



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 organised mammography screening vs. no mammography screening be used for early detection of breast cancer in women aged 70 to 74 ?

<b>POPULATION:</b>	early detection of breast cancer in women aged 70 to 74
<b>INTERVENTION:</b>	organised mammography screening
<b>COMPARISON:</b>	no mammography screening
<b>MAIN OUTCOMES:</b>	Breast cancer mortality; Other cause mortality; Stage IIA or higher (tumour size $\geq 20$ mm); Tumour size $\geq 50$ mm; Rate of mastectomies (women ages 40-74 at inclusion); Provision of chemotherapy (women ages 40-74 at inclusion); Quality of life (inferred from psychological effects); False-positive related adverse effects (psychological distress); False-positive related adverse effects (biopsies and surgeries); Overdiagnosis (population perspective); Overdiagnosis (woman perspective);
<b>SETTING:</b>	European Union
<b>PERSPECTIVE:</b>	Population (National Health System)
<b>BACKGROUND:</b>	Although mammography screening has both potential benefits and harms, many countries have organised programmes for women aged 50 or older. However, there continues to be debate about recommendations for mammography screening for women aged 70 and older.
<b>CONFLICT OF INTEREST:</b>	<u>Management of Conflicts of Interest (Col)</u> : Col for all Guideline Development Group (GDG) members were assessed and managed by the Joint Research Centre (JRC) following an established procedure in line with the 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: Roberto d'Amico, Jan Danes, Axel Gräwingholt, and Ruben van Engen.

## ASSESSMENT

<b>Problem</b> Is the problem a priority?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li><input type="radio"/> No</li> <li><input type="radio"/> Probably no</li> <li><input type="radio"/> Probably yes</li> <li><input checked="" type="radio"/> Yes</li> <li><input type="radio"/> Varies</li> <li><input type="radio"/> Don't know</li> </ul>	<p>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—accounting for 25% of all cancers (Ferlay 2013). Breast cancer ranks as the fifth leading cause of cancer death worldwide and the second leading cause of cancer-related death in developed regions (GLOBOCAN 2012). In the European Union, 367 090 women were diagnosed with breast cancer and 92 000 women died from the disease (Ferlay 2013). Breast cancer ranks fourth among the top five cancers with the highest disease burden (Tsilidis 2016).</p> <p>Annual incidence of breast cancer in the EU among women aged 70 to 74 is 3.0 per 1 000 and mortality is 0.8 per 1 000 (GLOBOCAN 2012)</p>	<p>The GDG prioritised this question for the ECIBC.</p>
<b>Desirable Effects</b> How substantial are the desirable anticipated effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li><input type="radio"/> Trivial</li> <li><input type="radio"/> Small</li> <li><input type="radio"/> Moderate</li> <li><input checked="" type="radio"/> Large</li> </ul>		<p>The mortality reduction, in relative terms, does not differ significantly from that observed in the 50 to 69 age group.</p>

o Varies  
o Don't know

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no mammography screening	Risk difference with organised mammography screening
Breast cancer mortality follow up: mean 20 years	18233 (2 RCTs) <sup>1,2,a</sup>	⊕⊕⊕⊕ HIGH <sup>b,c,d</sup>	RR 0.77 (0.54 to 1.09)	Low	
				900 per 100.000	<b>207 fewer per 100.000</b> (414 fewer to 81 more)
				High	
				3.000 per 100.000 <sup>e</sup>	<b>690 fewer per 100.000</b> (1.380 fewer to 270 more)
Other cause mortality follow up: mean 7.9 years <sup>f</sup>	17646 (2 RCTs) <sup>3,a</sup>	⊕⊕○○ LOW <sup>b,c</sup>	RR 1.01 (0.91 to 1.10)	Low	
				27.000 per 100.000 <sup>g</sup>	<b>270 more per 100.000</b> (2.430 fewer to 2.700 more)
Stage IIA or higher (tumour size ≥ 20 mm) <sup>f</sup>	97617 (1 RCT) <sup>4,a</sup>	⊕⊕○○ LOW <sup>c,h</sup>	RR 0.64 (0.55 to 0.73)	Moderate	
				1.070 per 100.000 <sup>g</sup>	<b>385 fewer per 100.000</b> (482 fewer to 289 fewer)
Tumour size ≥ 50 mm	97617 (1 RCT) <sup>4,a</sup>	⊕⊕○○ LOW <sup>c,h</sup>	RR 0.63 (0.45 to 0.89)	Moderate	
				170 per 100.000 <sup>g</sup>	<b>63 fewer per 100.000</b> (94 fewer to 19 fewer)
Overdiagnosis (population)	64117	⊕⊕⊕○	-	10.1% (95% CI 8.6%-11.6%) <sup>j</sup>	

