Living Evidence Synthesis Protocol
Joint Research Centre

Title

Digital breast tomo synthesis (including synthetic 2D images) vs. digital mammography for early detection of breast cancer in asymptomatic women in an organised screening programmes: a living systematic review (Protocol)

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Abstract

Screening programmes play a crucial role in early breast cancer detection; it can increase the chance of survival as well as have an impact on breast cancer mortality. Digital Mammography (DM) remains the best method to detect breast cancer in an early stage. DM is a technique of imaging which produces a 2D image of the 3D organ. Inevitably, this implies that lesions can be obscured by superposition of dense tissue. Indeed, the superposition of tissue can lead to false positives as well as false negatives. Digital Breast Tomosynthesis (DBT) is an imaging technique based on a series of low dose images of the breast taken from different angles and one compression, and has the potential to partly overcome tissue superposition thus improving detection of breast lesions through minimization of masking effects in DM.

Objective

To compare DBT versus DM for breast cancer screening.

Methods

In 2015, the European Commission Initiative on Breast Cancer (ECIBC) was launched to develop the European Guidelines on Breast Cancer Screening and Diagnosis. This systematic review informed the recommendations on the use of DBT compared to DM in organised screening programmes for early detection of breast cancer in asymptomatic women. Following a structured process, the ECIBC Guideline Development Group (GDG) selected intervention, comparison and outcomes relevant to this review. We will carry out a living systematic review including randomized controlled trials (RCT) and observational studies. Searches will be performed in Epistemonikos database and results will be incorporated into the L·OVE platform identified as "Three-dimensional mammography for breast cancer". We will evaluate the risk of bias of the included randomized trials using the ROB-2 tool, of the included observational studies using QUADAS – 2 tool and assess the certainty of evidence using the GRADE approach. We will monitor the L.OVE platform every two months searching for relevant observational studies and trials that could imply changes in the available evidence. The living process will end after 12 months of surveillance.

Background

Condition or domain being studied

Breast cancer is the second most common cancer in the world and, by far, the most frequent cancer among women, with an estimated 2 088 849 new cancer cases diagnosed in 2018 (11.6% of all cancers)1. Breast cancer ranks as the fourth cause of death from cancer overall (626 679 deaths)1. Screening programmes play a crucial role in early breast cancer detection; it can increase the chance of survival as well as have an impact on breast cancer mortality.

Why it is important to do this review

Digital mammography (DM) remains the best method to detect breast cancer in an early stage. DM is a technique of imaging which produces a 2D image of the 3D organ. Inevitably, this implies that lesions can be obscured by superposition of dense tissue. Indeed, the superposition of tissue can lead to false positives as well as false negatives. Digital breast tomosynthesis (DBT) is an imaging technique based on a series of low dose images of the breast taken from different angles and one compression, and has the potential to partly overcome tissue superposition thus improving detection of breast lesions through minimization of masking effects in DM2,3. The series of projections is then processed by a reconstruction algorithm to estimate the 3D appearance of the breast which can be viewed in successive slices. In screening trials, tomosynthesis has been used in addition to a 2D image done with 2D DM, regardless whether synthetic 2D images of the DBT series were available or not.

Through Epistemonikos - L.OVE platform we identified 8 SRs4-11 that potentially addressed our question (see section “Methods for identification of initial systematic reviews”).

We also considered the systematic review (Canelo-Aybar C. et al 2021, unpublished) that was specifically developed to inform the ECIBC recommendations on the use of DBT compared to DM in organised screening programmes for early detection of breast cancer in asymptomatic women.

Based on these SRs we developed an evidence matrix that revealed the primary studies that have been included in these reviews.

Considering the characteristics of the available evidence, with one high quality systematic review already available (Canelo-Aybar et al 2021, unpublished), and taking into account that the evidence on this therapy is on the rise, we propose to carry out a living systematic review with the aim of updating the existing systematic review with the new emerging evidence.

This SR will be developed as part of the Living Evidence to Inform Health Decisions project, which supports health system organizations in the implementation of the living evidence model for the development of evidence synthesis to inform health decisions12.

Objective

To compare digital breast tomosynthesis (DBT) versus digital mammography (DM) for breast cancer screening.

Types of studies to be included

We will include randomized controlled trials (RCTs) and observational studies.

