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Protocol Article

Risk-stratified breast cancer screening – a protocol for a non-blinded randomised trial

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ABSTRACT

INTRODUCTION. Breast cancer accounts for 14% of all cancer-related deaths among women. Women aged 50-69 years are offered biennial mammography, which reduces breast cancer-specific mortality. Simulations suggest that risk-stratified screening detects more early-stage cancers while lowering the number of unnecessary recalls, assessments and biopsies in low-risk women. This trial will investigate whether multifactorial risk-stratified screening, including polygenic score, is feasible, acceptable, cost-efficient and safe.

METHODS. A minimum of 962 consenting women aged 50-67 years will be randomised 1:1 into a control group receiving standard screening or an intervention group offered screening intervals based on individual risk. Risk factor data collection, communication and follow-up will occur online using a tool co-designed with women in the target group. The primary outcome will be the proportion of low-risk women who, within 800 days of their baseline mammogram, will refrain from their legally ensured two-year mammogram interval. Secondary outcomes include quality of life, anxiety and breast cancer worry, measured at baseline and repeated three times during follow-up. In addition, health economy analyses will be conducted.

CONCLUSIONS. The findings will inform the development of large-scale risk-stratified screening trials.

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Breast cancer is the most common cancer among women in Denmark, with nearly 5,000 new cases and 1,100 deaths annually, accounting for 14% of female cancer mortality [1]. To reduce mortality and minimise treatment intensity, women aged 50-69 years are legally entitled to biennial mammography. The current organised breast cancer screening, implemented nationwide in 2009, has not been changed since it was introduced in the 1990s. More than 80% of the invited women participate (n = 580,000 women biennially) [2]. The programme has low rates of false positives and false negatives, a high detection rate of cancers < 11 mm without lymph node involvement [3] and high overall satisfaction [4]. Breast cancer screening is also associated with overdiagnosis and overtreatment [5], anxiety, inconvenience and investigations due to false-positive findings in a population where seven out of eight women never develop breast cancer.

The current one-size-fits-all approach has several limitations: First, unrecognised low-risk women are screened too frequently, exposing them to disproportionate harm. Second, unrecognised high-risk women are screened too infrequently, with suboptimal investigations resulting in delayed detection and intensified treatments, associated with more late effects. Third, this situation places stress on the limited resources of trained mammography radiologists. Fourth, a third of breast cancers are currently detected between screenings [2]. Fifth, interval cancers are more frequent in high-risk women and are associated with adverse outcomes [6]. Therefore, these women might benefit from more frequent screening. Simulations suggest that risk-stratified screening could both detect cancers earlier and reduce unnecessary biopsies among healthy women [7].

The multifactorial breast cancer risk prediction model Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) integrates the latest polygenic score (PGS) for breast cancer based on 313 single-nucleotide polymorphisms (SNPs) [8], cancer family history, reproductive history, lifestyle and hormonal factors, and mammographic density [9]. BOADICEA was validated in the UK Biobank [10] and the KARMA study in Stockholm, Sweden [11] and implemented in the CanRisk tool, which received CE marking [12]. However, it remains unknown whether adjusting screening intervals after a BOADICEA risk assessment is acceptable to women attending their regular screening mammography.

We aim to develop an online tool to collect risk data, perform risk calculations and provide automated risk communication as part of a potential future screening programme; and, furthermore, to measure acceptance of risk-stratified breast cancer screening and its impact on quality of life, breast cancer worry and anxiety.

The Population-based Randomized Study Of a Novel breast cancer risk ALgorithm and stratified screening (PRSONAL) is a single-centre, interventional, randomised, two-armed 1:1 controlled trial without blinding.

Methods

In- and exclusion criteria

Women aged 50-67 years who could benefit from a programme change and provide informed consent will be eligible for inclusion. Prior to inclusion, participants will attend a screening mammography at a screening mammography clinic and receive information about the trial. The exclusion criteria will include women with a history of breast cancer, as these would likely not accept longer screening intervals, even though their estimated risk were low. Also, women with a known high risk of breast cancer will be excluded to avoid interfering with genetic counselling. Women with ethnic backgrounds for which the risk model has not been validated (e.g., women of sub-Saharan African descent) will also be excluded. As of 1 August 2021, these groups represented less than 2‰ of the target population. Participants will also have to be able to communicate and write in Danish, own a smartphone and use the Danish electronic identification solution (MitID).

Randomisation and blinding

Eligible women will be randomised in a 1:1 ratio by a study employee using a randomisation feature integrated into the risk communication software. Women in the control group will continue biennial screening, whereas women in the intervention group will be offered a breast cancer risk prediction requiring a blood sample and screening schedules adjusted accordingly, which prevents blinding.

