



The Saudi Center for Evidence Based Health Care

Breast Cancer

Clinical Practice Guideline on the Use of Screening Strategies for the Detection of Breast Cancer

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Executive summary

Introduction

Breast cancer is the most common cancer in women in both the developed and developing world. It is estimated that worldwide over 508,000 women died in 2011 due to breast cancer.¹ Although breast cancer is thought to be a disease of the developed world, almost 50% of breast cancer cases and 58% of deaths occur in less developed countries.² According to the 2009 Cancer Incidence Report of the Kingdom of Saudi Arabia,³ breast cancer is the most common among women representing 25.1% of all newly diagnosed female cancers. In 2009 the age-specific incidence rate was 22.7/100,000. The three regions with the highest incidence were Eastern region (33.1/100,000), Riyadh region (29.4/100,000), and Makkah region (26.4/100,000). The median age at diagnosis was 48 years (range 19 to 99 years). In Saudi Arabia, the infiltrating duct carcinoma (ICD-O-3, 8500) accounts for 78.2% of all morphological breast cancer variants.

Early detection of breast cancer in order to improve survival remains the cornerstone of breast cancer control.¹ There is widespread acceptance of the value of regular breast cancer screening as the single most important public health strategy to reduce breast cancer mortality.¹ The reason for this is that breast cancer can be more effectively treated at an early stage. On the other hand, it could also lead to over diagnosis and overtreatment.⁴ Mammography, clinical breast examination by a health care professional, and breast selfexamination can all identify tumors. Mammography can identify early stage breast cancer.

Methodology

This clinical practice guideline is a part of the larger initiative of the Ministry of Health of the Kingdom of Saudi Arabia (KSA) to establish a program of rigorous adaptation and de novo development of guidelines. The ultimate goals are to provide guidance for clinicians and reduce variability in clinical practice across the Kingdom.

The KSA guideline panel selected the topic of this guideline and all clinical questions addressed herein using a formal prioritization process. For all selected questions we updated existing systematic reviews that were used for the 2010 "Screening for Breast Cancer in Average-risk Women Aged 40 to 74" guideline by the Canadian Task Force on Preventive Health Care.⁵ We also conducted systematic searches for information that was required to develop full guidelines for the KSA, including searches for information about patients' values and preferences and cost (resource use) specific to the Saudi context. Based on the updated systematic reviews we prepared summaries of available evidence supporting each recommendation following the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach.⁶ We used this information to prepare the evidence to recommendation tables that served the guideline panel to follow the structured consensus process and transparently document all decisions made during the meeting (see Appendix 1). The guideline panel met in Riyadh on December 5, 2013 and formulated all recommendations during this meeting. Potential conflicts of interests of all panel members were managed according to the World Health Organization (WHO) rules.⁷

How to use these guidelines

The guideline working group developed and graded the recommendations and assessed the quality of the supporting evidence according to the GRADE approach.⁸ Quality of evidence (confidence in the available estimates of treatment effects) is categorized as: high, moderate, low, or very low based on consideration of risk of bias, directness, consistency and precision of the estimates. High quality evidence indicates that we are very confident that the *true* effect lies close to that of the estimate of the effect. Moderate quality evidence indicates moderate confidence, and that the *true* effect is likely close to the estimate of the effect, but there is a possibility



that it is substantially different. Low quality evidence indicates that our confidence in the effect estimate is limited, and that the *true* effect may be substantially different. Finally, very low quality evidence indicates that the estimate of effect of interventions is very uncertain, the *true* effect is likely to be substantially different from the effect estimate and further research is likely to have important potential for reducing the uncertainty.

The strength of recommendations is expressed as either strong ('guideline panel recommends...') or conditional ('guideline panel suggests...') and has explicit implications (see **Table 1**). Understanding the interpretation of these two grades is essential for sagacious clinical decision making.

Implications	Strong recommendation	Conditional (weak) recommendation
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not. Formal deci- sion aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situa- tion would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Adherence to this rec- ommendation according to the guideline could be used as a quality criterion or performance indicator.	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful helping in- dividuals making decisions consistent with their values and preferences.
For policy mak- ers	The recommendation can be adapted as policy in most situations	Policy making will require substantial debate and involvement of various stakeholders.

Table 1: Interpretation of strong and conditional (weak) recommendations

Key questions

- Should screening for breast cancer with mammography (digital) vs. no screening be used in women aged 40– 49 years?
- 2. Should mammography (digital) be used to screen for breast cancer among women aged 50-69?
- 3. Should mammography (digital) be used to screen for breast cancer among women aged 70-74?
- 4. Should breast self-examination be used to screen for breast cancer among women all ages?

5. Should clinical breast examination be used to screen for breast cancer among women all ages?



Recommendations

Recommendation 1:

The Ministry of Health of Kingdom of Saudi Arabia guideline panel suggests screening with mammography in women aged 40–49 years every 1 to 2 years. (Conditional recommendation; low-quality evidence)

Remarks:

Based on local cancer registry data, the incidence of breast cancer in the KSA seems to be higher than in the other countries in which studies were conducted. This fact may indicate that higher benefit on breast cancer mortality justifies a recommendation in favor of implementing breast cancer screening using mammography in this age group. Since the guideline panel determined that there is a close balance between desirable and undesirable consequences, they also suggest implementing shared-decision making strategies as a way to incorporate actively patients' perspective into the decision.

Recommendation 2:

The Ministry of Health of Saudi Arabia guideline panel suggests screening with mammography in women aged 50–69 years every 2 years. (Conditional recommendation; moderate-quality evidence)

Remarks:

Based on local cancer registry data, the incidence of breast cancer in the KSA for this age group is similar to the ones reported in the literature in other countries. The guideline panel determined that desirable consequences probably outweigh undesirable consequences in most settings.

Recommendation 3:

The Ministry of Health of Saudi Arabia guideline panel suggests no screening with mammography in women aged 70–74 years. (Conditional recommendation; low-quality evidence)

Remarks:

Giving the competing risks with other diseases, screening with mammography seems to be

not a priority for this age group. Based on local cancer registry data, the incidence of breast cancer in the KSA for this age group is similar to the ones reported in the literature in other countries. The guideline panel determined that undesirable consequences probably outweigh desirable consequences in most settings. In case this option is offered to women between 70 to 74 years old, the panel proposed that this should be done every 2 to3 years.

Recommendation 4:

The Ministry of Health of Saudi Arabia guideline panel suggests that self-breast examination not be used as a single method of screening for breast cancer in women of all ages. (Conditional recommendation; verylow quality evidence)

Remarks:

The panel determined that the strength of the recommendation should be weak/conditional based on the extensive level of uncertainty and lack of evidence. The guideline panel also highlighted that, when mammography is available, this option should always be offered first to patients. In this regard, breast self-examination plays a secondary role, especially in regions where mammography may not be offered.

Recommendation 5:

The Ministry of Health of Saudi Arabia guideline panel suggests that clinical breast examination by a health care professional not be used as a single method of screening for breast cancer in women of all ages. (Conditional recommendation; no evidence)

Remarks:

The panel determined that the strength of the recommendation should be weak/conditional based on the extensive level of uncertainty and lack of evidence. The guideline panel also highlighted that when mammography is available, this option should always be offered first to patients. Clinical breast examination could be used as method for breast cancer screening only when mammography is unavailable. This recommendation does not relate to rou-



tine physical examination. The option described in this recommendation c vers only clinical breast examination in the context of breast cancer screening.



Scope and purpose

The purpose of this document is to provide guidance about population-based screening strategies to detect breast cancer in women. The target audience of these guidelines includes primary care physicians and specialists in medical oncology and radiology in the Kingdom of Saudi Arabia. Other health care professionals, public health officers and policy makers may also benefit from these guidelines.

Given the importance of this topic, the Ministry of Health (MoH) of Saudi Arabia with the methodological support of the McMaster University working group produced clinical practice guidelines to assist health care providers in evidence-based clinical decision-making. This clinical practice guideline is a part of the larger initiative of the Ministry of Health of Saudi Arabia to establish a program of rigorous adaptation and de novo development of guidelines in the Kingdom; the ultimate goal being to provide guidance for clinicians and reduce variability in clinical practice across the Kingdom.

Introduction

Breast cancer is the most common cancer in women in both the developed and developing world. It is estimated that worldwide over 508,000 women died in 2011 due to breast cancer.¹ Although breast cancer is thought to be a disease of the developed world, almost 50% of breast cancer cases and 58% of deaths occur in less developed countries .² The incidence of breast cancer is increasing in the developing world, in part, due to the increase in life expectancy, urbanization and adoption of western lifestyles. Although some risk reduction could be achieved implementing prevention strategies, these policies cannot eliminate the majority of breast cancers in lowand middle-income countries where it is diagnosed in very late stages.

According to the 2009 Cancer Incidence Report of the Kingdom of Saudi Arabia (KSA),³

breast cancer is the most common among women representing 25.1% of all newly diagnosed female cancers. In 2009 the agespecific incidence rate was 22.7/100,000. The three regions with the highest incidence were Easter region (33.1/100,000), Riyadh region (29.4/100,000), and Makkah region (26.4/100,000). The median age at diagnosis was 48 years (range 19 to 99 years). In Saudi Arabia, the infiltrating duct carcinoma (ICD-O-3, 8500) accounts for 78.2% of all morphological breast cancer variants.

Early detection in order to improve breast cancer outcome and survival remains the cornerstone of breast cancer control.¹ There is widespread acceptance of the value of regular breast cancer screening as the single most important public health strategy to reduce breast cancer mortality.¹ The reason for this is that breast cancer can be more effectively treated at an early stage. On the other hand, it could also lead to overdiagnosis and overtreatment.⁴ Mammography, clinical breast examination by a health care professional, and breast self-examination can all identify tumors. Mammography can identify early stage breast cancer.

Methodology

To facilitate the interpretation of these guidelines; we briefly describe the methodology we used to develop and grade recommendations and quality of the supporting evidence. We present the details of the methodology in a separate publication.⁹

The Ministry of Health of the Kingdom of Saudi Arabia guideline panel selected the topic of this guideline and all clinical questions addressed herein using a formal prioritization process. For all selected questions we updated existing systematic reviews that were used for the 2010 "Screening for breast cancer in average-risk women aged 40 to 74" guideline by the Canadian Task Force on Preventive Health Care.⁵ We also conducted systematic searches for information that was required to develop full guidelines for the KSA, including



searches for information about patients' values and preferences and cost (resource use) specific to the Saudi context. Based on the updated systematic reviews we prepared summaries of available evidence supporting each recommendation following the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach (see **Appendix 2**).⁶ The guideline panel provided additional information, particularly when lack of published evidence was identified.

We assessed the quality of evidence using the system described by the GRADE working group.⁸ Quality of evidence is classified as "high", "moderate", "low", or "very low" based on decisions about methodological characteristics of the available evidence for a specific health care problem. The definition of each category is as follows:

- *High*: We are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- *Low*: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
- *Very low*: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

According to the GRADE approach, the strength of a recommendation is either strong or conditional (weak) and has explicit implications (see **Table 1**). Understanding the interpretation of these two grades – either strong or conditional – of the strength of recommendations is essential for sagacious clinical decision-making.

Based on this information and the input of KSA MoH panel members we prepared the *evidence-to-recommendation* tables that served the guideline panel to follow the struc-

tured consensus process and transparently document all decisions made during the meeting (see **Appendix 1**). The guideline panel met in Riyadh on December 5, 2013 and formulated all recommendations during this meeting. Potential conflicts of interests of all panel members were managed according to the World Health Organization (WHO) rules.⁷

How to use these guidelines

The Ministry of Health of Saudi Arabia and McMaster University Clinical Practice Guidelines provide clinicians and their patients with a basis for rational decisions about screening for breast cancer in women. Clinicians, patients, third-party payers, institutional review committees, other stakeholders, or the courts should never view these recommendations as dictates. No guidelines and recommendations can take into account all of the oftencompelling unique features of individual clinical circumstances. Therefore, no one charged with evaluating clinicians' actions should attempt to apply the recommendations from these guidelines by rote or in a blanket fashion.

Statements about the underlying values and preferences as well as qualifying remarks accompanying each recommendation are its integral parts and serve to facilitate an accurate interpretation. They should never be omitted when quoting or translating recommendations from these guidelines.

Key questions

The following is a list of the clinical questions selected by the KSA guideline panel as relevant for the Saudi context and addressed in this guideline. For details on the process by which the questions were selected please refer to the separate methodology publication.⁹

1. Should screening for breast cancer with mammography (digital) vs. no



screening be used in women aged 40–49 years?

- 2. Should mammography (digital) be used to screen for breast cancer among women aged 50-69?
- 3. Should mammography (digital) be used to screen for breast cancer among women aged 70-74?
- 4. Should breast self-examination be used to screen for breast cancer among women all ages?
- 5. Should clinical breast examination be used to screen for breast cancer among women all ages?

The question "Should magnetic resonance imaging be used as a strategy for breast cancer screening", which was addressed in the Canadian Task Force on Preventive Health Care 2010 guideline was not considered as relevant for the KSA context by the guideline panel.

Recommendations

I. Use of digital mammography for breast cancer screening

Question 1: Should screening for breast cancer with mammography (digital) vs. no screening be used in women aged 40–49 years?

