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

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QUESTION

Should **screening using tomosynthesis (including synthesised 2D images)** vs. **digital mammography** be used for **early detection of breast cancer in asymptomatic women**?

POPULATION:	early detection of breast cancer in asymptomatic women	**BACKGROUND:**	Breast cancer is the second most common cancer in the world and, by far, the most frequent cancer among women, with an estimated 1.67 million new cancer cases diagnosed in 2012 (25% of all cancers) (Ferlay 2012). Breast cancer ranks as the fifth cause of death from cancer overall (522 000 deaths), the most frequent cause of cancer death in women in less developed regions (324 000 deaths, 14.3% of total), and it is now the second cause of cancer death in more developed regions (198 000 deaths, 15.4%) after lung cancer (Ferlay 2012). 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 the rate of death from breast cancer. Mammography remains the best method to detect breast cancer in an early stage. Mammography 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 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 2007; Gur 2011). The series of projections is then processed by a reconstruction algorithm to estimate the 3D radiographic appearance of the breast which can be viewed in successive slices. Additional software can also
INTERVENTION:	screening using tomosynthesis (including synthesised 2D images)		
COMPARISON:	digital mammography		
MAIN OUTCOMES:	Breast cancer mortality, stage of breast cancer, breast cancer detection rate, interval cancer rate, recall rate, adverse effects, radiation induced cancers related to radiation dose, quality of life, other cause mortality		
SETTING:	European Union		
PERSPECTIVE:	Population (National Health System)		

			allow the construction of synthesised 2D images. Management of Conflicts of Interest (CoI): CoIs 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 CoI disclosure. Consequently, for this particular question, the following GDG members were recused from voting: Edoardo Colzani, Roberto d'Amico, Jan Danes, Solveig Hofvind, Miranda Langendam, Elsa Pérez, and Kenneth Young.

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Breast cancer ranks as the fifth cause of death from cancer overall (522 000 deaths), the most frequent cause of cancer death in women in less developed regions (324 000 deaths, 14.3% of total), and it is now the second cause of cancer death in more developed regions (198 000 deaths, 15.4%) after lung cancer (Ferlay 2012). Breast cancer is the fourth cancer with the highest disease burden (Tsilidis 2016). Digital mammography (DM) is widely used in screening and diagnosis of breast cancer. However, some aspects such as superposition of breast tissue reduce the sensitivity of mammography and increase false-positives and false negatives. Digital Breast Tomosynthesis (DBT) might provide better imaging and discriminative capacity in these cases.	
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small	**Outcomes** | **№ of** | **Quality of** | **Relative** | **Anticipated absolute effects* (95% CI)**	The currently included studies only present data from first round DBT plus DM screening.

	○ Moderate ○ Large ○ Varies ● Don't know						The included studies did not assess the outcomes of breast cancer mortality, quality of life, and other causes of mortality. The GDG agreed that DBT has a large effect on cancer detection rate. The anticipated effects on mortality, cancer stage, quality of life, and interval cancer detection rate are not known as the studies included did not examine these outcomes. Therefore, the GDG agreed that overall desirable anticipated effects were not known.
			participants (studies) Follow up	**the evidence (GRADE)**	**effect (95% CI)**	**Risk with digital mammography**	**Risk difference with***	
		Breast cancer detection rate	34344 (2 observational studies)[a]	⊕⊕◯◯ LOW[b]	**OR 1.45** (1.30 to 1.63)[c]	Study population		
						629 per 100.000[a]	**280 more per 100.000** (187 more to 392 more)	
		Recall rate	7500 (1 observational study)	⊕⊕◯◯ LOW[b]	**RR 1.43** (1.20 to 1.71)	Low		
						2.200 per 100.000[d]	**946 more per 100.000** (440 more to 1.562 more)	
						High		
						15.600 per 100.000[d]	**6.708 more per 100.000** (3.120 more to 11.076 more)	
		False positive recall	34174 (2 observational studies)[e]	⊕◯◯◯ VERY LOW[b f g]	**OR 1.75** (0.98 to 3.10)	Low		
						10.700 per 100.000[e]	**6.634 more per 100.000** (192 fewer to 16.384 more)	
						High		
						41.500 per 100.000[e]	**13.886 more per 100.000** (490 fewer to	
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small ○ Trivial ● Varies ○ Don't know						The results for overall recall rate and false positive recall rate came from different studies, and were not mutually consistent. In addition, the GDG agreed that based on the available evidence the effect on recall rate is likely to vary based on baseline recall rate in the population screened, conferring a reduction in recall in programmes with pre-existing high recall rates, and possibly an increase when existing rates are low (Gilbert, 2016).

