

Breast Cancer

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

April 2014

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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 self-examination 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 re-

duce 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.

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

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 decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Adherence to this recommendation 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 individuals making decisions consistent with their values and preferences.
For policy makers	The recommendation can be adapted as policy in most situations	Policy making will require substantial debate and involvement of various stakeholders.

Key questions

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?

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 to 3 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; 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.

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 covers 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 low- and 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 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 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 over-treatment.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 often-compelling 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 anx-

iety 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 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. 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, 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; 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.

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 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. 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:

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 ≥ 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 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. 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:

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 not be 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 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 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 mammography

Comparison: No screening

Setting: Outpatients

Perspective: Health system

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.

Evidence to recommendation framework 1

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS						
PROBLEM	Is the problem a priority?	No Probably No Uncertain Probably Yes Yes Varies ☐ ☐ ☐ ☐ ☒ ☐	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 low Low Moderate High ☐ ☐ ☒ ☐ ☐	<i>The relative importance or values of the main outcomes of interest:</i> <table><tr><th>Outcome</th><th>Relative importance</th><th>Certainty of the evidence</th></tr><tr><td></td><td></td><td></td></tr></table>	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
Outcome	Relative importance	Certainty of the evidence								

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS																																				
	Is there important uncertainty about how much people value the main outcomes?	Important uncertainty or variability Possibly important uncertainty or variability Probably no important uncertainty or variability No important uncertainty or variability No known undesirable outcomes ☐☒☐☐☐	Breast cancer mortality Critical Low All cause mortality Critical High False positive results Important Low Overdiagnosis Important Low Unnecessary biopsies or surgery Important Low Radiation exposure Important Low	important. After further input from a patient that attended the panel meeting, the outcome false positive results was rated down from critical to important.																																				
	Are the desirable anticipated effects large?	No Probably No Uncertain Probably Yes Yes Varies ☐☐☒☐☐☐	Anxiety, distress, or other psychological re-sponses Important Low																																					
	Are the undesirable anticipated effects small?	No Probably No Uncertain Probably Yes Yes Varies ☐☒☐☐☐☐	Summary of findings: Screening for breast cancer with mammography (digital) vs no screening (40-49 years) <table><tr><th>Outcome (follow-up: 11 yr)</th><th>Without screening</th><th>With mammography</th><th>Difference (per 1,000,000) (95%CI)</th><th>Relative effect (RR) (95%CI)</th><th>Certainty of the evidence (GRADE)</th></tr><tr><td>Breast cancer mortality</td><td>625 per 195,919</td><td>448 per 152,300</td><td>474 fewer (115 fewer to 792 fewer)</td><td>RR 0.85 (0.75 to 0.96)</td><td>LOW</td></tr><tr><td>All cause mortality</td><td>2,388 per 132,172</td><td>1,373 per 79,098</td><td>484 fewer (1,615 fewer to 726 more)</td><td>RR 0.97 (0.91 to 1.04)</td><td>HIGH</td></tr><tr><td>False positive results</td><td>-</td><td>32,700 per 100,000</td><td>-</td><td>-</td><td>LOW</td></tr><tr><td>Overdiagnose § (organized BCS)</td><td>-</td><td>500 per 100,000</td><td>-</td><td>-</td><td>LOW</td></tr><tr><td>Unnecessary biopsies or</td><td>-</td><td>500 Per 100,000</td><td>-</td><td>-</td><td>LOW</td></tr></table>	Outcome (follow-up: 11 yr)	Without screening	With mammography	Difference (per 1,000,000) (95%CI)	Relative effect (RR) (95%CI)	Certainty of the evidence (GRADE)	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	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	False positive results	-	32,700 per 100,000	-	-	LOW	Overdiagnose § (organized BCS)	-	500 per 100,000	-	-	LOW	Unnecessary biopsies or	-	500 Per 100,000	-	-	LOW	To save one life from breast cancer over about 11 years 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 - 690 women will have a false positive mammogram leading to unnecessary anxiety and follow-up testing
	Outcome (follow-up: 11 yr)	Without screening	With mammography	Difference (per 1,000,000) (95%CI)	Relative effect (RR) (95%CI)	Certainty of the evidence (GRADE)																																		
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Overdiagnose § (organized BCS)	-	500 per 100,000	-	-	LOW																																			
Unnecessary biopsies or	-	500 Per 100,000	-	-	LOW																																			
Are the desirable effects large relative to undesirable effects?	No Probably No Closely balanced Probably Yes Yes Varies ☐☐☒☐☐☐		§ Overdiagnose: Any invasive or noninvasive breast cancer detected by screening that would 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 EVIDENCE	ADDITIONAL CONSIDERATIONS																														
			<table><tr><td colspan="2">surgery</td><td></td><td></td></tr><tr><td>Radiation exposure</td><td>Annual screening (digital) in women 40–80 yr is associated with a lifetime risk of fatal breast cancer of 20 to 25 cases in 100,000</td><td>-</td><td>LOW</td></tr><tr><td>Anxiety, distress, or other psychological responses</td><td>-</td><td>See table below</td><td>LOW</td></tr></table> Psychological Effects of False-Positive Mammograms <table><tr><th>Effect</th><th>Increase effect size $\uparrow$ (95% CI)</th><th>Certainty of the evidence</th></tr><tr><td>Distress</td><td>0.16 (0.10 – 0.22)</td><td rowspan="7">LOW</td></tr><tr><td>Fear</td><td>0.88 (0.03 – 0.14)</td></tr><tr><td>Anxiety</td><td>0.22 (0.18 – 0.27)</td></tr><tr><td>Somatization</td><td>0.12 (0.05 – 0.19)</td></tr><tr><td>Perceived likelihood of getting breast cancer</td><td>0.09 (0.04 – 0.14)</td></tr><tr><td>Perceived benefits of mammography</td><td>0.11 (0.06 – 0.17)</td></tr><tr><td>Frequency of breast self examination</td><td>0.11 (0.04 – 0.19)</td></tr></table> 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	surgery				Radiation exposure	Annual screening (digital) in women 40–80 yr is associated with a lifetime risk of fatal breast cancer of 20 to 25 cases in 100,000	-	LOW	Anxiety, distress, or other psychological responses	-	See table below	LOW	Effect	Increase effect size $\uparrow$ (95% CI)	Certainty of the evidence	Distress	0.16 (0.10 – 0.22)	LOW	Fear	0.88 (0.03 – 0.14)	Anxiety	0.22 (0.18 – 0.27)	Somatization	0.12 (0.05 – 0.19)	Perceived likelihood of getting breast cancer	0.09 (0.04 – 0.14)	Perceived benefits of mammography	0.11 (0.06 – 0.17)	Frequency of breast self examination	0.11 (0.04 – 0.19)	Screening interval Screening with mammography on relative risk of death from breast cancer in women 40 to 49 years old <24 months: RR 0.82 (95%CI, 0.72 – 0.94) High quality evidence ≥24 months: RR 1.04 (95%CI 0.72 – 1.50) Low quality evidence $\uparrow$ Cohen's effect size 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 psychological effect of false-positive results and frequency of screening will have a lower value compared to the perceived benefits on mortality
surgery																																		
Radiation exposure	Annual screening (digital) in women 40–80 yr is associated with a lifetime risk of fatal breast cancer of 20 to 25 cases in 100,000	-	LOW																															
Anxiety, distress, or other psychological responses	-	See table below	LOW																															
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Frequency of breast self examination	0.11 (0.04 – 0.19)																																	

