms than age-only strategies.[4]

Studies that assess risk estimation, acceptability, feasibility, and the legal and ethical aspects of personalised screening strategies are underway. Two non-inferiority clinical trials comparing risk-based screening with age-based screening - the Women Informed to Screen Depending on Measures of risk (WISDOM) in the USA and My Personal Breast Screening (MyPeBS) in Europe - will complete their respective collections of information by 2025. In Canada, the Personalized Risk Assessment for Prevention and Early Detection of Breast Cancer: Integration and Implementation (PERSPECTIVE I&I) project, and in the United Kingdom, the Predicting the Risk of Cancer at Screening (PROCAS) study, aim to improve personalised risk assessment, perform cost-effectiveness analyses, and identify best practices to implement them in their respective National Health Systems.[4]

In 2019, the European Collaborative on Personalized Early Detection and Prevention of Breast Cancer (ENVISION) organized a consensus conference with international consortia leading the research on personalised breast cancer screening. The consensus statement identified several areas of research that require development to enable evidence-based personalised breast cancer screening and prevention programs. These include breast cancer subtype-specific risk assessment tools and implementation studies addressing feasibility and acceptability combined with modelling studies to evaluate the long-term population outcomes of risk-based screening.[4]

Figure 2. Outline of the proposed breast cancer risk prediction system using Machine Learning.



In the training phase, networks of interacting genetic and demographic risk factors for breast cancer are identified. These networks of features are then used to predict whether an unlabelled individual is a cancer case or a healthy control in the testing phase. This study provides two examples showing that a combination of interacting genetic variants (Single Nucleotide Polymorphisms) with breast cancer risk factors related to both familial history and oestrogen metabolism can increase breast cancer risk prediction accuracy. *Source: Behravan H, Hartikainen JM, Tengström M et al. Predicting breast cancer risk using interacting genetic and demographic factors and machine learning. Sci Rep 2020;10:11044.*

POTENTIAL ROLES OF ARTIFICIAL INTELLIGENCE IN PERSONALISED SCREENING

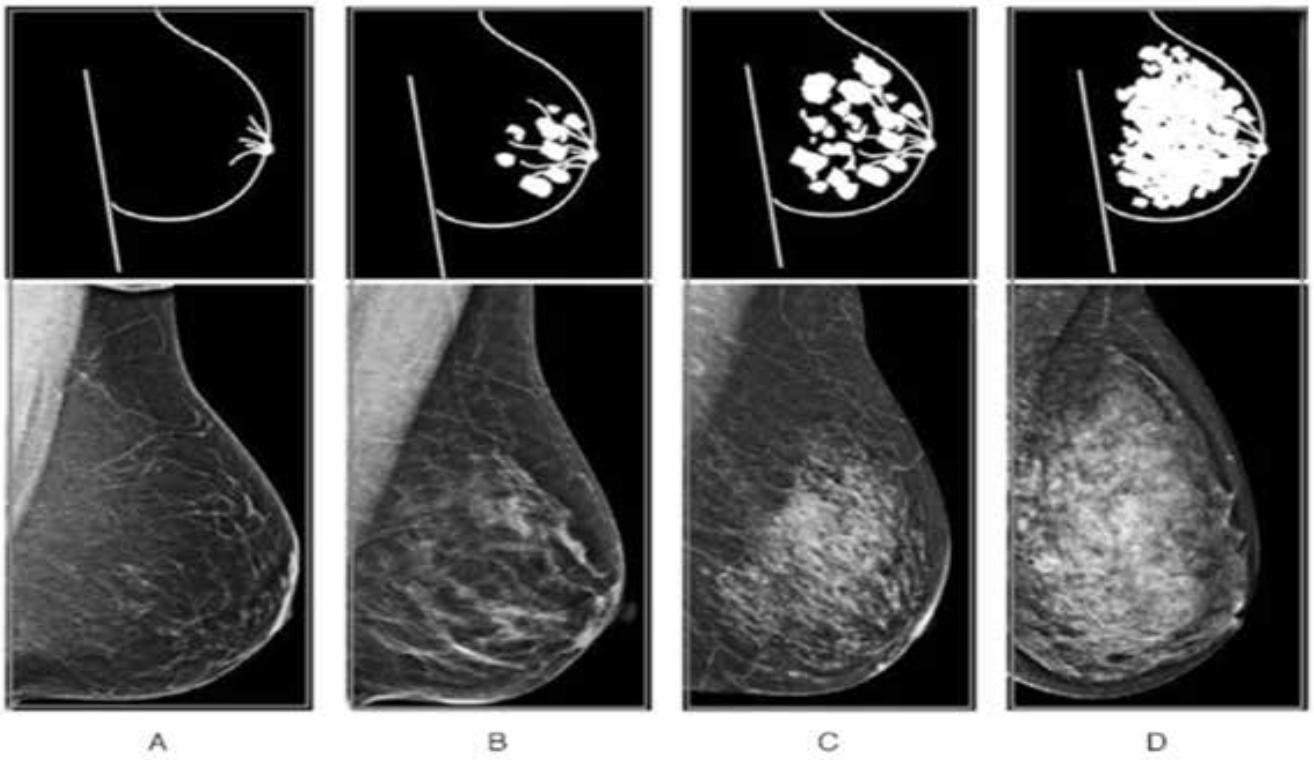
Artificial intelligence (AI) represents a real game changer in breast cancer imaging. Applications include assisted detection of tumour to increase diagnostic accuracy, reducing the rate of false negatives and false recalls, whilst improving radiologist workload; non-invasive tumour characterization (identification of tumour subtype, evaluation of tumour heterogeneity and microenvironment, etc) to plan targeted therapy and follow-up; prognostic/predictive applications regarding response to treatment, risk of relapse and overall survival; and lastly risk stratification, in order to achieve individualized screening programs through AI risk prediction modes (Figure 2).[5]

