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Genetic Factors in the Screening and Imaging for Breast Cancer

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Take-home points

- Genetic factors, including gene mutations, variants and polymorphisms as well as family history can have a significant impact on breast cancer screening recommendations.
- Mutations, variants and polymorphisms in a number of genes are associated with breast density and cancer risk.
- Artificial intelligence assisted breast imaging processing, in addition to breast cancer risk models, show promise in improving breast cancer risk assessment.
- Future directions for screening may be even more personalized based on personal and family history, genetic mutations and polymorphism, and artificial intelligence-guide imaging interpretation.

Keywords: Precision medicine; Breast cancer screening; Genetic testing; Artificial intelligence; Breast imaging

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INTRODUCTION

Breast cancer is the most common neoplasm in women worldwide, with an estimated incidence of 2179457 new cases and an estimated 655690 deaths in 2020. It is the highest leading cause of cancer-associated death among women worldwide [1]. The early diagnosis of breast cancer is important to reduce the mortality rate. Although screening mammography has improved the lives of innumerable women worldwide, it is not a perfect tool and has associated risks, including overdiagnosis, false positive results, overtreatment, radiation exposure, and psychosocial burdens of stress and anxiety [2]. Here, we review the new approaches and algorithms in breast cancer screening that improve the accuracy of clinical decision-making along with the traditional approaches.

Breast Cancer Screening Recommendations by ACR and Definition of High Risk

The principal goal of breast cancer screening is to detect small, non-palpable, node-negative breast cancers to allow the least morbid treatments and mortality. Regular mammographic screening results in a substantial reduction in breast cancer mortality across multiple study designs [3]. A number of organizations world-wide have established breast cancer screening recommendations based on risk factors. While there are many similarities and slight differences in many of these recommendations, we will focus on the criteria established by the American College of Radiology (ACR). The ACR recommends annual mammographic screening beginning at age 40 for women at average risk for developing breast cancer. The age to stop screening should be based on each woman's health

Korean Journal of Radiology
KJR

status rather than an age-based determination. Potential harms associated with screening mammography include overdiagnosis and treatment of cancer that would otherwise have been clinically insignificant in women's lives, as well as the unnecessary anxiety and additional testing that is associated with false-positive screening examination [4].

For high-risk groups of developing breast cancer, ACR recommends different screening ages and methods based on the types of high-risk factors (Table 1). Those factors include a calculated lifetime risk of 20% or more, a genetics-based increased risk (and their untested first-degree relatives), histories of chest radiation (cumulative dose of ≥ 10 Gy before age 30), personal histories of breast cancer and dense breast tissue or those diagnosed before age 50, personal histories with atypical ductal hyperplasia, atypical lobular hyperplasia, or lobular carcinoma in situ. All women, especially black women and those of Ashkenazi Jewish descent, should be evaluated for breast cancer risk no later than age 30 so that those at higher risk can be identified and can benefit from supplemental screening [5].

These ACR recommendations allow women to obtain the maximum life-extending benefits and provide improved treatment options for those diagnosed with breast cancer. Women should be helped to understand the risks of screening; weighing benefits and risks should be done by women, not for women. Overdiagnosis should not be a factor in deciding when to start screening or what screening interval to choose.

Breast Cancer Risk Assessment Model

Multiple statistical models have been developed to assess the risk of developing breast cancer and the risk of carrying a heritable genetic mutation and to identify those women who merit more aggressive and earlier screening. Identifying women at the highest risk of disease can direct the use of supplemental screening in addition to screening mammography [6]. Common models include the Claus model, BRCAPRO, BOADICEA, Gail model, and Tyrer-Cuzick. Each model incorporates and weighs different sets of risk factors (Table 2). Hence, the models can give different estimates for the same woman [7]. To improve discriminatory accuracy, a few models also include modifiable risk factors such as body mass index, alcohol use, exercise, and non-modifiable mammographic breast density.

The Breast Cancer Risk Assessment Tool (BCRAT), also known as the modified Gail model, has been widely used and validated. The Gail model, created in 1989 by Gail et al. [8], predicts the risk of developing breast cancer in women within the next five years and over their lifetime. It originally included five factors (age, number of first-degree relatives with breast cancer, age at birth of first child, age at menarche, and number of previous biopsies). Slight modifications were made over the years to allow for more accurate assessment. For example, the presence of atypical hyperplasia in a biopsy and women of different races and ethnicities, including Asian and Pacific Islander women, were added to the model [9,10]. This model has been shown to have a discriminatory accuracy of 0.55 (95% confidence interval [CI], 0.50–0.59). It has been used in the selection of women for chemoprevention. Although this model has worldwide validation, its applicability is questionable in some populations because it has significant limitations related to the absence of some risk factors in its formula [11].