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

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
RESOURCE USE	Are the resources required small?	No ☒ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☐ Varies ☐	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 of well-trained radiologists are needed.
	Is the incremental cost small relative to the net benefits?	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☒ Yes ☐ Varies ☐	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	Compared to no screening, both yielded a similar reduction in breast cancer mortality (13%) during the lifespan of the population 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 mammography screening for women aged 50 to 69 (Switzerland)
EQUITY	What would be the impact on health inequities?	Increased ☐ Probably increased ☐ Uncertain ☐ Probably reduced ☒ Reduced ☐ Varies ☐	None identified	The guideline panel agreed that since mammography for breast cancer screening is not systematically offered and widely available across the Kingdom, the implementation of this recommendation 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 No ☐ Uncertain ☐ Probably Yes ☐ Yes ☒ Varies ☐	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 No Uncertain Probably Yes Yes Varies ☐ ☐ ☐ ☐ ☒ ☐	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 *probably outweigh* desirable consequences in most settings



The balance between desirable and undesirable consequences *is closely balanced*



Desirable consequences *probably outweigh* undesirable consequences in most settings



Desirable consequences *clearly outweigh* undesirable consequences in most settings



Type of recommendation

We recommend against offering this option



We suggest not offering this option



We suggest offering this option



We recommend offering this option



Recommendation (text)

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; low-quality evidence)

Justification

Probably higher incidence than in the other countries in which studies were done; probably higher benefit on breast cancer mortality justifies a recommendation 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

No. of studies	Study design	Quality assessment					Quality	N° of participants		Effect		Importance
		Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias		Mammography	Control	Relative (95% CI)	Absolute per 1,000,000 (95% CI)	
Breast cancer mortality												
8	Randomized trials	Serious ¹	Serious ²	None ³	None ⁴	Undetected ⁵	⊕⊕⊖⊖ 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: median 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 positive 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 No Uncertain Probably Yes Yes ☐ ☐ ☐ ☐ ☒	Varies 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 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 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 over-treatment. 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 low Low Moderate High ☐ ☐ ☐ ☒ ☐	The relative importance or values of the main outcomes of interest: <table><tr><th>Outcome</th><th>Relative importance</th><th>Certainty of the evidence</th></tr><tr><td>Breast cancer mortality</td><td>Critical</td><td>Moderate</td></tr><tr><td>All cause mortality</td><td>Critical</td><td>High</td></tr><tr><td>False positive results</td><td>Important</td><td>Low</td></tr><tr><td>Overdiagnose</td><td>Important</td><td>Low</td></tr><tr><td>Unnecessary biopsies or surgery</td><td>Important</td><td>High</td></tr><tr><td>Radiation exposure</td><td>Important</td><td>Low</td></tr><tr><td>Anxiety, distress, or other psychological responses</td><td>Important</td><td>Low</td></tr></table>	Outcome	Relative importance	Certainty of the evidence	Breast cancer mortality	Critical	Moderate	All cause mortality	Critical	High	False positive results	Important	Low	Overdiagnose	Important	Low	Unnecessary biopsies or surgery	Important	High	Radiation exposure	Important	Low	Anxiety, distress, or other psychological responses	Important	Low	The opinion of panel members was divided – 2 thought the outcome false positives were critical, two thought it was important. After further input from a patient that attended the panel meeting, the outcome false positive results was rated down from critical to important.
	Outcome	Relative importance	Certainty of the evidence																									
Breast cancer mortality	Critical	Moderate																										
All cause mortality	Critical	High																										
False positive results	Important	Low																										
Overdiagnose	Important	Low																										
Unnecessary biopsies or surgery	Important	High																										
Radiation exposure	Important	Low																										
Anxiety, distress, or other psychological responses	Important	Low																										
Is there important uncertainty about how much people value the main outcomes ?	Important uncertainty or variability Possibly important uncertainty or variability Probably no important uncertainty or variability No important uncertainty or variability No known undesirable outcomes ☐ ☐ ☒ ☐ ☐																											

