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Evidence-Based Series 15-11 Version 3 REQUIRES UPDATING

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Magnetic Resonance Imaging Screening of Women at High Risk for Breast Cancer

The Expert Panel on MRI Screening of Women at High Risk for Breast Cancer

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An assessment conducted in January 2021 indicated that Evidence-Based Series (EBS) 15-11 Version 3 REQUIRES UPDATING. It is still appropriate for this document to be available while this updating process unfolds. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

EBS 15-11 consists of 4 sections. You can access the summary and full report here: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/2051

Section 1:	**Guideline Recommendations (ENDORSED)**
Section 2A:	**Systematic Review**
Section 2B:	**Systematic Review of Cost-Effectiveness Literature**
Section 3:	**EBS Development Methods and External Review Process**
Section 4:	**Document Review Summary and Tool**

January 24, 2018

For information about this report, the PEBC, and/or the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
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Guideline Report History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES AND KEY CHANGES
	Search Dates	Data		
Original version Apr 2007	1988-2006	Full Report	Peer-reviewed publication Web publication	N/A
Reviewed Version 2 Aug 2012	2006 –2011	New data found in Section 4 (Appendix A)		2007 recommendations are **ENDORSED**
Current Version 3 Jan 2018	2012-2017	New data found in Section 4: Document Review Summary and Tool		2012 recommendations are **ENDORSED**

Table of Contents

Evidence-Based Series 15-11 Version 3: Section 1

Magnetic Resonance Imaging Screening of Women at High Risk for Breast Cancer: Guideline Recommendations

The Expert Panel on MRI Screening of Women at High Risk for Breast Cancer

A Quality Initiative of the
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

These guideline recommendations have been ENDORSED, which means that the recommendations are still current and relevant for decision making.
Please see Section 4 (Document Review Summary and Tool) for a summary of updated evidence published between 2007 and 2017,
and for details on how this Clinical Practice Guideline was ENDORSED.

January 24, 2018

Questions
- What is the effectiveness of adding breast magnetic resonance imaging (MRI) to standard screening (mammography) compared to screening mammography alone?
- Does the addition of breast MRI to standard screening detect breast cancer at an earlier stage?
- What is the optimal frequency of MRI screening?
- Are there subgroups (risk category, age, or breast density) that benefit more from MRI screening than do others?
- What harms are associated with MRI screening, and are there any relative or absolute contraindications to its use?
- In the presence of an abnormal finding seen only on MRI imaging, what is the optimal workup and follow-up after screening?

Target Population
      Women at very high risk for breast cancer, 'very high risk' being defined as:
1. Known mutation in BRCA1, BRCA2 or other gene predisposing to a markedly elevated breast cancer risk.
2. Untested first-degree relative of a carrier of such a gene mutation

3. Family history consistent with a hereditary breast cancer syndrome and estimated personal lifetime cancer risk >25%.
4. High-risk marker on prior biopsy (atypical ductal hyperplasia, atypical lobular hyperplasia, lobular carcinoma in situ [LCIS]) or previous breast cancer.
5. Radiation therapy to chest (before age 30 and at least eight years previous but screening would not start before age 30. [e.g., a patient who is 35 and had radiation at age 29 would be eligible when she is 37. A patient who is 26 and had radiation at age 18 would be eligible at age 30. A patient who is 40 and had radiation at age 31 is not eligible]).

RECOMMENDATIONS
(The recommendations were slightly modified with respect to risk category 5 during the 2017 ENDORSEMENT)

MRI in addition to mammography is recommended for women in target population risk categories 1, 2, 3, and 5 above. The evidence is insufficient to recommend MRI screening for patients in risk category 4.

- Multiple studies, four in abstract form, were identified that evaluated MRI in comparison to mammography in women at high risk for breast cancer. These studies all found superior sensitivity for the detection of breast cancer with MRI compared to mammography. MRI was also found by most studies to have inferior specificity to mammography, with higher recall and biopsy rates associated with MRI.
- A meta-analysis done by the Working Group in 2007 of eight studies with the necessary data found MRI to have numerically superior discriminatory power overall compared to mammography in determining the true breast cancer status of high-risk women. The summary sensitivity was 80.1% (95% confidence interval [CI] 73.3% to 85.8%) for MRI and 36.8% (95% CI 29.6% to 44.5%) for mammography. The summary specificity was 93.0% (95% CI 92.5% to 93.6%) for MRI and 97.5% (95% CI 97.1% to 97.8%) for mammography. The overall diagnostic odds ratio for MRI was 77.338 (95% CI 29.117 to 205.41) versus 32.003 (14.633 to 69.989) for mammography. Due to the limited number of studies included, a direct statistical comparison of the two modalities was not possible.
- *Added to the 2017 Endorsement:* The risk of breast cancer by age 50 years is comparable to BRCA1 mutation carriers in category 5 patients; namely 35% and 31% in Hodgkin's Lymphoma survivors and BRCA1 carriers, respectively (Moskowitz CS, Chou JF, Wolden SL, et al. Breast cancer after chest radiation therapy for childhood cancer. J Clin Oncol. 2014;32(21):2217-23).

Expert Opinion and Qualifying Statements
- While there is insufficient evidence at this time to make a definitive recommendation regarding the appropriate screening frequency, it is the opinion of the Working Group that women should be screened annually, as this was the frequency typical of the identified studies on which the recommendation for screening is based.
- While there is insufficient evidence at this time to make a definitive recommendation regarding the ages of patients who should be screened, it is the opinion of the Working Group that women should be screened annually from 30 to 69 years of age. Age 30 is an appropriate age to begin screening as women at that age with BRCA mutations are at much greater risk of breast cancer than women aged 50 and older in the general population. Age 69 is an appropriate age to end screening because: the relative risk of cancer decreases with age in the population at hereditary risk; mammographic sensitivity increases with age; very few subjects were included in the studies greater than age 69; and the evidence

for mortality reduction from screening in the general population is lacking for women older than age 70.

Expert opinion and qualifying statements modified in the 2017 Endorsement:

- It is the opinion of the Working Group that the benefits of MRI in terms of increased sensitivity outweigh the potential harms of higher recall rates and biopsy rates for all women in risk category 5 who received ≥20 Gy radiation before the age of 30. For this group, screening should begin at age 30 or eight years after the chest irradiation, whichever is later, as the risk for breast cancer does not increase significantly until eight years after treatment (Koo E, Henderson MA, Dwyer M, Skandarajah AR. Management and prevention of breast cancer after radiation to the chest for childhood, adolescent, and young adulthood malignancy. Ann Surg Oncol. 2015 Dec;22 Suppl 3:S545-51).

- The Children's Oncology Group's Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancer (http://www.survivorshipguidelines.org/) recommends that for patients in risk category 5, annual screening with both mammography and MRI begin at age 25, a starting age consistent with U.S. MRI screening guidelines for the other high risk groups (National Comprehensive Cancer Network. Breast Cancer Screening and Diagnosis [Version 1.2017] https://www.nccn.org/professionals/physician_gls/pdf/breast-screening.pdf. Accessed 20 November 2017). This (Ontario) Working Group, however, did not find justification for screening from age 25 in this group (or any of the other high risk groups). In particular, a review of one prospective and 3 retrospective studies published since 2011 that looked at the results of adding MRI to mammography for screening risk category 5 found only 3 cases of breast cancer detected before age 30 out of a total of 51 cases and all 3 of these were detected by both MRI and mammography (See Section 4 for additional information).

- With respect to risk category 4, there are preliminary data that a subgroup of patients in risk category 4 might benefit from the addition of MRI to mammography (e.g., women who in addition to a high risk benign biopsy or previous breast cancer, also have breast density ≥50% and a family history of breast cancer though insufficient to put them in category 3 [Nadler M, Al-Attar H, Warner E, et al. MRI surveillance for women with dense breasts and a previous breast cancer and/or high risk lesion. Breast. 2017 Aug;34:77-82]). The Expert Panel members, however, consider the evidence to be insufficient to recommend MRI screening for risk category 4.

Contact Information
For information about this report, the PEBC, and/or the most current version of all reports,
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Evidence-Based Series 15-11 Version 3: Section 2A

Magnetic Resonance Imaging Screening of Women at High Risk for Breast Cancer: A Systematic Review

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A Quality Initiative of the
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

Please see Section 4 (Document Review Summary and Tool) for a summary of updated evidence published between 2007 and 2017.

Section Date: April 12, 2007

QUESTION(S)
- What is the effectiveness of adding breast magnetic resonance imaging (MRI) to standard screening (mammography) compared to screening mammography alone?
- Does the addition of breast MRI to standard screening detect breast cancer at an earlier stage?
- What is the optimal frequency of MRI screening?
- Are there subgroups (risk category, age, or breast density) that benefit more from MRI screening?
- What harms are associated with MRI screening, and are there any relative or absolute contraindications to its use?
- In the presence of an abnormal finding seen only on MRI imaging, what is the optimal workup and follow-up after screening?

Target Population
      Women at very high risk for breast cancer, very high risk being defined as:
1. Known mutation in BRCA1, BRCA2 or other gene predisposing to a markedly elevated breast cancer risk.
2. Untested first degree relative of a carrier of such a gene mutation
3. Family history consistent with a hereditary breast cancer syndrome and estimated personal lifetime cancer risk >25%.

4. High-risk marker on prior biopsy (atypical ductal hyperplasia, atypical lobular hyperplasia, lobular carcinoma in situ [LCIS]).
5. Radiation therapy to chest (before age 30 and at least 8 years previous).

INTRODUCTION

Since the discovery in the mid-1990's that inherited autosomal dominant mutations in the genes BRCA1 or BRCA2 confer an up to 85% lifetime risk of breast cancer, with substantial risk from age 30 onwards, tremendous attention has been focused on how to screen women with either proven mutations or a strong family history of breast cancer suggestive of an inherited predisposition. Moreover, because these women have an up to 65% risk of contralateral breast cancer after an initial breast cancer diagnosis (1), ongoing screening of this high-risk population is often the responsibility of the oncologist.

While the confirmation of a BRCA1 or BRCA2 mutation in a woman, either with or without a family history of breast/ovarian cancer, is considered to be the strongest known breast cancer risk factor to date, other groups of women would still be considered to be at very high risk. Their risk factors include the following:

- **Genetic factors:** Women who have rare inherited germline mutations (TP53 – Li-Fraumeni Syndrome, PTEN – Cowden Syndrome) (2) or who are untested first-degree relatives of a man/woman with a BRCA mutation are considered at high risk.

- **Family History:** Women in families with multiple relatives with early-onset breast cancer and/or epithelial ovarian cancer may have an inherited predisposition to breast cancer. Other features suggestive of inherited risk are bilateral breast cancer, breast and ovarian cancer in the same individual, or male breast cancer. Ashkenazi Jewish women are at particularly high risk, even with less striking family histories. In high-risk families, genetic testing may not be informative, because of the absence of affected relatives for testing or because of a false-negative genetic test (2). Moreover, in approximately 50% of families with a history highly suggestive of an inherited predisposition to breast cancer but no ovarian cancer, the cancer is not BRCA-related (3). Several models have been developed to estimate lifetime breast cancer risk in these families, including that by Claus (4) and BRACPRO (5) and the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) (6). The latter two models also provide an estimate of the risk of a woman carrying a BRCA1 or BRCA2 mutation.