One of the most popular risk prediction models is the International Breast Intervention Study (IBIS) model, or Tyrer-Cuzick (TC) model, a scoring system guiding breast cancer screening and prevention by accounting for age, genotype, family history of breast cancer, age at menarche and at first birth, menopausal status, atypical hyperplasia, lobular carcinoma *in situ*, height, and body mass index (BMI). Despite its widespread use, however, the IBIS/TC model demonstrated limited accuracy in some high-risk patient populations. AI can help integrate imaging features into predictive risk models increasing accuracy. For example, a study by Yala et al.[6] evaluated the performance of a hybrid deep learning AI model considering both traditional risk factors and mammograms, in comparison with the IBIS/TC model alone: the hybrid model placed 31% of patients in the top risk category, compared with 18% identified by the IBIS/TC model, and was able to identify the features associated with long-term risk beyond early detection of the disease.[7]

SUPPLEMENTAL SCREENING WITH CONTRAST-ENHANCED BREAST MRI FOR WOMEN WITH EXTREMELY DENSE BREASTS

Breast contain glandular tissue, fibrous connective tissue and fat. Breast density is a term used to describe the relative amount of these different tissue types as seen on mammography. The Breast Imaging

Figure 3. Breast density - The four levels.



Reporting and Data System (BI-RADS) classifies breast density into four categories, from A to D, from lowest to highest density.

Category A: entirely fatty breast.

Category B: scattered fibroglandular breast tissue – mostly fatty tissue with some areas of dense glandular and fibrous connective tissue.

Category C: heterogeneously dense breast tissue – many areas of dense glandular and fibrous connective tissue, with some areas of fatty tissue.

Category D: extremely dense breast tissue – breast is almost all dense glandular and fibrous connective tissue [Figure 3].

Women with extremely dense breasts have an increased risk of breast cancer. In addition, cancers in these women are also less likely to be detected on mammography since the sensitivity of mammography decreases with increasing breast density.[8]

Current mammographic screening programs are therefore not enough in this category of women. The results of recent studies, namely the DENSE trial and the EA1411 ECOG-ACRIN study, reporting on contrast-enhanced breast MRI as a screening method in women with extremely dense breasts provide compelling evidence that this cost-effective approach can enable a significant reduction in breast cancer mortality for these women. In light of the available evidence, the **European Society of Breast Imaging (EUSOBI) recommends that women aged 50 to 70 years with extremely dense breasts at average risk, should be offered supplemental screening with contrast-enhanced breast MRI every 2 to 4 years.**[5]

CONCLUSION

Breast cancer imaging continues to evolve and the near future predicts AI-based algorithms for risk-stratification models, moving towards a personalised screening approach.

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