Are the desirable anticipated effects large?	No ☐	Probably No ☐	Uncertain ☐	Probably Yes ☒	Yes ☐	Varies ☐	Summary of findings: Screening for breast cancer with mammography (digital) vs no screening (50-69 years) <table><tr><th>Outcome (follow-up: 11 yr)</th><th>Without screening</th><th>With mammography</th><th>Difference (per 1,000,000) (95%CI)</th><th>Relative effect (RR) (95%CI)</th><th>Certainty the evidence (GRADE)</th></tr><tr><td>Breast cancer mortality</td><td>743 per 115,206</td><td>639 per 135,068</td><td>1,387 fewer (622 fewer to 2,050 fewer)</td><td>RR 0.78 (0.68 to 0.90)</td><td>MODERATE</td></tr><tr><td>All cause mortality</td><td>690 per 19,694</td><td>734 per 19,711</td><td>220 more (140 fewer to 620 more)</td><td>RR 1.06 (0.96 to 1.2)</td><td>HIGH</td></tr><tr><td>False positive results</td><td>-</td><td>28,200 per 100,000</td><td>-</td><td>-</td><td>LOW</td></tr><tr><td>Overdiagnose § (organized BCS)</td><td>-</td><td>500 per 100,000</td><td>-</td><td>RR 1.40 (1.35 to 1.45)</td><td>LOW</td></tr><tr><td>Unnecessary biopsies or surgery</td><td>1,083 per 66,154</td><td>1,424 per 66,167</td><td>5,150 more (3,530 more to 6,902 more)</td><td>RR 1.3 (1.2 to 1.4)</td><td>HIGH</td></tr><tr><td>Radiation exposure</td><td colspan="2">Annual screening (digital) in women 40–80 years old is associated with a lifetime risk of fatal breast cancer of 20 to 25 cases in 100,000</td><td>-</td><td>-</td><td>LOW</td></tr><tr><td>Anxiety, distress, or other psychological responses</td><td>-</td><td>-</td><td>See table below</td><td>-</td><td>LOW</td></tr></table>	Outcome (follow-up: 11 yr)	Without screening	With mammography	Difference (per 1,000,000) (95%CI)	Relative effect (RR) (95%CI)	Certainty the evidence (GRADE)	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)	MODERATE	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	False positive results	-	28,200 per 100,000	-	-	LOW	Overdiagnose § (organized BCS)	-	500 per 100,000	-	RR 1.40 (1.35 to 1.45)	LOW	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	Radiation exposure	Annual screening (digital) in women 40–80 years old is associated with a lifetime risk of fatal breast cancer of 20 to 25 cases in 100,000		-	-	LOW	Anxiety, distress, or other psychological responses	-	-	See table below	-	LOW	To save one life from breast cancer over about 11 years 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
Outcome (follow-up: 11 yr)	Without screening	With mammography	Difference (per 1,000,000) (95%CI)	Relative effect (RR) (95%CI)	Certainty the evidence (GRADE)																																																			
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Are the undesirable anticipated effects small?	No ☐	Probably No ☒	Uncertain ☐	Probably Yes ☐	Yes ☐	Varies ☐																																																		
Are the desirable effects large relative to undesirable effects?	No ☐	Probably No ☐	Uncertain ☐	Probably Yes ☒	Yes ☐	Varies ☐																																																		
Psychological Effects of False-Positive Mammograms <table><tr><th>Effect</th><th>Increase effect size ¶ (95% CI)</th><th>Certainty of the evidence</th></tr><tr><td>Distress</td><td>0.16 (0.10 – 0.22)</td><td>LOW</td></tr></table>							Effect	Increase effect size ¶ (95% CI)	Certainty of the evidence	Distress	0.16 (0.10 – 0.22)	LOW	<24 months: RR 0.86 (95%CI, 0.75 – 0.98) High quality evidence																																											
Effect	Increase effect size ¶ (95% CI)	Certainty of the evidence																																																						
Distress	0.16 (0.10 – 0.22)	LOW																																																						

		<table><tr><td><i>Fear</i></td><td>0.88 (0.03 – 0.14)</td></tr><tr><td><i>Anxiety</i></td><td>0.22 (0.18 – 0.27)</td></tr><tr><td><i>Somatization</i></td><td>0.12 (0.05 – 0.19)</td></tr><tr><td><i>Perceived likelihood of getting breast cancer</i></td><td>0.09 (0.04 – 0.14)</td></tr><tr><td><i>Perceived benefits of mammography</i></td><td>0.11 (0.06 – 0.17)</td></tr><tr><td><i>Frequency of breast self examination</i></td><td>0.11 (0.04 – 0.19)</td></tr></table>	<i>Fear</i>	0.88 (0.03 – 0.14)	<i>Anxiety</i>	0.22 (0.18 – 0.27)	<i>Somatization</i>	0.12 (0.05 – 0.19)	<i>Perceived likelihood of getting breast cancer</i>	0.09 (0.04 – 0.14)	<i>Perceived benefits of mammography</i>	0.11 (0.06 – 0.17)	<i>Frequency of breast self examination</i>	0.11 (0.04 – 0.19)	≥24 months: RR 0.67 (95%CI 0.51 – 0.88) Moderate quality evidence
<i>Fear</i>	0.88 (0.03 – 0.14)														
<i>Anxiety</i>	0.22 (0.18 – 0.27)														
<i>Somatization</i>	0.12 (0.05 – 0.19)														
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<i>Frequency of breast self examination</i>	0.11 (0.04 – 0.19)														
			¶ Cohen's effect size interpretation 0.2 – Small 0.5 – Medium 0.8 – Large												
		Summary of the evidence for patients' values and preferences: <i>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.</i>	Based on local literature, clinical experience, and feedback from a representative from the patients, 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												