Summary of findings:

A recent Cochrane systematic review¹⁰ that included data from eight randomized controlled trials (RCT) showed that, in women below 50 years of age, the use of mammography compared to no screening reduces deaths ascribed to breast cancer in 15% without significant effect on all-cause mortality (See evidence to recommendation table 1). The systematic search update conducted did not retrieve any additional evidence. In absolute terms, to save one additional life from breast cancer over about 11 years of follow-up, in this age group, about 2,100 women would need to be screened every 2 to 3 years, 75 women would have an unnecessary breast biopsy, and 690 women will have a false positive mammogram leading to unnecessary anxiety and follow-up testing. Regarding screening interval, the evidence shows that when the option is implemented in intervals <24 months there is a reduction in the risk of death from breast cancer of 18% (RR 0.82 [95%CI, 0.72 – 0.94], High quality evidence), while the 95% confidence interval for screening ≥24 months includes both an important benefit and considerable harm (RR 1.04 [95%CI 0.72 – 1.50], Low quality evidence).

The guideline panel downgraded the quality of the evidence for the outcome breast cancer mortality from moderate to low due to serious indirectness. The panel agreed that there is considerable uncertainty regarding the baseline risk in this specify age subgroup. Their experience and additional local evidence brought to the discussion³ suggest that the baseline risk in Saudi population may be higher, and therefore, the absolute effect of mammography may also be higher. There was disagreement within the panel about the relative importance of the outcome false positive results. After further input from a patient that attended the panel meeting, the outcome of false positive results was rated down from critical to important. Then, the overall quality of the evidence for this recommendation was judged to be "low".

Values and preferences:

There are no local published data on women's values and preferences. However, three sources of data informed this topic: literature existing in other countries,¹¹⁻¹³ panel members' clinical experience, and the opinion of a representative from the patients that participated during the panel meeting. The literature reports that most women value mammography in particular for perceived reduction of mortality; few women consider issues of further testing or harm arising from falsepositives in their decision-making. However, many of the studies were done when participants were already in screening programs. Other women refuse breast cancer screening because of fear, fatalistic beliefs, absence of symptoms, or work or family responsibilities that do not allow for daytime appointments. The majority of women prefer to be jointly



involved in decision making with their care providers, but some would go for screening if recommended by their providers. Based on their clinical experience, the guideline panel decided that any psychological effect of falsepositive results and frequency of screening will have a lower value compared to the perceived benefits on mortality. Finally, the patient participating in the panel meeting corroborated panel's perception and, therefore, this recommendation places higher value for being alive and prevents death from breast cancer irrespective of the consequences of false positive results.

Resource use:

Under lack of local evidence on costs, the guideline panel agreed that the resources needed to allocate are not small. Among the costs related to this intervention can be listed: equipment, and human resources. Although digital mammogram equipment is widely available across regions in the Kingdom, a higher number of well-trained radiologists are needed.

Although there are no published or unpublished data on the cost-effectiveness of mammograms in the context of Saudi Arabia, a recent systematic review¹⁴ including 26 studies from other regions that incorporated cost-effectiveness data alongside randomized controlled trials, or used modelling techniques to estimate cost-effectiveness ratios, determined that mammography and clinical breast examination cost an additional USD 35,500 per quality-adjusted life year (QALY) saved compared with no screening. In addition the review stated that the cost per life years saved, from annual and biennial screening of women aged 40-49 was \$26,200 and \$14,000, respectively. A study mentioned that starting the screening at the age of 40 instead of 50 would cost between \$24,000 to \$65,000 US dollars per QALY gained. Moreover, the cost per QALY gained for triennial screening those aged 47 to 49 was about US\$45,000.¹⁵ The panel determined that probably the incremental cost is small relative to the net benefits.

Acceptability:

Panel members mentioned that they are informed of previous initiatives for implementing breast cancer screening using mammography in the Kingdom.¹⁶ From the panel's point of view, this option is acceptable for all the stakeholders.

Implementation considerations:

The panel highlights that this recommendation represents a good opportunity for shared decision-making. The access for women with disabilities should be guaranteed across the Kingdom. Availability of assessment clinics for women with positive (true & false) screening results should be guaranteed. In addition, the panel recognized the necessity for educating the population on the importance of breast cancer screening strategies.

Monitoring and evaluation:

The panel considered that control and audit the result of mammograms is important. They also mentioned that all radiologists diagnosing and reporting mammograms should be certified and be monitored periodically. Centers offering the service should also be regulated and monitored. In addition, the panel mentioned the need for closer monitoring via the implementation of a mammography national registry

Research priority:

The mammography national registry proposed by the panel also will inform further decisions using more accurate and direct evidence from the local context.

Recommendation 1:

The Ministry of Health of Saudi Arabia guideline panel suggests screening with mammography in women aged 40–49 years every 1 to 2 years. (Conditional recommendation; lowquality evidence)

Remarks:

Based on local cancer registry data, the incidence of breast cancer in the KSA seems to be higher than in the other countries in which studies were conducted. This fact may



indicate that higher benefit on breast cancer mortality justifies a recommendation in favor of implementing breast cancer screening using mammography in this age group. Since the guideline panel determined that there is a close balance between desirable and undesirable consequences, they also suggest implementing shared-decision making strategies as a way to incorporate actively patients' perspective into the decision.

Question 2: Should mammography (digital) be used to screen for breast cancer among women aged 50-69?

Summary of findings:

A recent Cochrane systematic review¹⁰ that included data from seven randomized controlled trials (RCT) showed that, in women at least 50 years of age, the use of mammography compared to no screening reduces deaths ascribed to breast cancer in 12% without significant effect on all-cause mortality (See evidence to recommendation table 2). The systematic search update conducted did not retrieve any additional evidence. In absolute terms, to save one additional life from breast cancer over about 11 years of follow-up, in this age group, about 720 women would need to be screened every 2 to 3 years, 26 women would have an unnecessary breast biopsy, 204 women will have a false positive mammogram leading to unnecessary anxiety and follow-up testing. Regarding screening interval, the evidence shows that when the option is implemented in intervals <24 months there is a reduction in the risk of death from breast cancer of 14% (RR 0.86 [95%CI, 0.75 - 0.98], High quality evidence). Implementing screening ≥24 months also suggests a reduction in breast cancer mortality (RR 0.67 [95%CI 0.51 -0.88], Moderate quality evidence). The overall quality of the evidence for this recommendation was judged to be "Moderate".

Values and preferences:

There are no local published data on women's values and preferences. However, three sources of data informed this topic: literature existing in other countries, ¹¹⁻¹³ panel members' clinical experience, and the opinion of a

representative from the patients that participated during the panel meeting. The literature reports that most women value mammography in particular for perceived reduction of mortality; few women consider issues of further testing or harm arising from falsepositives in their decision-making. However, many of the studies were done when participants were already in screening programs. Other women refuse breast cancer screening because of fear, fatalistic beliefs, absence of symptoms, or work or family responsibilities that do not allow for daytime appointments. The majority of women prefer to be jointly involved in decision making with their care providers, but some would go for screening if recommended by their providers. Based on their clinical experience, the guideline panel decided that any psychological effect of falsepositive results and frequency of screening will have a lower value compared to the perceived benefits on mortality. Finally, the patient participating in the panel meeting corroborated panel's perception and, therefore, this recommendation places higher value for being alive and prevents death from breast cancer irrespective of the consequences of false positive results.

Resource use:

Although there are no published or unpublished data on the cost-effectiveness of mammograms in the context of Saudi Arabia, a recent systematic review¹⁴ including 26 studies from other regions that incorporated cost-effectiveness data alongside randomized controlled trials, or used modeling techniques to estimate cost-effectiveness ratios, determined that mammography and clinical breast examination cost an additional USD 35,500 per quality-adjusted life year (QALY) saved compared with no screening. In addition the review stated that the cost per life years saved, from annual and biennial screening of women aged 40-49 was \$26,200 and \$14,000, respectively. A study mentioned that starting the screening at the age of 40 instead of 50 would cost between \$24,000 to \$65,000 US dollars per QALY gained. Moreover, the cost per QALY gained for triennial screening those aged 47 to 49 was about US\$45,000.15 The





panel determined that probably the incremental cost is small relative to the net benefits.

Acceptability:

Panel members mentioned that they are informed of previous initiatives for implementing breast cancer screening using mammography in the Kingdom.¹⁶ From the panel's point of view, this option is acceptable for all the stakeholders.

Implementation considerations:

The panel highlights that this recommendation represents a good opportunity for shared decision-making. The access for women with disabilities should be guaranteed across the Kingdom. Availability of assessment clinics for women with positive (true & false) screening results should be guaranteed. In addition, the panel recognized the necessity for educating the population on the importance of breast cancer screening strategies.

Monitoring and evaluation:

The panel considered that control and audit the result of mammograms is important. They also mentioned that all radiologists diagnosing and reporting mammograms should be certified and be monitored periodically. Centers offering the service should also be regulated and monitored. In addition, the panel mentioned the need for closer monitoring via the implementation of a mammography national registry

Research priority:

The mammography national registry proposed by the panel also will inform further decisions using more accurate and direct evidence from the local context. Cost effectiveness studies are also needed to inform future guidelines and stakeholders.

Recommendation 2:

The Ministry of Health of Saudi Arabia guideline panel suggests screening with mammography in women aged 50–69 years every 2 years (Conditional recommendation; moderate-quality evidence).

Remarks:

Based on local cancer registry data, the incidence of breast cancer in the KSA for this age group is similar to the ones reported in the literature in other countries. The guideline panel determined that desirable consequences probably outweigh undesirable consequences in most settings.

Question 3: Should mammography (digital) be used to screen for breast cancer among women aged 70-74?

Summary of findings:

A recent systematic review¹⁰ that conducted a meta-analysis of the two trials that reported results for women aged ≥70 years (Swedish Two County, East and West) found that screening led to a non-statistically significant reduction in breast cancer mortality (RR 0.68, 95% CI 0.45-1.01) (See evidence to recommendation table 3). The systematic search update conducted did not retrieve any additional evidence. In absolute terms, to save one additional life from breast cancer over about 11 years of follow-up, in this age group, about 450 women would need to be screened every 2 to 3 years, 11 women would have an unnecessary breast biopsy, 96 women will have a false positive mammogram leading to unnecessary anxiety and follow-up testing.

Regarding screening interval, the evidence shows that when the option is implemented in intervals \geq 24 months there is a 32% reduction in the risk of death ascribed to breast cancer (RR 0.68 [95%CI, 0.45 – 1.01], Low quality evidence), while the 95% confidence interval suggests an important benefit and a negligible harm. The overall quality of the evidence for this recommendation was judged to be "low". The panel considered that the option might not be relevant for this particular age group. Given other competing health risks, breast cancer is not a priority or a main health problem.

Values and preferences:

There are no local published data on women's values and preferences. However, three sources of data informed this topic: literature existing in other countries,¹¹⁻¹³ panel mem-



bers' clinical experience, and the opinion of a representative from the patients that participated during the panel meeting. The literature reports that most women value mammography in particular for perceived reduction of mortality; few women consider issues of further testing or harm arising from falsepositives in their decision-making. However, many of the studies were done when participants were already in screening programs. Other women refuse breast cancer screening because of fear, fatalistic beliefs, absence of symptoms, or work or family responsibilities that do not allow for daytime appointments. The majority of women prefer to be jointly involved in decision making with their care providers, but some would go for screening if recommended by their providers. Based on their clinical experience, the guideline panel decided that any psychological effect of falsepositive results and frequency of screening will have a lower value compared to the perceived benefits on mortality. Finally, the patient participating in the panel meeting corroborated panel's perception and, therefore, this recommendation places higher value for being alive and prevents death from breast cancer irrespective of the consequences of false positive results.

Resource use:

Although there are no published or unpublished data on the cost-effectiveness of mammograms in the context of Saudi Arabia, a recent systematic review¹⁴ including 26 studies from other regions that incorporated cost-effectiveness data alongside randomized controlled trials, or used modeling techniques to estimate cost-effectiveness ratios, determined that mammography and clinical breast examination cost an additional USD 35,500 per quality-adjusted life year (QALY) saved compared with no screening. In addition the review stated that the cost per life years saved, from annual and biennial screening of women aged 40-49 was \$26,200 and \$14,000, respectively. A study mentioned that starting the screening at the age of 40 instead of 50 would cost between \$24,000 to \$65,000 US dollars per QALY gained. Moreover, the cost per QALY gained for triennial screening those

aged 47 to 49 was about US\$45,000.¹⁵ The panel determined that probably the incremental cost is not small relative to the net benefits.

Acceptability:

Panel members mentioned that they are informed of previous initiatives for implementing breast cancer screening using mammography in the Kingdom.¹⁶ From the panel's point of view, this option is acceptable for all the stakeholders.

Implementation considerations:

The panel highlights that this recommendation represents a good opportunity for shared decision-making. The access for women with disabilities should be guaranteed across the Kingdom. Availability of assessment clinics for women with positive (true & false) screening results should be guaranteed. In addition, the panel recognized the necessity for educating the population on the importance of breast cancer screening strategies.

Monitoring and evaluation:

The panel considered that control and audit the result of mammograms is important. They also mentioned that all radiologists diagnosing and reporting mammograms should be certified and be monitored periodically. Centers offering the service should also be regulated and monitored. In addition, the panel mentioned the need for closer monitoring via the implementation of a mammography national registry

Research priority:

The mammography national registry proposed by the panel also will inform further decisions using more accurate and direct evidence from the local context. Cost effectiveness studies are also needed to inform future guidelines and stakeholders.



Recommendation 3:

The Ministry of Health of Saudi Arabia guideline panel suggests no screening with mammography in women aged 70–74 years (Conditional recommendation; low-quality evidence)

Remarks:

Giving the competing risks with other diseases, screening with mammography seems to be not a priority for this age group. Based on local cancer registry data, the incidence of breast cancer in the KSA for this age group is similar to the ones reported in the literature in other countries. The guideline panel determined that undesirable consequences probably outweigh desirable consequences in most settings. In case this option is offered to women between 70 to 74 years old, the panel proposed that this should be done every 2 to 3 years.