- **Clinical indicators of high risk:** Women receiving therapeutic chest irradiation before the age of 30 (e.g., for Hodgkin's disease) have a highly elevated risk from 15 years post-treatment onwards, but breast cancer has been reported as early as 8 years after treatment (7). Additionally, a benign biopsy showing lobular carcinoma in situ [6 to 10 fold increased risk vs. general population (8)] and benign biopsy showing atypical ductal or atypical lobular hyperplasia [(4-5 fold risk) (9)] are clinical indicators of high risk. Mammographic density has been consistently shown to be a strong independent risk factor for the development of breast cancer. In several studies, women with the greatest breast density have been found to have a 4-6 fold increased risk of breast cancer compared to women with the least dense breasts (10-14).

Several recent models have attempted to combine various risk factors to come up with a lifetime risk (14-18).

Until very recently, consensus guidelines for screening the high-risk population have relied chiefly on mammography (the only screening modality proven to reduce mortality in any population) with the exclusion of other modalities, because there had never been a screening trial directed at the 'very high risk' population (19,20). The most recent version of the National Comprehensive Cancer Network (NCCN) recommendations for breast cancer

screening and diagnosis, published in 2006, (21) states that annual MRI should be considered for women with BRCA mutations, as an adjunct to mammogram and clinical breast exam, but this is the first time this recommendation has appeared. The 2003 update to the American Cancer Society (ACS) guidelines for breast cancer screening (22), the most recent available, indicated that "the evidence currently available is insufficient to justify recommendations for any of these [i.e., MRI or ultrasound] screening approaches."

Since the alternative to breast screening for very high-risk women is bilateral prophylactic mastectomy, which is known to reduce mortality by over 90% (23), a recommendation for screening can be justified ethically only if the vast majority of tumours can be detected either prior to invasion (ductal carcinoma in situ [DCIS]) or at a very early stage of invasion (node-negative cancers ≤ 1 cm in diameter) for which the systemic recurrence rate is less than 10% (24-26). Unfortunately, studies of women who have inherited BRCA mutations undergoing conventional mammography-based screening have been extremely disappointing. In two prospective (27,28), one retrospective (29), and one series that included both retrospective and prospective data (30), very few cases of DCIS were detected, 40% to 78% of the invasive cancers were greater than 1cm in size, 20% to 56% had lymph node involvement, and the interval cancer rate ranged from 35% to 50%.

The relatively poor performance of mammography in these studies is not surprising. In the general population, the mortality reduction of screening mammography for women ages 40 to 49 is lower than for older women, mainly due to generally greater radiologic breast density (x-ray attenuating fibroglandular tissue) resulting in lower imaging sensitivity (31). In women younger than age 40, breast density is even greater. Moreover, BRCA1-related cancers are more often either mammographically occult or misread as benign compared to age-matched sporadic cancers because they tend to be cellular and fleshy with round pushing margins rather than scirrhous with irregular infiltrating margins (32), and because they are less likely to be associated with significant amounts of DCIS (33) (which often develops microcalcifications that lead to detection by mammography).

Given the drawbacks to the use of mammography in this population, there is a need for alternative screening modalities. The most promising candidate to date has been contrast-enhanced MRI of the breast. Breast MRI has been shown to have 94% or higher sensitivity for invasive breast cancer, when used as a diagnostic tool (34,35). The enhancement of the breast lesion reflects local tissue changes in blood flow, capillary permeability, and extracellular volume thought to be characteristic of tumour-related angiogenesis (36). Unlike mammography, MRI is not influenced by breast density and does not use ionizing radiation. Moreover, a combined analysis of kinetics and morphology has significantly improved MRI specificity (37). Many centers also have the technical capacity to do MR-guided needle localization biopsies; fewer centers can do MR-guided core biopsies. If MR-guided biopsies cannot be done, directed ultrasound frequently localizes the lesion. The use of MRI as a breast screening method for the general population is not practical on the basis of its high cost, limited availability, relatively low specificity, and the technical difficulty of sampling lesions visible only on MRI; however, applying it to a very high risk population is much more appropriate.

A number of prospective studies have been recently published in which women at very high risk for breast cancer, based on genetic testing or family history, underwent screening with MRI and mammography. Each study was performed either on the same day or within a very short time interval and read independently. A systematic review of this evidence was conducted for a clinical practice guideline on the utility of MRI screening.

METHODS

      This systematic review was developed by Cancer Care Ontario's Program in Evidence-based Care (PEBC), using the methods of the Practice Guidelines Development Cycle (38,39). Evidence was selected and reviewed by members of the PEBC Special Working Group on MRI Screening in Breast Cancer (the Working Group) and one methodologist.

      The systematic review is a convenient and up-to-date source of the best available evidence on MRI screening for women at high risk for breast cancer. The body of evidence in this review is comprised primarily of prospective comparative studies of MRI screening with mammography screening. That evidence forms the basis of a clinical practice guideline developed by the Working Group, published as Section 1 of this evidence-based series. The systematic review and companion practice guideline are intended to promote evidence-based practice in Ontario, Canada. The PEBC is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

Literature Search Strategy

      The search criteria and studies identified are described in Table 1. MEDLINE was searched to April 2006 using the search terms shown in Appendix 1. The Excerpta Medica database (EMBASE) was similarly searched up to April 2006 using the search terms shown in Appendix 1. Online conference proceedings from the American Society of Clinical Oncology (ASCO) annual meetings (http://www.asco.org/; 1999-2005), the annual San Antonio Breast Cancer Symposia (SABCS) (http://www.sabcs.org/; 2003-2005), and the Radiological Society of North America (RSNA) annual meetings (http://archive.rsna.org; 2001-2005) were also searched, using the methods shown in Table 1. The Canadian Medical Association Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp) and the National Guidelines Clearinghouse (http://www.guideline.gov/) were searched for existing evidence-based practice guidelines. Relevant articles and abstracts were selected and reviewed by two reviewers, and the reference lists from these sources were searched for additional trials, as were the reference lists from relevant review articles.

Table 1. Search criteria and studies identified.

	MEDLINE	EMBASE	ASCO	SABCS	RSNA
Search Method	OVID	OVID	ASCO web site search engine (allows up to three search terms)	Title/Abstract scan of applicable sessions in the conference proceedings	RSNA web site search engine (allows one search term and year selection)
Search criteria	See Appendix 1.	See Appendix 1.	MRI – Searched for "MRI", "breast", "screening" (Search 1) in abstract, and then title/abstract review of results.	NA	Searched for "breast", then title scan by year for "MRI" or "magnetic" followed by abstract review.
Number of articles identified by electronic search	39	64	117	NA	NA

	MEDLINE	EMBASE	ASCO	SABCS	RSNA
Number of articles marked for possible inclusion after title/abstract review	31	32	9	4	12
Number of articles included in review	8 + 2 systematic reviews and 1 systematic review identified through authors' personal files		3	2	3

Inclusion Criteria

- Systematic reviews, meta-analyses, and clinical practice guidelines that addressed the use of MRI in the screening of women at high-risk breast cancer were included.
- Randomized studies or prospective non-randomized studies of MRI compared to mammography with or without ultrasound and clinical breast examination for the screening of women at very high risk for breast cancer are included. Studies had to report at least one relevant measure of effectiveness/benefit, including sensitivity, specificity, positive or negative predictive value, accuracy, time to diagnosis, tumour stage information (size, proportion DCIS, etc.), or improvement in patient outcome (response or survival).
- The studies had to be relevant to the target population, that is, women at very high risk for breast cancer. 'Very high risk' was defined as:
  1. Known mutation in BRCA1, BRCA2 or other gene predisposing to a markedly elevated breast cancer risk.
  2. Untested first degree relative of a carrier of such a gene mutation
  3. Family history consistent with a hereditary breast cancer syndrome and estimated personal lifetime cancer risk >25%.
  4. High risk marker on prior biopsy (atypia, LCIS)
  5. Radiation therapy to chest (before age 30 and at least 8 years previous).

Exclusion Criteria

- Due to the lack of translation resources, non-English language reports were excluded.
- Because of changes in both mammographic and MRI technology, publications prior to 1995 were considered out-of-date and excluded.

Synthesizing the Evidence

The methods described by Moses et al (40,41), along with the guidelines described by Devillé et al (42), were used to evaluate the heterogeneity between the included studies of MRI compared to mammography, and, if possible, generate and compare summary receiver operating characteristic (ROC) curves for the two screening modalities. The Meta-DiSc software (43) (published by the Unit of Clinical Biostatistics of the Ramón y Cajal Hospital, Madrid, Spain and available at http://www.hrc.es/investigacion/metadisc_en.htm) was used in this analysis. An equally weighted least squares model was used to estimate the parameters of the summary ROC curves. Moses et al (41) suggested that weighted least squares modelling was appropriate only when the between-study variation is considered to be negligible compared to the within-study variation, an unwarranted assumption in this instance. The summary sensitivity was calculated using a random effects model with correction for overdispersion, and the specificity at this sensitivity was estimated from the summary ROC curve model.

Moses et al (40,41) provide a full discussion of the reasoning behind using special methods in the meta-analysis of screening test data. Briefly, the sensitivity and specificity measured in a study are not independent of each other but are dependent on the detection threshold associated with the study. The factors that influence this threshold are both obvious (i.e., different thresholds on the same scoring system, such as considering the Breast Imaging and Reporting Data System (BI-RADS) 3 instead of BI-RADS 4 as a positive examination) and not obvious (i.e., different radiologists, differences in equipment, or differences of interpretation of standard scoring systems). Aspects of these thresholds are often latent and not measured. For example, two different radiologists will report "normal" or "abnormal," but the threshold of evidence at which each radiologist moves from one classification to another is often not measured and cannot be compared. Therefore, not only must the meta-analytical methods used account for the dependence of sensitivity and specificity, but they must also account for possible differences in detection threshold.

The summary ROC method estimates the effect of variations in thresholds separately from the diagnostic odds ratio (DOR). The DOR is a summary measure of the relationship of sensitivity and specificity for a particular study. The greater the DOR, the more discriminatory power the test in question has. DOR is calculated as (42):

$$DOR = \frac{sens.}{1-sens.} \Big/ \frac{1-spec.}{spec.}$$

Two parameters were estimated from the Moses et al model (41): a slope parameter (B) and log-odds ratio parameter (A). A is the estimated log of the DOR of the summary ROC curve where the sensitivity and the specificity are equal. B is the slope of the transformed summary ROC curve and is a measure of the variation in threshold in the analysed data. When B is significantly different from zero, the implication is that the studies being analyzed vary in terms of their detection thresholds. A negative value of B suggests that a threshold is involved in the analyzed studies that increases specificity while decreasing sensitivity, while a positive value indicates the reverse. If B is not significantly different from zero, then the studies do not have important variation in their detection thresholds and the pooled DOR can be used to summarize the overall accuracy of the test. When this pooling was appropriate, it was done using a random effects model.

