Appendix 2: GRADE Evidence to Decision framework for health system and public health decisions

An interactive version of this framework that includes more subgroup information is available at: http://ietd.epistemonikos.org/#/frameworks/54cb8f762b3867639eed4c09/question

Authors: Andrew Oxman and Jenny Moberg
Interactive Evidence to Decision Framework Date: Jan 2015

5. Should routine screening mammography be used to screen women aged 40 to 49 for breast cancer? (Health system and public health recommendations or decisions)

QUESTION

Question details

Problem: Breast cancer in women aged 40 to 49
Option: Organized screening with biennial mammography for women aged 40 to 49
Comparison: No organized screening for women aged 40 to 49
Main outcomes: Total deaths, deaths from breast cancer, mastectomy or lumpectomy (some due to overdiagnosis), false positives, burden of screening
Setting: A European country
Perspective: Ministry of Health

Background

It is controversial whether the benefits of screening mammography outweigh the harms, particularly for women between the ages of 40 and 49 [1]. There have been strong reactions to clinical guidelines that have recommended against routine screening for women in this age group [2]. Many countries have organized programs for breast cancer screening. Although most programs have had a lower age limit of 50 [3], there continues to be debate about recommendations for screening mammography for women aged 40 to 49, whether there should be organized screening programs generally [4], and particularly for this age group [5].

ASSESSMENTS

Problem

Is the problem a priority?

Judgment

☐ Don’t know ☐ Varies ☐ No ☐ Probably No ☒ Probably Yes ☐ Yes
Research evidence
The 10 year risk of dying from breast cancer for 40 year old women without an organized screening program is approximately 3 per 1000 over 10 years[6].

Additional considerations
The 10 year risk of breast cancer for 40 year old women without an organized screening program is approximately 16 per 1000 women (based on US SEER data).

Desirable effects
How substantial are the desirable anticipated effects?

Judgment

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

Research evidence
Summary of findings: Effects of mammography screening for women aged 40-49
(See an interactive version here)

Overdiagnosis is diagnosis of "disease" that will never cause symptoms or death during a patient’s lifetime. Consequences of overdiagnosis of breast cancer include surgery, radiotherapy and endocrine therapy of women who would not be diagnosed or treated for breast cancer without screening. Psycho-social consequences include anxiety, depression, labeling and impacts on insurance status.

**Undesirable effects**

How substantial are the undesirable anticipated effects?

**Judgment**

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

**Research evidence**

See summary of findings table above.

**Certainty of the evidence**

What is the overall certainty of the evidence of effects?

**Judgment**

- No included studies
- Very low
- Low
- Moderate
- High

**Research evidence**

See summary of findings table above.

**Values**

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

**Judgment**

- Important uncertainty or variability
- Possibly important uncertainty or variability
- Probably no important uncertainty or variability
- No important uncertainty or variability
The relative importance or values of the main outcomes of interest:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Values</th>
<th>Research evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from breast cancer</td>
<td>No evidence</td>
<td>There is limited research about the importance or values that women place on the consequences of screening mammography, life after treatment of breast cancer or living with metastatic breast cancer. Both the average values of women and the extent of variability in how much they value avoiding the outcomes in the summary of findings table are uncertain[9][10].</td>
</tr>
<tr>
<td>Unnecessary surgery (overdiagnosis)</td>
<td>No evidence</td>
<td></td>
</tr>
<tr>
<td>False positive (recall for biopsy)</td>
<td>No evidence</td>
<td></td>
</tr>
<tr>
<td>Burden of screening</td>
<td>No evidence</td>
<td></td>
</tr>
</tbody>
</table>

Additional considerations
Many women have been exposed to information advocating the need for screening mammography and to conflicting recommendations about screening mammography for women age 40 to 49. Qualitative studies suggest that women perceive mammography as reducing breast cancer mortality [6].

**Balance of effects**

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

**Judgment**

<table>
<thead>
<tr>
<th></th>
<th>Don’t know</th>
<th>Varies</th>
<th>Favors the comparison</th>
<th>Probably favors the comparison</th>
<th>Does not favor either the option or the comparison</th>
<th>Probably favors the option</th>
<th>Favors the option</th>
</tr>
</thead>
</table>

Research evidence
See table values of the main outcomes of interest, and summary of findings table above.
Resources required

How large are the resource requirements (costs)?