Types of participants

Asymptomatic women attending an organised breast cancer screening programme

Setting

European Union

PICO question

Should screening using digital breast tomosynthesis vs. digital mammography be used in organised screening programmes for early detection of breast cancer in asymptomatic women?

Intervention

Screening using digital breast tomosynthesis (including synthesised 2D images)

Comparator

Screening using digital mammography

Types of outcome measures

Main outcomes

Breast cancer mortality

Breast cancer stage: assumes detecting cancer in stage I is better than stage II, better than stage III and better than stage IV, because the treatment is less invasive, there are less side effects and there is a better chance of survival;

Breast cancer detection rate: number of breast cancers detected per 1000 screened;

Interval breast cancer: primary breast cancer diagnosed in a woman who had a screening test with/without further assessment, which was negative for malignancy, either before the next invitation to screening or within a time period equal to a screening interval for a woman who has reached the upper age limit for screening (European Guidelines, 2001). Usually reported per 1000 persons screened with a negative result

Recall for assessment: proportion of screens called for further investigation due to suspicious mammogram.

Quality of life: includes anxiety caused or relieved by screening, anxiety caused by assessment of suspicious screening findings, longer length of life qualified by longer periods of life spent with a diagnosis of breast cancer, treatment side effects including psychosocial effects of body image following surgery.

Other cause mortality.

Adverse effects: includes radiation exposure, radiation induced cancers-related to radiation dose, over diagnosis related adverse effects, false positive related adverse effects.

Methods for identification of initial set of references

As a search source we used Epistemonikos database (https://www.epistemonikos.org), a comprehensive database of systematic reviews and other types of evidence, maintained by screening multiple information sources to identify systematic reviews and their included primary studies, including Cochrane Database of Systematic Reviews, MEDLINE, EMBASE, CINAHL, PsycINFO, LILACS, DARE, HTA Database, Campbell database, JBI Database of Systematic Reviews and Implementation Reports, EPPI-Centre Evidence Library13. We

designed and run a tailored search strategy in MEDLINE for the identification of primary studies. Based on the PICO characteristics the primary studies were either randomised and non-randomised clinical trials or observational studies.
Results from these searches were automatically included in the L.OVE platform of the Epistemonikos Foundation14. This platform has been validated as repository for the COVID-19 showing to be highly comprehensive source of evidence 13,15.
Our literature search was devised by the team maintaining the Epistemonikos-L·OVE platform (https://app.iloveevidence.com), using the following approach:
Identification of terms relevant to the population and intervention components of the search strategy, using Word2vec technology (10) to the corpus of documents available in Epistemonikos Database.
Discussion of terms with content and methods experts to identify relevant, irrelevant and missing terms.
Creation of a sensitive boolean strategy encompassing all the relevant terms.

Boolean search strategy

Epistemonikos

((((breast* OR mammary* OR mammography OR mastectomy) AND (cancer* OR neoplas* OR tumor* OR tumour* OR carcinoma* OR maligna* OR adenocar* OR metasta* OR mass OR masses OR nodul* OR oncolog*)) OR BRCA*) AND (("3-dimensional" OR "three-dimensional" OR "3 dimensional" OR "three dimensional" OR 3d OR "3 d" OR "3-d" OR threedimension*) AND (mammogra* OR ((imag* OR xray* OR "x-ray" OR "x ray" OR "x-rays" OR "x rays" OR radiograph*) AND (mamm* OR breast*)) OR birad* OR xeromammo* OR mastograph*)) OR ((digital AND breast AND tomosynth*) OR DBT))

MEDLINE

((((breast* OR mammary* OR mammography OR mastectomy) AND (cancer* OR neoplas* OR tumor* OR tumour* OR carcinoma* OR maligna* OR adenocar* OR metasta* OR mass OR masses OR nodul* OR oncolog*)) OR BRCA*) AND (("3-dimensional" OR "three-dimensional" OR "3 dimensional" OR "three dimensional" OR 3d OR "3 d" OR "3-d" OR threedimension*) AND (mammogra* OR ((imag* OR xray* OR "x-ray" OR "x ray" OR "x-rays" OR "x rays" OR radiograph*) AND (mamm* OR breast*)) OR birad* OR xeromammo* OR mastograph*)) OR ((digital AND breast AND tomosynth*) OR DBT)) AND ((randomi* OR RCT OR placebo* OR trial OR "controlled-trial" OR randomly*))

Evidence monitoring and surveillance plan (LIVING EVIDENCE)

In order to maintain the living evidence process for this review, the Epistemonikos-L.OVE platform14 will be used as technological enable to support the evidence identification, screening, and selection. We will keep a living search in the L·OVE platform to detect emerging reviews, observational studies and randomized controlled trials. Additionally, each three

months, we will manually search for ongoing studies in the WHO International Clinical Trials Registry Platform and the clinicaltrials.gov.

