



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 annual 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 against annual mammography screening over biennial mammography screening in the context of an organised screening programme (conditional recommendation, very low certainty in the evidence)

ASSESSMENT

POPULATION	Mammography screening in women 45-49 years
INTERVENTION	annual
COMPARISON	biennial mammography screening
MAIN OUTCOMES	Breast cancer mortality; Stage of breast cancer (IIB-IV); QALYs; All-cause mortality; False positive results; Biopsy recommendation; Overdiagnosis; Radiation induce breast cancer /death
SETTING	European Union
PERSPECTIVE	Population (National Health System)
BACKGROUND	<p>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).</p> <p>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</p>

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). 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. The balance between benefits and harms for the different intervals is still debatable, with recommended periodicity varying from annual to triennial for women from 50 to 59 years old. In the group of women aged between 45 to 49, the amount of evidence is even more scarce 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

In modelling studies events were calculated by subtracting estimation of 45 to 69 (or 74) screening years minus 50 to 69 (or 74) screening years. Effects are then incremental to the 50 to 69 (or 74) age year of screening. Observational studies from the United States for the 40 to 49 years age group showed a higher risk of stage II+ for biennial screening, along with smaller proportions of, false positive results and false positive biopsy recommendations.

More deaths averted with annual mammography screening and 80 fewer interval cancers detected.

The GDG agreed to review evidence from the randomised mammography screening trials as an indirect comparison of 2 years or more vs less than 2 years because the studies included did not have the exact annual vs. biennial screening period. There was concern that the CNBSS-1 (Miller, 2014) included a clinical breast examination prior to randomisation in the control group as well as the intervention group, which detected a substantial number of cancers in the control group, and which would be expected to dilute the difference between the intervention and control groups. However, a sensitivity analysis excluding CNBSS-1 from the annual mammography trials (Rate ratio 0.95; 95%CI 0.63 – 1.44) made only a small change to the relative risk comparing annual to biennial mammography screening.

The GDG discussed that the evidence reviewed is indirect, and that the evidence for this comparison is different from that reviewed for the triennial vs. biennial and annual vs. triennial.

As agreement could not be reached by consensus, voting among members of the GDG without Col was conducted, with the following results:
10 GDG members voted for 'small' 9 members voted for 'moderate'

How substantial are the undesirable anticipated effects?

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

Additional considerations

The GDG discussed concern with overdiagnosis results from the modelling study (Mandelblatt, 2016). These are the marginal effects assuming screening is undertaken from 45-74 years of age. The GDG noted that there was inconsistency with the rate of overdiagnosis in this age group 45-49 in the modelling research that is known in the literature and therefore interpreted the rate of overdiagnosis with caution.

The GDG discussed concern with the cumulative false positives rate identified of 22,000 per 100,000 women. In addition, these figures pertain to ten years of screening from age 40. Five years of screening from age 45 would give much smaller numbers.

The GDG expressed their concern about the false positive biopsy recommendation data, coming from the US, which are a lot higher than in Europe.

Death by radiation induced breast cancer was considered an undesirable effect (but is not included in Breast Cancer deaths averted).

The GDG agreed by consensus that 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
-

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 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).

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)

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 notes that the balance of effects favouring the comparison was interpreted despite the cost-effectiveness data, which demonstrated an effect contrasting to the increase in QALYs with this intervention.

☐ 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 noted the obvious increase in the cost if women between the ages of 45-49 are screened annually vs. biennially, as shown by the data coming from Spain and Slovenia.

The GDG noted the indirectness of this evidence due to the year of publication of the studies included (published in 2004-2005).

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

☒ Very low

☐ Low

☐ Moderate

☐ High

☐ No included studies

The certainty of the evidence of the magnitude of resources required 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 costs year value (2004, and 2005) 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 annual screening is low, the GDG noted that screening annually is clearly more expensive than biennially.

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

☐ Favors the comparison

Additional considerations

☒ Probably favors the comparison

☐ Does not favor either the intervention or the comparison

Differences between the amount of QALYS reported in the evidence of effects and the cost-effectiveness analysis are due to these QALYs having a 3% discount rate in the cost-effectiveness analysis.

☐ Probably favors the intervention

☐ Favors the intervention

☐ Varies

☐ No included studies

The GDG noted that the cost effectiveness evidence was of very low quality.

The GDG notes that its interpretation of the range for the ICER estimate was very wide.

As agreement could not be reached by consensus, voting was conducted: 13 members voted for 'probably favours the comparison'.

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 agrees health equity would vary across countries, depending on the current interval used for screening in their settings.

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

Healthcare providers: the GDG noted that there is variation between countries in Europe on the acceptability of annual vs biennial screening for women of this age.

In general the GDG felt that women would prefer annual screening, however, the acceptability would vary because some women also prefer a less frequent screening interval.

Policy-makers: acceptability may vary depending on the current practice in countries.

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 feasibility of this intervention will vary by country context

CONCLUSIONS

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

TYPE OF RECOMMENDATION	<div>Strong recommendation against the intervention</div> <div>○</div> <div>Conditional recommendation against the intervention</div> <div>⊗</div> <div>Conditional recommendation for either the intervention or the comparison</div> <div>○</div> <div>Conditional recommendation for the intervention</div> <div>○</div> <div>Strong recommendation for the intervention</div> <div>○</div>
RECOMMENDATION	For asymptomatic women aged 45 to 49 with an average risk of breast cancer, the ECIBC's Guidelines Development Group (GDG) suggests against annual mammography screening over 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 against annual screening was the result of the health effects that probably favour biennial screening, although the certainty of the evidence was very low.</p>
SUBGROUP CONSIDERATIONS	The GDG noted that women with a strong family history may be considered for more frequent screening within screening programmes (United Kingdom). Other countries do more intensive surveillance for high-risk women.
IMPLEMENTATION CONSIDERATIONS	

1. The GDG notes that there is variability in the acceptability between countries and that the current practice will impact the ease of implementation and the acceptability of this intervention to key stakeholders.

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

MONITORING AND EVALUATION Careful monitoring of interval cancer rates in this age group is warranted.

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).
3. The GDG notes that cost-effectiveness research would be helpful to further assess this screening interval in women aged 45 to 49.
4. The GDG notes that there is a lack of research on other imaging modalities between screening intervals with mammography for women of this age-group.
5. There was discussion in the GDG whether women with dense breasts in this age group should be screened at different intervals.
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. This priority may apply to all other screening interval recommendations.