Intervention

Blood is drawn and DNA is analysed for 313 SNPs. If consented to, the sample will remain in a research biobank until 2034, after which it will be discarded. Based on the BOADICEA predicted ten-year risk, women will be stratified into four risk groups: low, intermediate, elevated and high risk. Screening intervals will be adjusted

accordingly: every four years for low-risk, every two years for intermediate and annually for elevated and high-risk women. The elevated-risk group will receive supplemental tomosynthesis, and the high-risk will receive both supplemental breast magnetic resonance imaging and referral for consultation with a breast surgeon at a breast centre. The interventions in the elevated and high-risk groups are based on theoretical considerations backed by evidence of increased risk of interval cancers and benefit from intensified screening in high-risk women [13, 14].

Calculation of polygenic score and ten-year risk

PGS will be calculated using a custom iSelect array designed to measure 313 genotypes [8]. However, during the establishment of the method, 261 genotypes survived quality control [15] and were used to calculate PGS_{261}, as described previously [8].

The BOADICEA algorithm will be implemented in a locally developed interface to align with Danish practice. This will include translation into Danish and customisation to Danish cancer incidences. The tool will allow women to fill in risk factor information and healthcare professionals to calculate risks once the PGS becomes available. Using scrambled risk information from 20 women in a pilot produced ten-year risk estimates from the local model, identical to those generated by the online CanRisk.org tool, ensuring the accuracy of the local implementation.

Data

At baseline, risk factor information will be collected for all participants. This includes family history of breast cancer, lifestyle factors, reproductive history, mammographic Breast Imaging-Reporting and Data System (BI-RADS) breast density and measurements of height and weight. Additionally, psychosocial scales will be used to evaluate the mental health of all participants during the follow-up period. This approach will capture any particular adverse psychosocial developments among high-risk women. **Table 1** provides a detailed overview of the baseline data. There is no data monitoring committee in PRSONAL. Adverse events are reported in the risk communication software upon contact from participants. Audits are not planned. All data will be collected and maintained to protect confidentiality during and after the trial.

TABLE 1 Overview of risk information and clinical data provided by the participants.

Intervention group	Control group
Baseline, day 1	*Baseline, day 1*
Questionnaire about family history of breast cancer, lifestyle and reproductive history	Questionnaire about family history of breast cancer, lifestyl, and reproductive history
Measurement of height and weight	Measurement of height and weight
Mammogram obtained and BI-RADS density defined	Mammogram obtained and BI-RADS density defined
Complete questionnaires about quality of life, breast cancer worry and anxiety: psychosocial measuring scales	Complete questionnaires about quality of life, breast cancer worry and anxiety: psychosocial measuring scales
Randomisation, day 1	*Randomisation, day 1*
Provide a 4 ml blood sample for analysis of common genetic variants associated with the risk of breast cancer	Not applicable
Risk communication, day 90	*No risk communication, day 90*
Digital communication about the assignment of risk group and the risk-stratified screening schedule	Not applicable
Follow-up day 180, 365 and 800	*Follow-up day 180, 365 and 800*
Complete questionnaires about quality of life, breast cancer worry and anxiety: psychosocial measuring scales	Complete questionnaires about quality of life, breast cancer worry and anxiety: psychosocial measuring scales

BI-RADS = Breast Imaging-Reporting and Data System.

Data sharing statement

The study protocol can be accessed upon reasonable request. Please contact the corresponding author.

Public involvement

Women were involved in the exploration of attitudes towards risk-stratified screening [16], the design of PRSONAL and in co-creation of the website and risk communication.

Outcomes

The primary outcome will be the proportion of low-risk women who, within 800 days of their baseline mammogram, will refrain from their legally ensured two-year mammogram interval. This outcome will indicate the women's willingness to adapt to the proposed de-escalated screening. Secondary outcomes will include scales measuring the psychosocial consequences in terms of self-reported anxiety, breast cancer worry and quality of life at baseline and during the follow-up period, as well as the cost-effectiveness of personalised, stratified screening (**Table 2**).

TABLE 2 Overview and description of the planned outcome measures.