One reviewer will oversee the evidence that has entered the L.OVE of this question every month and apply the selection criteria presented above. If a potentially eligible study is found, a second reviewer will confirm its eligibility by reading the full text. Results of evidence surveillance will be collected and keep as part of the study records. Information on PRISMA will be updated accordingly. Criteria for selecting studies will be revised and change accordingly during the LE processes each 4 months.

All new eligible studies will undergo to data extraction process. The data synthesis will be update immediately, and the body of evidence for the outcomes of interest will be assessed following the GRADE approach accordingly looking for changes on the certainty assessment results.

The living process for this question will end after 12 months of surveillance updating the evidence synthesis report.

Statistical considerations for the living evidence synthesis

The inclusion of new studies identified as part of evidence surveillance and reporting on the outcomes of interest will follow this approach: We will perform a meta-analysis for each of the outcomes of interest reported by the new studies using a fixed-effect model to evaluate the statistical heterogeneity among included studies by using the I2 statistics. If new heterogeneity is detected (i.e. increase the heterogeneity previously identified or new heterogeneity arises where it was previously undetected), we will explore its potential sources by reviewing the new studies against previously included studies in order to identify reasons that may explain inconsistent results among studies. In presence of unexplained heterogeneity (I2> 70%), we will consider not to Meta-analyze them and explain the evidence synthesis narratively. If the I2 is below 90%, we will perform a meta-analysis by using the fixed effects of the random effects model, whichever pertinent.

Selection of studies

The results of the literature searches will be automatically incorporated into the L·OVE platform (automated retrieval) identified as “Three-dimensional mammography for breast cancer”.

Firstly, titles and abstracts will be independently screened by at least two reviewers against the inclusion criteria. We will resolve disagreements by consensus or by discussion with a third review author. Secondly, we will obtain the full reports for all records that appear to meet the inclusion criteria. We will record the reasons for excluding studies and show the study selection process in a PRISMA flow diagram.

Data extraction and management

We will use an excel spreadsheet to extract information about studies characteristics (characteristics of participants; inclusion-exclusion criteria; intervention and comparison description, outcomes and results). Data extraction will be performed by two authors.

Assessment of risk of bias of included studies

We will evaluate the risk of bias of the included randomized trials using the ROB-2 tool 16, and the risk of bias of the included studies on test accuracy using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool17 which includes the following four domains: patient selection, index test, reference standard, flow,and timing. Two independent review authors will do this assessment. Discrepancies will be resolved by consensus.

Measures of treatment effect

Studies results would be reported as pooled relative risks (RR), odds ratios (OR) for categorical outcomes or mean differences (MD) (or standardized mean differences, (SMD)) for continuous outcomes with the corresponding 95% confidence intervals (95% CI).

Data synthesis

We will evaluate the heterogeneity of the included studies with I2 as follows: I2 < 50% as low, heterogeneity, I2 > 50% and < 90% as high, and > 90% as very high. When heterogeneity is below 90%, we will perform a meta-analysis in RevMan 5.4.

Sensitivity analysis

We will perform a sensitivity analysis excluding the studies with high risk of bias.

Certainty of evidence

We will assess the certainty of evidence using the GRADE approach18, both for the evidence found as part of the initial or baseline review, and for the updates resulting from the living evidence process.

Two reviewers will independently define the certainty of evidence and discuss any disagreement to reach consensus. We will present the results using summary of findings tables.

Dissemination plan

We plan to communicate our review results as publication in a scientific journal.

If during the living process, new relevant results that imply changes in the current clinical practice are identified, we will update the report of this review and disseminate the update among potential users.

We will elaborate evidence technical reports to the hospital Health Assessment Committee. We will share the results through our social media channels. All periodical updates will be available in the LE_IHD project website (https://livingevidenceframework.com/en/).

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