For the mortality related outcomes, GDG members decided not to downgrade for imprecision because the relative effect is consistent with those in other age groups.

perspective)	(2 RCTs) <sup>5,6,a</sup>	MODERATE <sup>c,i</sup>		
Overdiagnosis (woman perspective)	64117 (2 RCTs) <sup>5,6,a</sup>	⊕⊕⊕○ MODERATE <sup>c,i</sup>	-	17.3% (95%CI 14.7%-20.0%) <sup>k</sup>
Rate of mastectomies (women ages 40-74 at inclusion)	249550 (5 RCTs) <sup>10,2,7,8,9</sup>	⊕⊕○○ LOW <sup>c,h,l</sup>	RR 1.20 (1.11 to 1.30)	Low
				900 per 100.000
Provision of chemotherapy (women ages 40-74 at inclusion)	99454 (2 RCTs) <sup>10,2,9</sup>	⊕○○○ VERY LOW <sup>b,c,m,n</sup>	RR 0.86 (0.52 to 1.41) <sup>p</sup>	Moderate
				400 per 100.000
Quality of life (inferred from psychological effects) <sup>f</sup>	(54 observational studies) <sup>11</sup>	⊕⊕○○ LOW <sup>p</sup>	-	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.
False-positive related adverse effects (psychological distress) <sup>f</sup>	(24 observational studies) <sup>12,13</sup>	⊕⊕○○ LOW	-	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 assessment was · for

				<p>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).</p>
False-positive related adverse effects (biopsies and surgeries) <sup>f</sup>	(4 observational studies) <sup>14</sup>	 VERY LOW <sup>g</sup>	-	<p>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).</p>
<ol style="list-style-type: none"> <li>1. Tabar L, Duffy SW, Yen MF, Warwick J, Vitak B, Chen HH, Smith RA.. All-cause mortality among breast cancer patients in a screening trial: support for breast cancer mortality as an end point.. J Med Screen; 2002.</li> <li>2. Nyström L, Andersson I, Bjurstam N, Frisell J, Nordenskjöld</li> </ol>				