II. Use of breast self-examination for breast cancer screening

Question 4: Should breast self-examination be used to screen for breast cancer among women all ages?

Summary of findings:

The evidence synthesis reported on the findings of two studies conducted in Russia¹⁷ and Shanghai.¹⁸ These trials reported that breast self-examination did not lead to significant differences between the option and control groups in all-cause mortality (RR 0.98 [95%CI 0.83-1.2]) (See evidence to recommendation table 4). The cited studies also detected an increased harm for benign breast biopsy. This raises concern for the potential harms of breast self-examination with the subsequent lack of evidence of their effectiveness in decreasing mortality. No new studies on the impact of breast self-examination on breast cancer mortality or all-cause mortality were located in the updated literature search.

The overall quality of the evidence for this recommendation was downgraded from

"moderate" to "very low" given that there is no data informing breast cancer mortality. Values and preferences:

There are no local published data on women's values and preferences. However, three sources of data informed this topic: literature existing in other countries,¹¹⁻¹³ panel members' clinical experience, and the opinion of a representative from the patients that participated during the panel meeting. Some women refuse breast cancer screening because of fear, fatalistic beliefs, absence of symptoms, or work or family responsibilities that do not allow for daytime appointments. The majority of women prefer to be jointly involved in decision making with their care providers, but some would go for screening if recommended by their providers. Based on their clinical experience, the guideline panel decided that any psychological effect of false-positive results and frequency of screening will have a lower value compared to the perceived benefits on mortality. Finally, the patient participating in the panel meeting corroborated panel's perception and, therefore, this recommendation places higher value for being alive and prevents death from breast cancer irrespective of the consequences of false positive results.

Resource use:

Given that there are no published or unpublished data on the cost-effectiveness of breast cancer mortality in the context of Saudi Arabia, the guideline panel determined that the relation between incremental cost and relative to the net benefits is uncertain.

Acceptability:

From the panel's point of view, this option is acceptable for all the stakeholders.

Implementation considerations:

The panel considered this option as feasible and easy to implement.

Research priority:

There is very limited evidence on the effectiveness of breast self-examination. The panel recognizes that more research in this area is needed in order to inform further recommendations on this regard.



Recommendation 4:

The Ministry of Health of Saudi Arabia guideline panel suggests that self-breast examination is not used as a single method of screening for breast cancer in women of all ages. (Conditional recommendation; very-low quality evidence)

Remarks:

The panel determined that the strength of the recommendation should be weak/conditional based on the extensive level of uncertainty and lack of evidence. The guideline panel also highlighted that, when mammography is available, this option should always be offered first to patients. In this regard, breast self-examination plays a secondary role, especially in regions where mammography may not be offered.

III. Use of clinical breast examination for breast cancer screening

Question 5: Should clinical breast examination be used to screen for breast cancer among women all ages?

Summary of findings:

No evidence was found indicating that Clinical Breast Examination reduces breast cancer mortality or all-cause mortality. (See evidence to recommendation table 5).

Values and preferences:

There are no local published data on women's values and preferences. However, three sources of data informed this topic: literature existing in other countries,¹¹⁻¹³ panel members' clinical experience, and the opinion of a representative from the patients that participated during the panel meeting. Some women refuse breast cancer screening because of fear, fatalistic beliefs, absence of symptoms, or work or family responsibilities that do not allow for daytime appointments. The majority of women prefer to be jointly involved in decision making with their care providers, but some would go for screening if recommended by their providers. Based on their clinical experience, the guideline panel decided that any

psychological effect of false-positive results and frequency of screening will have a lower value compared to the perceived benefits on mortality. Finally, the patient participating in the panel meeting corroborated panel's perception and, therefore, this recommendation places higher value for being alive and prevents death from breast cancer irrespective of the consequences of false positive results.

Resource use:

Under lack of local evidence on costs for this intervention, the guideline panel agreed that the resources needed to allocate probably are small. There are no published or unpublished data on the cost effectiveness of clinical breast examination.

Research priority:

There is very limited evidence on the effectiveness of clinical breast examination. The panel recognizes that more research in this area is needed in order to inform further recommendations on this regard

Recommendation 5:

The Ministry of Health of Saudi Arabia guideline panel suggests that clinical breast examination by a health care professional is not used as a single method of screening for breast cancer in women of all ages. (Conditional recommendation; no evidence).

Remarks:

The panel determined that the strength of recommendation should the he weak/conditional based on the extensive level of uncertainty and lack of evidence. The guideline panel also highlighted that when mammography is available, this option should always be offered first to patients. Clinical breast examination could be used as method for breast cancer screening only when mammography is unavailable. This recommendation does not relate to routine physical examination. The option described in this recommendation covers only clinical breast examination in the context of breast cancer screening.



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Appendices

- 1. Evidence-to-Recommendation Tables and Evidence Profiles
- 2. Search Strategies and Results



Appendix 1: Evidence-to-Recommendation Tables and Evidence Profiles

1. Should screening for breast cancer with mammography (digital) vs. no screening be used in women aged 40-49 years?

Problem: Women at average risk of disease (defined as those with no previous breast cancer, no history of breast cancer in a first degree relative, no known mutations in the BRCA1/BRCA2 genes or no previous exposure of the chest wall to radiation). **Option:** Screening for breast cancer using mam**Background:** Regular screening for breast cancer with mammography, breast self-examinations and clinical breast examination by a health care professional are widely recommended to reduce mortality due to breast cancer. Although controversy remains over which screening services should be provided and to whom (age groups), these methods are frequently used in contemporary practice.

Option: Screening for breast cancer using mammography Comparison: No screening Setting: Outpatients Perspective: Health system



Evidence to recommendation framework 1

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	Is the problem a priority?	No Probably Uncertain Probably Yes Varies No Yes □ □ □ □ ☑ □	According to the 2009 Cancer Incidence Report of the Kingdom of Saudi Arabia, breast cancer is the most common among women representing 25.1% of all newly diagnosed female cancers. In 2009 the age-specific incidence rate was 22.7/100,000. The three regions with the highest incidence were Easter region (33.1/100,000), Riyadh region (29.4/100,000), and Makkah region (26.4/100,000). The median age at diagnosis was 48 years (range 19 to 99 years). In Saudi Arabia, the infiltrating duct carcinoma (ICD-O-3, 8500) accounts for the 78.2% of all morphological breast cancer variants. Early detection in order to improve breast cancer outcome and survival remains the cornerstone of breast cancer control. There is widespread acceptance of the value of regular breast cancer screening as the single most important public health strategy to reduce breast cancer mortality. The reason for this is that breast cancer can be more effectively treated at an early stage. On the other hand, it could also lead to overdiagnosis and overtreatment. Mammography, clinical breast examination by a health care professional, and breast self-examination can all identify tumours. Mammography can identify early stage breast cancer.	Based on the data described in the 2009 Cancer Incidence Report of the Kingdom of Saudi Arabia, the Incidence of breast cancer is 25 per 100,000 Based on the data described in the 2009 Cancer Incidence Report of the Kingdom of Saudi Arabia, the guideline panel determined that the age-specific incidence has a bimodal presentation with picks at 45 and 60 years. From the panel's point of view, the pick at 45 years represents an earlier onset of the disease compared to statistics reported in the literature. Al-Eid HS, García AD. Saudi Cancer Registry: Cancer Incidence Report 2009. Saudi Arabia: Kingdom of Saudi Arabia, Ministry of Health; 2012.
	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
BENEFITS & HARMS OF THE OPTIONS	What is the overall certainty of this evidence?	No included studies Very Iow Low Moderate High	The relative importance or values of the main outcomes of interest: Outcome Relative importance Certainty of the evidence	The opinion of guideline panel members was divided – 2 thought the outcome false positives were critical, two thought it was



	CRITERIA	JUDGEMENTS	RESEARCH EV	RESEARCH EVIDENCE						ADDITIONAL CONSIDERATIONS
	Is there important uncertainty about how much	Possibly Probably no No Important important important No known uncertainty uncertainty uncertainty undesirable or variability or variability or variability outcomes	Breast cancer mortality C All cause mortality C False positive results Ir		CriticalLowCriticalHighImportantLow			important. After further imput from a patient that attended the panel meeting, the outcome false positve results was rated down from critical to important.		
	value the main outcomes?		Unnecessary biopsies or surgery Radiation exposure			Important Low Important Low				
	Are the desirable anticipated effects large?	No Probably Uncertain Probably Yes Varies No Yes	Anxiety, distress, or other psychological re- sponses Important Low Summary of findings: Screening for breast cancer with mammography (digital) vs no screening (40-49 years)							
	Are the undesirable anticipated	No Probably Uncertain Probably Yes Varies No Yes	Outcome (follow-up: 11 yr)	Without screening	With mammogra	iphy	Difference (per 1,000,000) (95%Cl)	Relative effect (RR) (95%CI)	Certainty of the evidence (GRADE)	To save one life from breast cancer over about 11 years in this age group, about:
	effects small?		Breast cancer mortality	625 per 195,919	448 per 152,300		474 fewer (115 fewer to 792 fewer)	RR 0.85 (0.75 to 0.96)	LOW	 - 2,100 women would need to be screened every 2 to 3 years - 75 women would have an unnecessary breast biopsy - 690 women will have a false
	Are the desirable effects large relative to undesirable effects?		All cause mortality	2,388 per 132,172	1,373 per 79,098		484 fewer (1,615 fewer to 726 more)	RR 0.97 (0.91 to 1.04)	HIGH	positive mammogram leading to unnecessary anxiety and follow- up testing
		No Probably Closely Probably Yes Varies No balanced Yes	False positive results Overdiagnose §	-	32,700 per 100,000 500		-	-	LOW	§ Overdiagnose: Any invasive or noninvasive breast cancer detected by screening that would not have been identified clinically
			(organized BCS) Unnecessary biopsies or	-	per 100,000 500 Per 100,000		-	-	LOW	not have been identified clinically or would not have resulted in symptoms or death in a person's lifetime is called overdiagnosis



CRITERIA	JUDGEMENTS	RESEARCH EV	IDENCE					ADDITIONAL CONSIDERATIONS
		surgery	· · · · · · · · · · · · · · · · · · ·	40			1.014	
		Radiation exposure	Annual screening (digital) in wo 80 yr is associated with a lifetim fatal breast cancer of 20 to 25 c 100,000	men 40– ne risk of cases in			LOW	Screening interval Screening with mammography on relative risk of death from breast
		Anxiety, distress, or other psychological responses			See table below	-	LOW	- cancer in women 40 to 49 years old <24 months: DD 0.02 (05% CL 0.72 - 0.04)
		·						High quality evidence
		Psychological Ef	fects of False-Positive Mam	mograms	iect size ¶ (95	% CI)	Certainty of the	 24 months: RR 1.04 (95%CI 0.72 – 1.50) Low quality evidence
		<u> </u>		0.40.00.40	0.00\		evidence	
		Distress		0.16 (0.10	- 0.22)			¶ Cohen's effect size interpreta-
		Anxiety		0.22 (0.18	- 0.1 4) - 0.27)			tion 0.2 – Small
		Somatization		0.12 (0.05	– 0.19)		LOW	0.5 – Medium
		Perceived likelihoo	od of getting breast cancer	0.09 (0.04	– 0.14)			0.8 – Large
		Perceived benefits	s of mammography	0.11 (0.06	– 0.17)			
		Frequency of brea	ast self examination	0.11 (0.04	– 0.19)			
		Summary of the of Most women value consider issues of However, many of Other women refu symptoms, or work majority of women	evidence for patients' values e mammography in particular i further testing or harm arising f the studies were done when se breast cancer screening be k or family responsibilities that prefer to be jointly involved in	s and prefe for perceive g from false participants ecause of fe t do not allo n decision n	erences: d reduction c positives in t were alread par, fatalistic l w for daytime naking with th	of mortality; their decisio y in screen beliefs, abs appointme peir care pro	few women on making. ing programs. ence of ents. The oviders, but	Based on local literature, clinical experience, and feedback from a representative from the patients, the guideline panel decided that any psycological effect of false- positive results and frequency of screening will have a lower value compared to the perceived benefits on mortality

CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
		some would go for screening if recommended by their providers.	



