



EUROPEAN COMMISSION
JOINT RESEARCH CENTRE

Directorate F - Health, Consumers & Reference Materials (Ispra)
Health in Society

European Commission Initiative on Breast Cancer (ECIBC): European guidelines on breast cancer screening and diagnosis

QUESTION	
Should screening using digital breast tomosynthesis in addition to digital mammography vs. digital mammography alone be used in organised screening programmes for early detection of breast cancer in asymptomatic women?	
POPULATION:	Asymptomatic women attending an organised breast cancer screening programme
INTERVENTION:	Screening using digital breast tomosynthesis (including synthesised 2D images or not) in addition to digital mammography
COMPARISON:	Digital mammography
MAIN OUTCOMES:	Breast cancer mortality, breast cancer stage, breast cancer detection (number of breast cancers detected per 1000 screened), interval breast cancer, recall for assessment, quality of life, other-cause mortality, adverse effects (including radiation exposure, radiation induced cancers-related to radiation dose, overdiagnosis related adverse effects, false positive related adverse effects)
SETTING:	European Union
PERSPECTIVE:	Population (National Health System)
BACKGROUND:	<p>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) (Ferlay J 2018). Breast cancer ranks as the fourth cause of death from cancer overall (626 679 deaths) (Ferlay J 2018).</p> <p>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.</p> <p>Digital breast tomosynthesis (DBT) is a pseudo-3D imaging technique based on a series of low dose images of the breast from different angles and therefore has the potential to overcome the tissue superposition issue thus improving detection of breast lesions (Rafferty 2013; Gur 2009). 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, tomosynthesis has been proposed to be used in addition to a 2D image (either done with DBT or mammography). This allows the comparison with previous mammographies that usually are available only in 2D and speeds up the process of interpreting images. 2D images can be obtained either through additional exposures, thus obtaining a regular DM, or through a software that allows the construction of synthesised 2D images. In this question we compare DBT in addition to DM, regardless if synthetic 2D is available, with DM alone.</p>

CONFLICT OF INTEREST:	<p><u>Management of Conflicts of Interest (Col)</u>: Cols for all Guidelines Development Group (GDG) members were assessed and managed by the Joint Research Centre (JRC) following an established procedure in line with European Commission rules. GDG member participation in the development of the recommendations was restricted, according to Col disclosure. Consequently, for this particular question, the following GDG members were recused from voting: Jan Danes, Solveig Hofvind, Elsa Pérez, and Kenneth Young. Miranda Langendam was not allowed to vote due to the established rules for external experts.</p> <p>The search strategies for this recommendation were updated on June 2018.</p>
------------------------------	--

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know 	<p>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), it ranks as the fourth cause of death from cancer overall (626,679 deaths) (Ferlay J 2018).</p> <p>DM is widely used in screening and diagnosis of breast cancer. However, some aspects such as superposition of breast tissue limits the sensitivity and specificity of mammography and false-positives and false negatives are an issue (JRC Technical Report PICO 1-3, contract FWC443094012015; available upon request). DBT might provide better imaging and discriminative capacity in these cases.</p>	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

- Trivial
- Small
- Moderate
- Large
- Varies
- Don't know

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with DM	Risk with screening using DBT in addition to DM				
Breast cancer detection	Study population		OR 1.89 (1.31 to 2.73)	19560 (1 RCT) ¹	⊕⊕⊕⊕ HIGH	
	450 per 100,000	847 per 100,000 (588 to 1,218)				
	Low					
	600 per 100,000	1128 per 100,000 (785 to 1,621)				
Breast cancer detection	Study population		OR 1.29 (1.13 to 1.47) ^a	91316 (4 observational studies) ^{2,3,4,5,6,7,8,b}	⊕⊕○○ LOW ^c	
	554 per 100,000 ^b	714 per 100,000 (626 to 812)				
Recall for assessment	Study population		OR 1.02 (0.87 to 1.18)	19560 (1 RCT) ¹	⊕⊕⊕○ MODERATE ^d	
	3,465 per 100,000	3532 per 100,000 (3,028 to 4,064)				
	Low					
	2,000 per 100,000	2039 per 100,000 (1,745 to 2,352)				
	Moderate					
	3,000 per	3058 per 100 000				

During the updating of the searches 4 new studies meeting the inclusion criteria for desirable effects were identified and added to the summary of findings table: 1 RCT (Pattacini 2018) and 3 observational studies (Skaane 2018, Houssami 2018, and Romero 2018).

The new studies provide additional information on breast cancer detection and breast cancer stage and new evidence is available for interval breast cancer (Skaane 2018, Houssami 2018). The critical outcomes breast cancer mortality, quality of life, or other-cause mortality are still not measured.

The currently included studies only present data from first round DBT in addition to DM screening.

The anticipated desirable effects were examined by the GDG and are reported per outcome as follows:

Breast cancer detection: the new available data (Pattacini 2018, Romero 2018) did not change the effect size; the effects were considered large as in the previous 2016 version. However there are still uncertainties about the clinical relevance of the increase in breast cancer detection as it may be a marker of overdiagnosis.

Breast cancer stage: the effects are still not known as there are no studies reporting the effect on incidence of breast cancer by stage. However, given the relative increase of 46% in invasive cancers detected, the technology is likely to confer a substantial reduction in late stage disease.

Interval breast cancer: The two new studies reporting interval breast cancer (Skaane 2018, Houssami 2018) suggest a very small or no reduction for this outcome.

Despite new studies being added during the update, including the new information about interval breast cancer, the GDG felt the information for the key outcomes (i.e.: breast cancer mortality, quality of life, other-cause mortality) was still needed to determine the truly anticipated desirable effects of DBT in addition to DM, as this information is still lacking in the new studies. This includes information on screening outcomes at subsequent (incident) screens.