Judgment

<table>
<thead>
<tr>
<th></th>
<th>Don’t know</th>
<th>Varies</th>
<th>Large costs</th>
<th>Moderate costs</th>
<th>Negligible costs or savings</th>
<th>Moderate savings</th>
<th>Large savings</th>
</tr>
</thead>
</table>

Research evidence

The unit costs of mammography vary across countries. An estimate of the direct cost of a single screening mammogram in Norway is about €100 (calculated using the capital costs of a mammogram, the number of radiologists and technicians needed for screening, costs of office space including heating and cleaning, and the number of screening mammograms carried out per year) [12]. For 3,000,000 women screened biennially the cost would be around €160,000,000 annually for mammograms. The full cost (including indirect costs, follow-up investigations and costs and savings from treatment) is not available.

Certainty of evidence of required resources

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

Judgment

<table>
<thead>
<tr>
<th></th>
<th>No included studies</th>
<th>Very low</th>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
</tr>
</thead>
</table>

Research evidence

The costs and cost-effectiveness of screening mammography in women aged 40 – 49 are very uncertain. There is substantial variation in models used, settings and estimates in cost effectiveness studies from 12 countries, and these studies do not specifically address organized screening for women aged 40 to 49 [13]. It is unlikely that screening mammography is cost effective in this age group [14].
**Cost-effectiveness**  
Does the cost-effectiveness of the option favor the option or the comparison?

**Judgment**

<table>
<thead>
<tr>
<th>☐</th>
<th>☐</th>
<th>☒ Favors the comparison</th>
<th>☐</th>
<th>☐</th>
<th>☐</th>
<th>☒ Favors the option</th>
</tr>
</thead>
<tbody>
<tr>
<td>Don’t know</td>
<td>Varies</td>
<td>Probably favors the comparison</td>
<td>Does not favor either the option or the comparison</td>
<td>Probably favors the comparison</td>
<td>Probably favors the comparison</td>
<td></td>
</tr>
</tbody>
</table>

**Research evidence**

The cost per quality adjusted life year (QALY) is €100,000 for screening every 3 to 4 years and €200,000 for screening every 2 years. The cost per QALY is less for some high-risk groups (see high-risk subgroup) [15].

**Equity**

What would be the impact on health equity?

**Judgment**

<table>
<thead>
<tr>
<th>☐</th>
<th>☐</th>
<th>☒ Reduced</th>
<th>☐</th>
<th>☒</th>
<th>☐</th>
<th>☒ Increased</th>
</tr>
</thead>
<tbody>
<tr>
<td>Don’t know</td>
<td>Varies</td>
<td>Reduced</td>
<td>Probably reduced</td>
<td>Probably no impact</td>
<td>Probably increased</td>
<td>Increased</td>
</tr>
</tbody>
</table>

**Research evidence**

There is evidence of lower utilization of screening mammography among low-income women and racial/ethnic minorities [16].

**Additional considerations**

Providing a screening mammography programme would increase equity only if the net benefits favoured screening.

**Acceptability**

Is the option acceptable to key stakeholders?

**Judgment**

<table>
<thead>
<tr>
<th>☐</th>
<th>☐</th>
<th>☒ No</th>
<th>☐</th>
<th>☒</th>
<th>☒</th>
<th>☒ Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Don’t know</td>
<td>Varies</td>
<td>No</td>
<td>Probably No</td>
<td>Probably Yes</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

**Research evidence**

No included studies
Additional considerations
Screening mammography is advocated by some people and organizations. Qualitative studies suggest that women perceive mammography as reducing breast cancer mortality [6], which may affect acceptability if the option is not recommended.

Feasibility
Is the option feasible to implement?

Judgment

<table>
<thead>
<tr>
<th>Don’t know</th>
<th>Varies</th>
<th>No</th>
<th>Probably No</th>
<th>Probably Yes</th>
<th>Yes</th>
</tr>
</thead>
</table>

Research evidence
Barriers to screening mammography include conflicting recommendations, knowledge and beliefs, expectations, competing priorities, lack of a usual health care provider, economic barriers, lack of access to screening services, appointment barriers, language barriers, social barriers and cultural norms [17].

