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1

Risk-based breast cancer screening strategies in women

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A B S T R A C T

The incidence of breast cancer continues to increase worldwide. Population-based screening is available in many countries but may not be the most efficient use of resources, thus interest in risk-based/stratified screening has grown significantly in recent years. An important part of risk-based screening is the incorporation of mammographic density (MD) and single nucleotide polymorphisms (SNPs) into risk prediction models to be combined with classical risk factors. In this article, we discuss different measures of MD and risk prediction models that are available. Risk-stratified screening options including supplemental or alternative screening modalities including digital breast tomosynthesis (DBT), automated ultrasound (ABUS) and magnetic resonance imaging (MRI) are discussed, as well as potential risk-based interventions (diet and lifestyle, chemoprevention and risk-reducing surgery). Furthermore, we look at risk feedback in practice and the cost-effectiveness and acceptability of risk-based screening, highlighting some of the current challenges.

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Introduction

Worldwide figures show a continuing upward trend in the incidence of breast cancer [1]. This is partly due to a shift in the distribution of risk factors. In developed countries such as the UK, there have been notable shifts in women giving birth later in life [2], and the number of women childless by age 45 [3]. Furthermore, adoption of more westernized lifestyles in developing countries has contributed to the increase in incidence. Breast cancer also contributes significantly to mortality, accounting for approximately 15% of all female cancer deaths [1]. Nevertheless, survival is high compared to other cancers, in particular in developed countries with 5-year survival rates ranging from approximately 40% in low-income countries to 80% or above in developed countries [4,5]. Higher survival rates in developed countries are in part due to screening, but also improvements in diagnosis and treatment over time.

Breast screening

Population-based screening programmes aim to detect the disease at an early stage, so effective treatment can be given leading to improved disease outcomes, including mortality. Earliest breast cancer screening programmes were established during the 1980s and screening is now well-established in several western countries, each producing their own clinical guidelines. Routine breast screening is offered to women from the age of 40 or 50 years, upwards to approximately 70 years, on a one, two, or three-yearly basis. Currently age is the only criterion used for inviting women, although women with a family history of breast cancer may receive increased surveillance and the option of preventive treatment through family history clinics commencing at a younger age [6].

Currently population-based screening programmes use mammographic imaging. Mammographic screening has evolved over the decades, with full field digital mammography (FFDM) and the routine use of two radiographic projections leading to improved early detection [7,8]. Although the introduction of breast screening has led to a reduction in mortality from breast cancer, the survival rate for more aggressive (triple negative) breast cancer is poorer compared to non-triple negative cancers [9].

Benefits and harms of screening

Despite the reduction in breast cancer mortality, there is continued debate about the benefits and harms of screening [10,11]. The most obvious benefit is a reduction in breast cancer mortality, which has been estimated to be approximately 20% in an independent review of 11 randomized controlled trials [12]. Overdiagnosis and overtreatment are the main shortcomings in population-based breast cancer screening. This occurs when a cancer is detected and treated, which in the absence of screening, would never have become symptomatic during a woman's lifetime. However, at present, it is not possible to know which cancers will become life-threatening or remain indolent, and consequently some women may undergo treatment for cancers, which may never have become symptomatic. Rates of overdiagnosis range widely largely due to study heterogeneity, but in studies with low risk of bias, estimates are in the region of 1–12% [10]. An independent review from the National Health Service Breast Screening Programme (NHSBSP) estimated that for every breast cancer death prevented, approximately three women are overdiagnosed and treated [12].

False positive results from screening may lead to additional tests and investigations potentially causing psychological distress and anxiety. In the UK, approximately 4% of women attending screening are recalled for further tests and investigations, of whom around 20% will be diagnosed with breast cancer [13]. The false-positive rate is higher in countries with more frequent screening intervals and in certain groups of women, e.g. those with increased breast density and attending their prevalent (first) screen. In contrast, false negatives (where no signs of abnormality are found in the mammograms of women with breast cancer) may falsely reassure women when a cancer actually may have been missed. Mammography can also cause pain and discomfort, which may prevent women attending in the future. In addition, exposure to radiation may pose a small increased risk of developing breast cancer due to the cumulative effect of screening over time [14].