	100,000	(2,620 to 3,521)				
Recall for assessment	Low		OR 0.95 (0.64 to 1.42)	35981 (3 observational studies) ^{2,4,5,6,7,8,e}	⊕○○○ VERY LOW ^{c,f,g}	
	2,200 per 100,000 ^e	2092 per 100,000 (1,419 to 3,095)				
	High					
	15,600 per 100,000 ^e	14937 per 100,000 (10,578 to 20,790)				
False positive recall for assessment	Study population		OR 0.88 (0.75 to 1.04)	19560 (1 RCT) ¹	⊕⊕⊕○ MODERATE ^d	
	3,015 per 100,000	2663 per 100,000 (2,279 to 3,132)				
False positive recall for assessment	Low		OR 1.22 (1.16 to 1.27)	73646 (4 observational studies) ^{10,3,4,5,6,7,9}	⊕⊕○○ LOW ^c	
	10,700 per 100,000 ^h	12754 per 100,000 (12,203 to 13,207)				
	High					
	41,500 per 100,000 ^h	46394 per 100,000 (45,143 to 47,394)				
Breast cancer stage (invasive)	Study population		OR 1.78 (1.20 to 2.63)	19560 (1 RCT) ¹	⊕⊕⊕⊕ i HIGH	
	399 per	707 per 100,000				

	100,000	(478 to 1,042)				
Breast cancer stage (invasive)	Study population		OR 1.46 (1.30 to 1.64)	39826 (2 observational studies) ^{4,5,6,7,8,b}	⊕⊕○○ LOW c,i	
	457 per 100,000 ^b	666 per 100,000 (593 to 747)				
Interval breast cancer	Study population		RR 0.99 (0.71 to 1.38)	87005 (2 observational studies) ^{11,12,j,k}	⊕○○○ VERY LOW ^l	
	180 per 100,000	179 per 100,000 (128 to 249)				
Radiation exposure	The median dose per examination was 6.40 mGy (IQR, 5.68–7.36 mGy) and 4.84 mGy (IQR, 4.24–5.72 mGy) for DBT and DM, respectively, meaning that the dose for DBT in addition to DM was 11.24 mGy (2.3 times higher than DM alone).		-	(1 RCT) ¹	⊕⊕⊕⊕ HIGH ^o	
Radiation exposure	Radiation doses for DBT in addition to DM were approximately twice that reported for DM alone. ^m		-	(3 observational studies) ^{13,14,7}	⊕⊕○○ LOW ^{n,o}	
Breast cancer mortality - not reported	-	-	-	-	-	
Quality of life - not reported	-	-	-	-	-	
Overdiagnose - not reported	-	-	-	-	-	
Radiation induced	-	-	-	-	-	

cancers-related to radiation dose - not reported						
Other causes of mortality - not reported	-	-	-	-	-	
<ol style="list-style-type: none"> 1. Pattacini P, Nitrosi A, Giorgi Rossi P, Iotti V, Ginocchi V, Ravaioli S, Vacondio R, Braglia L, Cavuto S, Campari C, Group., RETomo, Working. Digital Mammography versus Digital Mammography Plus Tomosynthesis for Breast Cancer Screening: The Reggio Emilia Tomosynthesis Randomized Trial. Radiology ; 2018. 2. Romero Martín S, Raya Povedano JL, Cara García M, Santos Romero AL, Pedrosa Garriguet M, Álvarez Benito M.. Prospective study aiming to compare 2D mammography and tomosynthesis + synthesized mammography in terms of cancer detection and recall.. Eur Radiol; 2018. 3. Bernardi D, Macaskill P, Pellegrini M, Valentini M, Fantò C, Ostilio L, Tuttobene P, Luparia A, Houssami N.. Breast cancer screening with tomosynthesis (3D mammography) with acquired or synthetic 2D mammography compared with 2D mammography alone (STORM-2): a population-based prospective study.. Lancet Oncol; 2016. 4. Skaane P, Bandos AI, Gullien R, Eben EB, Ekseth U, Haakenaasen U, et al.. Comparison of digital mammography alone and digital mammography plus tomosynthesis in a population-based screening program.. Radiology.; 2013. 5. Skaane P, Bandos AI, Gullien R, et al.. Prospective trial comparing full-field digital mammography (FFDM) vs. combined FFDM and tomosynthesis in a population-based screening programme using independent double reading with arbitration.. Eur Radiol; 2013. 6. Skaane P, Bandos AI, Eben EB, Jepsen IN, Krager M, Haakenaasen U, et al.. Two-view digital breast tomosynthesis screening with synthetically reconstructed projection images: comparison with digital breast tomosynthesis with full-field digital mammographic images. Radiology ; 2014. 7. Ciatto S, Houssami N, Bernardi D, Caumo F, Pellegrini M, Brunelli S, et al. Integration of 3D digital mammography with tomosynthesis for population breast-cancer screening (STORM): a prospective comparison study. The Lancet Oncology; 2013. 8. Houssami N, Macaskill P, Bernardi D, Caumo F, Pellegrini M, Brunelli S, et al. Breast screening using 2D-mammography or integrating digital breast tomosynthesis (3D-mammography) for single-reading or double-reading--evidence to guide future screening strategies. Eur J Cancer; 2014. 9. Lång K, Andersson I, Rosso A, Tingberg A, Timberg P, Zackrisson S. Performance of one-view breast tomosynthesis as a stand-alone breast cancer screening modality: results from the Malmö Breast Tomosynthesis Screening Trial, a population-based study. Eur Radiol; 2016 . 10. Lång K, Nergården M, Andersson I, Rosso A, Zackrisson S. False positives in breast cancer screening with one-view breast tomosynthesis: An analysis of findings leading to recall, work-up and biopsy rates in the Malmö Breast Tomosynthesis 						