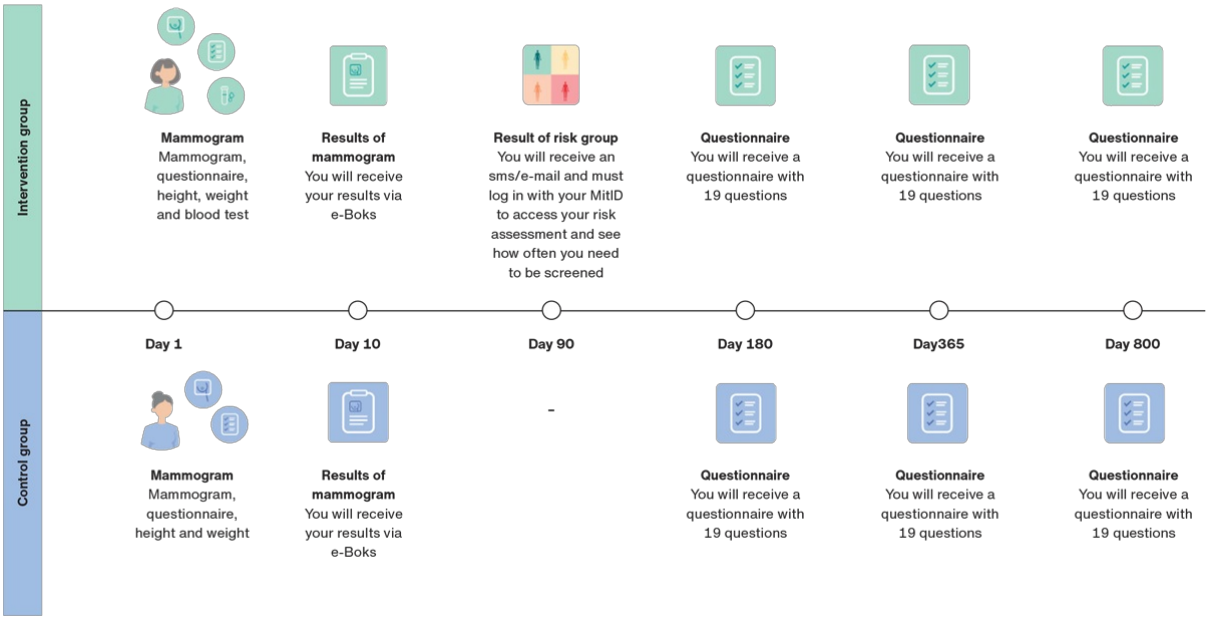
Outcome	Description	Timeframe
Primary measure		
The proportion of low-risk women who refrain from their law-ensured mammography within 800 days of baseline Trial success is defined as ≥ 70%	The proportion of the low-risk group that adapts to mammography 4 yrs after baseline, indicating willingness to de-escalate screening intervals Mammography of any indication; worry, clinically justified or screening will be registered	*In the low-risk group* 800 days after baseline
Secondary measures		
Subject anxiety	Level of anxiety will be measured using the PROMIS Item Bank v1.0 - Emotional Distress - Anxiety - Short Form 8a, in Danish: min. 37.1 – max 83.1[a]	*4 measurements in all risk groups and controls* Baseline 180 days 365 days 800 days
Subject breast cancer worry	Level of breast cancer worry will be measured using the Lerman Breast Cancer Worry Scale translated into Danish: min. 3 – max 13[a]	*4 measurements in all risk groups and controls* Baseline 180 days 365 days 800 days
Subject quality of life	Quality of life will be measured using the EQ-5D-5L instrument, EuroQol Research Foundation, in Danish *2 measures* Questionnaire: min. 5 – max 25[a] Health scale: min. 0 – max 100[b]	*4 measurements in all risk groups and controls* Baseline 180 days 365 days 800 days
Health economics: healthcare costs	Healthcare costs: costs associated with healthcare utilisation by study participants These will include primary care services, secondary care: in- and out-patient hospital and specialists, as well as prescription medication	*4 measurements in all risk groups and controls* Baseline 800 days 4 yrs 10 yrs
Health economics: cost-effectiveness	Cost-utility and -effectiveness of risk stratified screening, by comparing incremental cost per health outcome gained	*4 measurements in all risk groups and controls* Baseline 800 days 4 yrs 10 yrs

EQ-5D-5L = EuroQol 5 Dimension 5 Level; PROMIS = Patient-Reported Outcomes Measurement Information System.
a) A high score indicates a poorer outcome.
b) A high score indicates a better outcome.

Recruitment and consent

One week before their scheduled mammogram at Gentofte Hospital, Denmark, women aged 50-67 will receive an electronic study information letter with a link to the study website [16], detailed information about the trial and a timeline (**Figure 1**).

FIGURE 1 Timeline of the study.



After mammography, women may engage with recruitment staff or leave if uninterested. Recruitment staff will be unaware of invitees, ensuring voluntary participation. Final consent will follow in-person information on study details, criteria, procedures and risks, as approved by the Regional Scientific Ethical Committee. With the option of up to 24 hours of reflection, both parties will sign the consent form. Participants may withdraw at any time. Upon consent, questionnaires will be completed, height and weight measured, and randomisation will occur. If allocated to the intervention group, a blood sample will be drawn on-site.

