Editorial Commentary

Breast cancer screening programs: does one risk fit all?

Federica Pediconi, Francesca Galati

Department of Radiological, Oncological and Pathological Sciences, "Sapienza" University of Rome, Rome, Italy

Correspondence to: Prof. Federica Pediconi, Department of Radiological, Oncological and Pathological Sciences, "Sapienza" University of Rome, V.le Regina Elena, 324, 00161 Rome, Italy. Email: federica.pediconi@uniroma1.it.

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Breast cancer is the most common malignant tumour that affects women around the world.

Roughly one in eight woman suffers from breast cancer during her lifetime, and the average age of women with breast cancer has declined over the years. The European Society of Breast Imaging (EUSOBI) and 30 national breast radiology bodies support mammography for population-based screening, which has been shown to reduce breast cancer mortality and treatment impact (1). Considering the evidence from several cohort and case-control studies, the International Agency for Research on Cancer (IARC) showed its support for screening mammography as well (2), however the available data did not allow the IARC working group to define an optimal screening interval. Most European countries opted for biennial screening in the 50- to 69-year-old cohort, and annual interval for the 40- to 49-year-old cohort, giving the potential for higher BC growth rates and lower mammography sensitivity in presence of higher breast density (1). Current breast cancer screening guidelines recommend a general starting age for screening for all women, including those at increased risk, such as those with a family history of breast cancer. Based on expert opinion rather than empirical evidence, American Cancer Society guidelines recommend starting breast cancer screening at age 40 years or 10 years before the youngest relative with a breast cancer diagnosis.

In a recent study published in *JAMA Oncology*, Mukama *et al.* pointed out that the age-oriented screening approach that pays little attention to individual risks is sub-optimal and that personalized screening should be advocated (3). The aim of his paper, titled "Risk-Adapted Starting Age of Screening for Relatives of Patients with Breast Cancer" is to identify the risk-adapted starting age of breast cancer screening on the basis of a woman's detailed family history. This nationwide cohort study analyzed data recorded in Swedish family-cancer datasets. Data from January 1, 1958, to December 31, 2015, were collected and analyzed from October 1, 2017, to March 31, 2019. Patients population included 5,099,172 women born from 1,932 onward and with at least 1 known first degree relative (FDR) with a breast cancer diagnosis. Risk-adapted starting age of breast cancer screening varied by the number of affected first- or second-degree relatives and by age at diagnosis of first-degree relatives. In this model women with multiple affected first-degree relatives reached the screening risk level at age 27 to 36 years, depending on the youngest age at diagnosis in relatives; while mass screening was recommended at age 50 years. The risk-adapted starting age is similar to the starting age suggested by the American College of Radiology, which age is 30 years or 10 years earlier than the youngest relative with a breast cancer diagnosis. However, as the authors state, selecting other ages at diagnosis in relatives, the differences could be even greater, from –6 to +24 years, than observed. It has been established that

screening for high risk women should be started earlier, but is mammography the best imaging approach to screen women with above-average risk? Considering that, as the authors explain, tumours in young women tend to be biologically more aggressive and are associated with poor survival and that young women generally have dense breast and screening mammography does not work well.

Recently Vaughan wrote a review on new imaging approaches in screening. In addition to full-field digital mammography (FFDM), nine other imaging modalities have been identified for review (4). Of these, those suitable for young women since they do not expose the patient to ionizing radiation and are applicable as a screening tool in terms of sensitivity and specificity, are magnetic resonance imaging (MRI); automated breast ultrasound (ABUS) and tactile sensor imaging. From a screening point of view, as Vaughan said, MRI has four main disadvantages compared to mammography: long examination time; need for contrast agent; poor specificity; and cost of the equipment. In fact, with regard to the low specificity of MRI, in a recent article, Kuhl (5) argued that the positive predictive value (PPV) for MRI is the same as that of mammographic screening. In addition, recent literature data have reported increasing evidence that abbreviated screening protocol can be an interesting way to reduce MRI costs for acquisition and reading time in the screening setting. The original Kuhl and co-authors protocol (6) consisted of a single T1-weighted gradient-echo sequence before the Gadolinium-based contrast agent (GBCA) injection, repeated after the injection, for a total acquisition time of only 3 minutes. Thereafter, many studies (7-12) confirmed that the diagnostic performance of the abbreviated protocols was not significantly reduced compared to a standard full protocol, with a drastically reduced reading time (12,13). However, a limitation of abbreviated protocols may be the lack of biomarker information, provided by functional techniques (14). This perspective should be favored in the case of a general acceptance of the use of CE MRI for the screening of women with medium or at least intermediate-risk women. However, the recent controversy over the potential dangers associated with Gd retention in the brain after repeated administrations of GBCAs, has raised doubts about MRI screening of healthy women outside of those who have a real high-risk profile. Future large prospective studies will clarify the scenarios for the use of abbreviated contrast-enhanced (CE) MRI protocols in the screening setting, also in combination with DWI as an option without contrast (15). Although DWI lacks the spatial resolution of dynamic CE MRI, several groups of researchers are optimistic that recent technical advances in DWI will lead to improved sensitivity (16,17).