Use of Screening Strategies for Detection of Breast Cancer

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	Are the resources required small?	No Probably Uncertain Probably Yes Varies No Yes XI IIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIII	Mammography and clinical breast examination cost an additional USD 35,500 per quality-adjusted life year (QALY) saved compared with no screening.	Under lack of local evidence on costs, the guideline panel agreed that the resources needed to allocate are not small. Among the costs related to this intervention can be listed: equipment, and human resources. Although digital mammogram equipment is widely available across regions in the Kingdom, a higher number
RESOURCE USE	Is the incremental cost small relative to the net benefits?	No Probably Uncertain Probably Yes Varies No Yes IIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIII	In those aged less than 50, two studies from the US and UK were identified. The cost per life years saved, from annual and biennial screening of those aged 40-49 was \$26,200 and \$14,000, respectively. Barratt et al had reported that starting the screening from age 40 instead of 50 would cost \$24,000 to\$ 65,000 US dollars per QALY gained. Moreover, the cost per QALY gained for triennial screening those aged 47 to 49 was about US\$45,000. Rashidian, A., et al. Cost Effectiveness of Breast Cancer Screening Using Mammography; a Systematic Review. Iranian J Publ Health, Vol. 42, No.4, Apr 2013, pp. 347-357	of well-trained radiologists are needed. Compared to no screening, both yielded a similar reduction in breast cancer mortality (13%) during the lifespan of the popula- tion screened and a similar reduction in predicted breast cancer mortality rate (25%) 20 years after the start of the program. The 3% discounted cost-effectiveness ratio for organized screening was €11,512 per life year gained while opportunistic screening had twice the cost, with a ratio of €22,671 to €24,707 per life year gained Cost-effectiveness of opportunistic versus organized mam- mography screening for women aged 50 to 69 (Switzerland)
εαυιτγ	What would be the impact on health inequities?	Increased Probably Uncertain Probably Reduced Varies increased reduced	None identified	The guideline panel agreed that since mammography for breast cancer screening is not systematically offered and widely availa- ble across the Kingdom, the implementation of this recommenda- tion would reduce inequity in a way that larger population would be benefited from this screening strategy.
ACCEPTABILITY	Is the option acceptable to key stakeholders?	No Probably Uncertain Probably Yes Varies No Yes D D D D X D	None identified	Panel members mentioned that they are informed of previous small-scale initiatives for implementing breast cancer screening using mammography in the Kingdom. From the panel point of view, this option is acceptable for all the stakeholders.



	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
FEASIBILITY	Is the option feasible to implement?	No Probably Uncertain Probably Yes Varies No Yes	None identified	The panel highlights that this recommendation would represent a good opportunity for implementing shared decision-making. The access for women with disabilities should be guaranteed across the Kingdom.
				Availability of assessment clinics for women with positive (true + false positive) screening results.

Balance of consequences	Undesirable consequences clearly outweigh desirable consequences in most settings	Undesirable consequences <i>probably</i> <i>outweigh</i> desirable consequences in most settings	The balance between desirable and undesirable consequer is closely balanced	Desirable consequences probably outweigh undesirable consequences in most settings	Desirable consequences <i>clearly outweigh</i> undesirable consequences in most settings
			X		
Type of recommendation	We recommend against offering this option	We suggest no this opti	t offering on	We suggest offering this option	We recommend offering this option
				X	
Recommendation (text)	The Ministry of Health of Saudi Arabia dence)	guideline panel suggests screening wit	h mammography in women aged 40	-49 years every 1 to 2 years. (Condition	al recommendation; low-quality evi-
Justification	Probably higher incidence than in the o	ther countries in which studies were do	one; probably higher benefit on breas	st cancer mortality justifies a recommend	lation in favour of the option
Subgroup considerations	None				



Implementation considerations	 The panel highlights that this recommendation represents a good opportunity for shared decision-making. The access for women with disabilities should be guaranteed across the Kingdom. Availability of assessment clinics for women with positive (true + false) screening results.
Monitoring and evaluation	The panel considered that control and audit the result of mammograms is important. They also mentioned that all radiologists diagnosing and reporting mammograms should be certified and be monitored periodically. Centres offering the service should also be regulated and monitored. In addition, the panel mentioned the need for closer monitoring via the implementation of a national registry
Research priorities	The national registry proposed by the panel also will inform further decisions using more accurate and direct evidence from the local context



Evidence profile: 1. Should mammography vs. no intervention be used for breast cancer screening in women 40 to 49 years old? Author(s): Alonso Carrasco-Labra, Tejan Baldeh Date: 2013-11-28

			(Quality assessm	ient			N⁰ of par	ticipants	Effe	ect	
No. of studies	Study design	Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Quality	Mammography	Control	Relative (95% CI)	Absolute per 1,000,000 (95% CI)	Importance
Breast car	Breast cancer mortality											
8	Randomized trials	Serious ¹	Serious ²	None ³	None⁴	Undetected⁵	⊕⊕⊝⊖ Low	448/152,300	625/195,919	RR 0.85 (0.75 to 0.96)	474 fewer (115 fewer to 792 fewer)	CRITICAL
All-cause	mortality (follow	-up: media	an 11 years)						-		· ·	
2	Randomized trials	None	None ²	None ⁶	None ⁷	Undetected ⁸	⊕⊕⊕⊕ High	1,373/79,098 (1.7%)	2,388/132,172 (1.8%)	RR 0.97 (0.97 to 1.04)	484 fewer (1,615 fewer to 726 more)	CRITICAL
False posi	tive results								-		· · ·	
2	Observational studies	None	None	None	None	Undetected ⁹	⊕⊕⊝⊝ Low	32,700/100,000 (32.7%)	-	-	-	IMPORTANT

1. High risk of bias. Blinding and allocation concealment were unclear for five studies

2. The panel agreed that there is considerable uncertainty regarding the baseline risk in this subgroup. They provided evidence suggesting that the baseline risk in Saudi population may be higher

3. No serious heterogeneity; p-value for testing heterogeneity is 0.48 and I2 =0%

4. Total sample size is large and the total number of events is >300

5. Insufficient number of studies to assess publication bias

6. No serious heterogeneity; p-value for testing heterogeneity is 0.65 and I2 =0%

7. Sample size is large and total number of events is > 300

8. Insufficient number of studies to assess publication bias



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Evidence to recommendation framework 2

2. Should mammography (digital) be used to screen for breast cancer among women aged 50-69?

Problem: Women at average risk of disease (defined as those with no previous breast cancer, no history of breast cancer in a first degree relative, no known mutations in the BRCA1/BRCA2 genes or no previous exposure of the chest wall to radiation). **Option:** Screening for breast cancer using mammography **Comparison:** No screening **Setting:** Outpatients **Perspective:** Health system **Background:** Regular screening for breast cancer with mammography, breast self-examinations and clinical breast examinations are widely recommended to reduce mortality due to breast cancer. However, controversy remains over which screening services should be provided and to whom (age groups), these methods are frequently used in contemporary practice.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	Is the problem a priority?	No Probably Uncertain Probably Yes Varie: No Yes D D D I I	According to the 2009 Cancer Incidence Report of the Kingdom of Saudi Arabia, breast cancer is the most common among women representing 25.1% of all newly diagnosed female cancers. In 2009 the age-specific incidence rate was 22.7/100,000. The three regions with the highest incidence were Easter region (33.1/100,000), Riyadh region (29.4/100,000), and Makkah region (26.4/100,000). The median age at diagnosis was 48 years (range 19 to 99 years). In Saudi Arabia, the infiltrating duct carcinoma (ICD-O-3, 8500) accounts for the 78.2% of all morphological breast cancer variants. Early detection in order to improve breast cancer outcome and survival remains the cornerstone of breast cancer control. There is widespread acceptance of the value of regular breast cancer screening as the single most important public health strategy to reduce breast cancer mortality. The reason for this is that breast cancer can be more effectively treated at an early stage. On the other hand, it could also lead to overdiagnosis and overtreatment. Mammography, clinical breast examination by a health care professional, and breast self-examination can all identify tumours. Mammography can identify early stage breast cancer	Based on the data described in the 2009 Cancer Incidence Report of the Kingdom of Saudi Arabia, the Incidence of breast cancer is 25 per 100,000 Based on the data described in the 2009 Cancer Incidence Report of the Kingdom of Saudi Arabia, the guideline panel determined that the age-specific incidence



VENE CRITERIA JUDGEMENTS RESEARCH EVIDENCE ADDITIONA CONSIDER, What is the overail of this evidence? No included studies Very low Low Moderate High D The relative importance or values of the main outcomes of interest: The opinion of members was 2 thought the of Breast cancer mortality The relative important Moderate High Is there important value the main outcomes Important menetainty or variability or variability or variability or variability Probably no No important important Probably no No important important Probably no No important important The relative importance or values of the main outcomes of interest: The opinion of members was 2 thought the All cause mortality The relative important core mortality Critical Moderate The opinion of members was 2 thought the All cause mortality Important value the main outcomes Important important Probably no important important No important important important No important important Important important Low The opinion of members was 2 thought the All cause mortality The relative important Low The opinion of members was 2 thought the disciplication exposure The relative important Low The opinion of members was 2 thought the disciplication exposure Moderate High The opinion of members was 2 thought the disciplication exposure The relative important Low The opinion of members was 2 tho								has a bimodal presentation with picks at 45 and 60 years. From the panel's point of view, the pick at 45 years represents an earlier onset of the disease compared to statistics reported in the literature. AI-Eid HS, García AD. Saudi Cancer Registry: Cancer Incidence Report 2009. Saudi Arabia: Kingdom of Saudi Arabia, Ministry of Health; 2012.
What is the overall of this evidence? No included studies Very low Low Moderate High Is there important uncertainty outcomes Is there important uncertainty outcomes Is there important uncertainty outcomes Possibly or variability or variability Probably no No important No important Possibly important Probably no No important No important Important Important Low The relative importance or values of the main outcomes of interest: The opinion of important The opinio		CRITERIA	JUDGEMENTS		RESEARCH EVIDENCE			ADDITIONAL CONSIDERATIONS
Very low Low Moderate High Cutcome Relative importance Certainty of the evidence The opinion of members was 2 thought the 4 false positives critical vidence? Is there important uncertaint y about how much people value the main outcomes Probably no No No No No No False positive results Important Low The opinion of members was 2 thought the 4 false positives critical Moderate The opinion of members was 2 thought the 4 false positives critical Very low Important Important Important Important No known or variability or v		What is the overall	No		The relative importance or values of the main o	utcomes of interest:		
Or mis or mis or mis or mis or mis or mis members was 2 thought the false positives evidence? Important Important Important Important Important High false positives critical High false positives critical, two the was important further input fir false positives critical Hoderate 2 thought the false positives critical, two the was important further input fir false positives critical, two the was important further input fir palse positive results Important Low was important further input fir palse palse ourcertainty or variability or vari	S	certainty	included studies Very low Low Moderate High		Outcome	Relative importance	Certainty of the evidence	The opinion of panel
Is there important uncertaint y about how much people value the main outcomes Important uncertainty or variability or variabi	PTION	of this evidence?			Breast cancer mortality	Critical	Moderate	members was divided – 2 thought the outcome
Is there important uncertaint y about how much people value the main outcomes Important uncertainty or variability or variabi	io 里				All cause mortality	Critical	High	false positives were
Important uncertaint y about how much people value the main outcomes Important y about how much people value the main outcomes Important possibly rovariability Probably no important uncertainty No important uncertainty No important uncertainty No important uncertainty No important uncertainty Probably no important uncertainty No important uncertainty No important uncertainty Important uncertainty Important uncertainty Low further input fr patient that att the panel mee outcome false results was rait from critical to important.	S OF T	Is there			False positive results	Important	Low	was important. After
y about how much people value the main outcomes 2 2	IARMS	uncertaint			Overdiagnose	Important	Low	further input from a
be people value the main outcomes or variability or variability or variability or variability or variability outcomes Important Low Outcome false results was rai from critical to important.	ITS & H	y about how much	Possibly Probably no No Important important important No kno uncertainty uncertainty uncertainty undesira	own rable	Unnecessary biopsies or surgery	Important	High	the panel meeting, the
main outcomes 2	pe va	people value the	or variability or variability or variability or variability outcom	mes	Radiation exposure	Important	Low	outcome faise positve results was rated down
ſ		main outcomes ?		4	Anxiety, distress, or other psychological responses	Important	Low	from critical to important.

Are the desirable	No	Probably	Uncertain	Probably	Yes	Varies	Summary of finding (50-69 years)	is: Screening for b	reast cancer with mamme	ography (digital)	vs no scree	ning	To save one life from
anticipate d effects large?		No		Yes			Outcome (follow-up: 11 yr)	Without screening	With mammography	Difference (per 1,000,000) (95%Cl)	Relative effect (RR) (95%Cl)	Certainty the evide (GRADE)	about 11 years in this age group, about: - 720 women would
Are the undesirabl e	No	Probably No	Uncertain	Probably Yes	Yes	Varies	Breast cancer mortality	743 per 115,206	639 per 135,068	1,387 fewer (622 fewer to 2,050 fewer)	RR 0.78 (0.68 to 0.90)	MODERAT	need to be screened every 2 to 3 years - 26 women would have an unnecessary breast
effects small?		X					All cause mortality	690 per 19,694	734 per 19,711	220 more (140 fewer to 620 more)	RR 1.06 (0.96 to 1.2)	HIGH	biopsy - 204 women will have a false positive mammogram leading to
							False positive results	-	28,200 per 100,000	-		LOW	unnecessary anxiety and follow-up testing
							Overdiagnose § (organized BCS)	-	500 per 100,000	-	RR 1.40 (1.35 to 1.45)	LOW	§ Overdiagnose: Any invasive or noninvasive breast cancer detected
							Unnecessary biopsies or surgery	1,083 per 66,154	1,424 per 66,167	5,150 more (3,530 more to 6,902 more)	RR 1.3 (1.2 to 1.4)	HIGH	by screening that would not have been identified clinically or would not have resulted in
Are the desirable effects large	No	Probably No	Uncertain	Probably Yes	Yes	Varies	Radiation exposure	Annual screening (d years old is associat breast cancer of 20	igital) in women 40–80 ted with a lifetime risk of fatal to 25 cases in 100,000	-	-	LOW	person's lifetime is called overdiagnosis (20 yrs period)
undesirabl e effects?				X			Anxiety, distress, or other psychological responses	-	-	See table below	-	LOW	Screening interval Screening with mammography on
							Psychological Effec	ts of False-Positiv	re Mammograms				relative risk of death from breast cancer in women 50 to 69 years old
							Effect		Increase effect size	¶ (95% CI)	Certainty of tl evidence	10	<24 months: RR 0.86 (95%CI. 0.75 –
							Distress		0.16 (0.10 – 0.22)		LOW		0.98) High quality evidence

