



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 triennial vs. biennial mammography screening be used for early detection of breast cancer in women aged 45 to 49?

RECOMMENDATION

For asymptomatic women aged 45 to 49 with an average risk of breast cancer, the ECIBC's Guidelines Development Group (GDG) suggests either triennial or biennial mammography screening in the context of an organised screening programme (conditional recommendation, very low certainty in the evidence).

ASSESSMENT

POPULATION

Women between 45 to 49 years.

INTERVENTION

triennial

COMPARISON

biennial mammography screening

MAIN OUTCOMES

Breast cancer mortality; QALYs; False positive results; Biopsy recommendation; Overdiagnosis; Radiation induce breast cancer /death.

SETTING

European Union

PERSPECTIVE

Population (National Health System).

BACKGROUND

Breast cancer is the second most common cancer in the world and the most frequent cancer among women with an estimated 1.67 million new cancer cases diagnosed in 2012 (25% of all cancers) (Ferlay et al., 2013). In 2018 in Europe, it is estimated that 41,449 women between the ages of 45 and 49 will be diagnosed with breast cancer and 5,680 will die (Ferlay, 2018). Mammography screening has both potential benefits and harms. The Guidelines Development Group has conditionally recommended against screening in women between the ages of 40 and 44, but conditionally for screening for women between the ages of 45 and 49. Debate about the recommended interval for screening with mammography remains due to the theoretical advantage of earlier diagnosis but a potential increase in harms with shorter screening intervals. For example, the USPSTF recommended to individualise the decision of screening (Siu, 2016) in women aged 40 to 49 years, while the ACS recommended annual screening between the ages of 45 and 54 (Myers, 2015).

Management of Conflicts of Interest (Col): ColS 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: Roberto d'Amico and Chris de Wolf. Miranda Langendam, as external expert, was also not allowed to vote, according to the ECIBC rules of procedure. For more information please visit <http://ecibc.jrc.ec.europa.eu/gdg-documents>

JUDGEMENTS

Is the problem a priority?

- No
- Probably no
- Probably yes
- Yes
- Varies
- Don't know

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 et al., 2013). Breast cancer ranks as the fifth cause of death from cancer overall (522,000 deaths) and it is the second cause of cancer death in developed regions (198,000 deaths, 15.4%) after lung cancer. In 2018 in, Europe, it is estimated that 41,449 women between the ages of 45 and 49 will be diagnosed with breast cancer and 5,680 will die (Ferlay, 2018) Breast cancer is the fourth cancer with the highest disease burden (Tsilidis et al., 2016).

Although mammography screening is generally accepted as beneficial in reducing breast cancer mortality in women 50-69 years. The balance between benefits and harms for the different screening intervals is still debatable, with recommended periodicity varying between annual to triennial. In the group of women aged from 45 to 49, the amount of evidence is even scarcer and the topic is controversial.

Additional considerations

This question was prioritised by the GDG.

How substantial are the desirable anticipated effects?

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

Additional considerations

Events were calculated by subtracting estimation of 45 to 69 screening years minus 50 to 69 screening years. Effects are then incremental to the 50 to 69 screening, and may vary depending on the year of last screening.

In the 50 to 69 years age group, one randomised trial in the United Kingdom did not show higher risk of breast cancer mortality with triennial screening (Breast Screening Frequency Trial, 2002); observational studies from the United States reported larger proportions of interval cancer and lower proportions of false positive adverse events in the triennial schedule. The GDG noted that there would be 5 fewer breast cancer deaths averted and 12 fewer QALYs per 100,000 women with triennial vs biennial screening. The GDG noted that the data presented here refers to only a 5-year screening interval, as compared to the 20-year screening interval for the 50-69 age category.

In this age group, the deaths averted go in the same direction as the QALYs.

The GDG agreed the desirable effects, fewer overdiagnosis and fewer false positives, would be small.

How substantial are the undesirable anticipated effects?

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

Additional considerations

The fewer QALY and fewer breast cancer deaths averted refer only to the 5 year screening interval (for example, compared to approximately 300 QALYs in the 20 year screening interval in the age group of women between 50-69, here there are 12).

The GDG agreed the undesirable anticipated effects would be moderate.

What is the overall certainty of the evidence of effects?

Very low

Low

Moderate

High

No included studies

Additional considerations

There are no modelling studies that model these few years, so it was necessary to do the subtraction mentioned previously. This is why the GDG agreed that the quality of evidence of this data was very low.

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

A systematic review (JRC Technical Report PICO 10-11, contract FWC443094012015; available upon request) shows that women place a low value on the psychosocial and physical effects of false positive results and overdiagnosis. However, women generally consider these undesirable effects acceptable (*low confidence*). These findings are of limited value mainly given the significant concerns regarding the adequacy of the information provided to the participants, in order to take an informed decision. Also, acceptability of false positive results is based on studies of patients who have already received a false positive result, whose 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 patients' views. One of the main themes identified in the literature is that patients 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, women have a higher overall preference towards more comfortable, brief diagnostic procedures (*low confidence*).

No specific studies, neither focusing on the rest of the critical outcomes nor comparing different screening intervals, were identified. The findings, all from mammography studies, however, are likely to be generalizable to facing the decision of selecting different mammography schedules, as all screening intervals are associated with similar desirable and undesirable effects (e.g. false positive findings or overdiagnosis).

Additional considerations

The GDG agreed by consensus that there is possibly important uncertainty in how much people value the main outcomes.

