



**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

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

## RECOMMENDATION

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***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 triennial mammography screening in the context of an organised screening programme (conditional recommendation, very low certainty in the evidence).***

# ASSESSMENT

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<b>POPULATION</b>	Women between 45 to 49 years.
<b>INTERVENTION</b>	annual
<b>COMPARISON</b>	triennial mammography screening
<b>MAIN OUTCOMES</b>	Breast cancer mortality; QALYs; False positive results; Biopsy recommendation; Overdiagnosis; Radiation induce breast cancer /death.
<b>SETTING</b>	European Union
<b>PERSPECTIVE</b>	Population (National Health System).
<b>BACKGROUND</b>	<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 J, 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 (AL et al., 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>

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## 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 KK, 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 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.

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**How substantial are the desirable anticipated effects?**

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

**Additional considerations**

Events in the modelling study (QALY) 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 by the year of last screening.

For 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 inconsistency in different studies providing data on breast cancer mortality and QALYs for annual vs triennial mammography screening in the ages 45-49. While there were more breast cancer deaths and a greater number of false positives with annual screening, there were increased QALYs presented in the modelling data for annual vs triennial.

The model data was considered to be unstable in the age range 45 to 49 years old. It was considered that the model used was not internally consistent, and therefore, the GDG agreed they could not rely only on this data for this recommendation.

The GDG noted that there were fewer interval cancers (based on the study by (Klemi, 1997)). There was significant concern by the GDG in the data quality.

The GDG also noted that there is concern with the denominators used. In the actual study there were very few number of cancers detected, but the data was extrapolated in order to present it as a rate per 100,000 breast cancers. Based on the actual events in the study, this would be equivalent to approximately 25 fewer cancers per 100,000 women screened.

As agreement within the GDG could not be reached, voting among the members without Col resulted in the following: two members voted

"trivial" and 20 members voted "small"

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***How substantial are the undesirable anticipated effects?***

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

***Additional considerations***

Although there were more deaths with annual screening compared to triennial screening, the differences were small, and, given that no sensitivity analysis was reported, the GDG considered the difference was not significant.

The undesirable effects that the GDG focused on were the 36,000 more false positives and 7,000 more biopsy recommendations per 100,000 women screened using an annual screening interval.

Therefore, the GDG agreed that the undesirable effects were moderate.

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***What is the overall certainty of the evidence of effects?***

☒ Very low

☐ Low

☐ Moderate

☐ High

☐ No included studies

***Additional considerations***

The GDG agreed the overall certainty was very low, as mentioned previously, due to the problems with the modelling study and the indirectness of the evidence (looking at 40-49 age range and not the 45-49 age range).

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***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.

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***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 agrees there would be more health benefits with triennial screening compared to annual screening, given the large number of false positives.

☐ Probably favors the intervention

☐ Favors the intervention

☐ Varies

☐ Don't know

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***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***

As agreement within the GDG could not be reached, voting among the members without Col resulted in the following: seven members voted "moderate" and 15 members voted "large".

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***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 costs year value (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***

The GDG did not consider the modelling data on cost effectiveness because of the inconsistency of the modelling data.

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**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

The GDG discussed that there are large costs and that the evidence of effects data shows no net benefits for the intervention.

☐ Probably favors the intervention

☐ Favors the intervention

☐ Varies

☐ No included studies

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***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 depending on the current interval for screening in their setting.

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***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 there would be varying acceptability by different key stakeholders.

Women: probably not acceptable to have annual screening due to having to attend the screening programmes more frequently, although some women may prefer annual screening.

Policy-makers: acceptability varies, in certain context may be more or less acceptable depending on established practice and cost considerations. Healthcare providers: may favour increased frequency.

The GDG notes that the radiologists on the GDG believed it was not acceptable to do annual screening.

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***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 agreed the feasibility of implementing annual screening varies.

The GDG discussed the increased human resources needed as well as additional costs among the barriers to implementing annual screening in settings where this intervention is not currently in place, although in some areas it is already done. The GDG discussed that in this age group, breast density is also an issue to take into consideration.

## CONCLUSIONS

**Should annual vs. triennial 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 against annual mammography screening over triennial 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 recommendation was agreed by consensus.</p> <p>The recommendation was conditional due to no net health benefits with annual screening and large costs associated with it.</p>				
SUBGROUP CONSIDERATIONS	None were considered.				
IMPLEMENTATION	The GDG agreed that the possibility of using other imaging techniques in this subgroup of women may be relevant to consider.				

## **CONSIDERATIONS**

**MONITORING AND EVALUATION** Evaluate existing programmes that already have in place annual screening in order to have data for inter-country comparability.

## **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 small amount of evidence available and the very low certainty of it.
  2. More reliable data is necessary, particularly in this age group, as the only data comes from a small trial where the mammograms were taken in 1987.
  3. More research on the use of other imaging modalities was deemed by the GDG to be useful in this age group.
  4. There was discussion in the GDG whether women with dense breasts in this age group should be screened at different intervals.
  5. The use of more consistent modelling studies was also highlighted.
  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.
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