CONCLUSIONS
Type of recommendation

| ✔ Strong recommendation against the option | ❌ Conditional recommendation against the option | ❌ Conditional recommendation for either the option or the comparison | ❌ Conditional recommendation for the option | ✔ Strong recommendation for the option |

Recommendation
We recommend against the extension of a biennial organized mammography screening program for breast cancer in women aged 40 to 49 with no known increased risk of breast cancer.

We suggest that physicians offer screening mammography on an individual basis for women with one or more known risk factors for breast cancer, after discussion and assessment of the level of risk, and of the preferences of the individual.

Justification
We recommend against extending organized biennial screening mammography for women aged 40 to 49 with no known increased risk of breast cancer because the small reduction in the number of women being diagnosed with breast cancer is outweighed by the larger number of women experiencing serious undesirable effects, including unnecessary surgery.
**Detailed justification**

**Desirable effects:** There is moderately certain evidence that all-cause mortality is not reduced by screening mammography in women aged 40 to 49, and that mortality from breast cancer is only very slightly reduced in absolute terms (5 fewer per 10 000 women; 95%CI 1 to 8 fewer per 10 000 women).

**Undesirable effects:** A larger group of women are likely to experience unnecessary surgery, biopsies and anxiety due to overdiagnosis, and false positive results of screening. Most women experience some degree of burden associated with mammography screening.

**Balance of effects:** Extending organized biennial screening mammography for women aged 40 to 49 with no known increased risk of breast cancer would only slightly reduce the number of women who would die from breast cancer. This is outweighed by the larger number of women who would experience serious undesirable effects, including unnecessary surgery.

**Subgroup considerations**

We suggest that physicians offer screening mammography on an individual basis for women with one or more known risk factors for breast cancer, after discussion and assessment of the level of risk, and of the preferences of the individual.

**Implementation considerations**

- Media strategy and information addressing arguments raised by advocates of screening with explanation and supporting evidence for the decision not to recommend organized mammography screening for all women aged 40 to 49.
- Information for women aged 40 to 49, including the recommendation, justification and summary of findings.
- Information for health professionals explaining the recommendation.
- Information for women about how to assess their level of risk for breast cancer, possibly including the use of online risk calculators.
- Information for health professionals about which women (those with a high risk of breast cancer) should be offered biennial screening mammography.

**Monitoring and evaluation**

Not needed, beyond existing routinely collected data regarding breast cancer.

**Research priorities**

Measurement of how much women at higher risk value the main outcomes, and evaluation of patient information.
# EVIDENCE PROFILE

**Author(s):** Jenny Moberg  
**Date:** Jan 2015  
**Question:** Screening mammography compared to no screening for breast cancer in women aged 40 to 49  
**Setting:** Canada  

<table>
<thead>
<tr>
<th>Evidence assessment</th>
<th>№ of patients</th>
<th>Effect</th>
<th>Certainty (quality) of the evidence</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All-cause mortality. Follow up 11.4 years (follow up: median 11.4 years; assessed with: deaths)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 randomized trials</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td><strong>Breast cancer mortality (follow up: median 11.4 years; assessed with: deaths)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8 randomized trials</td>
<td>serious</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td><strong>Mastectomy or lumpectomy (estimated 30% due to overdiagnosis [4, 8]) (follow up: median 11.4 years; assessed with: surgery)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 randomized trials</td>
<td>not serious</td>
<td>not serious</td>
<td>serious</td>
</tr>
</tbody>
</table>

MD – mean difference, RR – relative risk

1. truly randomized  
2. no heterogeneity exists; p-value for testing heterogeneity is 0.65 and 12=0%  
3. the question addressed is the same for the evidence regarding the population, intervention, comparator and outcome  
4. sample size is large and total number of events is>300 (a threshold rule-of-thumb value)  
5. insufficient number of studies to assess publication bias  
6. 5 quasi-randomized and 3 truly randomized  
7. blinding and concealment were not clear for 5 studies, so only 3 trials were considered truly randomized  
8. no heterogeneity exists; p-value for testing heterogeneity is 0.48 and 12=0%  
9. no heterogeneity exists; p-value for testing heterogeneity is 0.87 and 12=0%  
10. population is all women 40-74
REFERENCES

1. Arie S. Switzerland debates dismantling its breast cancer screening programme. BMJ 2014; 348:g1625 doi: 10.1136/bmj.g16252