In order to evaluate the impact of screening with MRI plus mammography or MRI alone, the number needed to screen (NNS) to detect one additional case of cancer over what would have been detected by mammography alone, and the additional false positives (AFP) generated by screening these women, was calculated as described in Appendix 2.

RESULTS
Literature Search Results

The number of articles identified by the search, and the subsequent review, is described in Table 1. A number of articles were found to be consecutive reports from the same studies; only the most recent report was included, unless relevant data could be found in the earlier reports that had not been reprinted. Twelve prospective studies comparing MRI to mammography were identified, reported in fifteen included articles (44-58) (Table 2).

Overall Study Quality and Comparability

Several included studies have to date only been published in abstract form and without the complete reporting of methods, making it difficult to judge their overall quality. In addition, there are a number of important questions concerning the studies that have been fully published in peer-reviewed journals.

All of these studies compared mammography and MRI within the same patients. In addition, in all of the studies, the two imaging techniques were used within a very short time

period. Therefore, these studies all use an effective design to measure the relative performance of the two modalities in terms of sensitivity and specificity compared to each other, at least in the patient populations included in the study. In all the studies, biopsy-confirmed cancer was considered the definitive positive result, with sensitivity calculations being based on that standard.

There are notable differences, however, between the studies that affect their comparability. First, the criteria for defining positive and negative screening results were not completely consistent among the studies. One of the principle studies, the Magnetic Resonance Imaging Breast Screening (MARIBS) study (46), considered Breast Imaging Reporting and Data System (BIRADS) scores of 0, 3, 4, and 5 to be positive, while the other principle studies did not consider BIRADS 3 to be positive. However, this is only the most obvious difference in criteria. Other differences that are not apparent (differences in the use of the BIRADS classification scheme, differences in radiology practice, etc.) may mean that some studies were more likely to classify a given patient as positive (leading to higher sensitivity and/or lower specificity), while others were more likely to classify the same patient as negative.

Second, some of the studies included only those with known BRCA mutations, while others had a broader definition of high risk. If the effectiveness of MRI or mammography varies by the specific reason a person is classified as high risk, then those studies using broader definitions may have measured several different effects at once.

Third, while several of the studies were quite large in terms of the total number of patients enrolled, the number of cancers detected was small—no more than 45 in any study. The implication is that, while the specificity, based on the number of healthy patients, was precisely estimated, the estimate of sensitivity, based on the number of patients with cancer, was very imprecise.

Finally, a number of the studies included other screening techniques besides mammography and MRI; ultrasound, ductal lavage, and digital mammography, were all used in various studies (Table 2). In those studies, the cancers detected by the additional techniques might well have been interval cancers in the absence of those techniques, and therefore the interval cancer rates may not be comparable.

Technical Features of the MRI Examinations

All the MRI studies reviewed in this analysis involved the use of dynamic contrast-enhanced MRI. Some of the key technical details of the imaging methods are summarized in Table 3. The level of technical detail provided by these papers varied widely, with a few papers giving very specific information about the MRI methods and many providing virtually no information at all. Inspection of the images from those papers that provided them, demonstrated that the image quality did vary somewhat due to differences in manufacturers and the other equipment used, such as the breast coil technology. All the studies used T1-weighted MRI based on spoiled gradient-recalled MRI, with Gd-DTPA as the contrast agent. In most cases, the imaging was performed in either the axial or the coronal plane; however, a few studies used sagittal imaging. In most cases, the imaging scanned both breasts simultaneously; however, one study used a dual-imaging method in which two unilateral scans were performed, with the two injections of Gd-DTPA separated by several hours. In all cases, multiple sets of post-injection images were obtained to give information about tumour-enhancement kinetics.

Outcomes
MRI compared to Mammography

Key results of the twelve prospective studies of MRI compared to mammography identified for inclusion in this systematic review are summarized in Tables 4 and 5. Additional results of each of these studies are described below.

Table 2. Prospective studies comparing MRI to mammography.

Primary Author/Name of Study (if any)	Previous Breast Cancer?	Ages Allowed and Median or Mean Age	Mutation Status/Family History	Methods and Frequency
Kuhl/- (44)	Included	≥ 30 yrs or 5 yrs before youngest family member, median age 40	BRCA1/2 carrier or High familial risk	MRI, mammogramphy, CBE, and ultrasound, all done within 8 weeks, every year. CBE and ultrasound every 6 months, with follow-up if abnormal result.
Kriege/MRISC (45)	Not included	25 to 70 yrs, mean age 40	Cumulative lifetime risk ≥15% due to family or genetic predisposition	MRI and mammography, done where possible on same day, every year. CBE every 6 months.
MARIBS Study Group/MARIBS (46)	Not included	35 to 49 yrs, median age 40	*BRCA1/2* or *TP53* carrier, first-degree relative of carrier, strong family history of breast cancer, or family history consistent with Li-Fraumeni syndrome	MRI and Mammography every year, preferably on same day.
Warner/- (48,59) (designated Warner A)	Included	25 to 60 yrs, mean age 43	As Warner B, except that women with a first degree *BRCA1/2* mutation and women with three or more relatives with breast (diagnosed before age 50) or ovarian cancer, on the same side, were included.	MRI, Mammography, and ultrasound, and CBE done on same day, every year.
Warner/- (47,60,61) (designated Warner B)	Included	25 to 65 yrs, mean age 46.6	*BRCA1/2* carrier	MRI, Mammography, and ultrasound, done on same day, every year. CBE every 6 months, on the same day as imaging if appropriate.
Trecate/- (49)	Included	Ages allowed NR, age ranged from 30 to 61 years, median or mean age NR	*BRCA1/2* carrier or a 1:2 probability of being a carrier OR >50% risk of carrying a susceptibility gene.	MRI, mammography, and ultrasound every year. CBE every 6 months.
Hartman, Kurlan/- (50,51)	Included	≥25 yrs or 5 years younger than the earliest age at which a relative was diagnosed, median age 42.5	*BRCA1/2* carrier or >10% risk at 10 years for breast cancer	MRI, mammography, and ductal lavage every year. CBE every 6 months. All examinations completed with 8 weeks (2 weeks after 11/2002)
Lehman, Isaacs/- (52-54) [abstract]	Included	≥25 yrs, median or mean age NR	*BRCA1/2* carriers or ≥20% risk of BRCA1/2 mutation	MRI, mammography, and ultrasound within 90 days of each other.
Lehman/IBMC (55)	Included	≥25 yrs, mean age 45	*BRCA1/2* carriers or ≥25% lifetime risk of breast cancer.	CBE, mammography, and MRI within 90 days of each other.
Podo, Sardanelli/- (56,62)	Included	≥25 yrs, median or mean age 51 as of 2002	*BRCA1/2* carrier or first degree relative of carrier OR strong familial BC history	MRI, mammography, and ultrasound every year, for two years.
Rosen/- (57) [abstract]	Included	Ages allowed NR, median or mean age NR	History of prior contralateral breast cancer (contralateral) OR >25% lifetime risk, or prior proven ADH, ALH, or LCIS (high risk).	High-risk patients with heterogeneously dense breasts received MRI, DM, and ultrasound. Others randomized to one of DM, ultrasound, or MRI, or a combination. At least some received film/screen mammography (details not reported).

Primary Author/Name of Study (if any)	Previous Breast Cancer?	Ages Allowed and Median or Mean Age	Mutation Status/Family History	Methods and Frequency
Riedl/- (58) [abstract]	NR	Ages allowed NR, median or mean age NR	*BRCA1/2* mutation or high risk for breast cancer due to family history	MRI, mammography, CBE, and ultrasound every year.

Abbreviations: ADH, atypical ductal hyperplasia; ALH, atypical lobular hyperplasia; BC, breast cancer; CBE, clinical breast examination; DM, digital mammography; IBMC, International Breast MRI Consortium; LCIS, lobular carcinoma in situ; MARIBS, Magnetic Resonance Imaging Breast Screening; MRI, magnetic resonance imaging; MRISC, Magnetic Resonance Imaging Screening Study; NR, not reported.
* Reported details.

Table 3. Comparison of Breast MRI screening methods used in the included studies.[A]

Study	Imaging plane	Bilateral or Dual unilateral[B]	Field (Tesla) (manufacturer)	resolution	# of slices	TR (ms)	TE (ms)	angle (degrees)	fat suppression	dose Gd-DTPA (mmol/kg)	speed (sec)[C]	Single or Dual screen study[D]
Kuhl (44)	axial	B	1.5 (Philips)	256x256 400x512	NR	NR	NR	NR	NR	0.1	NR	S
MRISC (45)	axial	B	1.5 (mixed)	1mm isotropic	NR	NR	NR	NR	NR	0.1	NR	S
MARIBS (46)	coronal & sagittal	B	1.0 & 1.5 (mixed)	256x256	60-64	10-16	4.2-5.7	35	subtraction	0.2	90	D
Warner A (48,59) and Warner B (47,60,61)	sagittal	B	1.5 (GE)	256x256	56	18.4	4.3	40	subtraction	0.1	169	D
Trecate (49)	coronal	B	NR	256 x128	60	9	4	20	NR	0.1	70	S
Hartman/Kurlan (50,51)	sagittal	D	1.5 (GE)	188 x188	32	33	9	50	spectral-spatial	0.1	10.7	S*
Lehman/Isaacs (52-54)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
IBMC (55)	NR	NR	NR	256x128	32-60	50	4.5	NR	NR	NR	NR	NR
Podo/Sardanelli (56,62)	coronal or axial?	B	1 & 1.5 (mixed)	128x256 for coronal, adapted for axial?	40-48?	NR?	NR?	NR?	NR?	0.1	90	S
Rosen (57)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Riedl (58)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Abbreviations: DTPA, diethylenetriamine penta-acetic acid; Gd, gadolinium; NA - information not available from the reference; NR, not reported; TE, time delay prior to echo formation in milliseconds; TR, pulse sequence repetition time for each line in k-space measured in milliseconds.

[A] In all cases, the MR imaging was performed with a spoiled, gradient recalled sequence

[B] B - means a bilateral imaging method, D - a double imaging method where each breast is imaged separately with two injections of Gd-DTPA separately by several hours.

[C] This is the time in seconds to acquire images of both breasts once. This defines the temporal resolution of the dynamic data.

[D] S - a dynamic screening study was used for all breast MRI. D - a screening procedure was used and followed by a unilateral diagnostic exam of higher spatial resolution for patients with suspicious findings.

Table 4. Studies comparing MRI to mammography: patients included and cancers detected.