					27.242 more)
Radiation doses	0 (3 observational studies)	⨁⨁◯◯ LOW[h i]	-	Radiation doses for DBT vary by manufacturer and protocol but were approximately twice 20-30% higher than those reported for DM in these studies.[j]	

a. Median or mean of the control group of the included studies as appropriate unless otherwise specified.
b. Although only women with suggestive findings of malignancy were followed–up, it was 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.
c. Incremental cancer detection was 193 cancers per 100,000 women (from 107 more to 278 more).
d. Baseline risk calculated from Roman 2014 (PMID 24972452) and Hofvind (PMID 22972811).
e. Baseline risk calculated from Roman 2014 (PMID 24972452).
f. Although the STORM study (2013/2014) and MALMO study (2015) evaluated women recalled differently (radiologist vs. radiologist plus meeting arbitration) the results were consistent.
g. 95% CI probably crosses the clinical decision threshold (as the CI is wide, a different clinical decision regarding the intervention may be taken depending on whether the lower or the higher limit is considered).
h. Radiation exposure is a surrogate outcome of "other cancer related to radiation".
i. Results were consistent independently of the technology used (Hologic Selenia Dimensions or Siemens Mammomat Inspiration).
j. Doses levels are known to vary (diagnostic reference levels are typically country/region and system specific).

* Risk difference with screening using tomosynthesis (including synthesised 2D images).

False positive rates vary considerably between programmes, and in some programmes, rates are high (Roman, 2014).

The GDG considered that while there may be technique-and manufacturer specific differences in radiation doses, the dose from DBT alone is within the range currently accepted for DM alone.

CERTAINTY OF EVIDENCE

What is the overall certainty of the evidence of effects?

● Very low
○ Low
○ Moderate
○ High

○ No included studies

The GDG had no concerns on the evidence of greater test accuracy of DBT due to the higher breast cancer detection rate. However, due to the varied undesirable effects and the uncertainty of the overall effects because of lack of data on how the accuracy of DBT (the detection rate) relates to stage at diagnosis, aggressiveness of treatment

			and mortality, important patient-centred outcomes, the GDG agreed there was very low certainty of the evidence of effects**.**
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ● Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	No specific studies focusing in tomosynthesis 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 tomosynthesis, as both screening tests are associated with similar desirable and undesirable effects. 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 confidence). 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 have already received a false positive result. Their preferences 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. Regarding breast cancer diagnosis, there is very limited data available on people's 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 confidence). Also, people have a higher overall preference towards more comfortable, brief diagnostic procedures (moderate confidence).	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 rate (although there is uncertainty about how this affects breast cancer mortality), as well as the variation in recall rate, and the increase in radiation exposure are likely to be valued very differently by women. The preference for shorter examination times is of limited relevance, given that acquisition time for tomosynthesis is very similar to that for 2D mammography.

BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ 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		Given the lack of research and the uncertainty of the effects of DBT screening on mortality, the GDG could not reach consensus on whether the balance favours the intervention or comparison so voting was conducted: 10 members voted that the balance probably favours the intervention; six members voted don't know; two members abstained.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No relevant economic evaluations were identified.	The GDG agreed that the resources required for moving from digital mammography to tomosynthesis may be moderate. These resources may include, amongst other factors: costs of the technology, capital costs of the machines and the lifetime of the machine, capacity for data storage, and additional time for radiologists to read tomosynthesis images. One observational study (Wallis 2012) included in the systematic review of Gilbert et al. (Gilbert 2016) reported that radiologists' reading time would have an increase of approximately 100% (two times higher than DM alone) for tomosynthesis compared with digital mammography. Staff cost may vary depending on the country context and these costs are

			not transferable from one country to another. Although the studies reviewed above suggested an increase in recall rate with DBT, a number of excluded studies found the opposite (Gilbert 2016). Despite the savings that may occur with DBT due to a potential reduced recall rate, the extra costs mentioned above (equipment, additional radiologists time, etc) would probably not be outweighed.
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ○ High ● No included studies	No relevant economic evaluations were identified.	
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ 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	No relevant economic evaluations were identified.	

EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know		The GDG felt that within programmes there may be policy decisions to restrict the programme, if there are increased costs and the programme is unable to fund universal participation. This could have influences on equity in either direction.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	No specific studies focusing on tomosynthesis (including synthesised 2D images) were identified. The findings, all from mammography studies, however, are likely to be generalisable to tomosynthesis (including synthesised 2D images) in addition to digital mammography, as both screening tests are associated with similar desirable and undesirable effects. 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 mammography: (*a*) lack of knowledge and misperceptions regarding preventive medicine and breast health (high confidence in evidence), (*b*) poor communication skills of healthcare providers (high confidence in evidence), (*c*) poor accessibility to breast screening, especially among women with disabilities (high confidence in evidence), (*d*) fear and stress related to the procedure and the possibility of cancer diagnosis (high confidence in evidence), (*e*) pain and discomfort during the procedure (moderate confidence in evidence), (*f*) embarrassment and shyness during the procedure (moderate confidence in evidence), (*g*) lack of support and encouragement from family members, caregivers and social network (moderate confidence in evidence), (*h*) lack of information regarding the available resources (low confidence in evidence) and (*i*) low prioritisation of breast cancer screening (low confidence in evidence). Women and relevant stakeholders expressed similar opinions.	*Participants:* There is likely variability in acceptability for women. If there is a higher radiation dose women may be more concerned. On the other hand, women who come for screening may be concerned that 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 detection of cancers with DBT compared to DM. Participation rates in the trials reviewed are high, which may indicate their general acceptability of DBT. *Radiologists:* DBT may be preferred by radiologists reading screening tests because their certainty in the diagnosis may be higher when using DBT than when using DM.

			Policymakers: In settings with universal healthcare coverage, for directors of hospitals and screening programmes, it may not be an acceptable intervention, despite the increased detection capability, because there will likely be increased costs.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know		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. The need to establish standards for synthesised 2D imaging for implementation was mentioned by the GDG.

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
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	Probably favors the intervention	Favors the intervention	Varies	**No included studies**

SUMMARY OF JUDGEMENTS	JUDGEMENT						
			intervention or the comparison				
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

Conclusions

Should screening using tomosynthesis (including synthesised 2D images) vs. digital mammography be used for early detection of breast cancer in asymptomatic women?

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
	○	○	●	○	○
RECOMMENDATION	For asymptomatic women with an average risk of breast cancer, the ECIBC's Guidelines Development Group (GDG) suggests screening with either DBT or DM, in the context of an organised screening programme (conditional recommendation, very low certainty in the evidence). Since the GDG made a strong recommendation for screening at ages 50-69, this applies specifically to this age group. In settings and where the increased costs are not a barrier to implementation, the GDG felt that the increased breast cancer detection rate associated with DBT may warrant its implementation.				

JUSTIFICATION	**Overall justification** The GDG agrees that there is moderate quality evidence demonstrating a higher breast cancer detection rate using DBT as compared to DM. However, it has to be taken into account that at present the included studies only present data from first round DBT plus DM screenings and there is still a lack of studies on subsequent screening rounds. The GDG has concerns on the lack of evidence on direct outcomes such as interval breast cancer incidence, and reductions in incidence of advanced cancer and breast cancer mortality using DBT over DM. There are additional concerns on the lack of evidence of the harms of increased false positive rates. The GDG felt that there are important implementation considerations including the need for development of quality assurance frameworks for the technologies and programmatic standards. Finally, there is a lack of evidence on the cost effectiveness of DBT compared to DM. Conditions that the GDG felt are favourable towards the use of a particular screening test. DM: where costs or patient preference are in favour of DM, the GDG recommends considering continued use of DM. DBT: for research purposes and where the primary concern of the screening programme is increased detection rate, regardless of increased costs, DBT is recommended over DM. This recommendation was agreed by consensus within the GDG, with no need for voting. **Detailed justification** *Desirable Effects* The GDG agrees that DBT has higher cancer detection rates with a relative increase of 43% vs DM alone, but emphasises that research on the direct outcomes on interval cancer incidence, breast cancer stage at diagnosis and breast cancer mortality are not yet available. There was low certainty with this recommendation due to the inclusion of only one study in the systematic review that informed this recommendation. *Undesirable Effects* The GDG felt that the undesirable anticipated effects vary due to varied evidence on the recall and false positive rates, and a very small increased risk of developing other cancers due to a slight increased radiation dose of DBT. *Certainty of evidence of required resources* No research evidence addressing resource considerations was found, however, the GDG considered likely increases to the costs for DBT over DM based on a doubling of the time to interpret images, the costs of the technology and the data storage implications, with DBT requiring more storage and network infrastructure. These must be considered on a country-by-country basis depending on resources available for breast cancer screening programmes. In settings where the additional costs of DBT are a barrier to implementation, the GDG notes the uncertainty of the evidence of cost effectiveness of DBT. These 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 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. However, this group was not specifically considered in this question.
IMPLEMENTATION CONSIDERATIONS	- Evidence will be emerging from ongoing and newly starting screening trials on tomosynthesis that may influence the current recommendations. - In general, the GDG believed it is important to educate women and health professionals on the risk of radiation, and the very small increase in dose with DBT, in the context of possible benefits of screening.

