# ECIBC recommendation on mammography screening for women aged 40-44:

## Evidence profile

### Healthcare question
Should organised mammography screening vs. no mammography screening be used for early detection of breast cancer in women aged 40 to 44?

### Date
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### Authors

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### Abbreviations
- CI: Confidence interval
- RR: Risk ratio

<table>
<thead>
<tr>
<th>Certainty assessment</th>
<th>Nº of patients</th>
<th>Effect</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nº of studies</td>
<td>Study design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
<td>Indirectness</td>
</tr>
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<td>8 1234567a</td>
<td>randomised trials</td>
<td>not serious b</td>
<td>not serious c</td>
<td>not serious c</td>
</tr>
</tbody>
</table>

**Breast cancer mortality (short case accrual) for women aged 40 to 44 (follow up: mean 16.8 years)**
<table>
<thead>
<tr>
<th>№ of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>organised mammography screening</th>
<th>no mammography screening</th>
<th>Relative (95% CI)</th>
<th>Absolute (95% CI)</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>randomised trials</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>serious</td>
<td>none</td>
<td>736/152,344 (0.5%)</td>
<td>0.5%</td>
<td>RR 0.92 (0.83 to 1.02)</td>
<td>84 fewer per 100,000 (from 168 fewer to 14 more)</td>
<td>🌟🌟🌟◯</td>
<td>MODERATE</td>
</tr>
<tr>
<td>6</td>
<td>randomised trials</td>
<td>not serious</td>
<td>serious</td>
<td>serious</td>
<td>serious</td>
<td>none</td>
<td>3349/120,225 (2.8%)</td>
<td>2.5%</td>
<td>RR 1.04 (0.95 to 1.15)</td>
<td>100 more per 100,000 (from 125 fewer to 375 more)</td>
<td>🌟🌟🌟🌟</td>
<td>VERY LOW</td>
</tr>
<tr>
<td>5</td>
<td>randomised trials</td>
<td>serious</td>
<td>not serious</td>
<td>serious</td>
<td>serious</td>
<td>none</td>
<td>475/124,475 (0.4%)</td>
<td>0.4%</td>
<td>RR 0.88 (0.78 to 0.99)</td>
<td>46 fewer per 100,000 (from 84 fewer to 4 fewer)</td>
<td>🌟🌟🌟🌟</td>
<td>VERY LOW</td>
</tr>
<tr>
<td>4</td>
<td>randomised trials</td>
<td>not serious</td>
<td>not serious</td>
<td>serious</td>
<td>serious</td>
<td>none</td>
<td>95/112,681 (0.1%)</td>
<td>0.1%</td>
<td>RR 0.98 (0.74 to 1.29)</td>
<td>2 fewer per 100,000 (from 26 fewer to 26 more)</td>
<td>🌟🌟🌟🌟</td>
<td>LOW</td>
</tr>
</tbody>
</table>

Breast cancer mortality (longest case accrual available) for women for women aged 40 to 44 (follow up: mean 15.2 years)

Other cause mortality (follow up: mean 10.8 years)

Breast cancer stage IIA or higher (follow up: mean 13.6 years)

Breast cancer stage III+ or tumour size ≥40 mm (follow up: mean 13.5 years)
<table>
<thead>
<tr>
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<th>Importance</th>
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<td>Nº of studies</td>
<td>Study design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
<td>Indirectness</td>
</tr>
<tr>
<td>Rate of mastectomies</td>
<td>5</td>
<td>randomised trials</td>
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<td>not serious</td>
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<tr>
<td>Provision of chemotherapy</td>
<td>2</td>
<td>randomised trials</td>
<td>not serious</td>
<td>not serious</td>
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<tr>
<td>Overdiagnosis (population perspective)</td>
<td>1</td>
<td>randomised trials</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td>Overdiagnosis (woman perspective)</td>
<td>1</td>
<td>randomised trials</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td>Quality of life (inferred from psychological effects)</td>
<td>54</td>
<td>observational studies</td>
<td>not serious</td>
<td>not serious</td>
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<tr>
<td>False-positive related adverse effects (psychological distress)</td>
<td>24</td>
<td>observational studies</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td>Number of studies</td>
<td>Study design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
<td>Indirectness</td>
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</tr>
<tr>
<td>7</td>
<td>observational studies</td>
<td>not serious</td>
<td>not serious</td>
<td>serious *</td>
</tr>
</tbody>
</table>

False-positive related adverse effects (biopsies and surgeries)

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).
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 did use 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-1 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 the 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 and the quality control of screening and breast cancer care have improved. A large non-randomised study (Hellquist B 2011) showed a reduced risk for breast cancer deaths in women aged 40 to 49 years invited to screening, compared with women not invited (RR=0.74; 95%CI, 0.66-0.83) which is consistent with RCT results. The GDG did not rate downgrade for indirectness for breast cancer mortality but considered it serious for other outcomes.

d. 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).

e. Median or mean of the control group of the included studies unless otherwise specified


g. A large large non-randomised study (Hellquist 2011) showed a reduced risk for breast cancer deaths in women aged 40 to 49 years invited to screening, compared with women not invited (RR 0.74; 95%CI, 0.66 to 0.83) which is consistent with the results seen in the RCTs.

h. Unexplained inconsistency with statistical heterogeneity (I² = 62%, P = 0.02).

i. Importance of the outcome was lowered from 'critical' to 'important' because the GDG members felt this outcome influenced neither the direction nor the strength of the recommendation.

j. Some studies were sub-optimally randomised and had non-blinded assessment of stage of disease; when analysis was restricted to low risk of bias trials, the risk estimate was non-significant

k. Indirectness same as for women aged 50 to 69.

l. Population included women aged 40-74 years old. Therefore, a much broader age range than the 40-44 age group studied here. Observational studies do not confirm these results, instead they provide opposite results.

m. 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

n. Unexplained inconsistency with statistical heterogeneity (I² = 71%, P = 0.06).

o. Chemotherapy protocols and indications have significantly changed (e.g. node status was not determined in earlier studies).

p. Overdiagnosis calculated from CNBSS-1 trial, 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).

q. Overdiagnosis calculated from CNBSS-1 trial, 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).
r. Unexplained inconsistency for variability in anxiety in the group of women recalled for further testing.
s. Studies included women aged 50 to 69. Estimates for the 40 to 44 age stratum are likely to be higher.

References