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
RESOURCE USE	Are the resources required small?	No☒ Probably No☐ Uncertain☐ Probably Yes☐ Yes☐ Varies☐	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 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	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. Compared to no screening, both yielded a similar reduction in breast cancer mortality (13%) during the lifespan of the population 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 mammography screening for women aged 50 to 69 (Switzerland)
	Is the incremental cost small relative to the net benefits?	No☐ Probably No☐ Uncertain☐ Probably Yes☒ Yes☐ Varies☐		
EQUITY	What would be the impact on health inequities?	Increased☐ Probably increased☐ Uncertain☐ Probably reduced☒ Reduced☐ Varies☐	None identified	The guideline panel agreed that since mammography for breast cancer screening is not systematically offered and widely available across the Kingdom, the implementation of this recommendation 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 No☐ Uncertain☐ Probably Yes☐ Yes☒ Varies☐	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 No Uncertain Probably Yes Yes Varies ☐ ☐ ☐ ☐ ☒ ☐	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 <i>clearly outweigh</i> desirable consequences in most settings ☐	Undesirable consequences <i>probably outweigh</i> desirable consequences in most settings ☐	The balance between desirable and undesirable consequences <i>is closely balanced or uncertain</i> ☐	Desirable consequences <i>probably outweigh</i> undesirable consequences in most settings ☒	Desirable consequences <i>clearly outweigh</i> undesirable consequences in most settings ☐
Type of recommendation	We recommend against offering this option ☐	We suggest not offering this option ☐	We suggest offering this option ☒	We recommend offering this option ☐	
Recommendation (text)	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).				
Justification	-				
Subgroup considerations	None				
Implementation considerations	– The panel considered that shared decision making is crucial for this recommendation. The access for women with disabilities should be guaranteed across the Kingdom. Availability of assessment clinics for women with positive (true + false) screening results. 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. Centres offering the service should also be regulate and monitor. 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: 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

No. of studies	Study design	Quality assessment					Quality	N° of participants		Effect		Importance
		Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias		Mammography	Control	Relative (95% CI)	Absolute per 1,000,000 (95% CI)	
Breast cancer mortality (follow-up: median 11 years)												
7	Randomized trials	Serious ¹	None ²	None ³	None ⁴	Undetected ⁵	⊕⊕⊕⊖ 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: median 11 years)												
1	Randomized trials	None	None ²	None ⁶	None ⁷	Undetected ⁵	⊕⊕⊕⊕ 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 positive results												
2	Observational studies	None	None ²	None	None	Undetected ⁵	⊕⊕⊖⊖ 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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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

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 No ☒ Uncertain ☐ Probably Yes ☐ Yes ☐ Varies ☐	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 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 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	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 peaks at 45 and 60 years. From the panel's point of view, the peak 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	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS						
HARMS OF THE INTERVENTION	What is the overall certainty of this evidence?	No included studies Very low Low Moderate High ☐ ☐ ☒ ☐ ☐	The relative importance or values of the main outcomes of interest: <table><tr><th>Outcome</th><th>Relative importance</th><th>Certainty of the evidence</th></tr><tr><td>Breast cancer mortality</td><td>Critical</td><td>Low</td></tr></table>	Outcome	Relative importance	Certainty of the evidence	Breast cancer mortality	Critical	Low	The opinion of panel members was divided – 2 thought the outcome false positives were
Outcome	Relative importance	Certainty of the evidence								
Breast cancer mortality	Critical	Low								

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS																																										
	Is there important uncertainty about how much people value the main outcomes?	Important uncertainty or variability Possibly important uncertainty or variability Probably no important uncertainty or variability No important uncertainty or variability No known undesirable outcomes ☐☐☒☐☐	All cause mortality Critical - False positive results Important Low Overdiagnose Important Low Unnecessary biopsies or surgery Important Low Radiation exposure Important Low Anxiety, distress, or other psychological responses Important Low	critical, two thught it was important. After further input from a patient that attended the panel meeting, the outcome false positive results was rated down from critical to important. To save one life from breast cancer over about 11 years 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 § Overdiagnose: Any invasive or noninvasive breast cancer detected																																										
	Are the desirable anticipated effects large?	No Probably No Uncertain Probably Yes Yes Varies ☐☐☒☐☐☐	Summary of findings: Screening for breast cancer with mammography (digital) vs no screening (70-74 years) <table><tr><th>Outcome (follow-up: 11 yr)</th><th>Without screening</th><th>With mammography</th><th>Difference (per 1,000,000) (95%CI)</th><th>Relative effect (RR) (95%CI)</th><th>Certainty of the evidence (GRADE)</th></tr><tr><td>Breast cancer mortality</td><td>50 per 7,307</td><td>49 per 10,339</td><td>2,218 fewer (3,734 fewer to 39 more)</td><td>RR 0.68 (0.45 to 1.01)</td><td>LOW</td></tr><tr><td>All cause mortality</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr><tr><td>False positive results</td><td>-</td><td>21,200 per 100,000</td><td>-</td><td>-</td><td>LOW</td></tr><tr><td>Overdiagnose § (organized BCS)</td><td>-</td><td>500 per 100,000</td><td>-</td><td>RR 0.09 (0.88 to 0.96)</td><td>LOW</td></tr><tr><td>Unnecessary biopsies or surgery</td><td>-</td><td>500 per 100,000</td><td>-</td><td>-</td><td>LOW</td></tr><tr><td>Radiation exposure</td><td colspan="2">Annual screening (digital) in women 40–80 yr is associated with a lifetime risk of fatal breast</td><td>-</td><td>-</td><td>LOW</td></tr></table>		Outcome (follow-up: 11 yr)	Without screening	With mammography	Difference (per 1,000,000) (95%CI)	Relative effect (RR) (95%CI)	Certainty of the evidence (GRADE)	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)	LOW	All cause mortality	-	-	-	-	-	False positive results	-	21,200 per 100,000	-	-	LOW	Overdiagnose § (organized BCS)	-	500 per 100,000	-	RR 0.09 (0.88 to 0.96)	LOW	Unnecessary biopsies or surgery	-	500 per 100,000	-	-	LOW	Radiation exposure	Annual screening (digital) in women 40–80 yr is associated with a lifetime risk of fatal breast		-	-	LOW
	Outcome (follow-up: 11 yr)	Without screening	With mammography		Difference (per 1,000,000) (95%CI)	Relative effect (RR) (95%CI)	Certainty of the evidence (GRADE)																																							
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Radiation exposure	Annual screening (digital) in women 40–80 yr is associated with a lifetime risk of fatal breast		-	-	LOW																																									
Are the undesirable anticipated effects small?	No Probably No Uncertain Probably Yes Yes Varies ☒☐☐☐☐☐																																													
	Are the desirable effects large relative to undesirable effects?	No Probably No Closely balanced Probably Yes Yes Varies ☒☐☐☐☐☐																																												

To save one life from breast cancer over about 11 years 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