Study	# of Pts	# of Screens	# of Cancers detected[A]	Interval Cancers	Screens per Pt.	In situ[B]	Tumour size[C]	Node positive[D]
Kuhl (44)	529	1452[E]	43	3	Mean 2.7	20.9%	MRI median 1.1 cm, mammography median 1.2 cm	16%
MRISC (45)	1909	4169	45[F]	4	Mean 2.2	13.3%	43.2% ≤ 1 cm, 31.8% 1-2 cm, 25.0% > 2 cm	14.3%
MARIBS (46)	649	1881	35	2	Mean 2.9	17.1%	37.9% < 1 cm, 31.0% 1-2 cm, and 31.0% ≥ 2 cm	17.2%
Warner A (48)	196	196	6	NA	1	14.2%	100% < 1 cm	0%
Warner B (47)	236	457	22	1	Mean 1.9	27.2%	31.2% < 1 cm, 68.8% 1-2 cm	12.5%
Trecate (49)	23	23	4	NA	1	0%	NR	NR
Hartman/Kurlan (50,51)	68	68	1	NA	1	100%	NA[G]	NA[G]
Lehman/ Isaacs (52-54) [abstract]	171	171	6	NA	1	0%	16.7% T0, 50% T1, 16.7% T2	16.7%
IBMC (55)	367	367	4	NA	1	25%	33.3% < 1 cm, 66.7% 1-2 cm	0%
Podo/Sardanelli (56,62) [abstract]	235	321[H]	15[J]	0	Mean 1.4	NR[J]	0.3-1.9 cm	NR
Rosen (57) [abstract]	151	NR	4	NR	NR	NR	NR	NR
Riedl (58) [abstract]	234	340	17	0	Mean 1.5	NR	NR	NR

Abbreviations: NA, not applicable; NR, not reported

[A] Cancers detected by some other means (i.e. ultrasound) in the study and not detected by MRI or mammography; NA if no additional modality included.

[B] Percent of cancers detected.

[C] Percent of invasive cancers detected, if percentage provided.

[D] Proportion of invasive cancers with positive nodes.

[E] Included in sensitivity/specificity analysis, 1542 total surveillance rounds reported.

[F] Included in sensitivity/specificity analysis, 51 total cancers reported.

[G] No invasive cancers detected.

[H] Based on reported 86 completing 2nd round of planned two rounds.

[J] 18 cancers identified, but three cancers did not have complete evaluation with mammography, MRI, and ultrasound, and full results for those cancers were not reported. Of these 18, 3 (16.7%) were DCIS.

Table 5: Studies comparing MRI to mammography: sensitivity, specificity, PPV, and NPV.

Study	Definition of Positive	Mammography alone				MRI alone			
		Sens (%)	Spec (%)	PPV (%)	NPV (%)	Sens (%)	Spec (%)	PPV (%)	NPV (%)
Kuhl (44)	BI-RADS 4,5[A]	32.6	96.8	23.7	97.9[B]	90.7	97.2	50.0	99.7[B]
MRISC (45)	BI-RADS 0,4,5[C]	33.3	99.0	27.3	99.3[B]	64.4	96.4	16.4	99.6[B]
	BI-RADS 0,3,4,5[C]	40.0	95.0	8.0	99.3[B]	71.1	89.8	7.1	99.7[B]
MARIBS (46)	BI-RADS 0,3,4,5[D]	40	93	10	99	77	81	7.3	99
Warner A (48)[E]	BI-RADS 4,5	33	99.5	66	97	100	91	26	100
Warner B (47)[C]	BI-RADS 4,5	36	100[B]	88[B]	97[B]	77	95	46	99[B]
Trecate (49)	NR	0[B]	NR	NR	NR	100[B]	100[B]	100[B]	100[B]
Hartman/Kurlan (50,51)	See text	0[B]	99[B]	0[B]	99[B]	100[B]	76[B]	6[B]	100[B]
Lehman/ Isaacs (52-54) [abstract]	NR	33[B]	99[B]	50	98[B]	100[B]	95[B]	43	100[B]
IBMC (55)	BI-RADS 4,5[A]	25[B]	98[B]	12.5	99[B]	100[B]	93[B]	12.9	100[B]
Podo/Sardanelli (56,62) [abstract]	NR	60[B]	NR	75[B]	NR	93[B]	NR	74[B]	NR
Rosen (57) [abstract]	NR	25[B,F]	NR	NR	NR	100[B]	NR	NR	NR
Riedl (58) [abstract]	NR	53[G]	96	44	95	100	93	53	100

Abbreviations: NA, not applicable; NR, not reported; NPV, negative predictive value; PPV, positive predictive value; Sens, sensitivity; Spec, specificity.

[A] No BI-RADS 0 scores were assigned.
[B] Calculated from data provided.
[C] The reported sensitivity and specificity in the text of the abstract and paper was based on considering BI-RADS 0,3,4,5 positive. However, the paper also provided alternate cut-off information, which is reported here for comparability to the other included studies.
[D] The study used an alternate scoring system, but the authors claim the equivalence of a positive in this system to BI-RADS 0,3,4,5.
[E] The Warner A and Warner B studies have at least some subjects in common with each other.
[F] Digital mammography.
[G] Based on ten cancers out of 17 detected by mammography. The abstract reports a sensitivity of 40%. No explanation for this discrepancy is apparent.

The study by Kuhl et al (44) found that MRI was significantly more sensitive than mammography alone (p<0.001) but found no significant difference in specificity. This study also reported, or provided sufficient information to calculate the sensitivity (93.0%), specificity (96.1%), positive predictive value (PPV) (42.1%), and negative predictive value (NPV) (99.8%) of the combination of MRI and mammography. Out of the 43 total cancers, three (7.0%) were interval cancers, that is, cancers identified between screenings. Out of the 40 non-interval cancers, mammography identified fourteen (three DCIS and one recurrent DCIS), MRI identified 39 (eight DCIS), and the combination of MRI and mammography identified 40 (nine DCIS). Mammography detected ten invasive cancers with a median size of 1.2 cm. MRI detected 31 invasive cancers with a median size of 1.1 cm. Of the 25 minimal cancers (i.e., DCIS or less than 1 cm in size and node negative), mammography detected 20% and MRI detected 92%. Of the ten invasive cancers detected by mammography, four (40%) were node-positive; of the 31 invasive cancers detected by MRI, five (16%) were node-positive. None of the cancers detected only by MRI were node positive. The exact false-positive biopsy rate was not reported, but, based on the study protocol, the majority of the 45 false positives (2.6% of all screening rounds) due to mammography and the 39 false positives (2.3% of all screening rounds) due to MRI would have received a biopsy.

Of the 45 cancers reported in the Magnetic Resonance Imaging Screening (MRISC) study, reported by Kriege et al (45), 18 were detected by mammography, and 32 were detected by MRI. Thirty-nine of the cancers were invasive, and six were DCIS. Four of the identified cancers were interval cancers, 22 were prevalent (i.e., detected at the first screen of the study), and 19 were incident (i.e. detected on the second or subsequent screens). The sensitivity for the first mammography screening was 37.5% and on the second, 42.9% (p=0.71). For MRI, the sensitivity was 79.2% with the first screen, and 61.9% with the second (p=0.20). Based on a definition of BI-RADS scores 0, 3, 4, and 5 being positive, the sensitivity of mammography combined with MRI was 88.9%. For DCIS, the sensitivity of mammography was higher than that of MRI.

The MRISC study also reported accuracy data according to the BI-RADS cutoff, allowing for a direct comparison of MRI and mammography through the use of ROC curves. For mammography, the area under the ROC curve was 0.686, while for MRI it was 0.827; the difference in area was significant (0.141, 95% confidence interval [CI] 0.020 to 0.262, p<0.05). This significant difference in areas suggests that MRI has greater discriminatory power than mammography to correctly ascertain the disease status of a given individual.

Tumour stage in the MRISC study was compared to two age-matched control groups (one from a national cancer registry and one from a study of gene prevalence) in order to determine if the use of mammography and MRI allowed for the detection of breast cancer at an earlier stage. The proportion of tumours less than or equal to 1 cm in size (43.2%) was significantly higher that that found in the first control group (14.0%, p<0.001) or the second control group (12.5%, p=0.04). In addition, a significantly smaller proportion (14.3%) of the cancers in the study population were node positive, compared to 52.4% in the first control group (p<0.001) and 56.4% in the second control group (p=0.001).

Of the 25 biopsies performed in the MRISC study in women with mammographic BI-RADS scores of 3 or higher, seven (28.0%) showed no cancer. Of the 56 biopsies performed in women with MRI BI-RADS scores of 3 or higher, 24 (42.9%) showed no cancer.

The MARIBS study (46) found both MRI sensitivity and specificity (Table 5) were significantly different from mammography sensitivity (p=0.01) and specificity (p<0.0001). This study also reported a sensitivity of 94% and a specificity of 77% for the combination of MRI and mammography. The area under the ROC curve for MRI was 0.85 (95% CI 0.84 to 0.87) and for mammography it was 0.70 (0.68 to 0.72). The difference between these curves was significant (p=0.035).

Of the 35 cancers detected in the MARIBS study, 14 were detected by mammography and 27 by MRI. In addition, there were two interval cancers detected out of 1232 screening intervals. The sensitivity and specificity associated with the 20 prevalent cancers and the 15 incident cancers is summarized in Table 6. The sensitivity of mammography was higher than that of MRI for the detection of DCIS.

Table 6. MRI and mammography sensitivity and specificity by prevalent/incident cancers, adapted from MARIBS study report (46).

Group	Num. Cancers	Sensitivity MRI	Sensitivity Mammography	p	Specificity MRI	Specificity Mammography	p
Prevalent cancers	20	75%	40%	0.12	82%	93%	<0.0001
Incident cancers	15	80%	40%	0.11	81%	94%	<0.0001

The recall rate in the MARIBS study was 3.9% per woman year for mammography, 10.7% per woman year for MRI, and 12.7% per woman year for the combination of mammography and MRI. Two hundred forty-five of the 279 recalls in the study did not involve cancer. One hundred seven (38%) of the recalls required either a percutaneous fine-needle aspiration or core biopsy (91 women) or a surgical biopsy (16 women).

Two published studies by Warner et al had at least some patients in common. The study designated Warner B (47) in this systematic review included 96 of the BRCA1/2 mutation-carrying patients included in the study designated Warner A (48), which included women with a family history of breast cancer as well as mutation carriers. In the study designated Warner A (48), six cancers were identified, two detected by mammography and six by MRI. The addition of MRI to mammography led to fourteen biopsies that would not have been performed in its absence.

An abstract from the 2005 SABCS (59) reported the data from Warner A, which looked at the effect of a radiologist with special training in MRI interpretation. The data were broken down into two periods, before a specially trained radiologist was on staff (period A) and after (period B). Period A involved 225 women (487 screens), and period B involved 396 women (877 screens). Within period A, 16 cancers were detected, two of which (12%) were DCIS. Within period B, 27 cancers were detected, 12 of which (44%) were DCIS. The measured sensitivities were Period A MRI, 79%; Period A mammography, 43%; Period B MRI, 93%; and Period B mammography, 13%. Of particular note, for DCIS, the sensitivity of mammography was higher than that of MRI in period A, but in period B, the reverse was seen.

There were 25 cancers detected in the Warner B (47) study; eight were detected by mammography and 17 by MRI. Six of these cancers were DCIS. In addition, two cancers were detected only by ultrasound. MRI was found to be significantly more sensitive than mammography (p=0.02), and the sensitivity of MRI and mammography combined was 86%. The areas under the ROC curve were as follows: MRI 0.89, mammography 0.77, and MRI plus mammography 0.94. The mean sizes of tumours in the first and second rounds of screening were 1.1 cm and 1.3 cm, respectively.