- B,Rutqvist LE.. Long-term effects of mammography screening: updated overview of the Swedish randomised trials.. Lancet.; 2002.
3. Tabar L, Fagerberg G,Duffy SW,and N E Day. The Swedish two county trial of mammographic screening for breast cancer: recent results and calculation of benefit.. J Epidemiol Community Health; 1989 .
  4. Tabar L, Fagerberg G,Chen HH,Duffy SW,Smart CR,Gad A,et al.. Efficacy of breast cancer screening by age. New results from the Swedish Two-County Trial.. Cancer. ; 1995.
  5. Zackrisson S, Andersson I, Janzon L,Manjer J, Garne JP. Rate of over-diagnosis of breast cancer 15 years after end of Malmö mammographic screening trial: follow-up study. BMJ; 2006.
  6. Miller AB, To T,Baines CJ,Wall C.. Canadian National Breast Screening Study-2: 13-year results of a randomized trial in women aged 50-59 years.. J Natl Cancer Inst.; 2000.
  7. AB, Miller. The costs and benefits of breast cancer screening.. Am J Prev Med; 1993.
  8. J, Frisell. Mammographic screening for breast cancer [thesis]. Stockholm: Södersjukhuset; 1989.
  9. Andersson I, Aspegren K,Janzon L, Landberg T,Lindholm K,Linell F, et al. Mammographic screening and mortality from breast cancer: the Malmö mammographic screening trial.. 1988; 1988.
  10. Tabar L, Chen HH,Duffy SW,Krusemo UB.. Primary and adjuvant therapy, prognostic factors and survival in 1053 breast cancers diagnosed in a trial of mammography screening.. Jpn J Clin Oncol. ; 1999.
  11. Brett J, Bankhead C,Henderson B,Watson E,Austoker J.. The psychological impact of mammographic screening. A systematic review.. Psychooncology; 2005.
  12. Bond M, Pavey T,Welch K,Cooper C,Garside R,Dean S,et al.. Systematic review of the psychological consequences of false-positive screening mammograms.. Health Technol Assess; 2013.
  13. Salz T, Richman AR,Brewer NT. Meta-analyses of the effect of false-positive mammograms on generic and specific psychosocial outcomes.. Psychooncology. ; 2010.
  14. Hofvind S1, Ponti A,Patnick J,Ascunce 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.
- 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. For the mortality related outcomes, the GDG decided not to downgrade for imprecision because the relative effect is consistent with those in other age groups and that lends support that the estimate of the effect is close to what is reported here. This decision is also reinforced by the fact that, if the indirect evidence from the 50-69 age stratum were considered here, the certainty of the evidence for this outcome would also have been rated as 'moderate', as a result of downgrading that evidence from 'high' to 'moderate' by one level for indirectness and using it here.
  - 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 did not downgrade the quality of evidence for indirectness.
  - e. UK cancer registry data indicate a higher estimate, of 3% over 20 years.
  - f. The GDG changed the importance of the outcome from 'critical' to 'important' because the members felt this outcome influenced

- g. Median or mean of the control group of the included studies unless otherwise specified.
- h. Analysis includes women aged 40-74 years, however only about 13% of women were  $\geq 70$  years.
- i. Indirect data from women aged 50 to 69.
- j. Estimate from a meta-analysis of 2 trials including women aged 50 to 69 (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). Independent UK Panel on Breast Cancer Screening (2012).
- 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 during screening period in women invited for screening (woman perspective).
- l. Some studies were sub-optimally randomised and had non-blinded assessment of cause of death; however analysis restricted to low risk of bias trials provided a similar risk estimate.
- m. Chemotherapy protocols and their indications have significantly changed (e.g. node status was not determined in earlier studies).
- n. Unexplained inconsistency with statistical heterogeneity ( $I^2 = 71\%$ ,  $p = 0.06$ ).
- o. Same assumptions as in younger women can be made about lead time. This may be an even bigger issue in older women and it is influenced by life expectancy.
- p. Unexplained inconsistency for variability in anxiety in the group of women recalled for further testing.
- q. Studies included women aged 50 to 69. The estimates are likely lower within the stratum of women aged 70 and older.

## Undesirable Effects

How substantial are the undesirable anticipated effects?

### JUDGEMENT

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

### RESEARCH EVIDENCE

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no mammography screening	Risk difference with organised mammography screening
Breast cancer	18233	⊕⊕⊕⊕	RR 0.77	Low	

### ADDITIONAL CONSIDERATIONS

Overdiagnosis data was not available but the GDG members agreed that it could be extrapolated from the 50 to 69 age group.

There are more competing causes of death in this population.

Due to lead time (diagnosis time being brought forward with screening), 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.