§ Overdiagnose: Any invasive or noninvasive breast cancer detected

CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS																														
		<table><tr><td></td><td colspan="2">cancer of 20 to 25 cases in 100,000</td><td></td><td></td><td></td></tr><tr><td>Anxiety, distress, or other psychological responses</td><td>-</td><td>-</td><td>See table below</td><td>-</td><td>LOW</td></tr></table> Psychological Effects of False-Positive Mammograms <table><tr><th>Effect</th><th>Increase effect size $\uparrow$ (95% CI)</th><th>Certainty of the evidence</th></tr><tr><td>Distress</td><td>0.16 (0.10 – 0.22)</td><td rowspan="7">LOW</td></tr><tr><td>Fear</td><td>0.88 (0.03 – 0.14)</td></tr><tr><td>Anxiety</td><td>0.22 (0.18 – 0.27)</td></tr><tr><td>Somatization</td><td>0.12 (0.05 – 0.19)</td></tr><tr><td>Perceived likelihood of getting breast cancer</td><td>0.09 (0.04 – 0.14)</td></tr><tr><td>Perceived benefits of mammography</td><td>0.11 (0.06 – 0.17)</td></tr><tr><td>Frequency of breast self examination</td><td>0.11 (0.04 – 0.19)</td></tr></table> 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.		cancer of 20 to 25 cases in 100,000					Anxiety, distress, or other psychological responses	-	-	See table below	-	LOW	Effect	Increase effect size $\uparrow$ (95% CI)	Certainty of the evidence	Distress	0.16 (0.10 – 0.22)	LOW	Fear	0.88 (0.03 – 0.14)	Anxiety	0.22 (0.18 – 0.27)	Somatization	0.12 (0.05 – 0.19)	Perceived likelihood of getting breast cancer	0.09 (0.04 – 0.14)	Perceived benefits of mammography	0.11 (0.06 – 0.17)	Frequency of breast self examination	0.11 (0.04 – 0.19)	by screening that would not have been identified clinically or would not have resulted in symptoms or death in a person's lifetime is called overdiagnosis (20 yrs period) Screening interval Screening with mammography on relative risk of death from breast cancer in women 70 to 74 years old <24 months: Not available ≥24 months: RR 0.68 (95%CI 0.45 – 1.01) Low quality evidence $\uparrow$ Cohen's effect size interpretation 0.2 – Small 0.5 – Medium 0.8 – Large
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	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 psychological 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
RESOURCE USE	Are the resources required small?	No ☒ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☐ Varies ☐	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 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.	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.
	Is the incremental cost small relative to the net benefits?	No ☐ Probably No ☒ Uncertain ☐ Probably Yes ☐ Yes ☐ Varies ☐	Rashidian, A., et al. Cost Effectiveness of Breast Cancer Screening Using Mammography; a Systematic Review. Iranian J Publ Health, Vol. 42, No.4,	Compared to no screening, both yielded a similar reduction in breast cancer mortality (13%) during the lifespan of the population 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 mammography screening for women aged 50 to 69 (Switzerland)
EQUITY	What would be the impact on health inequities?	Increased ☐ Probably increased ☐ Uncertain ☐ Probably reduced ☒ Reduced ☐ Varies ☐	None identified	The guideline panel agreed that since mammography for breast cancer screening is not systematically offered and widely available across the Kingdom, the implementation of this recommendation 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 No ☐ Uncertain ☐ Probably Yes ☐ Yes ☒ Varies ☐	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 No ☐ Uncertain ☐ Probably Yes ☐ Yes ☒ Varies ☐	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 <i>clearly outweigh</i> desirable consequences in most settings ☐	Undesirable consequences <i>probably outweigh</i> desirable consequences in most settings ☒	The balance between desirable and undesirable consequences <i>is closely balanced or uncertain</i> ☐	Desirable consequences <i>probably outweigh</i> undesirable consequences in most settings ☐	Desirable consequences <i>clearly outweigh</i> undesirable consequences in most settings ☐
Type of recommendation	We recommend against offering this option ☐	We suggest not offering this option ☒	We suggest offering this option ☐	We recommend offering this option ☐	
Recommendation (text)	The Ministry of Health of Saudi Arabia guideline panel suggests no screening with mammography in women aged 70–74 years every 2 to 3 years (Conditional recommendation; low-quality evidence)				
Justification	In this group, the panel guideline considered that given other competing health risks, breast cancer is not a priority or a main health problem 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				
Subgroup considerations	None				
Implementation considerations	– The access for women with disabilities should be guaranteed across the Kingdom. Availability of assessment clinics for women with positive (true + false) screening results. 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. Centres offering the service should also be regulate and monitor. 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: 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