	<p>Screening Trial. Eur Radiol; 2016.</p> <ol style="list-style-type: none"> 11. Houssami N, Bernardi D, Caumo F, Brunelli S, Fantò C, Valentini M, et al. Interval breast cancers in the screening with tomosynthesis or standard mammography (STORM) population-based trial. Breast; 2018. 12. Skaane P, Sebuødegård S, Bandos AI, Gur D, Østerås BH, Gullien R, Hofvind S.. Performance of breast cancer screening using digital breast tomosynthesis: results from the prospective population-based Oslo Tomosynthesis Screening Trial. Breast Cancer Res Treat; 2018. 13. Paulis LE, Lobbes MB, Lalji UC, Gelissen N, Bouwman RW, Wildberger JE, et al. Radiation exposure of digital breast tomosynthesis using an antiscatter grid compared with full-field digital mammography. Invest Radiol; 2015. 14. Wallis MG, Moa E, Zanca F, Leifland K, Danielsson M. Two-view and single-view tomosynthesis vs. full-field digital mammography: high-resolution X-ray imaging observer study. Radiology; 2012. <ol style="list-style-type: none"> a. Relative effect was adjusted for paired design. b. Median or mean of the control group of the included studies as appropriate unless otherwise specified. c. Despite only women with suggestive findings of malignancy being followed-up, the panel agreed that there was not an important risk of information bias, as the same strategy was implemented in both arms of the included studies, and the effects were consistent across them. d. The panel believes that baseline recall rates interact with the effects of the intervention and relative estimates might be substantially different in scenarios with low, moderate or high baseline recall rates. e. Baseline risk calculated from Roman 2014 (PMID 24972452) and Hofvind 2012 (PMID 22972811) f. Despite the fact that the STORM study (2013/2014) and OTST study (2013) evaluated women recalled differently (radiologist vs. radiologist plus meeting arbitration) the results were consistent. g. Important statistical heterogeneity (Three studies with I2 of 99%, non - overlapping confidence intervals, and widely different point estimates). h. Baseline risk calculated from Roman 2014 (PMID 24972452). i. Invasive cancer stage is a surrogate outcome of cumulative incidence of advance breast cancer. j. Data from one round (most recent 2008-2009) included in control arm (DM) (Skane 2018) k. Houssami 2018 gives data from women who did not participate in OTST study (external cohort) included as control arm (DM) l. Wide 95%CI and low number of events. m. Doses are known to vary (diagnostic reference levels are typically country/region and technology specific). n. Radiation exposure is a surrogate outcome of "other cancer related to radiation". o. Results were consistent independently of the technology used (Hologic Selenia Dimension or Senographe Dimension). 	
--	--	--

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Large ○ Moderate ○ Small ○ Trivial ● Varies ○ Don't know 	See SoF table above	<p>During the updating of the searches 4 new studies meeting the inclusion criteria for desirable effects were identified and added to the SoF: 1 RCT (Pattacini 2018), and 3 observational studies (Skaane 2018, Houssami 2018, and Romero 2018).</p> <p>The new studies provide additional information on recall for assessment, false positive recall for assessment and radiation exposure. Critical outcomes such as breast cancer mortality, quality of life, or other-causes of mortality are still not measured.</p> <p>The currently included studies only present data from first round DBT in addition to DM screening.</p> <p>The anticipated undesirable effects were examined by the GDG:</p> <p><u>Recall for assessment:</u> the GDG notes that the recall for assessment may vary based on the baseline recall rate in the screening population (Hofvind 2012, Roman 2014). The relative effects from RCT and observational studies are similar.</p> <p><u>False positive recall for assessment:</u> The GDG agreed the effect would vary depending on the baseline rate (Bernardi 2016).</p> <p><u>Radiation induced cancers-related to radiation dose:</u> no data available. Although the dose would be increased by using DBT in addition to DM, the absolute increase in radiation induced cancers is likely to be small.</p> <p>Overall the GDG felt that the undesirable anticipated effects vary.</p>

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ● Very low ○ Low ○ Moderate ○ High ○ No included studies 		Due to indirectness and inconsistency of the estimates for the critical outcomes prioritised by the GDG the certainty of the evidence is very low.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ● Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes 	<p>No specific studies focusing in DBT were identified. The findings, all from mammography studies (JRC Technical Report PICO 10-11, contract FWC443094012015; available upon request), however, are likely to be generalisable to DBT, as both screening tests are associated with similar desirable and undesirable effects.</p> <p>A systematic review shows that participants in mammography screening programmes place a low value on the psychosocial and physical effects of false positive results and overdiagnosis (JRC Technical Report PICO 10-11, contract FWC443094012015). Women generally consider these undesirable effects acceptable (low certainty). However, these findings are of limited value, mainly given the significant concerns regarding the adequacy of the information provided to women, in order to make an informed decision about participation. Also, acceptability of false positive results is based on studies of participants who had already received a false positive result. Their preference may differ from the general population. Another finding is that breast cancer screening represents a significant burden for some women due to the associated psychological distress and inconvenience.</p> <p>Regarding breast cancer diagnosis, there is very limited data available on women' views. One of the main themes identified in the literature is that people disvalue highly the anxiety caused by delays in the receipt of results of diagnostic procedures, or by a lack of understanding of the tests due to suboptimal communication with physicians (moderate certainty). Also, people have a higher overall preference towards more comfortable, brief diagnostic procedures (moderate certainty).</p>	<p>During the updating no new study was identified.</p> <p>From the studies reviewed there was not much confidence in the findings and there is, therefore, uncertainty in how much people value the main outcomes. The GDG agreed that the increase in breast cancer detection, as well as the variation in recall rate, and the increase in radiation exposure are likely to be valued very differently by women.</p>

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● Don't know 		<p>In this updated recommendation, despite similar judgements made on some criteria (desirable effects, undesirable effects, certainty of the evidence and values) the GDG revised the previous judgment and decided to change from “probably favors the intervention” to “don't know “. This was mainly due to the lack of information about key outcomes such as mortality or validated surrogates (i.e. incidence of advanced stages) in the context of unexpected results for the outcome interval breast cancer.</p> <p>A decrease in interval breast cancer was expected as the sensitivity of the intervention has proved to be higher. The panel noted that all the studies reporting interval breast cancer suggest no or a very small reduction of this outcome. These results may be related with a risk of overdiagnosis. Therefore, the GDG was concerned about the increased cancer detection without knowing the clinical benefit (i.e. no difference in interval breast cancer).</p>