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

Favors the comparison

Additional considerations

Probably favors the comparison

Does not favor either the intervention or the comparison

The GDG agreed that the balance of the effects probably favours the comparison, biennial screening.

Probably favors the intervention

Favors the intervention

Varies

Don't know

How large are the resource requirements (costs)?

- Large costs
- Moderate costs
- Negligible costs and savings
- Moderate savings
- Large savings
- Varies
- Don't know

Additional considerations

The GDG agreed by consensus there would be moderate cost savings in triennial screening.

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

Very low

Low

Moderate

High

No included studies

The quality of the evidence of resource requirements was considered very low due to study design (models were based on observational data), inconsistency, and indirectness. Inconsistency in costs was due to differences in the year value of the costs (2004, 2005 and 2012) and settings (costs reported in Slovenia were higher than in Spain). Costs and resources used in Spain and Slovenia may not be applicable to other European settings.

Additional considerations

Although the certainty of the magnitude of resources required for triennial screening is very low, the GDG noted that screening biennially is more expensive than triennially.

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

Additional considerations

Triennial screening is less costly but has less QALYs and therefore the ICER is saving about 98.000 euros per QALY lost. In other words, it means that the ICER of biennial screening is about 98.000 per QALY compared to triennial screening.

The modelling study used may not be adequate since the data for this age group was estimated by subtracting the 40-44 years data from the 40 to 50 years data. Different from the effectiveness analysis, a 3% discount rate is applied in the cost-effectiveness analysis calculations. For this reason, the number of lost QALYs is higher here (38) than the 12 reported in the evidence of effects.

The GDG agreed that the evidence from this study was very low quality.

The GDG agreed the cost-effectiveness data probably favoured the intervention (triennial screening).

What would be the impact on health equity?

- Reduced
- Probably reduced
- Probably no impact
- Probably increased
- Increased
- Varies
- Don't know

No systematic review of the evidence was conducted.

Additional considerations

The GDG discussed that there would be reduced equity if you increase the screening frequency, because not all women would have an equitable screening opportunity, as it would depend on the existing protocol/resources in their setting. In situations where programmes are well implemented, changing from triennial to biennial screening may not affect particular subgroups of women.

In settings where already triennial screening is not reaching all women, of note low income women or women who are working, there may be even more challenges if they have to attend screening at increased frequencies.

In settings where reduced equity already exists, changing screening interval from triennial to biennial may further reduce equity.

The GDG agreed by consensus equity would therefore vary.

Is the intervention acceptable to key stakeholders?

- No
- Probably no
- Probably yes
- Yes
- Varies
- Don't know

No systematic review of the evidence was conducted.

Additional considerations

The GDG felt that it would be very difficult to convince women, and healthcare providers that the interval should decrease from biennial to triennial screening. However, in contexts where programmes are not already in place, it would be possible to consider triennial screening.

Policy-makers: may not be willing to decrease screening interval if biennial is currently being used in their context, but if they do not have any screening, they could consider triennial screening

Is the intervention feasible to implement?

- No
- Probably no
- Probably yes
- Yes
- Varies
- Don't know

No systematic review of the evidence was conducted.

Additional considerations

The GDG felt that it would be feasible to implement a less frequent screening interval

CONCLUSIONS

Should triennial vs. biennial mammography screening be used for early detection of breast cancer in women aged 45 to 49?

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 aged 45 to 49 with an average risk of breast cancer, the ECIBC's Guidelines Development Group (GDG) suggests either triennial or biennial mammography screening in the context of an organised screening programme (conditional recommendation, very low certainty in the evidence).				
JUSTIFICATION	<p>Overall justification</p> <p>The conditional recommendation for either triennial or biennial screening was agreed by the GDG by consensus.</p> <p>The reason for the conditional recommendation for either the intervention or the comparison was due mainly to the improved health effects with biennial screening, but moderate savings and favourable cost-effectiveness with triennial screening.</p>				
SUBGROUP CONSIDERATIONS	<ol style="list-style-type: none"> 1. Examine the conditions that the GDG identified and implement according to country-priorities. 				

IMPLEMENTATION CONSIDERATIONS

2. If there is no breast cancer screening programme already, triennial screening may be easier to implement as compared to biennial.

3. If screening in this age group is implemented (according to the conditional recommendation made by the ECIBC's GDG based on the screening ages) it is felt that it is better to have triennial screening than no screening programme at all.

4. The GDG agreed that the possibility of using other imaging techniques in this subgroup of women may be relevant to consider.

MONITORING AND EVALUATION

RESEARCH PRIORITIES

1. The GDG agreed that more research on the effectiveness of the different screening intervals, comparative studies, would be helpful due to the very low certainty of the evidence.
2. Less information is available for certain outcomes in this age group (e.g. interval cancer) and this information should be shared.
3. The GDG notes that cost-effectiveness research would be helpful to further assess this screening interval in women aged 45 to

49.

4. There was discussion in the GDG whether women with dense breasts in this age group should be screened at different intervals.

5. Evaluation of data on ongoing biennial opportunistic versus organised screening, particularly for this age group, and related equity issues. However, the GDG recognised that there may be difficulty and may be confounding effects when comparing different strategies for opportunistic screening.

6. The GDG felt that increased cost effectiveness data, having more contextualised costs and cost-effectiveness analysis and from other settings would be helpful for future recommendations; this included checking the consistency of cost-effectiveness models with new research from trials on breast cancer screening and natural history of breast cancer disease. Also many member states have cost analysis but they are in the grey literature and not publicly available, and this should be shared with the scientific community.
