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

Evidence profile

Healthcare question	Should organised mammography screening vs. no mammography screening be used for early detection of breast cancer in women aged 50 to 69?
Date	April 2016
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Abbreviations	**CI:** Confidence interval **RR:** Risk ratio

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Organised mammography screening	No mammography screening	Relative (95% CI)	Absolute (95% CI)		
Breast cancer mortality (short case accrual) (follow up: mean 17.6 years)												
6 [1,2,3,4,5,6,a]	randomised trials	not serious [b]	not serious	not serious [c,d]	not serious	none	616/134866 (0.5%)	0.6% [e]	**RR 0.77** (0.66 to 0.90)	**138 fewer per 100,000**	⊕⊕⊕⊕ HIGH	CRITICAL

										(from 204 fewer to 60 fewer)		
								1.0%		**230 fewer per 100,000** (from 340 fewer to 100 fewer)		
								2.1%		**483 fewer per 100,000** (from 714 fewer to 210 fewer)		
Breast cancer mortality (longest case accrual) (follow up: mean 15.5 years)												
6 [3,5,6,7,8,a]	randomised trials	not serious [b]	not serious	not serious [c,d]	not serious	none	740/134866 (0.5%)	0.8% [f]	**RR 0.77** (0.67 to 0.88)	**175 fewer per 100,000** (from 251 fewer to 91 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Breast cancer stage IIA or higher[g]												
4 [1,6,7,8,9,10,a]	randomised trials	serious [h]	serious [i]	serious [c]	serious [j]	none	652/143016 (0.5%)	0.7% [f]	**RR 0.80** (0.64 to 1.00)	**140 fewer per 100,000** (from 252 fewer to 0 fewer)	⊕◯◯◯ VERY LOW	IMPORTANT
Breast cancer stage III+ or tumour size ≥40 mm [g]												
3 [6,8,9,10,a]	randomised trials	serious [h]	not serious	serious [c]	not serious	none	99/93452 (0.1%)	0.2% [f]	**RR 0.62** (0.48 to 0.80)	**65 fewer per 100,000** (from 88 fewer to 34 fewer)	⊕⊕◯◯ LOW	IMPORTANT
Other cause mortality (follow up: mean 9.6 years)												
3 [9,11,a]	randomised trials	not serious	not serious	serious [c]	serious [j]	none	4479/66432 (6.7%)	6.6% [f]	**RR 0.99** (0.95 to 1.04)	**66 fewer per 100,000**	⊕⊕◯◯ LOW	IMPORTANT

										(from 330 fewer to 264 more)		
Overdiagnosis (population perspective)												
2 [9,12,a]	randomised trials	not serious	not serious	serious [c]	not serious	none	10.1% (95% CI 8.6%-11.6%) [k]				⊕⊕⊕◯ MODERATE	CRITICAL
Overdiagnosis (patient perspective)												
2 [9,12,a]	randomised trials	not serious	not serious	serious [c]	not serious	none	17.3% (95%CI 14.7%-20.0%) [l]				⊕⊕⊕◯ MODERATE	CRITICAL
Rate of mastectomies[g]												
5 [3,13,14,15,16,a]	randomised trials	not serious	not serious	very serious [c,m]	not serious	none	1542/144920 (1.1%)	0.9% [f]	**RR 1.20** (1.11 to 1.30) [n]	**180 more per 100,000** (from 99 more to 270 more)	⊕⊕◯◯ LOW	IMPORTANT
Provision of chemotheraphy[g]												
2 [3,15,16,a]	randomised trials	not serious	serious [o]	very serious [c,p]	serious [j]	none	252/59677 (0.4%)	0.4% [f]	**RR 0.86** (0.52 to 1.41) [n]	**56 fewer per 100,000** (from 192 fewer to 164 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Quality of life (inferred from psychological effects)[g]												
54 [17]	observational studies	not serious	not serious [q]	not serious	not serious	none	One systematic review with 54 studies included -no meta-analysis - (Brett 2005). Mammographic screening does not appear to create anxiety in women who are given a clear result after a mammogram and subsequently placed on routine recall. Mixed results about anxiety in women recalled for further testing: several studies reported transient or long term (from 6 months to 1 year after recall) anxiety, while other studies reported no differences in anxiety levels. The nature and extent of further testing seem to determine the extent of anxiety.				⊕⊕◯◯ LOW	IMPORTANT
False-positive related adverse effects (psychological distress)[g]												
24 [18,19]	observational studies	not serious	not serious	not serious	not serious	none	Two systematic reviews. One review included 17 studies and found that women who received a false-positive mammogram result had greater distress, fear, anxiety, and worry about breast cancer (Saltz 2010). The second review included 7 studies, the psychological distress using diseases-specific measurements, in women (age not specified) with a false-positive mammogram at 35 months after the last				⊕⊕◯◯ LOW	IMPORTANT