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know 	<p>Costs (2016 fees) used in the Medicaid model for 25,495 women aged 40 to 65 years in the US (1):</p> <p>1) DM screening fee per patient (including Computer-Assisted Diagnosis): 95.18 US Dollars.</p> <p>2) DM in addition to DBT screening fee per patient (including CAD): 132.04 US Dollars.</p>	<p>During the updating a new study was identified reporting data about costs (Miller 2017). The results from this study are reported under research evidence.</p> <p>The GDG agreed that resources required for moving from DM alone to DBT in addition to DM may include, amongst other factors: costs of the technology, capital costs of the machines and the lifetime of the machine, data transport and capacity for data storage, and additional time for radiologists to read DBT in addition to DM images, and increased time for the DBT in addition to DM compared to DM alone.</p> <p>Based on the information from three observational studies identified from the systematic review of Gilbert et al.</p>

		<p>(Gilbert 2016) radiologists' reading time would have an increase of between 100% and 200% for DBT in addition to DM compared with DM alone (Skaane 2013, Bernardi 2012a, Wallis 2012). This corresponds to absolute times of 77-191 seconds for DBT in addition to DM and 33-67 seconds for DM alone.</p> <p>Staff cost may vary depending on the country context and they are not transferable from one country to another.</p> <p>As consensus was not reached, voting was conducted among the GDG members: 9 members voted "large costs", 8 members voted "moderate costs".</p>
--	--	---

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Very low ● Low ○ Moderate ○ High ○ No included studies 	<p>The certainty of the evidence is low due to indirectness. The study of Miller et al. (Miller 2017) was performed in the US using data for women aged 40 to 65 years attending an annual DM screening.</p>	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies 	<p>According to Miller et al., the addition of DBT reduced the need of follow-up diagnostic tests (from 14.38% with DM alone to 10% with DBT in addition to DM) and improves the detection of invasive cancers, allowing earlier and less costly treatment, both of which more than offset the incremental cost of adding DBT to DM screening. The annual estimated per patient cost savings of using DBT was 8.14 US Dollars (Miller 2017).</p>	<p>During the updating one new study was identified (Miller 2017), but the GDG judged that its results may not be applicable to European screening programmes.</p> <p>The study of Miller et al. (1) was performed in the USA using data for women aged 40 to 65 years attending annual DM screening. Two main assumptions may not be applicable to European screening programmes. First, the recall rate was estimated to be 14.4% for DM and 10% for the combination of DBT in addition to DM. Second, the percentage of detected Stage 1 cancers was 32.9% for DM</p>

	DM	DM +DBT	Variation	Total savings due to use of DBT (per patient)	
Screened women	25,494	25,494			
Follow-up rate	14.38 % (N= 3,666)	10.00 % (N= 2,549)	Decrease of 4.38% (N=1,117)		
Screening cost per woman	95.18 USD	132.04 USD	Increase of 36.86 USD		
Follow-up cost per patient			Decrease of 30.44 USD		
	378.31 USD	333.31 USD			
Treatment cost per patient			Decrease of 14.56 USD		
Total cost of screening, follow-up and treatment per patient	473.49 USD	465.35 USD		8.14 USD	

and 40.1% for DBT in addition DM.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know 		<p>During the updating no new studies were identified.</p> <p>The GDG felt that within screening programmes there may be policy decisions to restrict the programme if there are increased costs and the screening programme is unable to fund universal participation. This could have an influence on equity in either direction.</p>

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know 	<p>No specific studies focusing on DBT in addition to DM were identified. The findings, all from DM studies, however, are likely to be generalisable to DBT in addition to DM, as both (DBT and DM) are associated with similar desirable and undesirable effects.</p> <p>However, a systematic review (JRC Technical Report PICO 16-17, contract FWC443094032016; available upon request) found the following barriers associated with breast cancer screening with DM: (a) lack of knowledge and misperceptions regarding preventive medicine and breast health (high certainty of evidence), (b) poor communication skills of healthcare providers (high certainty of evidence), (c) poor accessibility to breast screening, especially among women with disabilities (high certainty of evidence), (d) fear and stress related to the procedure and the possibility of cancer diagnosis (high certainty of evidence), (e) pain and discomfort during the procedure (moderate certainty of evidence), (f) embarrassment and shyness during the procedure (moderate certainty of evidence), (g) lack of support and encouragement from family members, caregivers and social network (moderate certainty of evidence), (h) lack of information regarding the available resources (low certainty of evidence) and (i) low prioritisation of breast cancer screening (low certainty of evidence). Women and relevant stakeholders expressed similar opinions.</p>	<p>During the updating no new studies were identified.</p> <p><u>Participants:</u></p> <p>There is likely variability in acceptability for women. If there is a higher radiation dose, women may be more concerned. Additional compression time for the test and/or additional compressions might be necessary depending on the manufacturer of the device. Women who come for screening may be concerned that if they only have DM, and are not offered DBT, they are not getting the screening technology with the highest detection rate. Women may appreciate the increased confidence in the screening result if there is higher breast cancer detection when screening with DBT in addition to DM compared to screening with DM alone. Participation rates in the trials reviewed are high, which may indicate their general acceptability of screening with DBT in addition to DM compared to DM alone.</p> <p><u>Radiologists:</u></p> <p>DBT may be preferred by radiologists reading screening tests because their certainty in the diagnosis may be higher when using DBT in addition to DM compared to using DM alone.</p> <p><u>Policy makers:</u></p> <p>In settings with universal healthcare coverage, for directors of hospitals and screening programmes, carrying out DBT as well as DM may not be acceptable because there will likely be increased costs.</p>

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know 		<p>During the updating no new studies were identified.</p> <p>The GDG felt that in contexts where there are the resources to support this and where there is access to new technologies that are capable of DBT, it is feasible. For other countries without the technology and resources to support this it may not be feasible. In addition, although DBT requires some extra training for radiologists, this was not seen by GDG as a major barrier to implementation.</p> <p>The need to establish quality standards for synthesised 2D imaging for implementation was mentioned by the GDG.</p>

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			No known undesirable outcomes
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know

	JUDGEMENT						
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention ○	Conditional recommendation against the intervention ●	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ○	Strong recommendation for the intervention ○
---	--	---	--	---

CONCLUSIONS

Recommendation

For asymptomatic women with an average risk of breast cancer, the ECIBC's Guidelines Development Group (GDG) suggests against screening with digital breast tomosynthesis (DBT) in addition to digital mammography (DM) versus digital mammography alone in the context of an organised screening programme (conditional recommendation, very low certainty of evidence).