	×			
		Fear Anxiety Sometization	0.88 (0.03 – 0.14) 0.22 (0.18 – 0.27) 0.12 (0.05 – 0.19)	≥24 months: RR 0.67 (95%Cl 0.51 – 0 88)
		Somalization	0.09(0.04 - 0.14)	Moderate quality
		Perceived henefits of mammography	0.05(0.04 - 0.17)	evidence
		Frequency of breast self examination	0.11 (0.04 – 0.19)	¶ Cohen's effect size
		Summary of the evidence for patients' valu	es and preferences:	0.2 – Small 0.5 – Medium 0.8 – Large
		Most women value mammography in particula issues of further testing or harm arising from fa studies were done when participants were alre cancer screening because of fear, fatalistic be that do not allow for daytime appointments. Th making with their care providers, but some wo	r for perceived reduction of mortality; few women consider alse-positives in their decision making. However, many of the eady in screening programs. Other women refuse breast liefs, absence of symptoms, or work or family responsibilities are majority of women prefer to be jointly involved in decision uld go for screening if recommended by their providers.	Based on local literature, clinical experience, and feedback from a representative from the patients, the guideline panel decided that any psycological effect of false-positive results and frequency of screening will have a lower value compared to the perceived benefits on mortality



	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	Are the resources required small?	No Probably Uncertain Probably Yes Varie No Yes XI IIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIII	Mammography and clinical breast examination cost an additional USD 35,500 per quality-adjusted life year (QALY) saved compared with no screening. In those aged less than 50, two studies from the US and UK were identi-	Under lack of local evidence on costs, the guideline panel agreed that the resources needed to allocate are not small. Among the costs related to this intervention can be listed: equipment, and human resources. Although digital mammogram equipment is
	Is the incremental cost small relative to the net benefits?	No Probably Uncertain Probably Yes Varie No Yes D D D II D	fied. The cost per life years saved, from annual and biennial screening of those aged 40-49 was \$26,200 and \$14,000, respectively. Barratt et al had reported that starting the screening from age 40 instead of 50 would cost \$24,000 to\$ 65,000 US dollars per QALY gained. Moreover, the cost per QALY gained for triennial screening those aged 47 to 49 was about US\$45,000. Rashidian, A., et al. Cost Effectiveness of Breast Cancer Screening Using Mam- mography; a Systematic Review. Iranian J Publ Health, Vol. 42, No.4, Apr 2013, pp. 347-357	of well-trained radiologists are needed. Compared to no screening, both yielded a similar reduction in breast cancer mortality (13%) during the lifespan of the popula- tion screened and a similar reduction in predicted breast cancer mortality rate (25%) 20 years after the start of the program. The 3% discounted cost-effectiveness ratio for organized screening was €11,512 per life year gained while opportunistic screening had twice the cost, with a ratio of €22,671 to €24,707 per life year gained Cost-effectiveness of opportunistic versus organized mam- mography screening for women aged 50 to 69 (Switzerland)
	What would be the impact on health inequities?	Increased Probably Uncertain Probably Reduced Valincreased reduced	es None identified	The guideline panel agreed that since mammography for breast cancer screening is not systematically offered and widely availa- ble across the Kingdom, the implementation of this recommenda- tion would reduce inequity in a way that larger population would be benefited from this screening strategy.
ACCEPTABILITY	Is the option acceptable to key stakeholders ?	No Probably Uncertain Probably Yes Varie No Yes D D D I X D	None identified	Panel members mentioned that they are informed of previous small-scale initiatives for implementing breast cancer screening using mammography in the Kingdom. From the panel point of view, this option is acceptable for all the stakeholders.



	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS		
FEASIBILITY	Is the option feasible to implement?	No Probably Uncertain Probably Yes Varies No Yes D D D D X D	None identified	The panel highlights that this recommendation would represent a good opportunity for implementing shared decision-making. In addition, the panel recognized the necessity for educating the population on the importance of breast cancer screening strategies. The access for women with disabilities should be guaranteed across the Kingdom. Availability of assessment clinics for women with positive (true + false positive) screening results.		



Balance of consequences	Undesirable consequences clearly outweigh desirable consequences in most settings	Undesirable consequences <i>probably</i> <i>outweigh</i> desirable consequences in most settings	The balance between desirable and undesirable consequenc is closely balanced or uncertain	Desirable consequences probably outweigh undesirable consequences in most settings	Desirable consequences clearly outweigh undesirable consequences in most settings
				X	
Type of recommendation	We recommend against offering this option	We suggest no this opti	ot offering V on	Ve suggest offering this option	We recommend offering this option
Recommendation (text)	The Ministry of Health of Saudi Arabia evidence).	guideline panel suggests screening wit	th mammography in women aged 50⊣	69 years every 2 years (Conditional reco	ommendation; moderate-quality
Justification	-				
Subgroup considerations	None				
Implementation considerations	 The panel considered that share Availability of assessment clinics the importance of breast cancer 	ed decision making is crucial for thi s for women with positive (true + fa screening strategies.	s recommendation. The access fo lse) screening results. In addition,	r women with disabilities should be the panel recognized the necessity	guaranteed across the Kingdom. for educating the population on
Monitoring and evaluation	The panel considered that control and a be monitored periodically. Centres offer registry	audit the result of mammograms is imp ring the service should also be regulate	portant. They also mentioned that all ra e and monitor. In addition, the panel m	adiologists diagnosing and reporting man nentioned the need for closer monitoring	nmograms should be certified and via the implementation of a national
Research priorities	The national registry proposed by the p	anel also will inform further decisions	using more accurate and direct eviden	ce from the local context	



Evidence profile: 2. Should mammography vs. no intervention be used for breast cancer screening in women 50 to 69 years old? Author(s): Alonso Carrasco-Labra, Tejan Baldeh Date: 2013-11-28

				Quality assessm	nent			Nº of par	ticipants	Ef	fect	
No. of studies	Study design	Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Quality	Mammography	Control	Relative (95% CI)	Absolute per 1,000,000 (95% Cl)	Importance
Breast car	ncer mortality (fo	ollow-up: r	nedian 11 years	6)								
7	Randomized trials	Serious ¹	None ²	None ³	None ⁴	Undetected⁵	⊕⊕⊕⊖ Moderate	639/135,068 (0.47%)	743/115,206 (0.65%)	RR 0.78 (0.68 to 0.90)	1,387 fewer (622 fewer to 2,050 fewer)	CRITICAL
All-cause	mortality (follow	-up: media	an 11 years)	•	•	•					•	
1	Randomized trials	None	None ²	None ⁶	None ⁷	Undetected⁵	⊕⊕⊕⊕ High	734/19,711 (3.7%)	690/19,694 (3.5%)	RR 1.06 (0.96 to 1.2)	220 more (140 fewer to 620 more)	CRITICAL
False pos	itive results		•	•	•	•			-		• /	
2	Observational studies	None	None ²	None	None	Undetected⁵	⊕⊕⊝⊝ Low	28,200/100,000 (28.2%)	-	-	-	IMPORTANT

1. High risk of bias. Blinding and allocation concealment were unclear for five studies

2. The question addressed is the same for the evidence regarding the population, intervention, comparator and outcome

3. No serious heterogeneity; p-value for testing heterogeneity is 0.12 and I2 =41%

4. Total sample size is large and the total number of events is >300

5. Insufficient number of studies to assess publication bias

6. Single study; heterogeneity not applicable

7. Sample size is large and total number of events is > 300

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Perspective: Health system

Evidence to recommendation framework 3

3. Should mammography (digital) be used to screen for breast cancer among women aged 70-74?

Problem: Women at average risk of disease (defined as those with no previous breast cancer, no history of breast cancer in a first degree relative, no known mutations in the BRCA1/BRCA2 genes or no previous exposure of the chest wall to radiation). **Option:** Screening for breast cancer using mammography **Comparison:** No screening **Setting:** Outpatients **Background:** Regular screening for breast cancer with mammography, breast self-examinations and clinical breast examinations are widely recommended to reduce mortality due to breast cancer. However, controversy remains over which screening services should be provided and to whom (age groups), these methods are frequently used in contemporary practice.



	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	Is the problem a priority?	No Probably Uncertain Probably Yes Varies No Yes	According to the 2009 Cancer Incidence Report of the Kingdom of Saudi Arabia, breast cancer is the most common among women representing 25.1% of all newly diagnosed female cancers. In 2009 the age-specific incidence rate was 22.7/100,000. The three regions with the highest incidence were Easter region (33.1/100,000), Riyadh region (29.4/100,000), and Makkah region (26.4/100,000). The median age at diagnosis was 48 years (range 19 to 99 years). In Saudi Arabia, the infiltrating duct carcinoma (ICD-O-3, 8500) accounts for the 78.2% of all morphological breast cancer variants. Early detection in order to improve breast cancer outcome and survival remains the cornerstone of breast cancer control. There is widespread acceptance of the value of regular breast cancer mortality. The reason for this is that breast cancer can be more effectively treated at an early stage. On the other hand, it could also lead to overdiagnosis and overtreatment. Mammography, clinical breast examination by a health care professional, and breast self-examination can all identify tumours. Mammography can identify early stage breast cancer	The panel considered that the intervention might not be relevant for this particular age group. Given other competing health risks, breast cancer is not a priority or a main health problem. Based on the data described in the 2009 Cancer Incidence Report of the Kingdom of Saudi Arabia, the Incidence of breast cancer is 25 per 100,000 Based on the data described in the 2009 Cancer Incidence Report of the Kingdom of Saudi Arabia, the guideline panel determined that the age-specific incidence has a bimodal presentation with picks at 45 and 60 years. From the panel's point of view, the pick at 45 years represents an earlier onset of the disease compared to statistics reported in the literature. Al-Eid HS, García AD. Saudi Cancer Registry: Cancer Incidence Report 2009. Saudi Arabia: Kingdom of Saudi Arabia, Ministry of Health; 201

	CRITERIA	JUDGEMEN	TS				RESEARCH EVIDENC	RESEARCH EVIDENCE				
F THE	What is the overall	No					The relative importance	The opinion of panel				
MS OI	certainty of	studies Very	low	Low	Moderate	High	Outcome	Relative importance	Certainty of the evidence	members was divide	əd –	
HAR	evidence?]	X			Breast cancer mortality	Critical	Low	false positives were	ne	

CRITERI	IA JUDGEMENTS	RESEARCH EV	IDENCE					ADDITIONAL CONSIDERATIONS
Is there important uncertain about how much people value the main outcomes Are the desirable	nt nty Dw Possibly Important uncertainty or variability Probably no important uncertainty or variability No important uncertainty or variability or variability No important uncertainty or variability No important or variability e Important uncertainty or variability Important uncertainty or variability Important uncertainty or variability No important uncertainty or variability Important uncertainty or variability or variability or variability e Important important Important uncertainty or variability Important uncertainty or variability Important uncertainty or variability e Important Important uncertainty Important uncertainty Important uncertainty e Important Important Important Important Important Important uncertainty e Important Important Important e Important Important e Important Important e Important Important e Important Important	All cause mortality False positive resu Overdiagnose Unnecessary biops surgery Radiation exposure Anxiety, distress, o psychological resp Summary of findia	Criti Its Imp Imp Sies or Imp e Imp r other onses Imp	cal ortant ortant ortant ortant ortant g for breast cance	- Low Low Low Low Low	nphy (digital) vs n	o screening	critical, two thnught it was important. After further input from a patient that attended the panel meeting, the outcome false positve results was rated down from critical to important.
anticipate effects large?		(70-74 years) Outcome (follow-up: 11 yr)	Without screening	With mammography	Difference (per 1,000,000) (95%Cl)	Relative effect (RR) (95%CI)	Certainty of the evidence	
Are the undesirat anticipate effects small?	able No Probably Uncertain Probably Yes Varies ted No Yes I	Breast cancer mortality	50 per 7,307	49 per 10,339	2,218 fewer (3,734 fewer to 39 more)	RR 0.68 (0.45 to 1.01)	(GRADE) LOW	To save one life from breast cancer over about 11 years in this age group, about:
		All cause mortality	-	-	-		-	- 450 women would need to be screened every 2 to 3 years
		False positive results	-	21,200 per 100,000	-	-	LOW	- 11 women would have an unnecessary breast
Are the desirable effects la	e No Probably Closely Probably Yes Varies	Overdiagnose § (organized BCS)	-	500 per 100,000	-	RR 0.09 (0.88 to 0.96)	LOW	- 96 women will have a false positive
relative to undesirat	to IX I I I I I I	Unnecessary biopsies or surgery	-	500 per 100,000	-	-	LOW	and follow-up testing
		Radiation exposure	Annual scree women 40–80 with a lifetime	I. ning (digital) in D yr is associated e risk of fatal breast	-	-	LOW	§ Overdiagnose: Any invasive or noninvasive breast cancer detected