Tyrer-Cuzick, also known as the International Breast Cancer Intervention Study (IBIS) model, maybe the most robust as it takes into account multiple factors, including

Table 1. ACR Screening Recommendation in High-Risk Females

Risk Factors	Screening Age	Screening Methods and Interval
Lifetime risk of 20% or more	Beginning at 30 years	Annual DM ± DBT, anuual MRI
Genetics-based increased risk (and their untested first-degree relatives)	Beginning at 30 years	Annual DM ± DBT, anuual MRI
Histories of chest radiation (cumulative dose of ≥ 10 Gy before age 30)	Beginning at age 25 or 8 years after radiation therapy, whichever is later	Annual DM ± DBT, anuual MRI
Personal histories of breast cancer and dense breast tissue or those diagnosed before age 50	From the time of diagnosis	Annual DM ± DBT, anuual MRI
Personal histories of ADH, atypical lobular hyperplasia, or LCIS	From the time of diagnosis	Annual DM ± DBT, consider anuual MRI

ACR = American College of Radiology, ADH = atypical ductal hyperplasia, LCIS = lobular carcinoma in situ, DM = diagnostic mammography, DBT = digital breast tomosynthesis, MRI = magnetic resonance imaging

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Table 2. Summary of Common Breast Cancer Risk Assessment Model

Risk Model	Claus	BRCAPRO	BOADICEA	Gail	IBIS (Tyrer-Cuzick)
Personal factors					
Age	0	0	0	0	0
Race	X	0	X	0	0
BMI	X	X	X	X	0
Age at menarche	X	X	X	0	0
Age at first birth	X	X	X	0	0
Age at menopause	X	X	X	X	0
Hx of piror biopsy	X	X	X	0	0
HRT	X	X	X	X	0
Breast density	X	X	X	X	0
Hx of ADH	X	X	X	0*	0
Hx of LCIS	X	X	X	X	0
Family history					
Age at onset of breast cancer	0	0	0	X	0
1st degree relatives	0	0	0	0	0
2nd degree relatives	0	0	0	X	0
3rd degree relatives	X	X	0	X	X
Male brest cancer	X	0	0	X	X
Bilateral breat cancer	X	0	0	X	0
Ovarian cancer	X	0	0	X	0
Gene mutations (*BRCA1/2*)	X	0	0	X	0

*History (Hx) of ADH was included in the modified Gail. IBIS = International Breast Cancer Intervention Study, BMI = body mass index, HRT = hormon replacement therapy, ADH = atypical ductal hyperplasia, LCIS = lobular carcinoma in situ

breast density, personal risk factors, and family history. The Tyrer-Cuzick model was developed in the United Kingdom. It provides a predicted 10-year and lifetime risk of developing invasive breast cancer. This model includes genetic information (mutation of *BRCA* and other breast cancer susceptibility genes) and originally nine other factors, namely, age, family history, menarche, age at first birth, menopause, atypical hyperplasia, lobular carcinoma in situ, height, and body mass index (BMI) [12]. In a validation study, with the addition of mammographic density, the discriminatory accuracy of this model improved from 0.59 (95% CI, 0.56–0.61) to 0.61 (95% CI, 0.58–0.63) [13].

A recent study on the 10-year performance of breast cancer risk models found that the Tyrer-Cuzick model was well calibrated, while the Gail model underpredicted risk (ratio of expected cases to observed cases was 1.03 [95% CI, 0.96–1.12] for Tyrer-Cuzick and 0.79 [95% CI, 0.73–0.85] for the Gail model) [14]. The Tyrer-Cuzick model is the most comprehensive but is also the most time intensive. Claus, BRCAPRO, and Tyrer-Cuzick are largely dependent on family history. In contrast, Gail model uses limited family history.

Genetic Testing in Women at High Risk

Women with a first-degree relative with breast cancer have about double the risk of breast cancer of the average woman. Mutations of *BRCA1* (chromosome 17q21) and *BRCA2* (chromosome 13q12-13q13) are responsible for 85% of hereditary breast cancer [15]. Recent genetic testing routinely screens the patient not only for *BRCA1/2* but for multiple genes (multigene panel testing), such as *PALB2*, *CHEK2*, *ATM*, *PTEN*, *TP53*, and others that identify women at high risk for breast cancer and other cancers [16]. Women who undergo multigene panel testing are also frequently found to have variants in many of these genes, which likely are not pathogenic and may or may not be predictive of a higher risk of breast cancer but do raise questions in the minds of the patients, their families and treating physicians regarding appropriate screening and preventive measures. Pathogenic alterations called deleterious mutation result in disease-associated phenotypes. Non-pathogenic alterations include variants of uncertain significance (VUS) and polymorphism. VUS is a mutation without clear disease association but may be associated pending further data or may move to classification as a known polymorphism.