Justification

Overall justification

As there was not agreement within the GDG for the direction of this recommendation, voting among members without CoI took place, the results of which were: 4 members voted for 'strong recommendation against the intervention'; 9 members voted for 'conditional recommendation against the intervention'; 1 member voted for 'conditional recommendation for the intervention'; 1 abstention.

The GDG agreed that there is high certainty for test accuracy of DBT in addition to DM over DM alone. However, it has to be taken into account that the included studies only present data from first round DBT in addition

to DM screenings and there is still a lack of studies on subsequent screening rounds.

In the updated recommendation, similar judgements were made on some criteria of the evidence to decision framework (i.e. desirable effects, undesirable effects, certainty of the evidence and values) as in the previous version of the recommendation. However, in this updated recommendation, differently to the previous version, the GDG agreed the balance between desirable and undesirable effects was unknown. This was mainly due to the lack of information about key outcomes such as mortality or validated surrogates (i.e. incidence of advanced stages) in the context of unexpected results showing very little or no decrease in interval breast cancers. A decrease in interval breast cancer was expected as the sensitivity of the intervention has proved to be higher, however, the two observational studies reporting interval breast cancer suggested a very small or no reduction of this outcome. These results may be related with a risk of overdiagnosis. Therefore, the GDG was concerned about the increased cancer detection without knowing the true clinical benefit (i.e. no difference in interval breast cancer).

During the updating a new study was identified reporting data about costs (Miller 2017) and the GDG judged that the resources required for DBT in addition to DM compared to DM alone are large.

Costs should be considered on a country-by-country basis, depending on resources available for breast cancer screening programmes. Evidence will be emerging from ongoing and newly starting screening trials on tomosynthesis that may influence the current recommendation.

Detailed justification

Desirable Effects

The evidence reviewed showed a large effect size in the increase of breast cancer detection; from 2 to 3 breast cancers detected per 1000 women at first round of DBT in addition to DM screening. However no evidence is available on key outcomes such as mortality or validated surrogates (i.e. incidence of advanced stages).

The information about interval breast cancer that became available with the updating of the search was inconsistent with the expectation: a decrease in interval cancer rate was expected as the sensitivity of the intervention has proved to be higher. The panel noted that the two studies reporting interval breast cancer suggest a very small or no reduction for this outcome.

In addition, there was no evidence on other desirable effects such as decreases in detection of advanced stage breast cancer or reduction in breast cancer mortality.

Undesirable Effects

The GDG agreed that the undesirable anticipated effects vary due to evidence on varying recall for assessment and false positive recall for assessment, and a small increased risk of developing other cancers due to increased radiation dose of DBT in addition to DM.

Certainty of evidence

The judgements were made in the context of very low certainty in the evidence of effects due to indirectness and inconsistency.

Resources required

The GDG judged that the resources required are large for screening using DBT in addition to DM. The resource considerations will also vary greatly based on the healthcare setting and health system funding for countries with universal healthcare coverage as compared to settings where DBT will be implemented in private healthcare settings. The GDG expressed their concern that this may lead to increased health inequities with varied implementation in different countries across Europe.

Subgroup considerations

Women with high mammographic breast density are likely to benefit most from the increased detection capability of DBT in addition to DM. However, this group was not specifically considered in this question.

Implementation considerations

- Evidence will be emerging from ongoing and future breast cancer screening trials on DBT that may influence the current recommendation.
- Inappropriate worry about radiation dose should be dealt with in case programmes that are using the DBT in addition to DM combination. In general, the GDG believes it is important to educate women and health professionals on the risk of radiation in the context of possible benefits of screening.
- There will be significantly increased data storage needs for screening programmes using DBT in addition to DM as compared DM alone.
- Additional time is needed for radiologists to read tomosynthesis images, and therefore even more for the DBT in addition to DM examination compared to DM alone.
- The GDG noted that health equity in access to screening should be considered due to different resource settings and the capacity for different countries to pay for DBT in addition to DM over DM alone.

Monitoring and evaluation

Standards should be developed in particular for the image quality of synthesised 2D images from the tomosynthesis technology.

Research priorities

- The currently included studies only present data from first round DBT in addition to DM screening studies, thus the effects for several patient-important outcomes, which need a longer follow-up period, could not be taken into account. Research on several screening rounds of DBT in addition to DM are warranted.
- Further research is needed to build the evidence on benefits and harms of DBT in addition to DM compared to DM alone through comparison of direct outcomes, including impacts of interval cancer detection, stage of breast cancer at detection and mortality reduction or projection of mortality reduction (i.e. modelling starting from incidence of advanced stages and interval cancer).
- Further research information on harms of DBT in addition to DM, including rates of overdiagnosis of breast cancer, are warranted.
- Research investigating the cost-effectiveness of a breast cancer screening programme using DBT in addition to DM is needed to inform decision-making on breast cancer screening.
- Research is needed to define the quality parameters that would need to be fulfilled for breast cancer screening programmes that decide to use DBT in addition to DM.
- Evidence on implementation challenges of screening programmes already using DBT in addition to DM should be collected.