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CRITERIA	JUDGEMENTS	RESEARCH EVI	DENCE						ADDITIONAL CONSIDERATIONS
			cancer of 20 to 25 100,000	cases in					by screening that would not have been identified clinically or would not
		Anxiety, distress, or other psychological responses	-	-	See table below	-	L	LOW	have resulted in symptoms or death in a person's lifetime is
		Psychological Effe	ects of False-Pos	itive Mam	nograms				called overdiagnosis (20 yrs period)
		Effect			Increase effect size ¶ (95	i% CI)	Certainty evidence	y of the e	
		Distress			0.16 (0.10 – 0.22)				
		Fear			0.88 (0.03 – 0.14)				Concerting integral
		Anxiety			0.22 (0.18 – 0.27)				Screening interval
		Somatization		1	0.12 (0.05 – 0.19)			LOW	mammography on
		Perceived likelihood	d of getting breast	cancer	0.09 (0.04 – 0.14)				from breast cancer in
		Perceived benefits	of mammography		0.11 (0.06 – 0.17)				women 70 to 74 years
		Frequency of breas	t self examination		0.11 (0.04 – 0.19)				old
									<24 months: Not available
		Summary of the e	vidence for patie	nts' values	and preferences:				≥24 months: RR 0.68 (95%CI 0.45 –
		Most women value issues of further tes	mammography in sting or harm arisi	particular f ng from fals	or perceived reduction of e-positives in their deci	of mortality; sion making	; few wome g. Howeve	en consider er, many of	1.01) Low quality evidence
		the studies were do cancer screening bu responsibilities that involved in decision their providers.	ne when participa ecause of fear, fai do not allow for d making with their	nts were al alistic belie aytime app care provid	ready in screening prog fs, absence of sympton ointments. The majority ders, but some would go	irams. Othe ns, or work of women o for screer	er women r or family prefer to b ning if reco	refuse breast ne jointly ommended by	¶ Cohen's effect size interpretation 0.2 – Small 0.5 – Medium 0.8 – Large



CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
			Based on local literature, clinical experience, and feedback from a representative from the patients, the guideline panel decided that any psycological effect of false-positive results and frequency of screening will have a lower value compared to the perceived benefits on mortality

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
SE	Are the resources required small?	No Probably Uncertain Probably Yes Varies No Yes X	Mammography and clinical breast examination cost an additional USD 35,500 per quality-adjusted life year (QALY) saved compared with no screening. In those aged less than 50, two studies from the US and UK were	Under lack of local evidence on costs, the guideline panel agreed that the resources needed to allocate are not small. Among the costs related to this intervention can be listed: equipment, and human resources. Although digital mammogram equipment is
RESOURCE US	Is the incremental cost small relative to the net benefits?	No Probably Uncertain Probably Yes Varies No Yes IX I II III	identified. The cost per life years saved, from annual and biennial screening of those aged 40-49 was \$26,200 and \$14,000, respectively. Barratt et al had reported that starting the screening from age 40 instead of 50 would cost \$24,000 to\$ 65,000 US dollars per QALY gained. Moreover, the cost per QALY gained for triennial screening those aged 47 to 49 was about US\$45,000. Rashidian, A., et al. Cost Effectiveness of Breast Cancer Screening Using Mammography; a Systematic Review. Iranian J Publ Health, Vol. 42, No.4,	widely available across regions in the Kingdom, a higher number of well-trained radiologists are needed. Compared to no screening, both yielded a similar reduction in breast cancer mortality (13%) during the lifespan of the popula- tion screened and a similar reduction in predicted breast cancer mortality rate (25%) 20 years after the start of the program. The 3% discounted cost-effectiveness ratio for organized screening

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
			Apr 2013, pp. 347-357	was €11,512 per life year gained while opportunistic screening had twice the cost, with a ratio of €22,671 to €24,707 per life year gained Cost-effectiveness of opportunistic versus organized mam- mography screening for women aged 50 to 69 (Switzerland)
ΕαυιτΥ	What would be the impact on health inequities?	Increased Probably Uncertain Probably Reduced Varies increased reduced	None identified	The guideline panel agreed that since mammography for breast cancer screening is not systematically offered and widely availa- ble across the Kingdom, the implementation of this recommenda- tion would reduce inequity in a way that larger population would be benefited from this screening strategy.
ACCEPTABILITY	Is the option acceptable to key stakeholders ?	No Probably Uncertain Probably Yes Varies No Yes D D D D XI	None identified	Panel members mentioned that they are informed of previous small-scale initiatives for implementing breast cancer screening using mammography in the Kingdom. From the panel point of view, this option is acceptable for all the stakeholders.
FEASIBILITY	Is the option feasible to implement?	No Probably Uncertain Probably Yes Varies No Yes D D D X D	None identified	The panel highlights that this recommendation would represent a good opportunity for implementing shared decision-making. In addition, the panel recognized the necessity for educating the population on the importance of breast cancer screening strate- gies. The access for women with disabilities should be guaranteed across the Kingdom. Availability of assessment clinics for women with positive (true + false positive) screening results.



Balance of consequences	Insequences Undesirable consequences Undesirable consequences probably The balance between clearly outweigh outweigh desirable consequences desirable consequences desirable consequences desirable consequences is closely balanced or uncertain in most settings in most settings in most settings		Desirable consequences probably outweigh undesirable consequences in most settings	Desirable consequences <i>clearly outweigh</i> undesirable consequences in most settings	
		Σ			
Type of recommendation	We recommend against offering this option	We suggest no this opti	ot offering ion	We suggest offering this option	We recommend offering this option
		X			
Recommendation (text)	The Ministry of Health of Saudi Arabia g evidence)	guideline panel suggests no screening	with mammography in women age	d 70–74 years every 2 to 3 years (Condition	onal recommendation; low-quality
Justification	In this group, the panel guideline consic In case this option is offered to women	dered that given other competing healt between 70 to 74 years old, the panel	th risks, breast cancer is not a priori proposed that this should be done	ty or a main health problem every 2 to 3 years	
Subgroup considerations	None				
Implementation considerations	 The access for women with disal results. In addition, the panel record 	bilities should be guaranteed acroscognized the necessity for educatir	ss the Kingdom. Availability of a ng the population on the importa	ssessment clinics for women with posi nce of breast cancer screening strates	itive (true + false) screening gies.
Monitoring and evaluation The panel considered that control and audit the result of mammograms is important. They also mentioned that all radiologic be monitored periodically. Centres offering the service should also be regulate and monitor. In addition, the panel mentior registry		I radiologists diagnosing and reporting ma I mentioned the need for closer monitoring	mmograms should be certified and via the implementation of a national		
Research priorities	The national registry proposed by the pa	anel also will inform further decisions	using more accurate and direct evid	lence from the local context	



Evidence profile: 3. Should mammography vs. no intervention be used for breast cancer screening in women 70 to 74 years old? Author(s): Alonso Carrasco-Labra, Tejan Baldeh

Date: 2013-11-28

	0 1 1	Quality assessment				N° of participants		Effect				
No. of studies	Study design	Risk of bias	Indirectness	Inconsisten- cy	Impreci- sion	Publica- tion bias	Quality	Mammography	Control	Relative (95% Cl)	Absolute (95% CI)	Importance
Breast car	ncer mortality	-		-	-	-		-	-			
2	Randomized trials	Serious ¹	None ²	None ³	Serious ⁴	Undetected⁵	⊕⊕⊝⊖ Low	49/10,339 (0.47%)	50/7,307 (0.7%)	RR 0.68 (0.45 to 1.01)	2,218 fewer (3,734 fewer to 39 more)	CRITICAL
All-cause i	mortality											
No stud- ies report- ing this outcome	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
False posi	tive results							-	•			
2	Observational studies	None	None ²	None	None	Undetected	⊕⊕⊝⊝ Low	21,200/100,000 (21.2%)	-	-	-	IMPORTANT

1. High risk of bias. Blinding and allocation concealment were unclear

2. The question addressed is the same for the evidence regarding the population, intervention, comparator and outcome

3. No serious heterogeneity; p-value for testing heterogeneity is 0.75 and I2 =0%

4. Serious imprecision. Total sample size is large, but the total number of events is <300

5. Insufficient number of studies to assess publication bias

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Evidence to recommendation framework 4



4. Should breast self-examination be used to screen for breast cancer among women all ages?

Problem: Women at average risk of disease (defined as those with no previous breast cancer, no history of breast cancer in a first degree relative, no known mutations in the BRCA1/BRCA2 genes or no previous exposure of the chest wall to radiation). **Option:** Screening for breast cancer using breast self-examination **Comparison:** No screening **Setting:** Outpatients

Perspective: Health system

Background: Regular screening for breast cancer with mammography, breast self-examinations and clinical breast examinations are widely recommended to reduce mortality due to breast cancer. However, controversy remains over which screening services should be provided and to whom (age groups), these methods are frequently used in contemporary practice.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	Is the problem a priority?	No Probably Uncertain Probably Yes Varies No Yes	According to the 2009 Cancer Incidence Report of the Kingdom of Saudi Arabia, breast cancer is the most common among women representing 25.1% of all newly diagnosed female cancers. In 2009 the age-specific incidence rate was 22.7/100,000. The three regions with the highest incidence were Easter region (33.1/100,000), Riyadh region (29.4/100,000), and Makkah region (26.4/100,000). The median age at diagnosis was 48 years (range 19 to 99 years). In Saudi Arabia, the infiltrating duct carcinoma (ICD-O-3, 8500) accounts for the 78.2% of all morphological breast cancer variants. Early detection in order to improve breast cancer outcome and survival remains the cornerstone of breast cancer control. There is widespread acceptance of the value of regular breast cancer mortality. The reason for this is that breast cancer can be more effectively treated at an early stage. On the other hand, it could also lead to overdiagnosis and overtreatment. Mammography, clinical breast examination by a health care professional, and breast self-examination can all identify tumours. Mammography can identify early stage breast cancer.	Based on the data described in the 2009 Cancer Incidence Report of the Kingdom of Saudi Arabia, the Incidence of breast cancer is 25 per 100,000 Based on the data described in the 2009 Cancer Incidence Report of the Kingdom of Saudi Arabia, the guideline panel determined that the age-specific incidence has a bimodal presentation with picks at 45 and 60 years. From the panel's point of view, the pick at 45 years represents an earlier onset of the disease compared to statistics reported in the literature. Al-Eid HS, García AD. Saudi Cancer Registry: Cancer Incidence Report 2009. Saudi Arabia: Kingdom of Saudi Arabia, Ministry of Health; 2012.



	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS	
	What is the overall certainty of this	No included studies Very Iow Low Moderate High	The relative importance or values of the main outcomes of interest: Outcome Relative importance Certainty of the evidence	The opinion of panel members was divided – 2 thought the outcome false	
	evidence?		Breast cancer mortality Critical -	positives were critical, two thought it was important.	
	Is there important uncertainty about how much people value the main outcomes?		All cause mortality Critical MODERATE	After further input from a	
		Possibly Probably no No	Paise positive results Important -	panel meeting, the outcome	
S & HARMS OF THE OPTIONS		t how Important important important important No kno uncertainty uncertainty u	Unnecessary biopsies or surgery Important -	false positve results was rated down from critical to important.	
			Anxiety, distress, or other psychological responses Important -	The overall quality of the	
	Are the		Summary of findings: Screening for breast cancer with breast self-examination vs no screening (all ages)	as very low given that there is no data informing breast cancer mortality.	
BENEFI	desirable anticipated effects large?	No Probably Uncertain Probably Yes Varies No Yes IX I I I I I I	Outcome (follow-up: 11 yr)Without screeningWith clinical breast examinationDifference (per 1,000,000) (95%CI)Relative effect (RR) (95%CI)Certainty of the evidence (GRADE)	No evidence was found indicating that Breast Self Exam reduces breast	
	Are the undesirable anticipated effects small?		Breast cancer of the second se	cancer mortality or all- cause mortality. Two large trials identified no reduction	
		No Probably Uncertain Probably Yes Varies No Yes	All cause mortality 289 per 193,763 292 per 193,596 30 fewer (254 fewer to 234 more) RR 0.98 (0.83 to 1.2) MODERATE	in breast cancer mortality associated with teaching Breast Self Exam to women aged 31 to 64, but found	
				ayeu 31 to 04, but toullu	



CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	RESEARCH EVIDENCE					
		False positive results		-	evidence of increased harm for benign breast biopsy. This rise concern for the			
		Overdiagnose § (organized BCS)		-	potential harms of Breast Self Exam and the			
		Unnecessary	-	-	evidence of their effectiveness in decreasing mortality.			
		Anxiety, distress, or other psychological responses	See table below	-	Breast self-exam has been suggested as a monthly			
					woman's breasts.			
Are the desirable		Psychological Effects of False-Positive Mammograms			Accuracy estimates: - Sensitivity: range from			
effects large relative to	No Probably Uncertain Probably Yes Varies No Yes I	Effect	Increase effect size ¶ (95% CI)	Certainty of the evidence	12% to 41% - Specificity: range from 66% and 81%			
undesirable effects?		Distress	0.16 (0.10 – 0.22)					
chicoto.		Fear	0.88 (0.03 – 0.14)					
		Anxiety	0.22 (0.18 – 0.27)					
		Somatization	0.12 (0.05 – 0.19)	LOW	§ Overdiagnose: Any			
		Perceived likelihood of getting breast cancer	0.09 (0.04 – 0.14)		breast cancer detected by			
		Perceived benefits of mammography	0.11 (0.06 – 0.17)		screening that would not			
		Frequency of breast self examination	0.11 (0.04 – 0.19)		have been identified clinically or would not have			
		Summary of the evidence for patients' valu	ies and preferences:		resulted in symptoms or death in a person's lifetime is called overdiagnosis (20 yrs period)			
		Most women value mammography in partic consider issues of further testing or harm However, many of the studies were done w	cular for perceived reduction of m arising from false-positives in the when participants were already in	ortality; few women ir decision making. screening programs.	¶ Cohen's effect size inter-			



CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
		Other women refuse breast cancer screening because of fear, fatalistic beliefs, absence of symptoms, or work or family responsibilities that do not allow for daytime appointments. The majority of women prefer to be jointly involved in decision making with their care providers, but some would go for screening if recommended by their providers.	pretation 0.2 – Small 0.5 – Medium 0.5 – Medium 0.8 – Large Based on local literature, clinical experience, and feedback from a representative from the patients, the guideline panel decided that any psycological effect of false-positive results and frequency of screening will have a lower value compared to the perceived
			benefits on mortality



	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS	
USE	Are the resources required small?	No Probably Uncertain Probably Yes Varies No Yes D D D D X D		Under lack of local evidence on costs for this intervention, the guideline panel agreed that the resources needed to allocate are	
RESOURCE	Is the incremental cost small relative to the net benefits?	No Probably Uncertain Probably Yes Varies No Yes I I IIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIII	None identified	small. Among the required resources it can be listed: healthy women educational programs, educational material, location for in-person sessions, health care professionals to deliver the message.	
ΕαυιτΥ	What would be the impact on health inequities?	Increased Probably Uncertain Probably Reduced Varies increased reduced	None identified	The guideline panel considered that health inequities would be reduced if this intervention were implemented, as long as the educational program is widely available across the Kingdom.	
ACCEPTABILITY	Is the option acceptable to key stakeholders ?	No Probably Uncertain Probably Yes Varies No Yes DDDDDDDDDDDDDDDDDDDDDDDDDDDDDDDDDDDD	None identified	The guideline panel thinks that the option is acceptable to all stakeholders with no exceptions.	
FEASIBILITY	Is the option feasible to implement?	No Probably Uncertain Probably Yes Varies No Yes	None identified	The panel considered this option as feasible and easy to imple- ment.	