							assessment was ; for women that needed further mammography RR=1.28 (95%CI 0.82-2.00); for women placed in early recall the RR=1.82 (95%CI 1.22-2.72); for women that needed a fine needle puncture aspiration RR=1.80 (95%CI 1.17-2.77); for women that needed a biopsy RR=2.07 (95%CI 1.22-3.52); no differences in generic measures of general anxiety and depression were observed at 6 weeks after assessment and 3 months after screening Bond (2013).		
False-positive related adverse effects (biopsies and surgeries)[g]									
4 [20]	observational studies	not serious	not serious	not serious	not serious	none	Results from literature review (4 studies, 390 000 women aged 50 to 69) showed an overall false-positive screening result of 19.7% in women undergoing 10 biennial screening tests (pooled risk estimate based on 3 studies; range 8 - 21%). This was related to a 2.9% pooled cumulative risk of an invasive procedure with benign outcome (range 1.8% to 6.3%; based on 2 studies) and 0.9% risk of undergoing surgical intervention with benign outcome (based on 1 study) (Hofvind 2012). Cross-sectional data from the EUNICE Project (women aged 50 to 69): 17 countries, 20 screening programmes, 1.7 million initial screens, 5.9 million subsequent screens; showed that 2.2% and 1.1% of all screening examinations resulted in needle biopsy among women without breast cancer (initial and subsequent screens, respectively). In addition, 0.19% and 0.07% of all screening examinations resulted in surgical interventions among women without breast cancer (initial and subsequent screens, respectively).	⊕⊕◯◯ LOW	IMPORTANT

Explanations

a. The reference listed in the evidence profiles correspond to the specific publications used to extract crude data for estimating the outcomes´ effect sizes. Additional reference describing the characteristics of the included studies can be found in the document´s main text of this systematic review.

b. Some studies used methods that would not be accepted for random allocation today. One study had non-blinded assessment of 'cause of death'. The GDG felt that the CNBSS-2 possibly had issues with achieving prognostic balance. The GDG felt that lack of allocation concealment in this set of studies did not lead to high risk of bias. Given that lack of single trials driving the overall results and similarity in effect sizes (the test for subgroup differences - low vs high risk of bias trials - was non-significant) and overlapping confidence intervals (CIs), the risk of bias was rated as 'not serious'.

c. Trials were conducted more than 20 years ago. Currently, women have higher adherence to breast cancer screening while quality control of screening and breast cancer care have improved.

d. Despite concerns about indirectness from the trials, including the fact that the population age range of 40 to 74 is broader than the age range in this question, after considering evidence from contemporary non-randomised studies (Broeders 2012) the GDG decided not to downgrade the quality of evidence for indirectness.
e. The GDG felt that baseline risks higher than 0.6% should be considered to evaluate absolute effects (Breast Cancer Screening, IARC Handbook of Cancer Prevention Volume 15)
f. Median or mean of the control group of the included studies unless otherwise specified.
g. Importance of the outcome was lowered from 'critical' to 'important' because the members felt this outcome influenced neither the direction nor the strength of the recommendation.
h. Non-blinded assessment of breast cancer stage is a serious concern. GDG members decided to downgrade to 'serious' for risk of bias.
i. Unexplained inconsistency with statistical heterogeneity (I^2 = 70%, P = 0.02). While one study shows clear benefit, in three studies the 95%CI does not exclude important benefit or harm.
j. 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).
k. Estimate from a meta-analysis of 2 trials (CNBSS-2 and Malmo I) in which women in the control group were not offered mammography screening at the end of the trial. Excess cancers as a proportion of cancers diagnosed over whole follow-up period in women invited for screening (population perspective).
l. Estimate from a meta-analysis of 2 trials (CNBSS-2 and Malmo I) in which women in the control group were not offered mammography screening at the end of the trial. Excess cancers as a proportion of cancers diagnosed during screening period in women invited for screening (woman perspective).
m. Observational studies do not confirm these results, instead they provide opposite results.
n. Due to lead time, there may be greater numbers of cancers to be treated in the screened group, during the period of observation, which may lead to an increased rate of chemotherapy and mastectomies in the screened group
o. Unexplained inconsistency with statistical heterogeneity (I^2 = 71%, P=0.06).
p. Chemotherapy protocols and indications have significantly changed (e.g. node status was not determined in earlier studies).
q. Unexplained inconsistency for variability in anxiety in the group of women recalled for further testing.

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