REFERENCES SUMMARY

- Bernardi D, Ciatto S, Pellegrini M, Anesi V, Burlon S, Cauli E, Depaoli M, Larentis L, Malesani V, Targa L, Baldo P, Houssami N.. Application of breast tomosynthesis in screening: incremental effect on mammography acquisition and reading time.. Br J Radiol; 2012.
- Bernardi D, Macaskill P, Pellegrini M, Valentini M, Fantò C, Ostilio L, Tuttobene P, Luparia A, Houssami N.. Breast cancer screening with tomosynthesis (3D mammography) with acquired orsynthetic 2D mammography compared with 2D mammography alone (STORM-2): a population-based prospective study.. Lancet Oncol; 2016.
- Bernardi D, Macaskill P, Pellegrini M, Valentini M, Fantò C, Ostilio L, Tuttobene P, Luparia A, Houssami N.. Breast cancer screening with tomosynthesis (3D mammography) with acquired orsynthetic 2D mammography compared with 2D mammography alone (STORM-2): a population-based prospective study.. Lancet Oncol; 2016.
- Ciatto S, Houssami N, Bernardi D, Caumo F, Pellegrini M, Brunelli S, et al. Integration of 3D digital mammography with tomosynthesis for population breast-cancer screening (STORM): a prospective comparison study. The Lancet Oncology; 2013.
- Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F (2018). Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available from: <https://gco.iarc.fr/today>, accessed [25 07 2019].
- Gilbert FJ, Tucker L, Young KC. Digital breast tomosynthesis (DBT): a review of the evidence for use as a screening tool. Clin Radiol; 2016.
- Hofvind S1, Ponti A, Patnick J, Asuncion N, Njor S, Broeders M, et al. False-positive results in mammographic screening for breast cancer in Europe: a literature review and survey of service screening programmes.. J Med Screen. ; 2012.
- Houssami N, Bernardi D, Caumo F, Brunelli S, Fantò C, Valentini M, et al. Interval breast cancers in the screening with tomosynthesis or standard mammography (STORM) population-based trial. Breast; 2018.
- Houssami N, Macaskill P, Bernardi D, Caumo F, Pellegrini M, Brunelli S, et al. Breast screening using 2D-mammography or integrating digital breast tomosynthesis (3D-mammography) for single-reading or double-reading--evidence to guide future screening strategies. Eur J Cancer; 2014.
- Lång K, Andersson I, Rosso A, Tingberg A, Timberg P, Zackrisson S. Performance of one-view breast tomosynthesis as a stand-alone breast cancer screening modality: results from the Malmö Breast Tomosynthesis Screening Trial, a population-based study. Eur Radiol; 2016 .
- Lång K, Nergården M, Andersson I, Rosso A, Zackrisson S. False positives in breast cancer screening with one-view breast tomosynthesis: An analysis of findings leading to recall, work-up and biopsy rates in the Malmö Breast Tomosynthesis Screening Trial. Eur Radiol; 2016.
- Miller JD, Bonafede MM, Herschorn SD, Pohlman SK, Troeger KA, Fajardo LL.. Value Analysis of Digital Breast Tomosynthesis for Breast Cancer Screening in a US Medicaid Population.. J Am Coll Radiol; 2017.
- Pattacini P, Nitrosi A, Giorgi Rossi P, Iotti V, Ginocchi V, Ravaioli S, Vacondio R, Braglia L, Cavuto S, Campari C, Group., RETomo, Working. Digital Mammography versus Digital Mammography Plus Tomosynthesis for Breast Cancer Screening: The Reggio Emilia Tomosynthesis Randomized Trial.. Radiology ; 2018.
- Paulis LE, Lobbes MB, Lalji UC, Gelissen N, Bouwman RW, Wildberger JE, et al. Radiation exposure of digital breast tomosynthesis using an antiscatter grid compared with full-field digital mammography. Invest Radiol; 2015.
- Roman M, Skaane P, Hofvind S. The cumulative risk of false-positive screening results across screening centres in the Norwegian Breast Cancer Screening Program. Eur J Radiol; 2014.
- Romero Martín S, Raya Povedano JL, Cara García M, Santos Romero AL, Pedrosa Garriguet M, Álvarez Benito M.. Prospective study aiming to compare 2D mammography and tomosynthesis + synthesized mammography in terms of cancer detection and recall.. Eur Radiol; 2018.
- Skaane P, Bandos AI, Eben EB, Jepsen IN, Krager M, Haakenaasen U, et al.. Two-view digital breast tomosynthesis screening with synthetically reconstructed projection images: comparison with digital breast tomosynthesis with full-field digital mammographic images. Radiology ; 2014.
- Skaane P, Bandos AI, Gullien R, Eben EB, Ekseth U, Haakenaasen U, et al.. Comparison of digital mammography alone and digital mammography plus tomosynthesis in a population-based screening program.. Radiology.; 2013.

- Skaane P, Bandos AI, Gullien R, et al.. Prospective trial comparing full-field digital mammography (FFDM) vs. combined FFDM and tomosynthesis in a population-based screening programme using independent double reading with arbitration.. Eur Radiol; 2013.
- Skaane P, Sebuødegård S, Bandos AI, Gur D, Østerås BH, Gullien R, Hofvind S.. Performance of breast cancer screening using digital breast tomosynthesis: results from the prospective population-based Oslo Tomosynthesis Screening Trial. Breast Cancer Res Treat; 2018.
- Tsilidis KK, Papadimitriou N, Capothanassi D, Bamia C, Benetou V, Jenab M, Freisling H, Kee F, Nelen A, O'Doherty MG, Scott A, Soerjomataram I, Tjønneland A, May AM, Ramon Quiros J, Pettersson-Kymmer U, Brenner H, Schottker B, Ordonez-Mena JM, Karina Dieffenbach A, Eriksson S, Bøgeberg Mathiesen E, Njølstad I, Siganos G, Wilsgaard T, Boffetta P, Trichopoulos D, Trichopoulou A.. Burden of Cancer in a Large Consortium of Prospective Cohorts in Europe. J Natl Cancer Inst; 2016.
- Wallis MG, Moa E, Zanca F, Leifland K, Danielsson M. Two-view and single-view tomosynthesis vs. full-field digital mammography: high-resolution X-ray imaging observer study. Radiology; 2012.
- Wallis MG, Moa E, Zanca F, Leifland K, Danielsson M. Two-view and single-view tomosynthesis vs. full-field digital mammography: high-resolution X-ray imaging observer study. Radiology; 2012.