In the UK, cancer screening identifies approximately one-third of invasive breast cancer diagnoses at all ages [15]. A significant proportion, approximately 3 per 1000 women screened, are also diagnosed as interval cancers, detected between screening intervals, some of which may have been missed at the time of screening [16]. Mammograms of women attending breast screening and diagnosed with an interval cancer are reviewed retrospectively. In approximately 20% of those reviewed cancer is visible but not identified during screening [17].

The rising incidence of breast cancer, associated overdiagnosis and treatment, and the potential for missed cancers all point to a need for change to breast screening programmes. The current 'one-size-fits-all' approach to breast screening may be suboptimal; alternatives such as risk-based (risk-stratified) screening have been proposed to optimize benefits of screening whilst minimizing harms [11]. Others have argued that such an approach will miss some breast cancers that population screening would detect [18].

Risk-based (stratified) screening

There is increasing interest in risk-based/stratified screening, with the number of publications in this area expanding rapidly over the last ten years. Risk stratification models offer a tailored approach to suit each woman's individual risk. Individuals are offered screening strategies based on their risk of developing cancer over the next five- or ten-year period, or on the suitability of mammography as a screening modality. According to Gilbert & Selamoglu (2018), there are two main considerations for implementing a more personalised approach to breast cancer screening: i) the risk of developing breast cancer for individual women and ii) the use of different imaging technologies depending on age and breast density.

Breast density

Breast density is a well-established risk factor for breast cancer, women with high density have a 4–6 times increased risk of developing breast cancer [20–23]. It is usually quantified as mammographic density (MD), the percentage of dense fibroglandular tissue in the mammogram. MD is also a risk for masking of the disease [23].

Measures of mammographic density

A number of methods exist for measuring MD. The American College of Radiology Breast Imaging Reporting and Data System (BIRADS) guidelines define breast density according to four categories, assessed visually [24]. Compared to the fourth edition, which was based on the percentage of dense tissue, the fifth edition places more of an emphasis on the masking effect of dense tissue [24]. As the BIRADS category increases, the sensitivity of mammography decreases as lesions may be obscured by dense fibroglandular tissue. One drawback of BIRADS is the considerable inter- and intraobserver variation between and within readers [25]. Nevertheless, BIRADS is widely used to classify breast density in mammograms.

Other visual assessment measures include Boyd categories [26] or visual analogue scales (VAS). VAS involves readers marking their estimate of breast density on four VAS, one for each mammographic view. Despite considerable intra- and interobserver variability [27], the measure is strongly associated with breast cancer risk [22,28].

Fully automated methods are becoming increasingly popular, many of which are currently used for research purposes but are not always commercially available. The mostly commonly used, and commercially available, automated software methods include VolparaDensity™ (Volpara Health Technologies, Wellington, New Zealand), Quantra™ (Hologic Inc, Bedford, MA, USA), Densitas (Densitas Inc, Halifax, NS, Canada) and more recently DenSeeMammo (Statlife, Boston, USA). Volpara and Quantra compute dense volume and volumetric percentage density using raw, or 'for processing' images, which rely on screening programmes specifically retaining these for the purpose of calculating MD. Densitas and DenSeeMammo are area-based methods that use processed, or 'for presentation' images; however, the latter provides only an estimate of BIRADS 5th edition categories. Fully

automated methods are entirely objective, and therefore, free from observer bias. Consequently, they provide the potential for screening to be tailored to women with an increased risk of developing breast cancer, and/or for women at the risk of masking where mammography may be less sensitive.