Fourteen percent of patients in the Warner B study had a biopsy for benign disease; most (approximately 95%) were detected by MRI or ultrasound. The benign biopsy rate was significantly different (p=0.05) between the different rounds of screening, being higher in the first round of screening (11%) than in the second (6.6%) or third (4.7%). For MRI, the false-positive rate (1 minus specificity, equivalent to the benign biopsy rate in this study) was 7% in year one, 3% in year two, and 1% in year three of the study. After the first round of

screening, 16.5% of the patients underwent a "diagnostic" (higher resolution) MRI; this percentage decreased to 9.6% in the second round and 7.1% in the third.

An abstract from the 2004 ASCO annual meeting (60,61) reported data from this same study by the screening program year. The repeat rates and benign biopsy rates were also provided by modality and year of program, (Table 7).

Table 7. MRI and mammography repeat and benign biopsy rates by year of screening, adapted from Warner et al (60,61).

	MRI			Mammography		
	First Year	Second Year	Third Year	First Year	Second Year	Third Year
Repeat Rate	24%	12%	9.5%	2.9%	1.1%	1.8%
Benign Biopsy Rate	6.1%	2.2%	1.2%	1.1%	0.5%	0%

Trecate et al (49), in a preliminary report of an ongoing study, stated that four cancers were detected by MRI, none of which were detected by mammography. No false-positive or false-negative results based on MRI were reported.

The published Hartman et al study (50), updated in abstract form at the 2005 SABCS (51), was a pilot study of MRI and mammography combined with ductal lavage. In this study, a positive MRI screen was considered a screen in which dominant lesions of ≥ 5 mm with either suspicious morphologic or dynamic enhancement features were identified. The definition of a positive mammography screen was not reported. The one cancer (DCIS) detected out of 68 patients was by MRI and was not detected by mammography. There were nine biopsies based on MRI that were false positives. The biopsy rate on the initial scan was significantly higher than that on subsequent scans (23.9% versus 4.5%, p=0.01) (51).

In the study reported in two abstracts and slides at the 2004 ASCO annual meeting by Lehman and Isaacs et al (52-54), six cancers were detected, all six by MRI and two by mammography. Four biopsies were conducted based on mammography (biopsy rate 2.3%), and 14 were conducted based on MRI (biopsy rate 8.2%). Mammography detected a T1 and a T2 cancer.

The study reported by Lehman et al (55), conducted by the International Breast MRI Consortium (IBMC), consisted of only one round of screening. Of four cancers detected, one was detected by mammography and four by MRI. Four biopsies were conducted due to mammography (2.2%), while 24 biopsies were conducted due to MRI (8.5%). However, it is important to note that an additional 11 women, including six with positive MRI, three with positive mammography, and two who received fine-needle aspiration, did not receive biopsies as dictated by the study protocol. The PPV of biopsy was 25.0% for mammography and 17% for MRI.

The preliminary results of an Italian study were first published by Podo et al (62), with more recent results published at the 2004 RSNA meeting by Sardanelli et al (56).   Two additional studies were reported at the 2004 RSNA annual meeting in abstract form, Rosen et al (57), and Riedl et al (58). These publications were short and provided little data beyond what is summarized in Tables 4 and 5.

While ultrasound is not the subject of this paper, in those studies that included ultrasound, sensitivity was no higher than that of mammography, and specificity was lower.
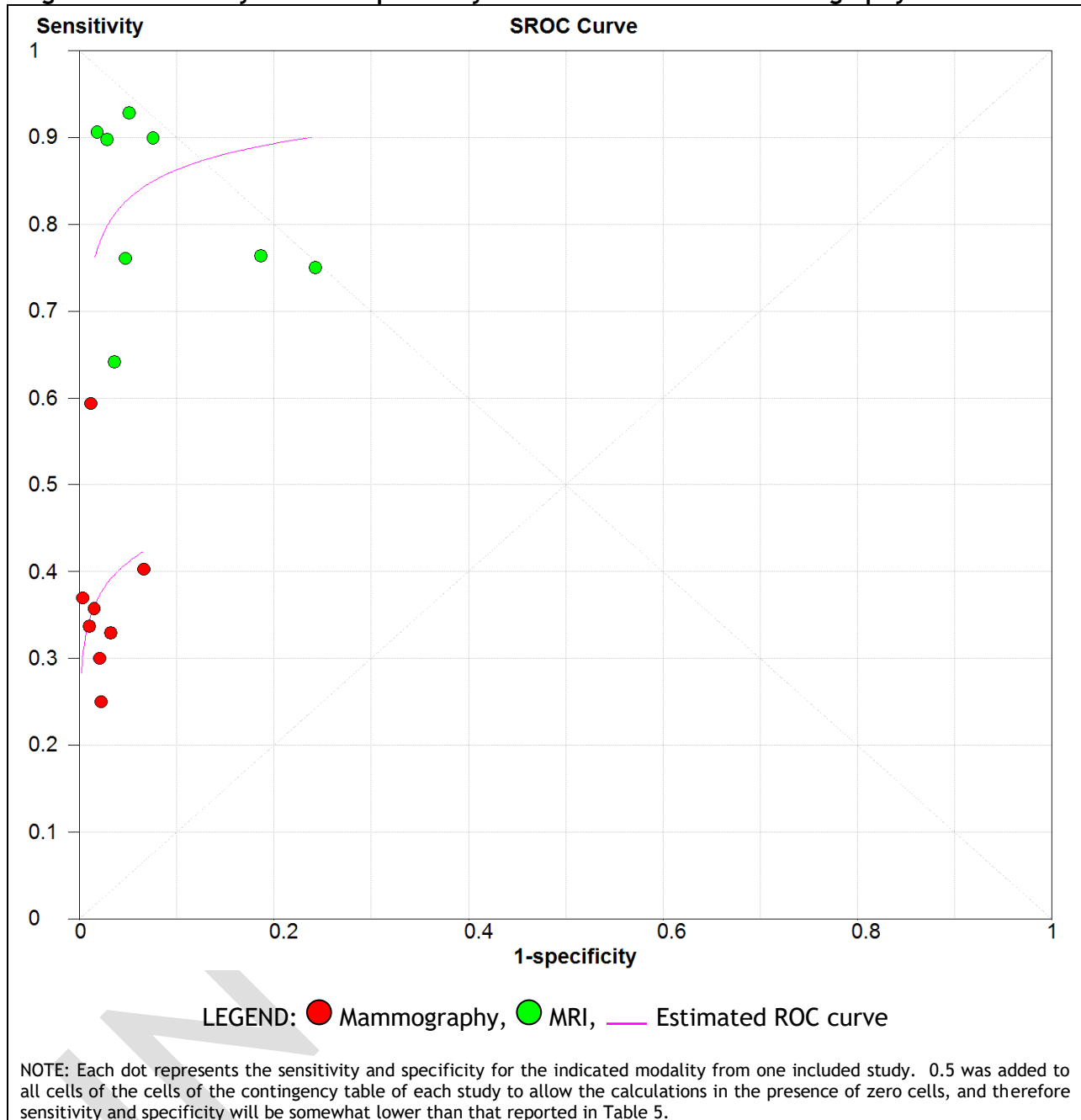
Meta-analysis

Based on the methods of Moses et al (40,41), only those studies for which the complete contingency table of true positives, false positives, true negatives, and false

negatives is either available or can be constructed can be combined into a meta-analysis. Out of the twelve included studies comparing MRI to mammography, eight (44-47,50-56) provided sufficient information to construct these tables. As the Warner B (47) and Warner A (48) study included at least some of the same patients, only the larger of the two (Warner B) was included in the analysis. The study reported by Trecate et al (49) provided only enough information to construct the contingency table for MRI and not enough for mammography and was excluded from the analysis. The contingency tables used for the analysis are summarized in Appendix 3. It should be noted that, in the analysis, in order to allow studies with zero subjects in a cell of the contingency tables to be included, 0.5 was added to all cells, as suggested by Moses et al (41).

Figure 1 is a plot of each study's sensitivity versus 1-specificity for each modality (MRI and mammography), which illustrates the relationship of these quantities and the differences between the imaging modalities. Figure 1 also shows the estimated summary ROC curve for both MRI and mammography plotted within the range of 1-specificities found in the studies. Note that the closer a particular study's dot for a particular modality lies to the upper left of the figure, the greater discriminatory power that modality had in that study to correctly determine the disease state of the included patients. The area of each dot is proportional to the inverse of the variance of the estimated values for that modality and study as calculated according to Littenberg and Moses (40) and gives an idea of the relative size of the included studies.

Figure 1: Sensitivity versus 1-Specificity of studies of MRI and mammography.

NOTE: Each dot represents the sensitivity and specificity for the indicated modality from one included study. 0.5 was added to all of the cells of the contingency table of each study to allow the calculations in the presence of zero cells, and therefore sensitivity and specificity will be somewhat lower than that reported in Table 5.

The parameters of the summary ROC curves were as follows: MRI, B=-0.483 (p=0.4341), A=3.865 (p=0.0032); mammography, B=-0.703 (p=0.0992), A=0.260 (p=0.8839). The A parameters above equate to the following DORs, where sensitivity equals specificity: MRI, 47.66; mammography, 1.30. As the B parameters for mammography and MRI were not significantly different from zero, indicating no significant threshold effect was involved, the pooled DOR was calculated from the underlying contingency tables, using a random effects model (see Table 8). The summary sensitivity was also estimated, and a corresponding specificity was calculated, using the estimated summary ROC curves (Table 7).

Table 8. Estimated sensitivity, specificity, and diagnostic odds ratio (DOR) from meta-analysis of studies that compared MRI to mammography.

Value	MRI	Mammography
Summary Sensitivity	80.1% (71.5% to 88.8%)	36.8% (30.7% to 43.0%)
- Specificity at this value[A]	97.0%	97.1%
- Heterogeneity	X^2 test p=0.018, I^2=58.4%	X^2 test p=0.630, I^2=0.0%
Diagnostic Odds Ratio	77.338 (29.117 to 205.41)	32.003 (14.633 to 69.989)
- Heterogeneity	X^2 test p<0.001, I^2=77.5%	X^2 test p=0.001, I^2=70.2%).

[A] As calculated from the estimated summary ROC curve.

Based on the summary sensitivity and specificity estimates in Table 8, the sensitivity and specificity of MRI and mammography combined was estimated to be 87.4% and 94.2% respectively. At a prevalence of breast cancer of 2% at time of screening in the target population, the number needed to screen (NNS) for MRI alone was 115 women to identify one additional cancer over what would be detected by mammography alone, with less than one additional false positive. The NNS for the combination of MRI and mammography was 99 women, with three additional false positives. Based on these data, out of 1000 women screened, one would expect 20 cancers to be identified. Using mammography alone, seven of these cancers would be detected, with 28 women falsely screened positive. Using MRI alone, 16 of these cancers would be detected, with 29 women falsely screened positive. Using MRI and mammography combined, 17 cancers would be detected, with 57 women falsely screened positive.