The evidence on supplemental ultrasound (US) long-term benefits in screening is limited, even if data literature demonstrate that US has high sensitivity for cancer detection, especially in younger women with dense breast tissue, in early-stage invasive cancers and reduces the frequency of interval cancers (18). From a screening point of view hand-held ultrasound (HHUS) is a suboptimal technique as it is time-consuming and, since its operator-dependency, it suffers from repeatability problems. In the past 15 years, dedicated ABUS devices have been developed to overcome the limitations of HHUS. In the face of the unique display mode, imaging features and artifacts in ABUS, which differ from those in HHUS, ABUS has exceeded mentioned HHUS limits. A recent review by Kim *et al.* shows that screening ABUS yielded a high diagnostic performance, similar to screening HHUS. As he reported supplemental ABUS screening increased breast cancer detection by 1.9–7.7 cases per 1,000 women; sensitivity increased by 21.6–41.0%, but specificity varied (18). The SomoInsight Study, a multicenter study conducted between 2009 and 2011 on a total of 15,318 women, additionally detected 1.9 cases of breast cancer per 1000 women (19), which was similar to the results of Japan Strategic Anti-cancer Randomized Trial (J-START) (20), but lower than the results of American College of Radiology Imaging Network 6,666 (21). Differences in the cancer detection rate are probably related to the different inclusion criteria. The SomoInsight study had an invasive cancers rate of 93.3%, mean breast lesion size of 12.9 mm, and proportion of node-negative cancers of 92.6% (19), which were similar to the results of HHUS screening (20,21). ABUS screening was effective in detecting small, invasive, and predominantly node-negative breast cancers, similar to HHUS screening. Despite the promising results, there are insufficient evidence for reduction in mortality with US and ABUS screening at the moment, so no recommendations have been established for the screening guidelines. However, the American College of Radiology (ACR) states that supplemental US screening is an option for women with dense breasts and supplemental magnetic resonance imaging may be performed depending on risk factors, such as a history of lobular carcinoma in situ in women with intermediate risk for breast cancers (22). An interesting future direction for screening will be the fusion of FFDM

or digital breast tomosynthesis (DBT) and ABUS in a single platform; although literature data are currently lacking, fusion techniques seem to be the next logical step in the screening evolution.

Another promising tool for early detection of breast cancer in countries with limited resources is the iBreastExam (iBE) (4): a tactile sensors which has secured both CE mark and FDA approvals. It is based on the principle of piezo-electric detectors that generate quantitative information on tissue compression and stiffness, as breast cancer tumours tend to be hard and stiff compared to normal breast tissue. There are just two clinical trials (23,24) testing iBE showing that the sensitivity and specificity are >80%, confirming the device's potential as a low-cost screening tool. Certainly further researches are needed to validate these results and be able to introduce iBEas a widespread screening tool.

Breast radiologists currently face challenging decisions in terms of choosing the right exam for breast screening, starting age and risk stratification based on personal risk factors (familiarity, ethnicity, mutations, breast density, lifestyle...), since most current screening programs rely on mammography at similar time intervals. These programs suggest annual or biennial mammography for all women, and consequently they are not clearly optimized for the detection of cancer on an individual level. The goal is to establish woman individual risk, as Pace and Keating said "the net benefit of screening depends greatly on baseline breast cancer risk, which should be in corporate into screening decision" (25). The study by Mukama *et al.* is in line with this statement, but the number of first and second degree family members and their age of tumour onset are sufficient to change the screening starting age? There are many other risk factors, including ethnicity, that help stratify risk and therefore change the starting age of screening. The main limitations of Mukama's work are that it is based on the only Swedish population, and that it considers only familial risk, while other risk factors are not investigated.

A variety of empiric and mathematical risk assessment models based on personal and familial risk factors have been developed to estimate a woman's risk of developing breast cancer, these models base their respective risk estimations on different aspects of a woman's personal and familial history and thus, are not equally well calibrated for all populations (26).

To date there are three types of risk modeling: estimation from pedigree data of the probability of carrying one or more high-risk mutations, using segregation analysis (Claus, BOADICEA, BRCAPRO); a regression model for cancer risk based on a number of risk factors (Gail, Gail with polygenic risk added , Gail with breast density added, Breast Cancer Surveillance Consortium (BCSC) model, BCSC model with SNPs added, iCARE); combination of the first two types models (Tyrer-Cuzick, Tyrer-Cuzick with density and polygenic risk added). Risk models differ because they have been developed for different populations, use different risk factors and may have different assumptions on the effect of risk factors (Tyrer-Cuzick is calibrated to breast cancer rates in the UK; the Gail model to rates in the United States).

In a recent article Dembrower *et al.* has developed a risk model that is based on a deep neural network, finding inherent advantages compared to other methods such as visual evaluation of mammographic density by the radiologist who may not be able to acquire all the information relevant to the risk in the image. The authors concluded that a deep neural network trained on mammographic screening images and breast cancer outcome can more accurately predict which women are at risk for future breast cancer than can density-based models, with lower false-negative rates for more aggressive cancers (27).

In conclusion risk prediction is a fundamental element of an individually adapted screening policy and artificial intelligence has the potential to improve risk prediction and guide future screening towards personalized medicine. Considering the individual characteristics of each subject for disease susceptibility and biology and developing imaging biomarkers that incorporate both phenotypic and genotypic metrics, it is therefore possible to better stratify patients for more precise therapeutic care.

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Footnote

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