No. of studies	Study design	Quality assessment					Quality	N° of participants		Effect		Importance
		Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias		Mammography	Control	Relative (95% CI)	Absolute (95% CI)	
Breast cancer mortality												
2	Randomized trials	Serious ¹	None ²	None ³	Serious ⁴	Undetected ⁵	⊕⊕⊖⊖ 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 mortality												
No studies reporting this outcome	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
False positive 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 No Uncertain Probably Yes Yes Varies ☐ ☐ ☐ ☐ ☒ ☐	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 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 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 peaks at 45 and 60 years. From the panel's point of view, the peak at 45 years represents an earlier onset of the disease compared to statistics reported in the literature. Al-Eid HS, Garcia 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 low Low Moderate High ☐☒☐☐☐	The relative importance or values of the main outcomes of interest: <table><tr><th>Outcome</th><th>Relative importance</th><th>Certainty of the evidence</th></tr><tr><td>Breast cancer mortality</td><td>Critical</td><td>-</td></tr><tr><td>All cause mortality</td><td>Critical</td><td>MODERATE</td></tr><tr><td>False positive results</td><td>Important</td><td>-</td></tr><tr><td>Overdiagnose</td><td>Important</td><td>-</td></tr><tr><td>Unnecessary biopsies or surgery</td><td>Important</td><td>-</td></tr><tr><td>Anxiety, distress, or other psychological responses</td><td>Important</td><td>-</td></tr></table>	Outcome	Relative importance	Certainty of the evidence	Breast cancer mortality	Critical	-	All cause mortality	Critical	MODERATE	False positive results	Important	-	Overdiagnose	Important	-	Unnecessary biopsies or surgery	Important	-	Anxiety, distress, or other psychological responses	Important	-	The opinion of panel members was divided – 2 thought the outcome false positives were critical, two thought it was important. After further input from a patient that attended the panel meeting, the outcome false positive results was rated down from critical to important.
	Outcome	Relative importance	Certainty of the evidence																						
	Breast cancer mortality	Critical	-																						
	All cause mortality	Critical	MODERATE																						
False positive results	Important	-																							
Overdiagnose	Important	-																							
Unnecessary biopsies or surgery	Important	-																							
Anxiety, distress, or other psychological responses	Important	-																							
Is there important uncertainty about how much people value the main outcomes?	Important uncertainty or variability Possibly important uncertainty or variability Probably no important uncertainty or variability No important uncertainty or variability No known undesirable outcomes ☐☐☒☐☐																								
Are the desirable anticipated effects large?	No Probably No Uncertain Probably Yes Yes Varies ☒☐☐☐☐☐	Summary of findings: Screening for breast cancer with breast self-examination vs no screening (all ages) <table><tr><th>Outcome (follow-up: 11 yr)</th><th>Without screening</th><th>With clinical breast examination</th><th>Difference (per 1,000,000) (95%CI)</th><th>Relative effect (RR) (95%CI)</th><th>Certainty of the evidence (GRADE)</th></tr><tr><td>Breast cancer mortality</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr><tr><td>All cause mortality</td><td>289 per 193,763</td><td>292 per 193,596</td><td>30 fewer (254 fewer to 234 more)</td><td>RR 0.98 (0.83 to 1.2)</td><td>MODERATE</td></tr></table>	Outcome (follow-up: 11 yr)	Without screening	With clinical breast examination	Difference (per 1,000,000) (95%CI)	Relative effect (RR) (95%CI)	Certainty of the evidence (GRADE)	Breast cancer mortality	-	-	-	-	-	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	The overall quality of the evidence was considered as very low given that there is no data informing breast cancer mortality.				
Outcome (follow-up: 11 yr)	Without screening	With clinical breast examination	Difference (per 1,000,000) (95%CI)	Relative effect (RR) (95%CI)	Certainty of the evidence (GRADE)																				
Breast cancer mortality	-	-	-	-	-																				
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Are the undesirable anticipated effects small?	No Probably No Uncertain Probably Yes Yes Varies ☐☐☒☐☐☐		No evidence was found indicating that Breast Self Exam reduces breast cancer mortality or all-cause mortality. Two large trials identified no reduction in breast cancer mortality associated with teaching Breast Self Exam to women aged 31 to 64, but found																						

CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS																								
Are the desirable effects large relative to undesirable effects?	No Probably No Uncertain Probably Yes Yes Varies ☐ ☒ ☐ ☐ ☐ ☐	<table><tr><td>False positive results</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr><tr><td>Overdiagnose § (organized BCS)</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr><tr><td>Unnecessary biopsies or surgery</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr><tr><td>Anxiety, distress, or other psychological responses</td><td colspan="2"></td><td>See table below</td><td>-</td><td>-</td></tr></table>	False positive results	-	-	-	-	-	Overdiagnose § (organized BCS)	-	-	-	-	-	Unnecessary biopsies or surgery	-	-	-	-	-	Anxiety, distress, or other psychological responses			See table below	-	-	evidence of increased harm for benign breast biopsy. This rise concern for the potential harms of Breast Self Exam and the corresponding lack of evidence of their effectiveness in decreasing mortality. Breast self-exam has been suggested as a monthly examination of the woman's breasts.
		False positive results	-	-	-	-	-																				
Overdiagnose § (organized BCS)	-	-	-	-	-																						
Unnecessary biopsies or surgery	-	-	-	-	-																						
Anxiety, distress, or other psychological responses			See table below	-	-																						
		Psychological Effects of False-Positive Mammograms <table><tr><th>Effect</th><th>Increase effect size ¶ (95% CI)</th><th>Certainty of the evidence</th></tr><tr><td>Distress</td><td>0.16 (0.10 – 0.22)</td><td rowspan="7">LOW</td></tr><tr><td>Fear</td><td>0.88 (0.03 – 0.14)</td></tr><tr><td>Anxiety</td><td>0.22 (0.18 – 0.27)</td></tr><tr><td>Somatization</td><td>0.12 (0.05 – 0.19)</td></tr><tr><td>Perceived likelihood of getting breast cancer</td><td>0.09 (0.04 – 0.14)</td></tr><tr><td>Perceived benefits of mammography</td><td>0.11 (0.06 – 0.17)</td></tr><tr><td>Frequency of breast self examination</td><td>0.11 (0.04 – 0.19)</td></tr></table> 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.	Effect	Increase effect size ¶ (95% CI)	Certainty of the evidence	Distress	0.16 (0.10 – 0.22)	LOW	Fear	0.88 (0.03 – 0.14)	Anxiety	0.22 (0.18 – 0.27)	Somatization	0.12 (0.05 – 0.19)	Perceived likelihood of getting breast cancer	0.09 (0.04 – 0.14)	Perceived benefits of mammography	0.11 (0.06 – 0.17)	Frequency of breast self examination	0.11 (0.04 – 0.19)	Accuracy estimates: - Sensitivity: range from 12% to 41% - Specificity: range from 66% and 81% § Overdiagnose: Any invasive or noninvasive breast cancer detected by screening that would not have been identified clinically or would not have resulted in symptoms or death in a person's lifetime is called overdiagnosis (20 yrs period) ¶ Cohen's effect size inter-						
Effect	Increase effect size ¶ (95% CI)	Certainty of the evidence																									
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	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
			<i>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.</i>	pretation 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 psychological 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
RESOURCE USE	Are the resources required small?	No Probably No Uncertain Probably Yes Yes Varies ☐ ☐ ☐ ☐ ☒ ☐	None identified	Under lack of local evidence on costs for this intervention, the guideline panel agreed that the resources needed to allocate are 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.
	Is the incremental cost small relative to the net benefits?	No Probably No Uncertain Probably Yes Yes Varies ☐ ☐ ☒ ☐ ☐ ☐		
EQUITY	What would be the impact on health inequities?	Increased Probably increased Uncertain Probably reduced Reduced Varies ☐ ☐ ☐ ☒ ☐ ☐	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 No Uncertain Probably Yes Yes Varies ☐ ☐ ☐ ☐ ☒ ☐	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 No Uncertain Probably Yes Yes Varies ☐ ☐ ☐ ☐ ☒ ☐	None identified	The panel considered this option as feasible and easy to implement.