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Korean Journal of Radiology
KJR

Polymorphism is a variant that is common and thought to be a "normal" variation. Single nucleotide polymorphisms are substitutions in single bases in the DNA sequence, which are estimated to occur in 1/100–1/1000 base pairs [17]. These variations account for human genetic variation. Therefore, most unrelated individuals are more than 99% identical. While we are genetically 99% similar, polymorphisms, insertions, deletions, and other mutations and variations clearly result in distinct breast density, breast imaging, risk of tumor development, the response of the tumor to treatment, and the response of normal tissues to treatment, the pattern of failure, and prognosis.

Polygenic Risk Score

Approximately 20% of familial/genetic risk can be attributed to mutations in high or moderate-risk genes. The remaining 80% may be attributable to a combination of variations or polymorphisms in a number of genes associated with breast cancer risk (Fig. 1). These combined polymorphisms can be modeled to generate a score (polygenic risk score) that can be used to estimate breast cancer risk and potential screening recommendations [18]. Two ongoing trials (My Personal Breast Cancer Screening and Screen Depending on Breast Cancer Risk] are testing the age-based vs. risk-based screening [19,20]. Overall, this study demonstrated that compared with following general population guideline strategies for women of average risk, risk-tailored screening has the potential to prevent more breast cancer deaths and extend lives for identifiable groups of women at high risk due to their breast cancer family history and polygenic risk.

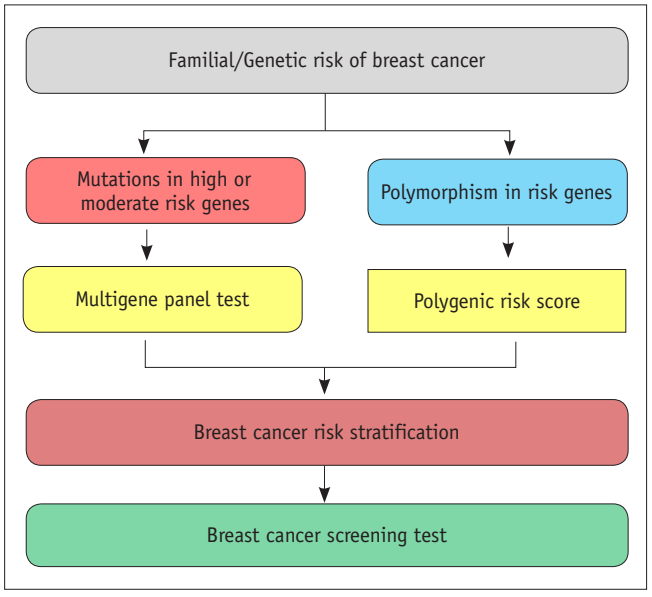

Fig. 1. Breast cancer genetic screening model in high-risk females. Females with a high risk of breast cancer undergo both studies of mutations (multigene panel test) and polymorphism (polygenic risk score) in breast cancer risk-associated genes. These tests stratify the breast cancer risk and provide personalized screening plans.

Breast density is a significant risk factor for breast cancer. Multiple factors contribute to breast density which include BMI, hormonal use, age, tamoxifen, menopausal status, diet, and other environmental, biological, and genetic factors. There are likely genetic determinants of breast density. Women with breast density > 50% have a significantly higher rate of breast cancer cumulative risk compared to women with a density < 50% [21]. Prior studies showed that polymorphisms in multiple genes, including *IGF-1*, *BCL-2*, *ADAMTS8/9*, growth factor genes (*INHA*, *IGFBP1/3*), multiple loci, and genes in estrogen pathway are associated with breast density and cancer risk [22–25]. Despite the promising result of the polygenic risk model, it is unclear if polygenic risk stratification will contribute to cost-effective cancer screening given the absence of robust evidence on the costs of polygenic risk stratification, the effects of differential ancestry, potential downstream economic sequelae, and how large volumes of polygenic risk data would be collected and used [26].