Balance of consequences	Undesirable consequences <i>clearly outweigh</i> desirable consequences in most settings	Undesirable consequences <i>probably</i> <i>outweigh</i> desirable consequences in most settings	The balance between desirable and undesirable consequence is uncertain	Desirable consequences es probably outweigh undesirable consequences in most settings	Desirable consequences clearly outweigh undesirable consequences in most settings
			X		
Type of recommendation	We recommend against offering this option	We suggest no this opti	ot offering W	Ve suggest offering this option	We recommend offering this option
		X			
Recommendation (text) The Ministry of Health of Saudi Arabia guideline panel suggests th recommendation; very-low quality evidence)		guideline panel suggests that self-brea ence)	ast examination is not used as a single	method of screening for breast cancer i	n women of all ages. (Conditional
Justification	The panel determined that the strength ed that when mammography is availab mammography may not be offered.	of the recommendation should be we le, this option should always be offered	ak/conditional based on the extensive l d first to patients. In this regard, breast	level of uncertainty and lack of evidence self-examination plays a secondary role	e. The guideline panel also highlight- e, especially in regions where
Subgroup considerations	None				
Implementation – The panel considered this option as feat considerations		n as feasible and easy to implemer	nt.		
Monitoring and evaluation	-				
Research priorities	There is very limited evidence on the e this regard.	ffectiveness of breast self-examination	. The panel recognizes that more rese	arch in this area is needed in order to in	form further recommendations on



Evidence profile: 4. Should breast self-examination vs. no intervention be used for breast cancer screening in women of all ages? Author(s): Alonso Carrasco-Labra, Tejan Baldeh Date: 2013-11-28

			Quality assessment					N° of participants		Effect		
No. of studies	Study design	Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Quality	Breast self- examination	Control	Relative (95% CI)	Absolute (95% CI)	Importance
Breast cance	er mortality	-	-	-	-	-	-	-	-		-	
No studies reporting this outcome	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
All-cause mo	ortality											
2	Randomized trials	Serious ¹	None ²	None ³	None ⁴	Undetected⁵	⊕⊕⊕⊝ Moderate	292/193,596 (0.15%)	298/193,763 (0.15%)	RR 0.98 (0.84 to 1.15)	30 fewer (254 fewer to 234 more)	CRITICAL
False positiv	e		•			•	-				•	
No studies reporting this outcome	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

1. High risk of bias. Blinding and allocation concealment were unclear

2. The question addressed is the same for the evidence regarding the population, comparator and outcome

3. No serious heterogeneity; p-value for testing heterogeneity is 0.58 and I2 =0%

4. Sample size is large and total number of events >300

5. Insufficient number of studies to assess publication bias

REFERENCES

- Thomas DB, Gao DL, Ray RM, Wang WW, Allison CJ, Chen FL, Porter P, Hu YW, Zhao GL, Pan LD, Li W, Wu C, Coriaty Z, Evans I, Lin MG, Stalsberg H, and Self SG. Randomized trial of breast self-examination in Shanghai: final results. J Natl Cancer Inst. 2002; 94(19): 1445-57. PM:12359854.

- Semiglazov VF, Moiseyenko VM, Bavli JL, Migmanova NS, Seleznyov NK, Popova RT, Ivanova OA, Orlov AA, Chagunava OA, and Barash NJ. The role of breast self-examination in early breast cancer detection (results of the 5-years USSR/WHO randomized study in Leningrad). Eur J Epidemiol. 1992; 8(4): 498-502. PM:1397215.



Evidence to Recommendation Framework 5

5. Should clinical breast examination be used to screen for breast cancer among women all ages?

Problem: Women at average risk of disease (defined as those with no previous breast cancer, no history of breast cancer in a first degree relative, no known mutations in the BRCA1/BRCA2 genes or no previous exposure of the chest wall to radiation). **Option:** Screening for breast cancer using clinical breast examination **Comparison:** No screening **Setting:** Outpatients **Perspective:** Health system **Background:** Regular screening for breast cancer with mammography, breast self-examinations and clinical breast examinations are widely recommended to reduce mortality due to breast cancer. However, controversy remains over which screening services should be provided and to whom (age groups), these methods are frequently used in contemporary practice.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	Is the problem a priority?	No Probably Uncertain Probably Yes Varies No Yes	According to the 2009 Cancer Incidence Report of the Kingdom of Saudi Arabia, breast cancer is the most common among women representing 25.1% of all newly diagnosed female cancers. In 2009 the age-specific incidence rate was 22.7/100,000. The three regions with the highest inci- dence were Easter region (33.1/100,000), Riyadh region (29.4/100,000), and Makkah region (26.4/100,000). The median age at diagnosis was 48 years (range 19 to 99 years). In Saudi Ara- bia, the infiltrating duct carcinoma (ICD-O-3, 8500) accounts for the 78.2% of all morphological breast cancer variants. Early detection in order to improve breast cancer outcome and survival remains the cornerstone of breast cancer control. There is widespread acceptance of the value of regular breast cancer screening as the single most important public health strategy to reduce breast cancer mortality. The reason for this is that breast cancer can be more effectively treated at an early stage. On the other hand, it could also lead to overdiagnosis and overtreatment. Mammography, clinical breast examination by a health care professional, and breast self-examination can all identify tumours. Mammography can identify early stage breast cancer.	Based on the data described in the 2009 Cancer Incidence Report of the Kingdom of Saudi Arabia, the Incidence of breast cancer is 25 per 100,000 Based on the data described in the 2009 Cancer Incidence Report of the Kingdom of Saudi Arabia, the guideline panel determined that the age-specific incidence has a bimodal presentation with picks at 45 and 60 years. From the panel's point of view, the pick at 45 years represents an earlier onset of the disease compared to statistics reported in the literature.



CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
			Al-Eid HS, García AD. Saudi Cancer Registry: Cancer Incidence Report 2009. Saudi Arabia: Kingdom of Saudi Arabia, Ministry of Health; 2012.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	What is the overall	No included	The relative importance or values of the main outcomes of interest:	
	this	studies Very low Low Moderate High	Outcome Relative importance Certainty of the evidence	The opinion of panel members was divided –
6	evidence?		Breast cancer Critical -	2 thought the outcome false positives were
TIONS	Is there important		All cause mortality Critical -	critical, two thought it
= THE OP	uncertainty about how	Possibly Probably no No Important important important _{No known}	False positive Important - results	further input from a patient that attended the
MS OI	much people	uncertainty uncertainty uncertainty uncertainty undesirab or variability or variability or variability or variability outcomes	Overdiagnose Important -	panel meeting, the
ITS & HAR	value the main		Unnecessary biop- sies or surgery Important -	results was rated down from critical to important.
BENEF	outcomes?		Anxiety, distress, or other psychological Important - responses	
	desirable anticipated effects	No Probably Uncertain Probably Yes Varies No Yes	Summary of findings: Screening for breast cancer with clinical breast examination vs no screening	
	large?			No evidence was found



CRITERIA	JUD	GEMEN	TS			RESEARCH EV	IDENCE					ADDITIONAL CONSIDERATIONS
Are the undesirable anticipated effects	No	Probably No	Uncertain	Probably Yes	Yes Varies	Outcome (follow-up: 11 yr)	Without screening	With clinical breast examination	Difference (per 1,000,000) (95%Cl)	Relative effect (RR) (95%CI)	Certainty of the evidence (GRADE)	indicating that Clinical Breast Examination reduces breast cancer mortality or all-cause mortality.
small?						Breast cancer mortality	_	_	_		_	'
						All cause mortality		-	-	-	-	Accuracy of clinical breast examination: - sensitivity: range from
						False positive results	-	-	-	-	-	40% to 69% - specificity: range from 88% to 99%
						Overdiagnose § (organized BCS)	-	-	-	-	-	- positive predictive value: 4% to 50%
						Unnecessary biopsies or surgery	-	-	-		-	§ Overdiagnose: Any invasive or noninvasive
Are the desirable	No	Probably	Uncertain	Probably	Yes Varies	Anxiety, distress, or other psychological responses			See table below	-	-	breast cancer detected by screening that would not have been identified
effects large relative to undesirable		No	X	Yes			L			I		clinically or would not have resulted in symptoms or death in a
effects?						Psychological Ef	fects of False-Po	sitive Mammo	grams			person's lifetime is called overdiagnosis (20 yrs
						Effect		Inc	rease effect size ¶ (95%	Cl) Certain eviden	nty of the ice	period)
						Distress		0.1	6 (0.10 – 0.22)			
						Fear		0.8	8 (0.03 – 0.14)			
						Anxiety		0.2	2 (0.18 – 0.27)			
						Somatization		0.1	2 (0.05 – 0.19)			
						Perceived likelihoo	od of getting breas	t cancer 0.0	9 (0.04 – 0.14)			5 01 1 5 5 1 1
						Perceived benefits	of mammography	/ 0.1	1 (0.06 – 0.17)			¶ Cohen's effect size



CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
		Frequency of breast self examination 0.11 (0.04 – 0.19) Summary of the evidence for patients' values and preferences: Most women value mammography in particular for perceived reduction of mortality; few women consider issues of further testing or harm arising from false-positives in their decision making. However, many of the studies were done when participants were already in screening programs. Other women refuse breast cancer screening because of fear, fatalistic beliefs, absence of symptoms, or work or family responsibilities that do not allow for daytime appointments. The majority of women prefer to be jointly involved in decision making with their care providers, but some would go for screening if recommended by their providers.	interpretation 0.2 – Small 0.5 – Medium 0.8 – Large Based on local literature, clinical experience, and feedback from a representative from the patients, the guideline panel decided that any psycological effect of false-positive results and frequency of screening will have a lower value compared to the perceived benefits on mortality



Use of Screening Strategies for Detection of Breast Cancer

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
USE	Are the resources required small?	No Probably Uncertain Probably Yes Varies No Yes D D D X D		Index look of local ovidence on costs for this intervention the
RESOURCE	Is the incremental cost small relative to the net benefits?	No Probably Uncertain Probably Yes Varies No Yes D D X D D	None identified	guideline panel agreed that the resources needed to allocate probably are small.
εαυιτγ	What would be the impact on health inequities?	Increased Probably Uncertain Probably Reduced Varies increased reduced	None identified	The guideline panel considered that health inequities would be reduced if this intervention were implemented.
ACCEPTABILITY	Is the option acceptable to key stakeholders ?	No Probably Uncertain Probably Yes Varies No Yes D D D D D X D	None identified	The guideline panel determined that this option is acceptable to key stakeholders
FEASIBILITY	Is the option feasible to implement?	No Probably Uncertain Probably Yes Varies No Yes D D D D X D	None identified	The panel considered this option as feasible and easy to imple- ment.



Balance of consequences	Undesirable consequences <i>clearly outweigh</i> desirable consequences in most settings	Undesirable consequences <i>probably</i> <i>outweigh</i> desirable consequences in most settings	The balance between desirable and undesirable consequence <i>is uncertain</i>	Desirable consequences probably outweigh undesirable consequences in most settings	Desirable consequences clearly outweigh undesirable consequences in most settings
			Σ		
Type of recommendation	We recommend against offering this option	We suggest no this opti	t offering W	le suggest offering this option	We recommend offering this option
		X			
Recommendation (text)	The Ministry of Health of Saudi Arabia of women of all ages. (Conditional recomm	guideline panel suggests that clinical b nendation; no evidence)	reast examination by a health care pro	ofessional is not used as a single metho	d of screening for breast cancer in
Justification	The panel determined that the strength ed that when mammography is availabl mammography is unavailable. This reco the context of breast cancer screening.	of the recommendation should be weat e, this option should always be offered ommendation does not relate to routine	ak/conditional based on the extensive l first to patients. Clinical breast examin e physical examination. The option des	level of uncertainty and lack of evidence nation could be used as method for brea scribed in this recommendation covers o	 The guideline panel also highlight- ast cancer screening only when only clinical breast examination in
Subgroup considerations	None				
Implementation considerations					
Monitoring and evaluation	-				
Research priorities	There is very limited evidence on the effectiveness of clinical breast examination. The panel recognizes that more research in this area is needed in order to inform further recommon this regard				



Evidence profile: 5. Should clinical breast examination vs. no intervention be used for breast cancer screening in women of all ages? Author(s): Alonso Carrasco-Labra, Tejan Baldeh Date: 2013-11-28

				Quality assessme	ent			N° of part	icipants	Effe	ect	
No. of studies	Study design	Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Quality	Clinical breast exam- ination	Control	Relative (95% Cl)	Absolute (95% CI)	Importance
Breast cancer	mortality											
No studies reporting this outcome	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
All-cause mor	tality	<u>.</u>	•		•	•	•	•	•	•	•	•
No studies reporting this outcome	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
False positive	results		•			•			-	•		
No studies reporting this outcome	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT



Appendix 2: Search Strategies and Results

Question: Should mammography, clinical breast examination, and self-breast examination be used to screen for breast cancer?