Balance of consequences	Undesirable consequences <i>clearly outweigh</i> desirable consequences in most settings ☐	Undesirable consequences <i>probably outweigh</i> desirable consequences in most settings ☐	The balance between desirable and undesirable consequences <i>is uncertain</i> ☒	Desirable consequences <i>probably outweigh</i> undesirable consequences in most settings ☐	Desirable consequences <i>clearly outweigh</i> undesirable consequences in most settings ☐
Type of recommendation	We recommend against offering this option ☐	We suggest not offering this option ☒	We suggest offering this option ☐	We recommend offering this option ☐	
Recommendation (text)	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)				
Justification	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.				
Subgroup considerations	None				
Implementation considerations	– The panel considered this option as feasible and easy to implement.				
Monitoring and evaluation	-				
Research priorities	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.				

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

No. of studies	Study design	Quality assessment					Quality	N° of participants		Effect		Importance
		Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias		Breast self-examination	Control	Relative (95% CI)	Absolute (95% CI)	
Breast cancer mortality												
No studies reporting this outcome	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
All-cause mortality												
2	Randomized trials	Serious ¹	None ²	None ³	None ⁴	Undetected ⁵	⊕⊕⊕⊖ 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 positive												
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

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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 No Uncertain Probably Yes Yes ☐ ☐ ☐ ☐ ☒ Varies ☐	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 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 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 peaks at 45 and 60 years. From the panel's point of view, the peak 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																					
BENEFITS & HARMS OF THE OPTIONS	What is the overall certainty of this evidence?	No included studies ☒ Very low ☐ Low ☐ Moderate ☐ High ☐	The relative importance or values of the main outcomes of interest: <table><tr><th>Outcome</th><th>Relative importance</th><th>Certainty of the evidence</th></tr><tr><td>Breast cancer mortality</td><td>Critical</td><td>-</td></tr><tr><td>All cause mortality</td><td>Critical</td><td>-</td></tr><tr><td>False positive results</td><td>Important</td><td>-</td></tr><tr><td>Overdiagnose</td><td>Important</td><td>-</td></tr><tr><td>Unnecessary biopsies or surgery</td><td>Important</td><td>-</td></tr><tr><td>Anxiety, distress, or other psychological responses</td><td>Important</td><td>-</td></tr></table> Summary of findings: Screening for breast cancer with clinical breast examination vs no screening (all ages)	Outcome	Relative importance	Certainty of the evidence	Breast cancer mortality	Critical	-	All cause mortality	Critical	-	False positive results	Important	-	Overdiagnose	Important	-	Unnecessary biopsies or surgery	Important	-	Anxiety, distress, or other psychological responses	Important	-	The opinion of panel members was divided – 2 thought the outcome false positives were critical, two thought it was important. After further input from a patient that attended the panel meeting, the outcome false positive results was rated down from critical to important.
	Outcome	Relative importance		Certainty of the evidence																					
	Breast cancer mortality	Critical		-																					
All cause mortality	Critical	-																							
False positive results	Important	-																							
Overdiagnose	Important	-																							
Unnecessary biopsies or surgery	Important	-																							
Anxiety, distress, or other psychological responses	Important	-																							
Is there important uncertainty about how much people value the main outcomes?	Important uncertainty or variability ☐ Possibly important uncertainty or variability ☐ Probably no important uncertainty or variability ☒ No important uncertainty or variability ☐ No known undesirable outcomes ☐																								
Are the desirable anticipated effects large?	No ☐ Probably No ☐ Uncertain ☒ Probably Yes ☐ Yes ☐ Varies ☐																								

CRITERIA		JUDGEMENTS						RESEARCH EVIDENCE						ADDITIONAL CONSIDERATIONS
Are the undesirable anticipated effects small?		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%CI)	Relative effect (RR) (95%CI)	Certainty of the evidence (GRADE)	indicating that Clinical Breast Examination reduces breast cancer mortality or all-cause mortality.
		☐	☐	☒	☐	☐	☐	Breast cancer mortality	-	-	-	-	-	
Are the desirable effects large relative to undesirable effects?								All cause mortality	-	-	-	-	-	Accuracy of clinical breast examination: - sensitivity: range from 40% to 69% - specificity: range from 88% to 99% - positive predictive value: 4% to 50%
								False positive results	-	-	-	-	-	
								Overdiagnose § (organized BCS)	-	-	-	-	-	
								Unnecessary biopsies or surgery	-	-	-	-	-	
								Anxiety, distress, or other psychological responses			See table below	-	-	
								Psychological Effects of False-Positive Mammograms						

CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
		<i>Frequency of breast self examination</i> 0.11 (0.04 – 0.19) Summary of the evidence for patients' values and preferences: <i>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.</i>	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 psychological 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
RESOURCE USE	Are the resources required small?	No Probably No Uncertain Probably Yes Yes Varies ☐ ☐ ☐ ☒ ☐ ☐	None identified	Under lack of local evidence on costs for this intervention, the guideline panel agreed that the resources needed to allocate probably are small.
	Is the incremental cost small relative to the net benefits?	No Probably No Uncertain Probably Yes Yes Varies ☐ ☐ ☒ ☐ ☐ ☐		
EQUITY	What would be the impact on health inequities?	Increased Probably increased Uncertain Probably reduced Reduced Varies ☐ ☐ ☐ ☒ ☐ ☐	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 No Uncertain Probably Yes Yes Varies ☐ ☐ ☐ ☐ ☒ ☐	None identified	The guideline panel determined that this option is acceptable to key stakeholders
FEASIBILITY	Is the option feasible to implement?	No Probably No Uncertain Probably Yes Yes Varies ☐ ☐ ☐ ☐ ☒ ☐	None identified	The panel considered this option as feasible and easy to implement.