Evidence profile

Healthcare question	Should screening using digital breast tomosynthesis in addition to digital mammography vs. digital mammography alone be used in organised screening programmes for early detection of breast cancer in asymptomatic women?
Date	June 2018
Authors	Guideline Development Group (GDG): Mariangela Autelitano, Bettina Borisch, Mireille Broeders, Xavier Castells, Roberto D'Amico, Edoardo Colzani, Jan Daneš, Chris De Wolf, Stephen Duffy, Patricia Fitzpatrick, Markus Follmann, Livia Giordano, Paolo Giorgi Rossi, Axel Gräwingholt, Solveig Hofvind, Lydia Ioannidou-Mouzaka, Susan Knox, Miranda Langendam, Annette Lebeau, Helen McGarrigle, Lennarth Nyström, Elsa Pérez Gómez, Cecily Quinn, Peter Rabe, Holger Schünemann, Alberto Torresin, Ruben Van Engen, Cary Van Landsveld-Verhoeven, Sue Warman, Kenneth Young. Systematic Review team: Mónica Ballesteros, Pablo Alonso Coello, Nadia Montero, Iván Solà, Margarita Posso, Alexander Mathioudakis. JRC Healthcare Quality team: Zuleika Saz-Parkinson, Donata Lerda
Abbreviations	CI: Confidence interval OR: Odds Ratio RR: Risk ratio

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	screening using digital breast tomosynthesis in addition to digital mammography	digital mammography	Relative (95% CI)	Absolute (95% CI)		
Breast cancer detection												
1 ¹	randomised trials	not serious	not serious	not serious	not serious	none	83/9777 (0.8%)	44/9783 (0.4%)	OR 1.89 (1.31 to 2.73)	397 more per 100,000 (from 139 more to 769)	⊕⊕⊕⊕ HIGH	CRITICAL

										more)		
								0.6%		528 more per 100,000 (from 185 more to 1,021 more)		
Breast cancer detection												
4 2,3,4,5,6,7,8	observational studies	not serious ^a	not serious	not serious	not serious	none	329/45658 (0.7%)	253/45658 (0.6%) ^b	OR 1.29 (1.13 to 1.47) ^c	160 more per 100,000 (from 72 more to 258 more)	⊕⊕○○ LOW	CRITICAL
Recall for assessment												
1 ¹	randomised trials	not serious	not serious	serious ^d	not serious	none	344/9777 (3.5%)	339/9783 (3.5%)	OR 1.02 (0.87 to 1.18)	67 more per 100,000 (from 437 fewer to 598 more)	⊕⊕⊕○ MODERATE	CRITICAL
								2.0%		39 more per 100,000 (from 255 fewer to 352 more)		

								3.0%		58 more per 100,000 (from 380 fewer to 521 more)		
Recall for assessment												
3 2,4,5,6,7,8	observational studies	not serious ^a	serious ^{e,f}	not serious	not serious	none	1339/35981 (3.7%)	2.2% ^g	OR 0.95 (0.64 to 1.42)	108 fewer per 100,000 (from 781 fewer to 895 more)	⊕○○○ VERY LOW	CRITICAL
								15.6% ^g		663 fewer per 100,000 (from 5,022 fewer to 5,190 more)		
False positive recall for assessment												
1 ¹	randomised trials	not serious	not serious	serious ^d	not serious	none	261/9777 (2.7%)	295/9783 (3.0%)	OR 0.88 (0.75 to 1.04)	352 fewer per 100,000 (from 737 fewer to 117 more)	⊕⊕⊕○ MODERATE	CRITICAL

False positive recall for assessment												
4 3,4,5,6,7,9,10	observational studies	not serious ^a	not serious	not serious	not serious	none	1929/36823 (5.2%)	10.7% ^h	OR 1.22 (1.16 to 1.27)	2,054 more per 100,000 (from 1,503 more to 2,507 more)	⊕⊕○○ LOW	CRITICAL
								41.5% ^h		4,894 more per 100,000 (from 3,643 more to 5,894 more)		
Breast cancer stage (invasive)												
1 ¹	randomised trials	not serious	not serious	serious ⁱ	not serious	none	69/9777 (0.7%)	39/9783 (0.4%)	OR 1.78 (1.20 to 2.63)	309 more per 100,000 (from 79 more to 643 more)	⊕⊕⊕○ MODERATE	CRITICAL
Breast cancer stage (invasive)												
2 ^{4,5,6,7,8}	observational studies	not serious ^a	not serious	serious ⁱ	not serious	none	133/19913 (0.7%)	91/19913 (0.5%) ^b	OR 1.46 (1.30 to 1.64)	209 more per 100,000 (from 136 more to 290 more)	⊕○○○ VERY LOW	CRITICAL

Interval breast cancer												
2 ^{11,12,j,k}	observational studies	not serious	not serious	not serious	serious ^l	none	60/31593 (0.2%)	100/55412 (0.2%)	RR 0.99 (0.71 to 1.38)	2 fewer per 100,000 (from 52 fewer to 69 more)	⊕○○○ VERY LOW	CRÍTICO
Radiation exposure												
1 ¹	randomised trials	not serious	not serious	not serious ^m	not serious	none	The median dose per examination was 6.40 mGy (IQR, 5.68–7.36 mGy) and 4.84 mGy (IQR, 4.24–5.72 mGy) for DBT and DM, respectively, meaning that the dose for DBT in addition to DM was 11.24 mGy (2.3 times higher than DM alone).			⊕⊕⊕⊕ HIGH	CRITICAL	
Radiation exposure												
3 ^{4,13,14}	observational studies	not serious	not serious ^m	serious ⁿ	not serious	none	Radiation doses for digital mammography plus tomosynthesis were approximately twice that reported for digital mammography alone. ^o			⊕○○○ VERY LOW	CRITICAL	
Breast cancer mortality - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Quality of life - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Radiation induced cancers-related to radiation dose - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Overdiagnosis - not reported - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Other causes of mortality - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	