However, different methods do not always agree [23,29,30]. Brandt et al. (2016) found differences of up to 14% in the classification of dense tissue (BIRADs 4th edition categories 3 & 4) for Volpara (51%), Quantra (37%), and BIRADS (43%), and an external systematic review for the UK National Breast Screening Committee found that even fully automated methods were not concordant, despite being more reliable than visual methods [23]. This may in turn impact screening recommendations and/or clinical management. Assessment by clinicians results in better discrimination between cases and controls with higher area under the curve (AUC) statistics reported for BIRADS [29] and VAS [22] compared to automated methods. Volpara and Densitas percentage density also had strong, but attenuated, associations with breast cancer, and may offer a practical solution to breast density assessment for risk-based screening [22]. Assessment by clinicians may incorporate mammographic features other than breast density, such as pattern and texture [31,32].

More recently artificial intelligence and machine learning approaches have been developed to estimate breast density from mammograms. For example, Ionescu et al. [33] developed a method using convolutional neural networks to predict VAS scores from FFDM, which was comparable to human performance (radiologist VAS) in predicting breast cancer.

Breast density awareness

In the United States, the Food and Drug Administration (FDA) has announced the requirement that all women attending for breast screening should receive information about their breast density [34], to help inform women and health care professionals about the options in relation to supplemental screening using, for example, the risk-stratification algorithm developed by the Massachusetts Breast Risk Education and Assessment Task Force (MA-BREAST) [35].

Single nucleotide polymorphisms (SNPs)

In women with pathogenic variants in BRCA1 and BRCA2, the risk of developing breast cancer may be as high as 80% by the age of 80 [36]. BRCA1 and BRCA2 mutations are also associated with an increased risk of ovarian cancer. Pathogenic variants in other genes have been associated, to a lesser extent, to breast cancer risk including TP53, PTEN, CDH1, STK11 and PALB2 being associated with high risk (>40% lifetime), and CHEK2 and ATM moderate risk (20–30% risk). Inherited genetic pathogenic variants account for a relatively small proportion of all breast cancers (4–5%), and the majority of women who develop breast cancer do not have a pathogenic variant in an actionable gene. Individual breast cancer susceptibility variants (single nucleotide polymorphisms (SNPs)) also account for a small increase in risk, but a combination of these variants, may lead to a considerable increase in risk. A polygenic risk score (PRS) is the combined effect of individual breast cancer susceptibility variants identified by genome-wide association studies. The number of variants identified has increased over the past decade and currently 313 SNPs have shown an increase in the risk of developing breast cancer for individual women [37]. The 313 SNP PRS has also been shown to be associated with specific subtypes of breast cancer (ER+ and ER-disease).

Breast cancer risk models

Models for predicting an individual's breast cancer risk are well-established and incorporate a number of classical breast cancer risk factors. Recent developments have included other established risk factors e.g. MD and SNPs.

Cintolo-Gonzalez et al. [38] and Louro et al. [39] provide an overview of breast cancer risk prediction models. Five risk models were identified that predict breast cancer and are available as web-based applications/platforms. Some focus on family history and genetic factors e.g. BRCAPRO and the

Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) [40–42], whilst others include classical risk factors e.g. Tyrer-Cuzick [43,44], Gail (Breast Cancer Risk Assessment Tool - BRCAT) [45,46] and the Breast Cancer Surveillance Consortium (BCSC) [47] model (Table 1).

Incorporation of breast density and SNPs

Currently only two web-based models incorporate breast density: Tyrer-Cuzick and BCSC. Incorporating breast density into BCSC, as measured by BIRADS 4th edition, was well calibrated (E:O ratio 1.03, 95% CI 0.99–1.06) with an AUC of 0.66 (95% CI 0.65–0.67). However, the AUC was lower (0.62) after adjustment for age [48]. Brentnall et al. [44] demonstrated in a different population that the addition of MD to the Tyrer-Cuzick model increased the AUC by 0.04 from 0.57 to 0.61. The addition of MD also accurately identified more low- and high-risk women. MD was assessed by VAS, and found to be an independent predictor for breast cancer risk with an odds ratio per interquartile range of 1.47 (95% CI 1.33–1.62) after adjusting for Tyrer-Cuzick risk score. Tyrer-Cuzick version 8, now enables MD to be added to the model using either Volpara percentage density, percentage MD as estimated by VAS, or BIRADS 5th edition categories.

