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

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QUESTION

Should annual vs. triennial mammography screening be used for early detection of breast cancer in women aged 70 to 74?

RECOMMENDATION

For asymptomatic women aged 70 to 74 with an average risk of breast cancer, the ECIBC's Guidelines Development Group (GDG) recommends against annual mammography screening over triennial mammography screening, in the context of an organised screening programme (strong recommendation, very low certainty in the evidence).

ASSESSMENT

POPULATION	Mammography screening in women 70 years or older
INTERVENTION	annual
COMPARISON	triennial mammography screening
MAIN OUTCOMES	Stage of breast cancer (IIB-IV); False positive results; Biopsy recommendation.
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 54,490 women between the ages of 70 and 74 will be diagnosed with breast cancer and 15,149 will die (Ferlay, 2018).The Guidelines Development Group has conditionally recommended in favour of screening for women between the ages of 70 and 74. However, there continues to be debate about the recommended interval for screening with mammography, particularly for ages 70 and above. Management of Conflicts of Interest (CoI): CoIs 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 54,490 women between the ages of 70 and 74 will be diagnosed with breast cancer and 15,149 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 between 70 to 74, the amount of evidence is even more scarce and the topic 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

For the modelling study, events were calculated by subtracting estimation of 50 to 74 screening years minus 50 to 69 screening years. Effects are then incremental to those observed in the 50 to 69 screening age group and might vary by the year of last screening. Differences between triennial versus annual screening is small and given that no sensitivity analysis was carried out, the GDG considered that there would be no significant differences in the breast cancer deaths averted.

For the breast cancer deaths averted, false positive results and false positive biopsy recommendations, data was available from two modelling studies that were internally consistent and consistent between them so the GDG agreed to use this data.

For the QALYs the data presented was estimated from one model. It appears that there are breast cancer deaths averted, but at the same time there is a reduction in the number of QALY which seems contradictory. This is primarily driven by the issues around overdiagnosis and false positive results. In addition, the QALY modelling study is based on different evidence than the breast cancer mortality evidence that is coming from a trial and which the GDG agrees is better evidence. In addition, the QALY data from the modelling study may not be consistent for the 70-74 and 45-49 age group ranges as it was modelled for a much larger age group, and therefore the model becomes unstable in the smaller and marginal age groups (there is no direct data on those two small extreme age groups).

The GDG agreed that the breast cancer deaths averted corresponded to a small desirable effect.

How substantial are the undesirable anticipated effects?

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

Additional considerations

The QALYs is an aggregate measure of the false positive results and the false positive biopsy recommendations, they are not additive outcomes.

The GDG agreed that the decrease in QALYs for annual screening corresponded to moderate undesirable effects.

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 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
- ⊗ Probably favors the comparison
- ◯ Does not favor either the intervention or the comparison
- ◯ Probably favors the intervention
- ◯ Favors the intervention
- ◯ Varies
- ◯ Don't know

Additional considerations

The GDG agreed that due to the moderate undesirable effects and small desirable effects of annual screening, the balance probably favours the comparison (triennial screening).

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 that there would be moderate costs for annual screening compared to 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 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. The study performed in Slovenia reported data for women aged 71 to 75 years.

Additional considerations

The certainty according to the evidence presented was very low but the GDG was certain that annual screening is much more costly than triennial screening.

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

No relevant research evidence was identified.

Additional considerations

The GDG discussed that while there is no research evidence, it is assumed that there are moderate costs for annual screening and from the modelling evidence there is net harm (small benefits and moderate harms). The GDG therefore thought that the cost effectiveness 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 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 annual 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 annual may further reduce equity.

As agreement within the GDG for the impact on health equity could not be reached, voting among the members without CoI resulted in the following: 12 members voted in favour of ‘varies’, and 3 members voted in favour of ‘reduced’ (it is noted that all GDG patient representatives voted that it would be reduced), 1 member voted "probably no impact".

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

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: the GDG felt that they may not be willing to decrease the screening interval, particularly if annual screening is currently being used in their context.

In addition, the radiologists of the GDG agreed that the acceptability would be low if there is more harm than benefit, taking into account the associated increased costs with doing annual screening.

Therefore, GDG agreed that most stakeholders would probably not find the intervention acceptable.

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

In areas where not even triennial screening is in place, it will be even more difficult to do it annually.

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.

As agreement within the GDG for the feasibility could not be reached, voting among the members without CoI resulted in the following: 13 members voted in favour of ‘probably no’, 8 members voted in favour of ‘varies'.

CONCLUSIONS

Should annual vs. triennial mammography screening be used for early detection of breast cancer in women aged 70 to 74?

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 70 to 74 with an average risk of breast cancer, the ECIBC's Guidelines Development Group (GDG) recommends against annual mammography screening over triennial mammography screening, in the context of an organised screening programme (strong recommendation, very low certainty in the evidence).

JUSTIFICATION

Overall justification

The strong recommendation against annual screening was agreed by the GDG by consensus.

The GDG agreed that there is a net harm, moderate costs and the annual screening is probably not acceptable to key stakeholders and it is probably not feasible to implement.

SUBGROUP CONSIDERATIONS	None considered.
IMPLEMENTATION CONSIDERATIONS	The GDG does not feel that annual screening programmes are currently in place in any jurisdictions in Europe and therefore there would be no implementation considerations for this strong recommendation.
MONITORING AND EVALUATION	None considered.
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. 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.