Other Systematic Reviews

Three systematic reviews were identified, two (63,64) by the systematic search and an additional review (65) through personal communication.

The earliest review is an assessment produced by the Technology Evaluation Center of the Blue Cross Blue Shield Association (65), published in 2003. This review included five study reports, one of which is included in this review (48), three that have since had more complete results published (44,45,49), and another study (66) that does not meet the inclusion criteria for this review. No meta-analysis was conducted. This review concluded that MRI screening of women at high risk for breast cancer improved net health outcomes and was as beneficial as established alternatives.

A systematic review by Irwig et al (64), published in 2004, included one study report that is included in this review (48), one that has since had more recent results published (44), and two that do not meet the inclusion criteria of this review (66,67). No meta-analysis was conducted. The Irwig et al review made no conclusions or recommendations regarding MRI, other than to state that its "potential role in screening (if any) is in women at high risk of breast cancer."

The most recent review, reported by Elmore et al (63) in 2005, broadly covered screening in breast cancer and included MRI. Within the MRI section, six separate studies were included, two of which did not meet the inclusion criteria for this review (66,68), two that are included in this review (45,47), and two that have since had more recent results published (44,56). No meta-analysis was conducted. The Elmore review reported sensitivity for mammography in the range of 13% to 40%, sensitivity for MRI in the range of 71% to 100%, the rate of biopsies performed as a result of MRI in the range of 2.9% to 16%, and the PPV of these biopsies in the range of 24% to 89%. The review made no conclusions or recommendations regarding MRI in high-risk women.

DISCUSSION

Since approximately 75% of women with proven BRCA mutations and a much higher percentage of other high-risk populations decline prophylactic mastectomy, development of an effective and acceptable screening regimen for these women is essential.

What is the effectiveness of adding breast MRI to standard screening (mammography)?

The meta-analysis of the eight comparative studies of screening MRI and mammography for which sufficient data was provided to conduct the analysis found the combination of MRI and mammography to have numerically superior discriminatory power overall, compared to mammography alone, in determining the true breast cancer status of high-risk women. The sensitivity and specificity of the combination of MRI and mammography was estimated at 87.4% and 94.2%, respectively. By screening 99 women in the target population one would expect to detect one additional cancer, at a cost of three additional false positives. If one assumes a prevalence of 2%, this means that out of 1,000 women screened, one would expect 20 cancers to be identified. Using mammography alone, seven of these cancers would be detected, with 28 women falsely screened positive. Using MRI and mammography combined, 17 cancers would be detected, with 57 women falsely screened positive. Therefore, ten extra cancers would be detected at a cost of 29 extra false positive screens.

While there was considerable statistical heterogeneity, particularly with respect to the sensitivity threshold of mammography, this almost certainly reflects the heterogeneity of the varying characteristics of the patient populations of the studies (age, risk status, and previous breast cancer) as well as the experience and possibly the MRI technique of the study centres. Since these studies were almost exclusively confined to women with known BRCA mutations, or very high familial risk based on family history, the relative sensitivity of MRI compared to mammography for other high-risk groups is still unknown.

In those studies in which patients had two or more rounds of screening, including a more recent MRISC publication (69) (released after the time frame of the literature search in this document), MRI had significantly higher sensitivity than mammography on the incident screens as well as the prevalent screens. Moreover, the specificity of MRI was higher from the second screen onwards compared to the initial round or screening.

The estimates above for the combination of MRI and mammography are surrounded by some uncertainty, especially the estimate of sensitivity. This estimate is based on the assumption that MRI and mammography are uncorrelated in their detection capabilities. Positive correlation would lead to overestimation of the sensitivity of the combination, while negative correlation would lead to underestimation. In addition, the estimates of sensitivity for the individual modalities are themselves uncertain, leading to uncertainty in the estimate for the combination. Based on the 95% confidence intervals of the MRI and mammography sensitivities, the combination sensitivity could range from as little as 80% to as high as 94%. However, this difference in sensitivity does not make a substantial difference in the number needed to screen to find one additional cancer, which could be as high as 120 in the worst case.

Does the addition of breast MRI to standard screening detect breast cancer at an earlier stage?

A comparison of the studies of high risk women that included MRI compared to those that did not suggests that, with MRI screening, cancers are detected at a smaller size and, correspondingly, are less likely to have spread to axillary lymph nodes. In all the studies that included MRI, fewer than 20% of tumours had spread to the axillary lymph nodes compared to 33% to 50% in the studies in which only mammography was performed. The ability of MRI to

detect DCIS before it is visible by mammography seems to be dependent on the experience of the centre and improves substantially over time (59).

What is the optimal frequency of MRI screening?

      All the MRI studies reported used a screening interval of one year. However, it is conceivable that this is not the ideal screening interval for all risk groups and at all ages. Tumour doubling time increases with age (70) and may be longer in BRCA-related cancers. Although mammography and MRI were performed at the same time in the studies and are still done that way in clinical practice in most centres, it has been suggested that staggering the two modalities by six months might lower the interval cancer rates, particularly in women under 40. There is no evidence regarding the efficacy of this approach compared to simultaneous screening.

Are there subgroups (risk category, age, or breast density) that benefit more from MRI screening than do others?

      Since the probability of detecting cancer with MRI varies with risk and the false positive rate does not, it is reasonable to assume that on average lower risk women will benefit less from MRI than will higher risk women. However, within the high-risk populations studied, it is not clear whether certain groups benefit more from MRI or not.

      With respect to breast density, since breast density decreases with age and mammographic sensitivity increases accordingly in the general population, one might expect a similar trend in high-risk women. Few of the studies included a substantial proportion of older women. However, in the study by Warner et al. (61) the relative sensitivity of MRI compared to mammography was if anything greater in the woman ages 50 and over than it was in the younger women. A more recent abstract released after the time frame of the literature search in this document (71) found that although mammographic sensitivity was somewhat higher in fatty breasts than in dense breasts, the majority of cancers in women with low breast density were missed by mammography.

      There is no data regarding the optimal age at which to begin MRI screening. For women with BRCA mutations, age 30 would be reasonable, as the annual risk of breast cancer at this age is already 0.74% for women with BRCA1 mutations and 0.36% for women with BRCA2 mutations (72), significantly higher than the incidence of breast cancer for women in the general population ages 50 and over. Earlier screening might be considered if there is a family history of breast cancer prior to this age. There is also no data about the upper age limit. Considering the facts that:
1. Relative risk of cancer decreases with age for high risk women;
2. Mammographic sensitivity increases with age;
3. There is minimal data from MRI screening studies for women over age 65; and
4. Evidence for mortality reduction from screening in the general population is lacking for women age 70 and over;

it would be reasonable to stop MRI screening and perform annual mammography alone after age 65 or 70. As mentioned above, in view of the slower doubling time in older women, it might be reasonable to perform MRI every two years after age 60, with mammography performed annually.

      All studies of MRI to date have focused on women at increased risk due to family history or genetic status. The benefit of MRI in the other high-risk populations targeted by this review (women with LCIS or atypical ductal/lobular hyperplasia, or women with a history of radiation to the chest before age 30) is unknown. It is conceivable that the benefit of screening MRI could differ in subgroups of patients at similar numerical cancer risk but with a different profile of risk factors. Differences in the biology of cancers developing in these

other high-risk groups and the biology of 'hereditary cancers' could affect either the relative sensitivity of MRI compared to mammography or the clinical significance of detection lead time.

What harms are associated with MRI screening, and are there any relative or absolute contraindications to its use?

In all the studies, the specificity of MRI was significantly lower than that of mammography, with more recalls as well as biopsies for benign findings. While lower specificity is acceptable in a small and very high-risk population, in dealing with lower risk populations, the positive predictive value of MRI drops substantially. The fact that MRI costs approximately 10 times more than mammography (approximately $1000 per scan) cannot entirely be ignored. Moreover, the cost of investigating a positive finding is disproportionately higher for MRI than for mammography. In addition to financial costs, there are undoubtedly psychological costs to false positives in this already highly anxious population. Although this could not be demonstrated objectively in two studies reported to date (45,73,74), in a recent study by the Toronto group (Warner E, unpublished data) women recalled for additional investigations because of an MRI abnormality were found to have significantly higher breast cancer-related anxiety than women not recalled. It is not yet known whether the anxiety level of these women returns to baseline once the benignity of the abnormality is demonstrated.

For premenopausal women, to optimize sensitivity and specificity, MRI should be performed during the second week of the menstrual cycle.

Not all women can undergo MRI–it is contraindicated in women with pacemakers or aneurysm clips. Some women become too claustrophobic to lie prone for 30 minutes in the magnet, even after sedation. Obese women, particularly those with broad shoulders may not fit into the magnet.

In the presence of an abnormal finding seen only on MRI imaging, what is the optimal workup and follow-up after screening?

Differentiating benign enhancement, including physiologic enhancement, at MRI from malignant enhancement can be challenging. The *Breast Imaging Reporting and Data System® (BI-RADS®) Atlas*, with the included lexicon for MRI, has been published as guide to aid in breast MRI interpretation and optimize sensitivity and specificity (75). An MRI should be interpreted in conjunction with recent mammography, with the objective of correlating any lesion identified at MRI with the mammograms.

Lesions that fulfil criteria for a benign lesion at MRI, including some fibroadenomas, intramammary lymph nodes, cysts, fat necrosis, fibroadenolipomas, scars, postoperative hematomas, and seromas, require no specific lesion follow-up.

Any mammographically occult lesion that does not fulfill the criteria of a benign lesion, should be categorized as follows, with the workup tailored accordingly (75).

1. BI-RADS 3 is a probably benign finding, found usually on a baseline study. The majority of lesions in this category are presumed persistent findings, such as a probable fibroadenoma or fibrocystic change. Similar to the practice established for mammography, a six-month follow-up is initially indicated, and if the lesion remains stable, it is followed up again at six months and one year with MRI. Two years of stability is required for a classification of benign. Ultrasound evaluation could be considered as an additional means to characterize a lesion as probably benign and serve as an alternative means to perform follow-up of the lesion. Mass lesions, particularly those > 5mm, are more likely to be visible at ultrasound compared with non-mass lesions (76,77). Use of ultrasound in the post-MRI work-up should be at the

radiologist's discretion. If there were uncertainty about an ultrasound lesion corresponding to the MRI abnormality in question, MRI follow-up would be indicated.

In the context of significant background parenchymal enhancement, a hormonally induced, non-mass enhancing lesion may occasionally present with a less typical appearance. BI-RADS 3 is also used less commonly in such instances where an abnormality is thought to be transient and benign. A short interval follow-up in three months, timed to week two of the menstrual cycle or after discontinuing hormone replacement therapy (HRT) is indicated. If truly physiologic, this enhancement should decrease or resolve. For those lesions that do not improve or actually progress at follow-up, the lesion should be reclassified as a BI-RADS 4, and biopsy would be indicated.