None of the current models, with the exception of Tyrer-Cuzick v8, incorporate polygenic SNP scores. Others, however, have investigated the addition of SNPs to risk models and shown they are significant independent predictors of breast cancer risk. A review by Willoughby et al. [49] included validation studies incorporating PRS, the number of SNPs incorporated increased from SNP-5 to SNP-313, with a trend to suggest that discrimination between cases and controls improves with larger numbers of SNPs. The majority of studies included in the review were validated using the Tyrer-Cuzick or Gail model, but few also incorporated MD [49]. We have recently shown that incorporation of 18 SNPs improved discrimination between cases and controls with the AUC increasing from 0.58 for classical risk factors, to 0.64 after incorporating MD, and to 0.67 after also adding SNPs [50]. In addition, the number of cases reclassified as high risk were 16% and 9.5% for MD and SNPs respectively, compared with only 5 and 4% of non-cancers.

The BOADICEA model has recently been modified to incorporate non-genetic risk factors including MD, PRS, and other classical risk factors [51]. MD is based on BIRADS, and other risk factors on a self-report questionnaire. It is hoped that the model may be used in clinical practice, but still requires further validation, and the web interface is currently under development.

Comparison of performance of risk models

Recent studies have compared the performance of the different web-based risk assessment models discussed above, and found that the Tyrer-Cuzick model performs consistently better than other models in predicting breast cancer overall [44,47,53–56] and amongst subgroups [54,56]. Terry et al. [56] also compared BOADICEA and BRCAPRO models finding that Tyrer-Cuzick and BOADICEA performed better than BRCAPRO and BRCAT. Most comparisons do not include models that incorporate MD and SNPs. Terry et al. [56] concluded that models incorporating multigenerational family history were better at predicting breast cancer, but by using a 'hybrid' model there was potential for further improvement. Other non-web-based risk models exist and show promise, for example, Choudhury et al. (2019) demonstrated their recently developed iCARE models perform as well, or better, than BRCAT and Tyrer-Cuzick [57].

For the purpose of risk-based screening, it is important that risk models are easily accessible and user friendly with web-based applications that may be used within clinical practice to facilitate identification of individuals who may need to be counselled on their risk, or may require supplemental screening, or other interventions, as a result of their increased risk of developing breast cancer. However, it should be noted that the majority of research on breast cancer risk assessment models, particularly in relation to PRS, has been validated on predominantly white women living within Europe and the United States [58,59].

Table 1
Factors included in online/web-based applications of risk models for breast cancer suitable for use in the general population.

	BCRAT (Gail)	BOADICEA	Tyrer-Cuzick (IBIS)	BCSC	BRCAPRO
Personal characteristics	Age Race/ethnicity	Age Height* BMI* Alcohol intake* Country* Ashkenazi inheritance* Birth cohort (year of birth)*	Age Weight Height Ashkenazi inheritance	Age Race/ethnicity	Age Race/ethnicity
Reproductive characteristics	Age menarche Age first full-term pregnancy	Age menarche* Age first full-term pregnancy* Number of children* Menopausal status* Age at menopause*	Age menarche Age first full-term pregnancy Number of children Menopausal status Age at menopause		
Hormonal		Oral contraceptives* HRT use:* Never Former Current – type	HRT use: Never/Ever/Current Length of use Type		
Previous biopsies	Previous biopsies Number of biopsies Atypical hyperplasia		Previous biopsies Hyperplasia Atypical hyperplasia LCIS	Prior biopsies Benign breast disease	
Personal history breast cancer	Eligibility question for risk calculation – women must not have: a history of breast cancer, DCIS, LCIS, or previous radiation therapy to the chest for treatment of Hodgkin's lymphoma	Provides a risk of breast cancer in unaffected individuals and risk of contralateral breast cancer for affected individuals	Not suitable for women with a previous diagnosis of breast cancer	Eligibility question for risk calculation – women must not have: a history of breast cancer, DCIS, breast augmentation, or mastectomy	Provides risk of breast cancer in unaffected individuals and risk of contralateral breast cancer for affected individuals Oophorectomy Mastectomy
Family history breast cancer FDR	Yes	Yes	Yes	Yes	Yes
Family history FDR age	No	Yes	Yes	No	Yes
Family history breast cancer SDR/TDR	No	SDR TDR Identical twins	SDR TDR	No	SDR TDR Identical twins