Explanations

- a. Despite only women with suggestive findings of malignancy being followed-up, the panel agreed that there was not an important risk of information bias, as the same strategy was implemented in both arms of the included studies, and the effects were consistent across them.
- b. Median or mean of the control group of the included studies as appropriate unless otherwise specified.
- c. Relative effect was adjusted for paired design.
- d. The panel believes that baseline recall rates interact with the effects of the intervention and relative estimates might be substantially different in scenarios with low, moderate or high baseline recall rates.
- e. Despite the fact that the STORM study (2013/2014) and OTST study (2013) evaluated women recalled differently (radiologist vs. radiologist plus meeting arbitration) the results were consistent.
- f. Important statistical heterogeneity (Three studies with I² of 99%, non -overlapping confidence intervals, and widely different point estimates).
- g. Baseline risk calculated from Roman 2014 (PMID 24972452) and Hofvind 2012 (PMID 22972811)
- h. Baseline risk calculated from Roman 2014 (PMID 24972452).
- i. Invasive cancer stage is a surrogate outcome of cumulative incidence of advance breast cancer.
- j. Data from one round (most recent 2008-2009) included in control arm (DM) (Skane 2018)
- k. Houssami 2018 gives data from women who did not participate in OTST study (external cohort) included as control arm (DM)
- l. Wide 95%CI and low number of events
- m. Results were consistent independently of the technology used (Hologic Selenia Dimension or Senographe Dimension).
- n. Radiation exposure is a surrogate outcome of "other cancer related to radiation".
- o. Doses are known to vary (diagnostic reference levels are typically country/region and technology specific).

References

1. Pattacini P, Nitrosi A, Giorgi Rossi P, Iotti V, Ginocchi V, Ravaioli S, Vacondio R, Braglia L, Cavuto S, Campari C, Group., RETomo, Working. Digital Mammography versus Digital Mammography Plus Tomosynthesis for Breast Cancer Screening: The Reggio Emilia Tomosynthesis Randomized Trial. *Radiology* ; 2018.
2. Romero Martín S, Raya Povedano JL, Cara García M, Santos Romero AL, Pedrosa Garriguet M, Álvarez Benito M. Prospective study aiming to compare 2D mammography and tomosynthesis + synthesized mammography in terms of cancer detection and recall. *Eur Radiol*; 2018.
3. Bernardi D, Macaskill P, Pellegrini M, Valentini M, Fantò C, Ostilio L, Tuttobene P, Luparia A, Houssami N. Breast cancer screening with tomosynthesis (3D mammography) with acquired or synthetic 2D mammography compared with 2D mammography alone (STORM-2): a population-based prospective study. *Lancet Oncol*; 2016.
4. Skaane P, Bandos AI, Gullien R, Eben EB, Ekseth U, Haakenaasen U, et al. Comparison of digital mammography alone and digital mammography plus tomosynthesis in a population-based screening program. *Radiology*; 2013.
5. Skaane P, Bandos AI, Gullien R, et al. Prospective trial comparing full-field digital mammography (FFDM) vs. combined FFDM and tomosynthesis in a population-based screening programme using independent double reading with arbitration. *Eur Radiol*; 2013.
6. Skaane P, Bandos AI, Eben EB, Jøbsen IN, Krøger M, Haakenaasen U, et al. Two-view digital breast tomosynthesis screening with synthetically reconstructed projection images: comparison with digital breast tomosynthesis with full-field digital mammographic images. *Radiology* ; 2014.
7. Ciatto S, Houssami N, Bernardi D, Caumo F, Pellegrini M, Brunelli S, et al. Integration of 3D digital mammography with tomosynthesis for population breast-cancer screening (STORM): a prospective comparison study. *The Lancet Oncology*; 2013.
8. Houssami N, Macaskill P, Bernardi D, Caumo F, Pellegrini M, Brunelli S, et al. Breast screening using 2D-mammography or integrating digital breast tomosynthesis (3D-mammography) for single-reading or double-reading--evidence to guide future screening strategies. *Eur J Cancer*; 2014.

9. Lång K, Andersson I, Rosso A, Tingberg A, Timberg P, Zackrisson S. Performance of one-view breast tomosynthesis as a stand-alone breast cancer screening modality: results from the Malmö Breast Tomosynthesis Screening Trial, a population-based study. *Eur Radiol*; 2016 .
10. Lång K, Nergården M, Andersson I, Rosso A, Zackrisson S. False positives in breast cancer screening with one-view breast tomosynthesis: An analysis of findings leading to recall, work-up and biopsy rates in the Malmö Breast Tomosynthesis Screening Trial. *Eur Radiol*; 2016.
11. Houssami N, Bernardi D, Caumo F, Brunelli S, Fantò C, Valentini M, et al. Interval breast cancers in the screening with tomosynthesis or standard mammography (STORM) population-based trial. *Breast*; 2018.
12. Skaane P, Sebuødegård S, Bandos AI, Gur D, Østerås BH, Gullien R, Hofvind S.. Performance of breast cancer screening using digital breast tomosynthesis: results from the prospective population-based Oslo Tomosynthesis Screening Trial. *Breast Cancer Res Treat*; 2018.
13. Paulis LE, Lobbes MB, Lalji UC, Gelissen N, Bouwman RW, Wildberger JE, et al. Radiation exposure of digital breast tomosynthesis using an antiscatter grid compared with full-field digital mammography. *Invest Radiol*; 2015.
14. Wallis MG, Moa E, Zanca F, Leifland K, Danielsson M. Two-view and single-view tomosynthesis vs. full-field digital mammography: high-resolution X-ray imaging observer study. *Radiology*; 2012.