2. BI-RADS 4 and 5 lesions have suspicious features at MRI for malignancy and require biopsy. Ultrasound evaluation can be helpful to identify a sonographic correlate to guide percutaneous biopsy. Mass lesions are more likely to be ultrasound visible than non-mass lesions (77). Smaller lesions (< 5mm), are less likely to be ultrasound visible and less likely to be malignant than are larger lesions (76-78). With this in mind, similar to BI-RADS 3b lesions, it is recommended that post-MRI ultrasound evaluation be at the radiologist's discretion, depending on the lesion in question. Lesions with an ultrasound correlate have a higher PPV for malignancy than those lesions not ultrasound visible (76,77). However, as there are a significant number of breast cancers that are only visible at MRI, MRI-guided biopsy capability is a mandatory part of any breast MRI screening program. If a lesion is suspicious based on MRI, it requires biopsy regardless of it being mammographically or ultrasound visible.

Other Issues

While the significantly greater sensitivity of MRI is unquestionable, as with any screening intervention, its ultimate clinical effectiveness depends on its ability to reduce mortality, as opposed to simply increasing lead time. The greatest challenge in reviewing the evidence for the effectiveness of MRI screening is the lack of any randomized trials. Once preliminary evidence from comparative pilot studies of MRI and mammography was available, randomized studies were no longer considered to be feasible, and perhaps not even ethical. In addition, the follow-up in the published comparative studies discussed in this review is still too short for recurrence and survival data to be available for women with MRI-detected cancers. Therefore, the recommendations for MRI screening in this guideline are based on indirect evidence and certain assumptions, according to the following rationale:

1. Randomized trials of screening mammography, which downstages cancers (relative to no screening) in the general population, have demonstrated a mortality decrease of 20% to 30%.
2. Since MRI screening downstages cancers (relative to mammography) in a particular high-risk population in prospective comparative studies, it likely decreases mortality in that high-risk population.

Several additional caveats should be mentioned. While all groups have reported a higher sensitivity for MRI compared to mammography for invasive cancer, in the two large multicentre studies (45,46), as well as in the earlier cohort of the Warner B study, mammography was more sensitive than MRI for DCIS. This is likely due to the 'MRI learning curve,' which is steeper for DCIS with its more subtle presentation than for invasive cancer. Accordingly, MRI can not yet be recommended as a replacement for mammography but should be used in addition to mammography. If mammography reveals a cancer on a particular round of screening, MRI is still indicated, as multiple primary lesions occur fairly commonly in this population (44). Even in highly experienced centres mammography is still recommended

because it remains the only screening modality proven to date to reduce breast cancer mortality in any population.

Although there has been some theoretical concern about the possible risk of mammography inducing breast cancer in young women in general and in women with BRCA mutations in particular (as these genes have a role in repairing DNA damage), a recent study by Goldfrank et al. is reassuring (79). In that study of 213 women with BRCA mutations no association was found between mammogram exposure and breast cancer risk. Similar results were found in a recent study by Narod et al (80). Furthermore, even if there were a tiny increase in cancer risk attributable to screening mammography, which would make one cautious about using this modality in young low risk women, this would be more than offset by the much greater likelihood of early mammographic detection of cancer in the very high risk patient.

The accreditation of centres performing MRI is not yet available but should be a priority. Centres differ with respect to the sophistication of their magnet and other hardware, computer software and the experience of the physicists, technologists, and radiologists. Not all centres are capable of performing MRI-guided biopsies for lesions that cannot be visualized by other modalities, even in retrospect. The capacity to perform such biopsies is particularly important for identifying DCIS, particularly in women with BRCA1 mutations whose tumours tend to become invasive more quickly than other breast cancers.

Finally, in counselling very high-risk women who are trying to choose between risk-reducing mastectomy and screening, the point should be made that, although the sensitivity of MRI is excellent, it is less than 100%. Therefore, women who opt for screening should strongly consider other risk-reducing measures (e.g., chemoprevention and/or oophorectomy) and must be able to accept some risk.

ONGOING TRIALS

The United States National Cancer Institute (NCI) Clinical Trials database (http://www.cancer.gov/search/clinical_trials/) was searched for breast cancer screening trials. Two ongoing trials were identified (81,82) in a review of the resulting trial protocols that involved the evaluation of MRI in the screening of high-risk women. It is likely that there are additional ongoing studies that are not registered in the NCI database.

CONCLUSIONS

Screening high risk women with MRI in addition to mammography significantly increases sensitivity, with a moderate but acceptable decrease in specificity. MRI screening likely reduces breast cancer mortality, but conclusive data is not yet available, and randomized trial data will never be available. At present, the sensitivity and specificity of MRI screening differs significantly between centres, largely due to varying levels of experience in using MRI. Ideally, breast screening for high risk women should be combined with risk reduction strategies. The recommendations in this document will undoubtedly change over time as new evidence accumulates.

CONFLICT OF INTEREST

All the authors were asked to declare any potential conflict of interest. DP indicated ownership of stock valued in excess of CDN$5000 in a manufacturer of MRI equipment; all other authors reported no conflict of interest.

JOURNAL REFERENCE

The following systematic review based on this EBS has been published by the *Annals of Internal Medicine* (http://www.annals.org/):

- Warner E, Messersmith H, Causer P, Eisen A, Shumak R, Plewes D. Systematic review: using magnetic resonance imaging to screen women at high risk for breast cancer. Ann Intern Med. 2008 May 6;148(9):671-9.

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Appendix 1. Search criteria for MEDLINE and EMBASE.

MEDLINE	EMBASE
1 exp Magnetic Resonance Imaging/	1 magnetic resonance imaging.ti
2 magnetic resonance imaging.ti	2 MRI.ti
3 MRI.ti	3 (breast or mammary).tw
4 1 or 2 or 3	4 (cancer or carcinoma or neoplasm).tw
5 breast neoplasms/ or carcinoma, ductal, breast/	5 screening.mp
6 (breast or mammary).tw	7 high risk.mp
7 (cancer or carcinoma or neoplasm).tw	8 hereditary.mp
8 5 or (6 and 7)	9 brca.mp
9 screening.mp	10 (familial or family history).mp
11 high risk.mp	11 (prior or previous).mp
12 hereditary.mp	12 (radiotherapy or radiation).mp
13 brca.mp	13 7 or 8 or 9 or 10 or 11 or 12
14 (familial or family history).mp	15 exp Mass Screening/
15 (prior or previous).mp	16 5 or 15
16 (radiotherapy or radiation).mp	18 exp Health Education/
17 11 or 12 or 13 or 14 or 15 or 16	19 exp health promotion/
19 exp Mass Screening/	20 exp Retrospective Studies/
20 9 or 19	21 (letter or editorial or comment or news).pt
22 8 and 17 and 20	22 review.pt. not systematic.mp
23 limit 22 to english language	23 questionnaires/ or health surveys/
24 limit 23 to yr="1995 - 2006"	24 exp nuclear magnetic resonance imaging/
25 exp Health Education/	25 exp Breast Cancer/
26 exp health promotion/	26 24 or 1 or 2
27 24 not (25 or 26)	27 25 or (3 and 4)
28 exp Retrospective Studies/	28 27 and 13 and 16
29 case reports.pt	29 28 not (18 or 19 or 20 or 21 or 22 or 23)
30 27 not (28 or 29)	30 limit 29 to (english language and yr="1995 - 2006")
31 (letter or editorial or comment or news).pt	31 30 and 26
32 30 not 31	
33 review.pt. not systematic.mp	
34 questionnaires/ or health surveys/	
35 32 not (33 or 34)	
36 35 and 4	

Appendix 2. Calculation of number needed to screen, additional false positives, and sensitivity and specifity of MRI and mammography combined.

Number Needed to Screen (NNS) and Additional False Positives (AFP)
The proportion of true positives (PTP) and proportion of false positives (PFP) of any screening modality is calculated based on the prevalence (P) of disease in the screened population as follows:

$$PTP = Sens \times P$$
$$PFP = Spec \times (1-P)$$

Given two cancer screening modalities, A and B, where A is the more sensitive of the two, the number needed to screen (NNS) is the number of individuals who need to be screened by modality A to detect one additional case of cancer over what would have been detected by modality B in the same population. In the process, if the specificity of A is lower than B, a number of additional false positives (AFP) will be generated. These values are calculated as follows:

$$NNS = \frac{1}{PTP_A - PTP_B}$$
$$AFP = NNS \times (PFP_A - FPR_B)$$

Sensitivity and Specificity of MRI Combined with Mammography
While the available data does not allow the direct measurement of the sensitivity and specificity of MRI combined with mammography, several things can said about the range these values could take, and estimates of their values can be made based on the assumption that they are uncorrelated.

For sensitivity and specificity, assuming that mammography has a lower sensitivity and a higher specificity than MRI, then:

$$Sens_{MRI} \leq Sens_{Comb} \leq Minimum(Sens_{MRI} + Sens_{Mammo}, 100\%)$$
$$Maximum(Spec_{MRI} + Spec_{Mammo} - 100\%, 0\%) \leq Spec_{Comb} \leq Spec_{MRI}$$

To illustrate the above, if there is positive correlation between MRI and mammography sensitivity (i.e. they are detecting the same cancers and leaving the same cancers undetected by either), then the sensitivity of the combination will approach the sensitivity of MRI alone. If there is negative correlation (i.e. they are detecting different cancers, each catching the cancers the other misses), then the sensitivity will approach the sum of the two sensitivities, or 100%. Similarly, if MRI and mammography specificity are positively correlated (i.e. they are falsely detecting cancer in the same people), then the specificity for the combination will approach that of MRI. If they are negatively correlated (i.e. they are falsely detecting cancer in different people), then the combined specificity will approach the sum of the individual specificities minus 100%, or 0% in the worst case.

In order to estimate the sensitivity and specificity of MRI combined with mammography from the available data, one must assume that the sensitivities of the two modalities, as well as the specificities, are uncorrelated with each other. If this assumption is valid, then the MRI/mammography combined sensitivity and specificity can be estimated as follows:

$$Sens_{Combined} = (Sens_{MRI} \times Sens_{Mammo}) + [Sens_{MRI} \times (1 - Sens_{Mammo})] + [(1 - Sens_{MRI}) \times Sens_{Mammo}]$$
$$Spec_{Combined} = Spec_{MRI} \times Spec_{Mammo}$$

Appendix 3. Complete data used for meta-analysis.

Study	Number of patients	Number of Screenings	Number of Cancers	Mammography				MRI			
				TP	FP	TN	FN	TP	FP	TN	FN
Kuhl (44)	529	1452	43	14	45	1364	29	39	39	1370	4
MRISC (45)	1909	4169	45	15	40	4084	30	29	148	3976	16
MARIBS (46)	649	1881	35	14	121	1725	21	27	344	1502	8
Warner B (47)	236	457	22	8	1	434	14	17	20	415	5
Hartman (50,51)	68	68	1	0	1	66	1	1	16	51	0
Lehman (52-54)	171	171	6	2	2	163	4	6	8	157	0
IBMC (55)	367	367	4	1	7	356	3	4	27	336	0
Sardanelli (56)	235	321	15	9	3	303	6	14	5	301	1

Abbreviations: FN, false negative; FP, false positive; IBMC, International Breast MRI Consortium; MARIBS, Magnetic Resonance Imaging Breast Screening; MRISC, Magnetic Resonance Imaging Screening Study; TN, true negative; TP, true positive.