Family history breast cancer other features	No	Bilaterality ER status PR status HER2 CK14 CK5/6	Bilaterality	No	Bilaterality ER status HER2
Family history other cancers	No	Ovarian Prostate Pancreatic	Ovarian	No	Ovarian
Genetic testing	No	BRCA1, BRCA2, PALB2, CHEK2, and ATM	BRCA1, BRCA2	No	BRCA1, BRCA2
Common genetic variants (SNPs)	No	Yes*	Yes	No	No
Mammographic density	No	BIRADS*	VAS BIRADS Volpara	BIRADS	No

BRCAPRO (https://projects.iq.harvard.edu/bayesmendel/brcapro)
BRCAT - Breast Cancer Risk Assessment Tool (Gail) (https://bcrisktool.cancer.gov/calculator.html)
BOADICEA – Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm;
* indicates those risk factors that have been incorporated into the extended model, but that are yet to be incorporated into their online platform (https://ccge.medschl.cam.ac.uk/boadicea/boadicea-web-application/)
BCSC – Breast Cancer Surveillance Consortium (https://tools.bcsc-scc.org/BC5yearRisk/intro.htm).
Tyrer-Cuzick (IBIS – International Breast cancer Intervention Study) (http://www.ems-trials.org/riskevaluator/)
BMI – body mass index, HRT – hormone replacement therapy, FDR – first degree relatives, SDR – second degree relatives, TDR – third degree relatives, ER – estrogen receptor, PR – progesterone receptor, VAS – visual analogue scale, BIRADS – Breast Imaging Reporting and Data System.

The risk-based models produce a 5- or 10-year risk score, which can further be categorized into risk groups for stratification. These risk groups can then be used to aid clinical decisions.

Risk-stratified screening options

Interventions with relatively few side effects, such as lifestyle or dietary interventions are likely to be beneficial within the wider population, and to reduce the risk of other diseases e.g. cardiovascular disease, stroke and diabetes. Conversely, interventions with more side effects, such as additional screening and/or chemoprevention need to be considered in terms of the potential harms and benefits, and are more likely to be useful for a smaller subset of the population, i.e. by targeting those at increased risk [60].

Generally risk-stratified programmes propose less screening in women below average risk (e.g. <2% 10-year risk), no change in screening frequency for women at average risk (e.g. 2 to <5% 10-year risk) and an increase in screening for women above average risk (e.g. >5% 10-year risk), particularly in those with dense breasts as measured by mammograms at the time of screening. Lifestyle advice is recommended for all groups, while chemoprevention may be an option for those at above average risk and risk-reducing surgery for those at very high risk (e.g. >8% 10-year risk).

Supplemental or alternative screening modalities

Mammography is the routine standard for population-based screening programmes; however, other screening modalities may be useful for women with an above average or high risk of developing breast cancer, and with dense breast tissue. Modalities proposed for stratified screening include: digital breast tomosynthesis (DBT), ultrasound and automated breast ultrasound (ABUS) and magnetic resonance imaging (MRI).

Digital breast tomosynthesis (DBT)

DBT provides multiple image projections, which helps to overcome the problem of overlapping tissue in 2D mammography. Evidence suggests that DBT (in combination with 2D mammography) increases cancer detection rates and reduces the number of recalls and false positives [61]. The main drawback is the increased reading time; however, this needs to be considered in relation to the potential benefits [62].