	mortality follow up: mean 20 years	(2 RCTs) <sup>1,2,a</sup>	HIGH <sup>b,c,d</sup>	(0.54 to 1.09)	900 per 100.000	<b>207 fewer per 100.000</b> (414 fewer to 81 more)	False-positive rates have been observed to be lower in this age group compared to younger age groups.
					High		
					3.000 per 100.000 <sup>e</sup>	<b>690 fewer per 100.000</b> (1.380 fewer to 270 more)	
	Other cause mortality follow up: mean 7.9 years <sup>f</sup>	17646 (2 RCTs) <sup>3,a</sup>	⊕⊕○○ LOW <sup>b,c</sup>	<b>RR 1.01</b> (0.91 to 1.10)	Low		
					27.000 per 100.000 <sup>g</sup>	<b>270 more per 100.000</b> (2.430 fewer to 2.700 more)	
	Stage IIA or higher (tumour size ≥ 20 mm) <sup>f</sup>	97617 (1 RCT) <sup>4,a</sup>	⊕⊕○○ LOW <sup>c,h</sup>	<b>RR 0.64</b> (0.55 to 0.73)	Moderate		
					1.070 per 100.000 <sup>g</sup>	<b>385 fewer per 100.000</b> (482 fewer to 289 fewer)	
Tumour size ≥ 50 mm	97617 (1 RCT) <sup>4,a</sup>	⊕⊕○○ LOW <sup>c,h</sup>	<b>RR 0.63</b> (0.45 to 0.89)	Moderate			
				170 per 100.000 <sup>g</sup>	<b>63 fewer per 100.000</b> (94 fewer to 19 fewer)		
Overdiagnosis (population perspective)	64117 (2 RCTs) <sup>5,6,a</sup>	⊕⊕⊕○ MODERATE <sup>c,i</sup>	-	10.1% (95% CI 8.6%-11.6%) <sup>j</sup>			
Overdiagnosis (woman perspective)	64117 (2 RCTs) <sup>5,6,a</sup>	⊕⊕⊕○ MODERATE <sup>c,i</sup>	-	17.3% (95%CI 14.7%-20.0%) <sup>k</sup>			
Rate of mastectomies (women ages 40-74 at inclusion)	249550 (5 RCTs) <sup>10,2,7,8,9</sup>	⊕⊕○○ LOW <sup>c,h,l</sup>	<b>RR 1.20</b> (1.11 to 1.30)	Low			
				900 per 100.000	<b>180 more per 100.000</b> (99 more to 270 more)		

	Provision of chemotherapy (women ages 40-74 at inclusion)	99454 (2 RCTs) <sup>10,2,9</sup>	⊕○○○ VERY LOW <sup>b,c,m,n</sup>	<b>RR 0.86</b> (0.52 to 1.41) <sup>p</sup>	Moderate  400 per 100.000 <b>56 fewer per 100.000</b> (192 fewer to 164 more)
	Quality of life (inferred from psychological effects) <sup>f</sup>	(54 observational studies) <sup>11</sup>	⊕⊕○○ LOW <sup>p</sup>	-	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.
	False-positive related adverse effects (psychological distress) <sup>f</sup>	(24 observational studies) <sup>12,13</sup>	⊕⊕○○ LOW	-	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 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) <sup>f</sup>	(4 observational studies) <sup>14</sup>	 VERY LOW <sup>g</sup>	-	<p>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).</p>
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  - 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 did not downgrade the quality of evidence for indirectness.
  - e. UK cancer registry data indicate a higher estimate, of 3% over 20 years.
  - f. The GDG changed the importance of the outcome from 'critical' to 'important' because the members felt this outcome influenced neither the direction nor the strength of the recommendation.
  - g. Median or mean of the control group of the included studies unless otherwise specified.
  - h. Analysis includes women aged 40-74 years, however only about 13% of women were ≥ 70 years.
  - i. Indirect data from women aged 50 to 69.
  - j. Estimate from a meta-analysis of 2 trials including women aged 50 to 69 (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). Independent UK Panel on Breast Cancer Screening (2012).
  - 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 during screening period in women invited for screening (woman perspective).
  - l. Some studies were sub-optimally randomised and had non-blinded assessment of cause of death; however analysis restricted to low

	<p>risk of bias trials provided a similar risk estimate.</p> <ul style="list-style-type: none"> <li>m. Chemotherapy protocols and their indications have significantly changed (e.g. node status was not determined in earlier studies).</li> <li>n. Unexplained inconsistency with statistical heterogeneity (<math>I^2 = 71\%</math>, <math>p = 0.06</math>).</li> <li>o. Same assumptions as in younger women can be made about lead time. This may be an even bigger issue in older women and it is influenced by life expectancy.</li> <li>p. Unexplained inconsistency for variability in anxiety in the group of women recalled for further testing.</li> <li>q. Studies included women aged 50 to 69. The estimates are likely lower within the stratum of women aged 70 and older.</li> </ul>	
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## Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li>○ Very low</li> <li>○ Low</li> <li>● Moderate</li> <li>○ High</li> <li>○ No included studies</li> </ul>	<p>The overall certainty (i.e. quality) of the evidence was moderate, as this was the lowest quality (corresponding to the quality of the evidence for overdiagnosis) of the two critical outcomes—namely, breast cancer mortality and overdiagnosis.</p>	