Risk communication without health care staff

We will develop a web-based risk communication tool and a study website [16] based on relevant studies [17] and systematic user involvement. The content and the user interface/experience will be developed by UI/UX designers, women (targeted users), and the Danish Cancer Society. Once the individual PGS is calculated, the absolute ten-year risk will be calculated, and the primary investigator will release a notification by email or phone text message, after which the women will access their personal website with the risk communication using MitID .

Statistics and sample size

Risk groups were defined a priori based on risk percentiles: low (1st-46th), intermediate (47th-90th), increased (91st-98.4th) and high (98.5th-100th), corresponding to absolute ten-year risks of < 2.45%, 2.45-5.15%, 5.16-8.00% and > 8.00%, respectively, for this 50-67-year aged group. These cut-offs were calculated by extrapolating results from the KARolinska Mammography Project for Risk Prediction of Breast Cancer (KARMA) study [11], while adjusting for differences in incidences and composition of birth year. There is currently no consensus regarding risk cut-offs; however, in this study, the chosen risk groups were designed to maximise the size of the low-risk group while still offering the two-year interval to women in the 50th risk percentile. Additionally, to study safety and efficacy in higher-risk groups, these were further subdivided as described.

PRSONAL will primarily be powered to measure the acceptance of de-escalated screening among low-risk women. If more than 70% of low-risk women accept a longer screening interval and refrain from a mammography within 800 days of baseline, PRSONAL will have achieved its goals in terms of acceptance and economic sustainability.

When calculating the required sample size based on the primary outcome, the following assumptions were applied: 95% of women attending screening mammography will be eligible for participation. Among these, 50% will participate in the randomisation. Among those randomised to the intervention group, 10% will regret their decision. Among the remaining participants, 46% will be classified as low-risk women. To achieve 90% statistical power at a 0.05 significance level for detecting a dropout rate of 30% or less among low-risk women, a minimum of 962 women will have to be randomised.

Predefined outcomes will be calculated using standard statistics in the STATA 18 software package.

Ethics

Women will be informed of their risk electronically and urged to contact the study personnel if they have any concerns. In case of very high anxiety and/or breast cancer worry by day 180 after baseline, the study staff will contact the patient to offer consultation. Any such instances will be documented in the database.

The study will be conducted in accordance with the World Medical Association Declaration of Helsinki. The protocol has been approved by the Regional Scientific Research Committee, which also approves amendments. The study is registered with ClinicalTrials.gov.

Trial registration: ClinicalTrials.gov Identifier: NCT06060938. Registration date: 11092023. Scientific Ethical Committee, Capital Region, Denmark: Approval H-23017474, 1 June 2023, of protocol version .

Discussion

This protocol adheres to the SPIRIT statement (Checklist in the Supplemental material). The primary outcome will be the proportion of low-risk women refraining from a mammography within 800 days of baseline.

The lack of extensive interviews of all participants is a limitation of PRSONAL, but after consulting the participants of the qualitative study [17], it was deemed sufficient for the goals of the study to offer contacts by phone and e-mails to capture concerns and reservations among participants. The intervention was planned conservatively in terms of de-escalating screening, as some degree of caution might be called for when feasibility studies, such as PRSONAL, are conducted. Ideally, the exact risk cut-offs defining the risk groups and their intervention would be decided on evidence of benefit on breast cancer mortality.

Breast cancer mortality has decreased impressively in the past decades, and although debated, screening does seem to contribute a large part of the causes of this reduced mortality, after improved treatment of stage I-III and metastatic breast cancer [18]. Nevertheless, these findings support efforts to reconsider the one-size-fits-all approach and highlight the importance of initiatives like PRSONAL.

Two ongoing international randomised trials of risk-stratified breast cancer screening, Women Informed to Screen Depending On Measures of risk (WISDOM) [19] and My Personal Breast Cancer Screening (MyPeBS) [20] with a combined recruitment target of 185,000 women, will have the statistical power to analyse tumour stage distribution at diagnosis, mortality and other variables associated with breast cancer screening, such as sensitivity and specificity. Measurement of overdiagnosis, however, would require a randomisation arm not receiving any screening at all and follow all women until at least ten years after cessation of any screening. This is hard to imagine in the real world, but overdiagnosis as a potential screening side effect remains a motivation behind the de-escalated screening in the PRSONAL low-risk group. If risk-stratified versus biennial breast cancer screening proves to be comparable to or more effective in terms of short-term efficacy, acceptability and psychological safety, and if long-term results from both WISDOM and MyPeBS support risk-stratified screening, health authorities may consider national implementation.

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Use of artificial intelligence: ChatGPT-4o has been used by the authors for language corrections of some paragraphs.

References can be found with the article at ugeskriftet.dk/dmj

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Supplementary material: https://content.ugeskriftet.dk/sites/default/files/2025-08/supplementary_a03250154.pdf

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