Ultrasound and automated breast ultrasound (ABUS)

Handheld ultrasound may be a useful adjunct to FFDM, particularly amongst women with dense breast tissue. However, limitations include time to perform and interpret examinations, as well as operator dependence and high recall rates [19]. ABUS, developed to automate and overcome some of these limitations, has been found to be comparable, or in some cases better, in terms of breast cancer detection rates. ABUS, as an adjunct to FFDM, detects cancers that are smaller and at an earlier stage [63]. Nevertheless, some of the limitations of hand-held ultrasound persist e.g. interpretation time and high recall rates, but ABUS may be an attractive option as it is safe and relatively inexpensive. Currently the evidence for supplemental ultrasound is unclear and study quality is poor [23].

Magnetic resonance imaging (MRI)

MRI has a high sensitivity; however, it also has a relatively high recall rate (~10%). A recent systematic review of 11 published studies reported a sensitivity of 0.75 for mammography and 0.92 for MRI; however, specificity was 0.71 and 0.72, respectively [64]. Weighted area under the summary ROC curves was significantly higher for MRI (0.93 versus 0.73 for mammography). MRI is recommended in many screening guidelines for women at high risk of developing breast cancer [6,65], and can detect

smaller breast cancers at an earlier stage. MRI is perhaps most important in BRCA1 and TP53 pathogenic variant carriers [6]. The main drawback is cost but also the time taken to perform the examination, and the use of a contrast agent means it carries a risk of toxicity [66]. Abbreviated, or fast MRI, which can be performed in about a tenth of the time for standard MRI, has been found to be as effective as standard MRI [19] and may be favoured in the future.

There are a number of other available imaging modalities, Zhang et al. [67] performed a network meta-analysis on 19 different imaging methods for diagnosis of breast cancer. Direct comparisons of modalities were limited because of the number and quality of included studies; however, in addition to MRI, several methods including breast-specific gamma imaging, mammography plus scintimammography, and contrast-enhanced MRI demonstrated better diagnostic value in breast cancer detection and may be promising techniques for the future.

Interventions for those at increased risk

Lifestyle advice

Lifestyle advice stresses the importance of maintaining a healthy weight, physical activity, and reducing alcohol intake [68]. As noted earlier, this will benefit the wider population as well as those at increased risk of developing breast cancer.

Chemo-prevention drugs

A number of clinical guidelines recommend the use of chemoprevention drugs (e.g. tamoxifen or raloxifene) amongst women at a high or moderate risk of developing breast cancer [6,69], but benefits must be weighed against potential adverse effects, which depending on the drug can be troublesome in a number of women. Mocellin et al. [70] performed a network meta-analysis of randomized controlled trials for breast cancer chemoprevention drugs. The network, or multiple treatment, meta-analysis enables efficacy (how effective the drug is) and acceptability (using data on side effects as a measure of toxicity) to be examined concurrently to determine, which drugs are most successful in terms of meeting both requirements. Results showed a high level of evidence for aromatase inhibitors (anastrozole and exemestane) and lasofoxifene, and a moderate level of evidence for arzoxifene, raloxifene, tamoxifen and tibolone. Tamoxifen remains the only effective chemoprevention drug in premenopausal women, and no drugs have been shown to be effective in reducing oestrogen receptor negative (ER-) disease [70]. Identifying individuals who are most likely to benefit from chemoprevention drugs remains a challenge and research is currently ongoing in this area. National Institute for Health and Care Excellence (NICE) guidance in the UK favours anastrozole for postmenopausal women and tamoxifen for premenopausal women [6].

Risk-reducing surgery

Risk-reducing surgery is only recommended in those at high risk of developing breast cancer [6], usually with a family history of the disease. Risk-reducing mastectomy was found to be extremely effective in reducing the risk of developing breast cancer in a prospective cohort study of 550 women from 10 European countries offering genetic counselling services [71]. No breast cancers were found in 3334 women-years of follow-up compared to 34 breast cancers expected based on life tables. Careful consideration should be given before undergoing risk-reducing surgery.