## 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"> <li>○ Important uncertainty or variability</li> <li>● Possibly important uncertainty or variability</li> <li>○ Probably no important uncertainty or variability</li> <li>○ No important uncertainty or variability</li> <li>○ No known undesirable outcomes</li> </ul>	<p>A systematic review shows that participants place a low value on the psychosocial and physical effects of false-positive results and overdiagnosis (JRC Technical Report PICO 10-11, contract FWC443094012015; available upon request). Women generally consider these undesirable effects acceptable (low confidence in evidence). 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 participants due to the associated psychological distress and inconvenience (moderate confidence in evidence).</p> <p>Regarding breast cancer diagnosis, very limited data is available addressing people's views. One of the main themes identified in the literature is that people disvalue highly the anxiety caused by delays in receiving diagnostic results, or by a lack of understanding of the tests due to suboptimal communication with physicians (moderate confidence in evidence). Also, people have a higher overall preference towards more comfortable, brief diagnostic procedures (moderate confidence in evidence). (JRC Technical Report PICO 10-11, contract FWC443094012015; available upon request).</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"> <li>○ Favors the comparison</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>○ Probably favors the intervention</li> <li>● Favors the intervention</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>		

## Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li>○ Large costs</li> <li>○ Moderate costs</li> <li>○ Negligible costs and savings</li> <li>○ Moderate savings</li> <li>○ Large savings</li> <li>● Varies</li> <li>○ Don't know</li> </ul>	<p>Similarly to the findings of a prior systematic review (1), we did not identify any European economic evaluation related to this question. However, one study, based on data from the United States, assessing mammography screening in women aged 80 to 85 was identified (2).</p>	<p>Although there is no direct evidence addressing this question, it is reasonable to hypothesise that the resources required might be moderate. These resources, for screening older women, might be similar to those required for the extension of current screening standards (in women aged 50 to 69) to women aged 40 to 49.</p> <p>As in the younger age groups, GDG members believed that these costs would differ by country and would be influenced by the presence of opportunistic screening.</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"> <li>○ Very low</li> <li>○ Low</li> <li>○ Moderate</li> <li>○ High</li> <li>● No included studies</li> </ul>	<p>No research evidence was identified</p>	<p>We did not identify any European economic evaluation studies assessing the question of interest. Required resources are reported in (2); however, they are not applicable to Europe.</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"> <li>○ Favors the comparison</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>○ Probably favors the intervention</li> <li>○ Favors the intervention</li> <li>○ Varies</li> <li>● No included studies</li> </ul>	No research evidence was identified.	

## Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li>○ Reduced</li> <li>○ Probably reduced</li> <li>○ Probably no impact</li> <li>○ Probably increased</li> <li>○ Increased</li> <li>○ Varies</li> <li>● Don't know</li> </ul>		A systematic review on this topic has not been conducted. However, the utilisation of cancer screening services may largely depend on the availability of national public screening programmes; although European findings highlight that inequalities are larger in countries without population-based screening programmes (Palència, 2010).

## Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li>○ No</li> <li>○ Probably no</li> <li>○ Probably yes</li> <li>● Yes</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	A systematic review (JRC Technical Report PICO 16-17, contract FWC443094032016; available upon request) found the following barriers associated with breast cancer screening: (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.	

## Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

<ul style="list-style-type: none"> <li>○ No</li> <li>○ Probably no</li> <li>● Probably yes</li> <li>○ Yes</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>		A systematic review on this topic has not been conducted. Some countries do not have screening programmes in place and may not be able to implement them mainly due to lack of resources and/or infrastructure.
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## SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	<b>Yes</b>		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	<b>Large</b>		Varies	Don't know
UNDESIRABLE EFFECTS	Large	<b>Moderate</b>	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	<b>Moderate</b>	High			No included studies
VALUES	Important uncertainty or variability	<b>Possibly important uncertainty or variability</b>	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	<b>Favors the intervention</b>	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	<b>Varies</b>	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			<b>No included studies</b>
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	<b>No included studies</b>
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	<b>Don't know</b>
ACCEPTABILITY	No	Probably no	Probably yes	<b>Yes</b>		Varies	Don't know
FEASIBILITY	No	Probably no	<b>Probably yes</b>	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	<b>Conditional recommendation for the intervention</b>	Strong recommendation for the intervention
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## CONCLUSIONS

### Recommendation

For asymptomatic women aged 70 to 74 with an average risk of breast cancer, the ECIBC's Guidelines Development Group (GDG) suggests mammography screening over no mammography screening, in the context of an organised screening programme (conditional recommendation, moderate certainty of the evidence).

### Justification

#### Overall justification

The conditional recommendation (rather than strong) in favour of mammography screening over no mammography screening, in the context of an organised screening programme, was the result of a balance of the health effects that favours mammography screening, in the context of moderate quality evidence about these effects; despite possibly important uncertainty or variability in how much women value the main outcomes. As agreement within the GDG for the direction of this recommendation could not be reached, voting among members without CoI resulted in the following: 14 members voted in favour of 'conditional recommendation', 6 members voted in favour of 'strong recommendation', and 2 members abstained.

#### Detailed justification

##### *Desirable Effects*

Mammography, compared to no screening, reduces the risk of breast cancer mortality (690 fewer breast cancer deaths per 100 000, with a range from 270 more to 1380 fewer deaths, or 207 fewer breast cancer deaths per 100 000, with a range from 81 more to 414 fewer deaths, using 3% and 0.9% baseline risk, respectively) (high quality evidence). It also reduces the risk of stage IIA breast cancer or higher (385 fewer cases per 100 000 women) (low quality evidence) and tumour size  $\geq$  50 mm (63 fewer tumours size  $\geq$  50mm per 100 000 women) (low quality evidence). However, these findings were not statistically significant.

##### *Undesirable Effects*

Women aged 40 to 74 randomised to invitation to screening were more likely to undergo mastectomy (180 more mastectomies per 100 000 women) (low quality evidence). Overdiagnosis data was not available but was extrapolated from the 50 to 69 age group (10.1% (moderate quality evidence) from a population perspective and 17.3% from the perspective of a woman invited to screening (moderate quality evidence)). Mammography screening compared with no screening did not increase the number of women aged 43 to 74 treated with chemotherapy (very low quality evidence). Women who had further testing following their routine mammogram experienced significant short-term anxiety. Estimated cumulative risk of a false-positive screening result in women aged 50 to 69 undergoing 10 biennial screening tests was 19.7% with 2.2% of women having a needle biopsy after an initial screening mammogram. False-positive mammograms are also associated with greater anxiety and distress about breast cancer as well as negative psychological consequences that may last up to three years (low quality evidence).

### Subgroup considerations

This recommendation does not apply to high-risk women (see recommendations for women with high breast density).

### Implementation considerations

Continued screening in this age group should be guided by life expectancy.

Alternative strategies may be needed to extend screening to age groups that were screened at a younger age.

## Monitoring and evaluation

Future monitoring and evaluation of screening services should consider risks and benefits in the context of evolving treatment and management protocols.

Monitoring and evaluation criteria are being developed within the ECIBC initiative.

## Research priorities

1. Explore other treatment options such as active surveillance/monitoring.
2. Further evaluation needed regarding the incremental benefits and harms of additional screening from age 70 onwards in women who have been regularly screened before age 70.
3. Carry out context-specific cost-effectiveness research.

## REFERENCES SUMMARY

1. Rashidian A, Barfar E, Hosseini H, Nosratnejad S, Barooti E.. Cost effectiveness of breast cancer screening using mammography; a systematic review.. Iran J Public Health; 2013.
2. Rosenquist CJ, Lindfors KK.. Screening mammography in women aged 40-49 years: analysis of cost-effectiveness.. Radiology; 1994.