Artificial Intelligence Risk Model

Artificial intelligence (AI) and deep learning (DL) have exciting potential to transform the field of medical imaging. Breast imaging is well suited for AI algorithm development since the diagnostic question is straightforward (e.g., malignant vs. benign) and there is widespread availability of standard imaging data. A DL risk model, based on the patient's mammogram images alone, has proven superior predictive accuracy in future breast cancer risk assessment compared with traditional risk models across 7 global institutions, including patients of diverse races and ethnicities [27]. The DL model has advantages beyond accuracy, as it does not require knowledge of the patient's family history or personal history of prior biopsy and pathology, hormone use, menopausal status, or other risk factors required by traditional risk models [28]. Multiple DL-based models, including Hybrid DL and Image-Only DL, were developed. A recent and promising model is Mirai [29].

Mirai is a mammogram-based breast cancer risk model using AI. It primarily focuses on mammograms and leverages

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nonimage risk factors (for example, age and hormonal factors) if they were available. Mirai works following steps. First, the mammogram image is put through an "image encoder." Each image representation, as well as which view it came from, is aggregated with other images from other views to obtain a representation of the entire mammogram. With the mammogram, a patient's traditional risk factors are predicted using a Tyrer-Cuzick model, which includes age, weight, and hormonal factors. If the risk factor information is unavailable, predicted values are used. Finally, with this information, the additive hazard layer (a statistical model) predicts a patient's risk for each year over the next five years (Fig. 2). Mirai showed better performance compared with Tyrer-Cuzick and previous DL models at identifying both 5-year breast cancer risk and high-risk patients across multiple international cohorts. Mirai also performed similarly across race and ethnicity categories [30]. However, Mirai contained few African American and Hispanic women, making up 5 and 1% of the dataset, respectively.

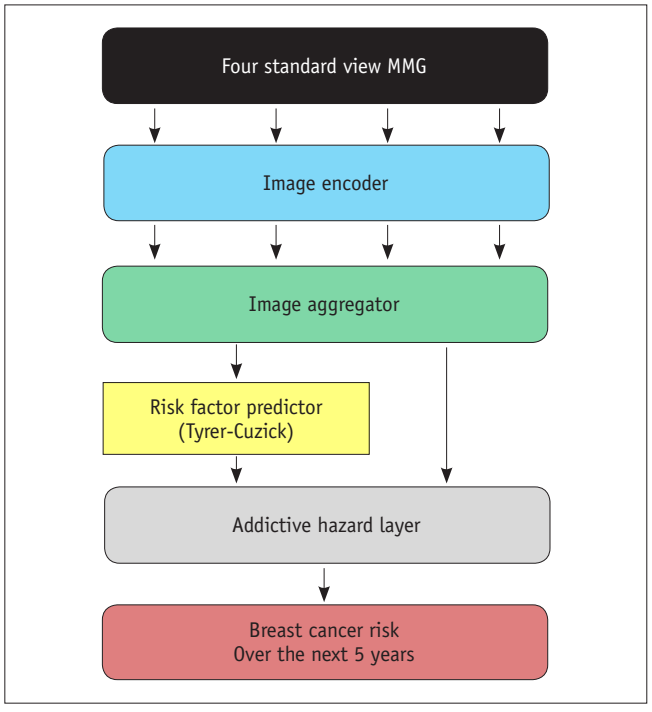

Fig. 2. Mirai-artificial intelligence mammography based breast cancer risk model. The four standard views of an individual mammogram (MMG) were mapped by an image encoder and converted to the four vectors. The image aggregator combined the four vectors into a single vector for the MMG. The risk factor predictor module predicted all the risk factors used in the Tyrer-Cuzick model from the MMG vector. The additive hazard layer combined information from both the image aggregator and risk factor predictor to estimate breast cancer risk over the next 5 years. Figure 2 is modified from Yala et al. [30], *Sci Transl Med* 2021;13:eaba4373. Reprinted with permission from the American Association for the Advancement of Science (AAAS).

Future Directions

Each woman has unique socioeconomic and physiobiological factors which require personalized breast cancer screening. Personal and family history, genetic testing for high-risk genes, polygenic risk score with validated polymorphisms, and AI and DL-guided mammogram (MMG) interpretation will be leveraged to estimate breast cancer risk and adapt screening frequency. With additional studies and validation, one can imagine personalized screening ranging from biennial MMG for very low risk, annual MMG for low risk, annual MMG and magnetic resonance imaging (MRI) (from age 40) for moderate risk, annual MMG and MRI (from age 30) for high risk, and twice yearly MMG and MRI for very high risk woman (These are possible future directions and not recommendations). Future studies are warranted to continue to personalize breast cancer screening recommendations in an effort to optimize cost effectiveness and early detection in the women at risk for breast cancer.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: all authors. Funding acquisition: Bruce George Haffty. Supervision: Bruce George Haffty. Validation: Bruce George Haffty. Visualization: Jongmyung Kim. Writing—original draft: all authors. Writing—review & editing: all authors.

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