	- The GDG identified variability in the quality of DBT machines currently available and their methods of capturing images. The MBTST study used a machine that has a wide-angle form of DBT image capture and may result in different breast cancer detection rates. The Malmo study used a single view DBT format. - The GDG notes that new quality assurance standards of technologies and screening programmes must be considered in choosing DBT over DM. The GDG emphasised that specific standards for synthesised 2D imaging, and their use in comparison to previously captured DM screening images will be necessary in order to implement this recommendation. - There will be significantly increased data storage needs for screening programmes using DBT as compared to DM. - The GDG noted that health equity in access to screening should be considered for countries choosing DBT-based screening programmes, due to different resource settings and the capacity for different countries to be able to pay for DBT over DM which may lead to increased health inequities.
MONITORING AND EVALUATION	- Quality control/standardisation of the technology for better image storage should be undertaken. - Quality standards should be developed, in particular for the image quality of synthesised 2D images from the tomosynthesis technology.
RESEARCH PRIORITIES	- Evidence will be emerging from ongoing and newly starting screening trials on tomosynthesis that may influence the current recommendations. - Collecting evidence relevant to implementation challenges of DBT-based screening programmes. - Further research information on harms of DBT, including rates of overdiagnosis of breast cancer are warranted. - Further research is needed to build the evidence on benefits and harms of DBT vs DM through comparison of direct outcomes, including impacts of interval cancer incidence, stage of breast cancer at detection and mortality reduction. - Research investigating the cost-effectiveness of a breast cancer screening programme using DBT is needed to inform decision-making on breast cancer screening. - Research is needed to define the quality parameters that need to be fulfilled for DBT-based breast cancer screening programmes to be implemented.

Evidence profile

Healthcare question	Should screening using tomosynthesis (including synthesised 2D images) vs. digital mammography be used for early detection of breast cancer in asymptomatic women?
Date	April 2016
Authors	ECIBC 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, Ivan Sola, Margarita Posso, Alexander Mathioudakis. JRC Healthcare Quality team: Zuleika Saz-Parkinson, Donata Lerda
Abbreviations	**CI:** Confidence interval **OR:** Odds Ratio **RR:** Risk ratio

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Screening using tomosynthesis (including synthesised 2D images)	Digital mammography	Relative (95% CI)	Absolute (95% CI)		
Breast cancer detection rate												
2	observational studies	not serious [a]	not serious	not serious	not serious	none	152/17172 (0.9%)	108/17172 (0.6%) [b]	**OR 1.45** (1.30 to 1.63) [c]	**280 more per 100,000** (from 187 more to 392 more)	⊕⊕◯◯ LOW	CRITICAL
Recall rate												
1	observational studies	not serious [a]	not serious	not serious	not serious	none	282/7500 (3.8%)	2.2% [d]	**RR 1.43** (1.20 to 1.71)	**946 more per 100,000** (from 440 more to 1,562 more)	⊕⊕◯◯ LOW	CRITICAL
								15.6% [d]		**6,708 more per 100,000** (from 3,120 more to 11,076		

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Screening using tomosynthesis (including synthesised 2D images)	Digital mammography	Relative (95% CI)	Absolute (95% CI)		
										more)		
False positive recall												
2	observational studies	not serious [a]	not serious [e]	not serious	serious [f]	none	459/17087 (2.7%)	10.7% [g]	**OR 1.75** (0.98 to 3.10)	**6,634 more per 100,000** (from 192 fewer to 16,384 more)	⊕◯◯◯ VERY LOW	CRITICAL
								41.5% [g]		**13,886 more per 100,000** (from 490 fewer to 27,242 more)		
Radiation doses												
3	observational studies	not serious	not serious [h]	not serious [i]	not serious	none	Radiation doses for DBT vary by manufacturer and protocol but were approximately twice 20-30% higher than those reported for DM in these studies [j]				⊕⊕◯◯ LOW	
Breast cancer mortality - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Interval cancer rate - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Quality of life - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Radiation induced cancers-related to radiation dose - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Other causes of mortality - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	

Explanations

a. Although only women with suggestive findings of malignancy were followed–up, it was 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. Incremental cancer detection was 193 cancers per 100,000 women (from 107 more to 278 more).

d. Baseline risk calculated from Roman 2014 (PMID 24972452) and Hofvind (PMID 22972811).

e. Although the STORM study (2013/2014) and MALMO study (2015) evaluated women recalled differently (radiologist vs. radiologist plus meeting arbitration) the results were consistent.
f. 95% CI probably crosses the clinical decision threshold (as the CI is wide, a different clinical decision regarding the intervention may be taken depending on whether the lower or the higher limit is considered).
g. Baseline risk calculated from Roman 2014 (PMID 24972452).
h. Results were consistent independently of the technology used (Hologic Selenia Dimensions or Siemens Mammomat Inspiration).
i. Radiation exposure is a surrogate outcome of "other cancer related to radiation".
j. Doses levels are known to vary (diagnostic reference levels are typically country/region and system specific).

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