Balance of consequences	Undesirable consequences <i>clearly outweigh</i> desirable consequences in most settings ☐	Undesirable consequences <i>probably outweigh</i> desirable consequences in most settings ☐	The balance between desirable and undesirable consequences <i>is uncertain</i> ☒	Desirable consequences <i>probably outweigh</i> undesirable consequences in most settings ☐	Desirable consequences <i>clearly outweigh</i> undesirable consequences in most settings ☐
Type of recommendation	We recommend against offering this option ☐	We suggest not offering this option ☒	We suggest offering this option ☐	We recommend offering this option ☐	
Recommendation (text)	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)				
Justification	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 routine physical examination. The option described in this recommendation covers only clinical breast examination in the context of breast cancer screening.				
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 recommendations on 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

No. of studies	Study design	Quality assessment					Quality	N° of participants		Effect		Importance
		Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias		Clinical breast examination	Control	Relative (95% CI)	Absolute (95% CI)	
Breast cancer mortality												
No studies reporting this outcome	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
All-cause mortality												
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. exp breast neoplasms/ 2. exp neoplasms/di 3. exp breast/ 4. 2 and 3 5. 1 or 4 6. exp mass screening/ 7. (screen\$ or (rountine\$ adj3 (test\$ or check\$ or diagnos\$ 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. 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 controlled trial) 26. (random\$ or rct).mp. 27. 24 and 26 28. (meta-analy\$ or metaanaly\$ or (systematic\$ adj10 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
1. ((breast\$ or mammary) adj3 (neoplas\$ or tumor\$ or cancer\$ or carcinom\$)).mp. 2. (screen\$ or (routine\$ adj3 (test\$ or check\$ or diagnos\$ or detect\$))).mp. 3. ((clinical\$ or physical\$) adj3 (exam\$ or detect\$ or diagnos\$)).mp. 4. 2 or 3 5. 1 and 4 6. limit 5 to yr="2010 -Current" Study Types: Randomized controlled trials	
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
1. ((breast\$ or mammary) adj3 (neoplas\$ or tumor\$ or cancer\$ or carcinom\$)).mp. 2. (screen\$ or (routine\$ adj3 (test\$ or check\$ or diagnos\$ or detect\$))).mp. 3. ((clinical\$ or physical\$) adj3 (exam\$ or detect\$ or diagnos\$)).mp. 4. 2 or 3 5. 1 and 4 6. limit 5 to last 2 years 7. ((breast\$ or mammary) adj3 (neoplas\$ or tumor\$ or cancer\$ or carcinom\$)).kw. 8. 1 not 7 9. 4 and 7 10. limit 9 to last 2 years Study Types: Systematic reviews of Randomized controlled trials	
Records Retrieved	2

Database: Cochrane database of systematic reviews	
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: Systematic reviews of Randomized controlled trials	
Records Retrieved	1

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 erroneous\$) adj3 (result\$ or find-	

ing\$ or test\$ or diagnos\$)).mp.
 19. ((inappropriat\$ or unnecess\$ or unneed\$) adj3 (treat\$ or Surg\$ or therap\$ or regimen\$)).mp.
 20. (observ\$ adj3 bias\$).mp.
 21. or/14-20
 22. 8 and 21
 23. exp "wounds and Injuries"/ci, et
 24. exp stress, psychological/
 25. exp prejudice/
 26. exp stereotyping/
 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 randomized controlled trial)
 32. exp evaluation studies/
 33. comparative study.pt.
 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/
 4. ((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

45

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/
7. (screen\$ or (routin\$ adj3 (test\$ or check\$ or diagnos\$ 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
1. ((breast\$ or mammary) adj3 (neoplas\$ or tumor\$ or cancer\$ or carcinom\$)).mp. 2. (screen\$ or (routine\$ 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	3

Database: Cochrane database of systematic reviews	
Search strategy: Costs	Date of search: 11/2013
1. ((breast\$ or mammary) adj3 (neoplas\$ or tumor\$ or cancer\$ or carcinom\$)).mp. 2. (screen\$ or (routine\$ 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: Systematic reviews of randomized controlled trials and economic evaluations	
Records Retrieved	2

Database: EBSCO CINAHL	
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]	

Study Types: Randomized controlled trials and observational studies	
Records Retrieved	125

Database: OVID Medline	
Search strategy: Patients values and preferences	Date of search: 11/2013
1 breast cancer screening.ti. 2 exp *Breast Neoplasms/di 3 exp *Mammography/ 4 or/1-3 5 *mass screening/ 6 exp *Breast neoplasms/ 7 5 and 6 8 4 or 7 9 *"patient acceptance of healthcare"/ or *patient compliance/ or *patient participation/ or patient satisfaction/ or patient preference/ or *treatment refusal/ 10 (women? adj3 (acceptance or preference? or satisfaction or experience?)).tw. 11 (consumer? adj3 (acceptance or preference? or satisfaction or experience?)).tw. 12 (patient? adj3 (acceptance or preference? or satisfaction or experience?)).tw. 13 willingness to pay.tw. 14 ((conjoint or contingent) adj3 (valuation or analysis)).tw. 15 or/9-14 16 8 and 15 17 limit 16 to (english or french) 18 limit 17 to yr="2010 -Current" Study Types: Randomized controlled trials and observational studies	
Records Retrieved	305

Database: OVID Medline	
Search strategy: Breast cancer screening frequency	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/ 7. (screen\$ or (routine\$ adj3 (test\$ or check\$ or diagnos\$ 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. 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 Abstract Review)	
No. Excluded:	445
Included for Full Text review:	10
Selection (Full Text Review)	
No. Excluded:	6