Database: OVID Medline		
Search strategy: screening		Date of search: 11/2013
1 even breast peoplasms/		
2 evo neonlasms/di		
2. exp heoptains/di		
A 2 and 3		
$5 1 \text{ or } \Lambda$		
6 evo mass screening/		
7 (screens or (rountines adi3 (tests or checks or dia	gnoss or detects)))	mn
8 6 or 7		p.
9 5 and 8		
10 exp physical examination/		
11. exp breast/		
12. exp breast neoplasms/		
13. 11 or 12		
14. 10 and 13		
15. exp mammography/		
16.9 and 14		
17.9 and 15		
18. exp mortality/		
19. mo.fs.		
20. 18 or 19		
21. 16 and 20		
22. 17 and 20		
23. 21 or 22		
24. limit 23 to (english language and humans)		
25. limit 24 to (meta analysis or practice guideline or	randomized contro	lled trial)
26. (random\$ or rct).mp.		
27. 24 and 26		
28. (meta-analy\$ or metaanaly\$ or (systematic\$ adj1	.0 review\$)).mp.	
29. 24 and 28		
30. 25 or 27 or 29		
31. 24 not 30		
32. limit 31 to ed=20101001-20131115		
33. limit 30 to ed=20101001-20131115		
Study Types: Randomized controlled trials		
Records Retrieved	30	



Database: Cochrane Central						
Search strategy: screening in general Date of search: 11/2013						
 ((breast\$ or mammary) adj3 (neoplas\$ or tumor\$ d (screen\$ or (rountine\$ adj3 (test\$ or check\$ or dia ((clinical\$ or physical\$) adj3 (exam\$ or detect\$ or d 2 or 3 1 and 4 limit 5 to yr="2010 -Current" Study Types: Randomized controlled trials 	or cancer\$ or carcing gnos\$ or detect\$))). diagnos\$)).mp.	om\$)).mp. mp.				
Records Retrieved	22					

Database: Cochrane Central					
Search strategy: digital mammography	Date of search: 11/2013				
 1. ((digital\$ or computer\$) adj7 mammogra\$).mp. 2. limit 1 to yr="2010 -Current" Study Types: Randomized controlled trials 					
Records Retrieved	1				

Database: Cochrane database of systematic reviews						
Search strategy: screening in general Date of search: 11/2013						
 I. ((breast\$ or mammary) adj3 (neoplas\$ or tumor\$ 2. (screen\$ or (rountine\$ adj3 (test\$ or check\$ or dia 3. ((clinical\$ or physical\$) adj3 (exam\$ or detect\$ or 4. 2 or 3 5. 1 and 4 6. limit 5 to last 2 years 7. ((breast\$ or mammary) adj3 (neoplas\$ or tumor\$ 6. 1 not 7 9. 4 and 7 10. limit 9 to last 2 years Study Types: Systematic reviews of Randomized contacts 	or cancer\$ or carcing gnos\$ or detect\$))). diagnos\$)).mp. or cancer\$ or carcing trolled trials	om\$)).mp. mp. om\$)).kw.				
Records Retrieved 2						

Database: Cochrane database of systematic reviews	
Search strategy: digital mammography	Date of search: 11/2013
1 ((digital f or computer f) adi7 mammagraf) mp	
1. ((digitals or computers) adj/ mammogras).mp.	

2. limit 1 to yr="2010 -Current"



Cm

Study Types: Systematic reviews of Randomized controlled trials

Records Retrieved

Database: OVID Medline	
Search strategy: Ductal carcinoma in situ	Date of search: 11/2013
1. exp carcinoma, intraductal, noninfiltrating/	
2. exp breast neoplasms/	
3. 1 and 2	
4. overdiagnos\$.mp.	
5. over-diagnos\$.mp.	
6. (overtreat\$ or over-treat\$).mp.	
7. exp Diagnostic errors/	
8. exp mass screening/	
9. exp mammography/	
10. 8 or 9	
11. 3 and 7 and 10	
12. 4 or 5 or 6	
13. 3 and 12	
14. limit 13 to ed=20101001-20131115	
Study Types: Randomized controlled trials	
Records Retrieved 24	

Database: OVID Medline	
Search strategy: Adverse effects	Date of search: 11/2013
1. exp mammography/	
2. exp physical examination/	
3. exp mass screening/	
4. 1 or 2 or 3	
5. exp breast/	
6. exp breast diseases/di, ep	
7. 5 or 6	
8. 4 and 7	
9. exp mammography/ae, ct	
10. exp physical examination/ae, ct	
11. exp mass screening/ae, ct	
12. 9 or 10 or 11	
13. 7 and 12	
14. exp diagnostic errors/	
15. (overtest\$ or overdiagnos\$ or over-test\$ or over-diagnos\$).mp.	
16. misdiagnos\$.mp.	
17. (false\$ adj (positiv\$ or negativ\$)).mp.	
18. ((incorrect\$ or false\$ or wrong\$ or bias\$ or mistake\$ or error\$ or err	oneous\$) adj3 (result\$ or find-



ing\$ or test\$ or diagnos\$)) mp	
19 (linanpropriat\$ or unnecess\$ or unnec	ed\$) adi3 (treat\$ or Surg\$ or theran\$ or regimen\$)) mp
20 (observ(\$ adi3 bias\$) mn	
21 or/1/-20	
22. 8 and 21	
23 exp "wounds and Injuries"/ci_et	
24 exp stress nsychological/	
25 exp prejudice/	
26 exp stereotyning/	
27 or/23-26	
28.8 and 27	
29 13 or 22 or 28	
30 limit 29 to english language	
31 limit 30 to (meta analysis or randomize	ed controlled trial)
32 exp evaluation studies/	
33 comparative study nt	
34 exp epidemiologic studies/	
35, 32 or 33 or 34	
36, 30 and 35	
37, 31 or 36	
38. limit 37 to ed=20101001-20131115	
Study Types: Randomized controlled trials	and observational studies
Records Retrieved	147

Database: Cochrane Central	
Search strategy: Adverse effects	Date of search: 11/2013
1. exp mammography/	
2. mammogra\$.mp.	
3. exp physical examination/	
((physical\$ or clinical\$ or manual\$) adj3 exam\$).mp.	
5. exp mass screening/	
6. screen\$.mp.	
7. or/1-6	
8. exp breast/	
9. exp breast diseases/di, ep	
10. (breast\$ or mammar\$).mp.	
11. or/8-10	
12. 7 and 11	
13. ((advers\$ adj3 effect\$) or harm\$ or contraindicat\$).mp.	
14. ae.fs.	
15. or/13-14	
16. 12 and 15	
17. exp mammography/ae, ct	
18. exp physical examination/ae, ct	
19. exp mass screening/ae, ct	
20. or/17-19	
21. 11 and 20	

22. exp diagnostic errors/ 23. (overtest\$ or overdiagnos\$ or over-test\$ or over-diagnos\$).mp. 24. (false\$ adj (result\$ or positiv\$ or negativ\$)).mp. 25. (observ\$ adj3 bias\$).mp. 26. (diagnos\$ adj3 (error\$ or mistak\$ or incorrect\$)).mp. 27. or/22-26 28.12 and 27 29. exp "wounds and Injuries"/ci, et 30. exp stress, psychological/ 31. exp prejudice/ 32. exp stereotyping/ 33. (anxiet\$ or anxious\$ or fear\$ or discriminat\$ or unfair\$ or prejudic\$ or stigma\$ or stereotyp\$).mp. 34. or/29-33 35. 12 and 34 36. 16 or 21 or 28 or 35 37. limit 36 to yr="2010 -Current" Study Types: Randomized controlled trials and observational studies

Records Retrieved

Database: OVID Medline	
Search strategy: Costs	Date of search: 11/2013
1. exp breast neoplasms/	
2. exp neoplasms/di	
3. exp breast/	
4. 2 and 3	
5. 1 or 4	
6. exp mass screening/	
(screen\$ or (rountine\$ adj3 (test\$ or check\$ or diag	gnos\$ or detect\$))).mp.
8. 6 or 7	
9. 5 and 8	
10. exp physical examination/	
11. exp breast/	
12. exp breast neoplasms/	
13. 11 or 12	
14. 10 and 13	
15. exp mammography/	
16. 9 and 14	
17. 9 and 15	
18. 16 or 17	
19. exp "Costs and Cost Analysis"/	
20. 18 and 19	
21. limit 20 to english language	
22. limit 21 to ed=20101001-20131115	
Study Types: Economic evaluation and cost-effectiveness studies	
Records Retrieved	64

Database: Cochrane Central		[
Search strategy: Costs		Date of search: 11/2013
 Search strategy. Costs 1. ((breast\$ or mammary) adj3 (neoplas\$ or tumor\$ or cancer\$ or carcinom\$)).mp. 2. (screen\$ or (rountine\$ adj3 (test\$ or check\$ or diagnos\$ or detect\$))).mp. 3. ((clinical\$ or physical\$) adj3 (exam\$ or detect\$ or diagnos\$)).mp. 4. (cost or costs or costing or economic\$ or financial\$).mp. 5. 1 and (2 or 3) and 4 6. limit 5 to yr="2010 -Current" Study Types: Randomized controlled trials 		
Records Retrieved	2	
Database: Cochrane database of systematic reviews		
Search strategy: Costs		Date of search: 11/2012
Search Shalegy. CUSIS		
 Study Types: Systematic reviews of randomized controlled trials and economic evaluations 		
Records Retrieved	2	
Database: EBSCO CINAHL		r
Search strategy: Patients values and preferences		Date of search: 11/2013
 S1. TI breast cancer screening S2. (MH "Breast Neoplasms/DI") S3. (MM "Mammography") S4. S1 or S2 or S3 S5. (MM "Cancer Screening") S6. (MM "Breast Neoplasms+") S7. S5 and S6 S8. S4 or S7 S9. MM "Patient Compliance" or MM "Consumer Participation" or MH "Patient Satisfaction" or MH "Treatment Refusal" or MH "Consumer Satisfaction" S10. TX women? N3 preference? or TX women? N3 acceptance or TX women? N3 satisfaction or TX women? N3 experience? S11. TX consumer? N3 preference? or TX consumer? N3 acceptance or TX consumer? N3 satisfaction or TX consumer? N3 experience? S12. TX consumer? N3 choice? or TX patient? N3 choice? or TX women* N3 choice? S13. S9 or S10 or S11 or S12 S14. S8 and S13 S15. S8 and S13 [Limiters - Publication Year from: 2010-2013; Language: English, French] 		
515. 58 and 513 [Limiters - Publication Year from: 2010-2013; Language: English, French]		

Study Types: Randomized controlled trials and observational studies

Records Retrieved

Database: OVID Medline		
Search strategy: Patients values and preferencesDate of search: 11/2013		
Search strategy: Patients values and preferencesDate of search: 11/20131 breast cancer screening.ti. 2 exp *Breast Neoplasms/di 3 exp *Mammography/ 4 or/1-3		
Records Retrieved	305	
Database: OVID Medline		
Search strategy: Breast cancer screening frequency	Date of search: 11/2013	
 exp breast neoplasms/ exp neoplasms/di exp breast/ 2 and 3 5. 1 or 4 exp mass screening/ (screen\$ or (rountine\$ adj3 (test\$ or check\$ or diagnos\$ or detect\$))).mp. 6 or 7 5 and 8 exp physical examination/ exp breast/ exp breast neoplasms/ 11 or 12 14. 10 and 13 exp mammography/ 		

16.9 and 14		
17 9 and 15		
18 exp mortality/		
19 mo fs		
20 18 or 19		
21 16 and 20		
22 17 and 20		
23 21 or 22		
24. limit 23 to (english or french)		
25. limit 24 to humans		
26. (biannual or bi-annual).tw.		
27. schedule.tw.		
28. frequency.tw.		
29. (interval not confidence interval).tw.		
30. (annual* or yearly).tw.		
31. biennial.tw.		
32. 26 or 27 or 28 or 29 or 30 or 31		
33. 25 and 32		
34. limit 33 to yr="2010 -Current"		
Study Types: Randomized controlled trials		
Records Retrieved	62	
Database: Google - Grey literature search		
Search strategy:		Date of search: 11/2013
 "breast cancer screening AND harms" "mammography AND harms" "mammography AND costs" "breast cancer screening AND costs" 		
The search was limited to Saudi Arabia		
Study Types: Randomized controlled trials, observational studies, registries		
Records Retrieved	Relevant: 2	



Summary of Searches

Total No. Retrieved:	835
Cochrane:	76
Medline:	632
Embase:	-
Other:	127
Duplicates:	380
No. Total	455
Without duplicates:	
Screening (Title and Al	ostract Review)
No. Excluded:	445
Included for Full Text	10
review:	
Selection (Full Text Re	view)
No. Excluded:	6