Cost effectiveness of a risk-stratified programme

In 2013, in England, the NHSBSP was estimated to cost £96 million per year [72], and a recent economic analysis of the NHSBSP suggested that breast screening is cost-effective under a number of scenarios, with only the worst case scenario exceeding the lower NICE guideline threshold of £20,000 per quality-adjusted life year (QALY) [73]. However, they conclude that the screening programme should continue to be offered but economic evidence reviewed in the near future when additional data become available.

Two studies have examined the cost-effectiveness of risk-based screening in the NHSBSP. Pashayan et al. [74] examined three scenarios: no screening, the current screening model with women aged 50–69 years offered 3 yearly mammograms, and a risk-stratified screening group where women aged 50 years and above a specific risk threshold were offered 3 yearly screening until the age of 69 years. They concluded that compared to age-based screening (among 10,000 women screened aged 50–69 years and followed to 85 years of age) not offering screening to women in the lowest tertile of risk (1.69% 10-year risk) could improve cost-effectiveness (£20,066 less) and overdiagnosis (26.7% fewer), whilst resulting in a small excess of breast cancer deaths (7/329–2.9% more deaths).

Similarly, Gray et al. [75] performed a cost-effectiveness analysis using a number of scenarios for a stratified NHSBSP compared to the current breast screening programme and no screening alternative. Risk-stratified scenarios included:

i) 10-year risk based on the Tyrer-Cuzick model incorporating breast density and texture assessment: <3.5% screened every 3 years, 3.5–8% every 2 years and >8% annually
ii) as above but risk categories split by tertiles – lowest tertile screened every 3 years, middle tertile every 2 years and highest tertile annually
iii) as currently but additional screening for those with a high risk of masking assessed by Volpara Density Grades (VDG categories 3 and 4, which correspond to BIRADS 4th edition categories 3 and 4). High risk of masking offered supplemental ultrasound and those with high risk of masking and 10-year Tyrer-Cuzick >8% supplemental MRI
iv) combined approach of i) and iii)

All scenarios were considered cost-effective when compared to no screening, and scenarios i) and ii) were considered cost-effective compared to current screening with incremental cost-effectiveness ratios (ICERs) of £16,689 and £23,924 per QALY, respectively. Approaches based on the risk of masking (iii and iv) were not judged to be cost-effective compared to the status quo. The study demonstrates that risk-based screening may be an efficient use of health care resources.

Acceptability of risk-based screening

Success of risk-based screening programmes depends on acceptability to health care professionals and women attending breast screening. Rainey et al. [76] found those with a perceived increased risk of breast cancer were accepting of more frequent screening, lifestyle changes, chemoprevention, and surgical intervention, whereas those with low perceived risk were not accepting of less frequent screening. Women also identified communication as key, both for health care providers and for providing risk information to family members. However, health care professionals from the UK, Netherlands and Sweden felt risk-stratified screening may induce 'anxiety/worry' relating to: 'personal breast cancer risk, (late) detection of breast cancer, confrontation with an unhealthy lifestyle, chemoprevention, and potential impact on relatives'. Furthermore, they felt there may be psychological consequences [77].

Focus group research in Australia examined views of family history clinicians and women on their website iPrevent (www.petermac.org/iprevent), which gives individual risk assessment (based on the Tyrer-Cuzick or BOADICEA model depending on entered risk factor data), tailored screening recommendations, and risk-reducing options, as well as useful prescribing tips for recommended drugs [78]. Family history clinicians had concerns about meeting the additional demands for advice and management. They felt primary care professionals lacked experience or confidence to assess risk and prescribe chemoprevention drugs, but viewed it as a means of providing consistent information. From the woman's perspective, receiving risk information was not seen as a priority for some, whilst others felt it was empowering. Perceived problems included 'overload of information' and 'lack of confidence in primary care professionals', but they felt it would enable participation in informed discussions with primary care providers.

