The Tomosynthesis study in Bergen

The To-Be follow-up trial

Synopsis - Study 1a in the main protocol

Approved by the Regional Committees for Medical and Health Research Ethics in the South East of Norway (official record number 2015/424) and registered at ClinicalTrials.gov (NCT03669926)

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Study title	Digital breast tomosynthesis – the future screening tool for breast cancer? Interval and subsequent round breast cancer in a randomized controlled trial comparing digital breast tomosynthesis and digital mammography screening
Study phase	We will collect information about women screened with digital breast tomosynthesis (DBT) after originally being screened with DBT (DBT after DBT) or standard digital mammography (DM) (DBT after DM) in the To-Be 1 trial in 2016 and 2017 and are diagnosed with interval or subsequent round screen-detected breast cancer during a two years follow up period (2018-2019).
Background	Prevalent DBT has shown higher cancer detection rates and lower recall rates compared to DM. Yet, there is insufficient evidence to draw any conclusions about the downstream benefits and harms after the prevalent round of DBT in a population-based screening program and there is no data on interval and subsequent round screen-detected cancer rates and histopathologic tumor characteristics from a randomized controlled trial.
Study aim	To investigate interval cancer and histopathologic tumor characteristics for women screened with DBT or DM and subsequent round screen-detected cancer and histopathologic tumor characteristics for women screened with DBT after DBT or DBT after DM.
Study setting	The breast center at Haukeland University hospital, as a part of the national screening program, BreastScreen Norway.
Study design	Follow-up from a randomized controlled trial and a single-group clinical trial.
Outcome measures	*Primary outcomes:* Interval and subsequent round screen-detected breast cancer rates *Secondary outcomes:* Histopathologic tumor characteristics of interval and subsequent round screen-detected breast cancer *Other outcome measures:* Sensitivity, specificity, recall rates, biopsy rates, positive predictive values of recalls and biopsies
Study population	We expect 90% of the women attending the screening unit at Danmarksplass to participate in To-Be-2, based on preliminary results from To-Be 1. We therefore expect to screen 32 400 women with DBT, where 13 000 have a prior DBT, and 13 000 a prior DM. About 6400 women will be prevalently screened with DBT.
Inclusion/exclusion criteria	Inclusion criteria: Women who attend BreastScreen Norway in Bergen 2018-2019 with a complete screening examination, signed informed consent, and a prior examination in the To-Be 1 trial. Exclusion criteria: Women with breast implants, prior history of breast cancer, metastases, other primary cancers, women who report breast symptoms, and those prevalently screened with DBT in To-Be 2.
Study groups	Group 1: Women originally screened with DBT in To-Be 1, and DBT in To-Be 2. Group 2: Women originally screened with DM in To-Be 1, and DBT in To-Be 2.
Procedures	Screening with two-view DBT. Independent double reading of the screening mammograms, by a pool of seven breast radiologists. All cases with a positive

	score are discussed at a consensus meeting where the decision of whether to recall the women for further assessment will be taken.
Assessments	Women recalled will undergo further assessment, such as additional imaging and needle biopsy.
Sample size calculation	Our primary outcome of interest is the difference in rate of screen-detected cancer between the two scenarios, with a significance level of 0.05. Using a two-sided chi-squared test, group sample sizes of 13 000 in both groups achieve 80% power to detect a difference of 0.3 percentage points in screen-detected cancer rates between the two groups. This assumes the rate of screen-detected cancer in-group 1 is 0.6% under the null hypothesis.
Statistical analysis	Variables will be described and tested using chi squared tests, t-tests, one way analysis of variance (ANOVA) and Z tests. The primary outcome will be analyzed with a log-binomial regression model and presented as crude risk ratios with 95% confidence intervals.
Safety considerations	In addition to adhering to the ethical approvals obtained, the study followed a rigorous quality assurance plan with monthly reporting. The results were only available for the steering committee.
Project management	Consortium: Haukeland University Hospital Cancer Registry of Norway University of Oslo The consortium appointed a Steering Committee. The project group is led by PI Solveig Hofvind
Study sponsor	Cancer Society of Norway, Radiological department, Haukeland University Hospital and the Cancer Registry of Norway.