Risk feedback to individuals

It is important that risk is communicated to individuals to help in their decision-making process. The Predicting Risk Of Cancer at Screening (PROCAS) study found 95% of women wanted to receive risk feedback [79]. Face-to-face or telephone risk feedback appointments were offered to all women identified as being at high risk, and a proportion of those at moderate and low risk. Perhaps unsurprisingly, women identified as high and moderate risk were more likely to accept a risk feedback consultation (76.8% and 73.1%, respectively) compared to those at low risk (54.9%). High-risk women were also more likely to attend their next screening appointment (94.4% versus 84.2% attendance in low risk).

Information discussed at feedback sessions included: 10-year and lifetime risk of breast cancer, factors that increased/decreased individual risk and dietary and lifestyle advice. For those at high and moderate risk, information was given regarding additional mammographic screening and chemoprevention drugs (tamoxifen and raloxifene) [79]. Women not invited for risk counselling were sent risk feedback by letter. The study showed that providing risk feedback to women as a part of the NHSBSP is both feasible and acceptable. Further work in relation to how best to provide risk feedback in a timely manner is currently underway in PROCAS-2 (https://preventbreastcancer.org.uk/breast-cancer-research/research-projects/early-detection-screening/procas/). PROCAS-2 involves the use of online questionnaires, and real-time calculation of breast density and risk assessment using automated methods. Silver et al. [80] also concluded that implementing a risk-based screening programme delivered by breast health genetic counsellors (BHGCs) in three Californian breast imaging centres was feasible, but resource intensive.

Because of practicalities of changing the screening interval for a proportion of individuals (i.e. those at moderate and high risk) two potential models exist – individuals may be seen within established family history clinics or alternatively at static screening sites for intermediate screening visits.

Challenges to risk-based screening

There are a number of challenges and questions that still exist prior to implementing risk-based screening. Technical challenges include: which method is best to measure breast density, which risk model should be used, which combination of risk factors – classical, breast density, SNPs, what is the optimum screening interval, which subgroups of women benefit from chemoprevention drugs, is it possible to determine which individuals will have a response to treatment? Practical and logistical challenges include: how should risk information be fed back to individuals, who should perform risk feedback, who is best placed to advise on risk-reducing chemoprevention drugs, how easy is it to change the screening interval for subgroups of women?

Summary

The ‘one-size-fits-all’ approach to breast cancer screening is currently widely debated, and there is a drive towards risk-based/stratified screening. Automated density methods and web-based breast cancer risk models may help to facilitate this; however, different methods and models can produce conflicting results. Risk-based strategies exist for those at an increased risk of masking due to high breast density (supplemental screening), and for those at an increased risk of developing breast cancer (lifestyle interventions, chemoprevention and risk-reducing surgery). Cost-effectiveness models demonstrate that risk-based screening may be an efficient use of health care resources, when based on individual risk scores and incorporating MD assessment. However, incorporating supplemental screening based on risk of masking does not appear to be cost-effective. Methods of risk feedback seem to be feasible but resource intensive, and on the whole the risk-based screening approach appears to be acceptable to both health care professionals and women.

Declaration of Competing Interest

DGE has received travel grants from AstraZeneca.

Practice points

- Breast cancer incidence continues to increase worldwide
- The current one-size-fits-all approach to breast screening may be suboptimal
- Risk-based screening could optimize benefits whilst minimizing harms
- Automated density assessment methods are increasingly available
- Risk-based/stratified models incorporating breast density and SNPs, perform better than those incorporating classical risk factors alone
- Digital breast tomosynthesis, automated ultrasound and MRI may be helpful as supplementary screening modalities for risk-stratified screening
- Preventive options are recommended for women at increased risk of developing breast cancer
- Risk-based screening appears to be cost-effective, feasible and acceptable

Research agenda

- Further work to determine, which method for measuring breast density is best
- Further work to incorporate breast density and SNPs into risk prediction models and to validate models to determine, which are best for predicting the risk of breast cancer
- Further studies to determine, which women will benefit the most from chemoprevention drugs
- Further studies to determine how and who should perform risk feedback to women
- Further studies to determine how risk-stratified screening can be implemented in practice

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