Evidence-Based Series 15-11 Version 3: Section 2B

Magnetic Resonance Imaging Screening
of Women at High Risk for Breast Cancer:
A Systematic Review of the Cost Effectiveness Literature

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A Quality Initiative of the
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

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**This cost-effectiveness systematic review was not updated
as part of the updated search described in Section 4
(Document Review Summary and Tool).**

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Section Date: April 12, 2007

INTRODUCTION

As a companion to the systematic review of the clinical evidence found in Section 2 of this evidence-based series, a systematic review of the cost-effectiveness literature regarding the use of MRI in the screening of women at high risk for breast cancer was undertaken. This systematic review was conducted with assistance from the Program for Assessment of Technology in Health (PATH).

METHODS
Data Sources and Searches

MEDLINE, EMBASE, the Cochrane Library, and Office of Health Economics (OHE) Health Economics Evaluations Database (HEED) were searched to October 2006. The search criteria used were similar to those used in Section 2 of this evidence-based series, with the addition of appropriate terms to identified economic evaluation studies.

Study Selection

Studies were selected if they investigated the cost effectiveness of MRI in the screening of women at high risk for breast cancer compared to or in addition to mammography.

Data Extraction and Quality Assessment

Data was extracted by one reviewer. No formal assessment of the quality of the included studies was performed.

Data Synthesis and Analysis

No meta-analysis was performed.

RESULTS

One hundred and twenty-five separate items were retrieved from all the databases combined. Of these, two studies (1,2) were eligible for inclusion in this systematic review.

Griebsch et al (1) conducted a cost-effectiveness analysis comparing mammography alone, MRI alone, and the combination of MRI and mammography, from the perspective of the United Kingdom National Health Service. "Additional cancers detected" was used as the measure of effectiveness. This study used data from the MARIBS study (3) as the basis for its analysis. The time frame of the analysis was one year.

In this study, the cost per additional cancer detected was estimated to be £28,284 for the combination of mammography and MRI using the baseline assumptions of the analysis, for the entire population included in the MARIBS study (BRCA1/2 and TP53 carriers, first degree relatives of carriers, or strong family history of breast or ovarian cancer), and £15,302 for BRCA2 carriers alone. MRI alone was dominated by the combination of mammography and MRI. In the MARIBS study, there were no additional cancers detected with the combination of MRI and mammography over MRI alone in BRCA1 carriers, so the cost per additional cancer detected was only estimated for MRI alone; £11,731. An uncertainty analysis, based on a decision makers willingness to pay for an additional cancer detected, found that, for the entire population, the probability that the combination of MRI and mammography was cost effective, compared to mammography alone, was 0.06 if the decision maker were willing to pay £20,000, and 0.67 if the decision maker were willing to pay £30,000. In a sensitivity analysis, the cost-effectiveness of the combined modalities was most sensitive to the costs of the MRI screening itself and the costs of further investigations to establish a diagnosis.

Plevritis et al (2) conducted a model-based cost-effectiveness analysis comparing mammography alone to the combination of MRI and mammography, from a societal perspective. Quality-adjusted life years (QALYs) gained by screening was the measure of effectiveness. The analysis was conducted using a simulated cohort of BRCA1/2 mutation carriers followed over their lifetimes using Monte Carlo simulation methods. An extensive mathematical model of the natural history of invasive breast cancer was used to estimate the incidence of disease and its mortality. Costs were based on United States Medicare reimbursement costs and other sources.

In this study, the cost per QALY gained from the combination of MRI and mammography over mammography alone for women aged 25 to 69 years was US$88,651 for BRCA1 carriers and US$188,034 for BRCA2 carriers. In women aged 35 to 54 years, the cost per QALY gained for the addition of MRI to mammography was US$55,420 for BRCA1 carriers and US$130,695 for BRCA2 carriers. For women younger than 50 years with extremely dense breasts on mammography, the cost per QALY gained was US$41,183 for BRCA1 carriers and US$98,454 for BRCA2 carriers. In the case of BRCA2 mutation carriers, biennial, as opposed to annual, mammography and MRI screening yielded a cost per QALY gained of US$98,679 in women aged 35 to 54 years. The authors concluded that, at a threshold of US$100,000 per QALY gained, adding annual MRI to mammography was cost effective for all BRCA1 carriers ages 35 to 54 and for BRCA2 carriers for whom mammography is insensitive. Biennial MRI was cost-effective at that threshold in all BRCA2 carriers. The authors also concluded that MRI plus mammography was not cost effective, at the above threshold, in younger women ages 25 to 34 years or older women aged 55 or older.

DISCUSSION

There is evidence from these two studies (1,2) that the addition of MRI to mammography is cost effective for some women at high risk for breast cancer, assuming a threshold of US$100,000 per QALY as did Plevritis et al. Specifically, MRI and mammography is more cost effective in women at the highest risk of breast cancer and in women for whom mammography is less sensitive.

In both the included studies, a number of assumptions were made regarding recall rates, underlying incidence of breast cancer and its natural history, costs, etc. A full treatment of these assumptions is not possible in this document. The original articles should be reviewed to gain an understanding of the assumptions made by the study authors. This is especially true regarding the costs incorporated into these studies and whether these costs are relevant to an Ontario perspective.

ACKNOWLEDGEMENTS

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Evidence-Based Series 15-11 Version 3: Section 3

Magnetic Resonance Imaging Screening of Women at High Risk for Breast Cancer: Guideline Development and External Review - Methods and Results

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A Quality Initiative of the
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This Section describes the original development of Version 1 of this document. See Section 4 (Document Review Summary and Tool), for details on the assessment and review process that led to this document's endorsement

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Section Date: April 12, 2007

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, called Disease Site Groups (DSGs) and Guideline Development Groups (GDGs), mandated to develop the PEBC products. These panels are comprised of clinicians, other health care providers, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based practice guideline reports, using the methods of the Practice Guidelines Development Cycle (1, 2). The PEBC reports consist of a comprehensive systematic review of the clinical evidence on a specific cancer care topic, an interpretation of and consensus agreement on that evidence by our DSGs and GDGs, the resulting clinical recommendations, and an external review by Ontario clinicians in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each clinical practice guideline report, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original clinical practice guideline information.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES
Development and Internal Review

This evidence-based series was developed by the Special Working Group on MRI Screening in Breast Cancer (the Working Group) of CCO's PEBC. The series is a convenient and up-to-date source of the best available evidence on MRI screening for women at high risk for breast cancer, developed through systematic review, evidence synthesis, and input from practitioners in Ontario.

Report Approval Panel

Prior to the submission of this evidence-based series report for external review, the report was reviewed and approved by the PEBC Report Approval Panel, which consists of two members, including an oncologist, with expertise in clinical and methodology issues. **It is important to note that Section 2-A (the cost-effectiveness systematic review) was not reviewed by the Report Approval Panel.** Key issues raised by the Panel, with the response of the authors, included:

- Both the magnitude of the benefit of MRI screening and the costs in terms of additional false positives were not presented in a way easily understandable to the target audience of the document. The Panel suggested several alternative values, including a number-needed-to-screen, to put these benefits and costs into perspective. RESPONSE: The presentation of the results of the meta-analysis was edited in order to increase readability and clarity, and the suggested additional values were reported.
- Concern was raised regarding the lack of evidence from randomized controlled trials. The Panel asked for additional clarification and discussion of this issue. RESPONSE: A discussion of the reasons why randomized controlled trial data was not available and not likely to become available was included.
- The Panel pointed out that the evidence in the document suggests that the magnitude of the benefit of MRI decreases with the age of the patient and questioned the age range of patients covered by the recommendations (ages 30 to 69). RESPONSE: Several statements were added to the discussion to address this issue, suggesting that a biannual schedule of screening may be appropriate after age 60.
- The Panel suggested that the evidence could be interpreted as supporting MRI as a replacement for mammography as opposed to its use in combination with mammography. The Panel also pointed out that, while the questions address mammography combined with MRI versus mammography alone, most of the data deals with the comparison of MRI to mammography. They asked for a discussion of these issues. RESPONSE: A discussion of the reasons why mammography remains necessary in the screening of the target population was added. Also, additional analysis was presented that more directly addressed the question of MRI plus mammography versus mammography alone.
- The Panel questioned the value added by a non-systematic review of the mammography literature and asked for additional discussion of this issue. RESPONSE: This section was removed.

Based on the response to the Panel, the report was approved on January 10, 2007.

External Review by Ontario Clinicians

Following the review and discussion of Sections 1 and 2 of this evidence-based series and review and approval of the report by the PEBC Report Approval Panel, the Working Group circulated the clinical practice guideline and systematic review to clinicians in Ontario for review and feedback. **It is important to note that Section 2-A (the cost-effectiveness**

systematic review) was not included in the draft sent for practitioner feedback. Box 1 summarizes the draft clinical recommendations and supporting evidence developed by the panel.

BOX 1: DRAFT RECOMMENDATIONS (approved for external review January 10, 2007)

Target Population
Women at very high risk for breast cancer, 'very high risk' being defined as:
1. Known mutation in BRCA1, BRCA2 or other gene predisposing to a markedly elevated breast cancer risk.
2. Untested first-degree relative of a carrier of such a gene mutation
3. Family history consistent with a hereditary breast cancer syndrome and estimated personal lifetime cancer risk >25%.
4. High-risk marker on prior biopsy (atypia, lobular carcinoma in situ [LCIS])
5. Radiation therapy to chest (before age 30 and at least eight years previous).

Recommendations

MRI in addition to mammography is recommended for women in target population subgroups 1, 2, and 3 above. It is the expert opinion of the working group that these women should be screened annually from 30 to 69 years of age.

There is insufficient evidence to make a recommendation for or against MRI in addition to mammography for target population subgroups 4 and 5 above. However, it is the expert opinion of the working group that the benefits of MRI in terms of increased sensitivity outweigh the potential harms of higher recall rates and biopsy rates for these latter two subgroups.

- Twelve studies, four in abstract form, were identified that evaluated MRI in comparison to mammography in women at high risk for breast cancer. These studies all found superior sensitivity for the detection of breast cancer with MRI compared to mammography. MRI was also found by most studies to have inferior specificity to mammography, with higher recall and biopsy rates associated with MRI.
- A meta-analysis of these studies found MRI to have numerically superior discriminatory power overall compared to mammography in determining the true breast cancer status of high-risk women. The summary sensitivity was 80.1% (95% confidence interval [CI] 73.3% to 85.8%) for MRI and 36.8% (95% CI 29.6% to 44.5%) for mammography. The summary specificity was 93.0% (95% CI 92.5% to 93.6%) for MRI and 97.5% (95% CI 97.1% to 97.8%) for mammography. The overall diagnostic odds ratio for MRI was 77.338 (95% CI 29.117 to 205.41) versus 32.003 (14.633 to 69.989) for mammography. Due to the limited number of studies included, a direct statistical comparison of the two modalities was not possible.

Methods

Feedback was obtained through a mailed survey of 57 practitioners in Ontario. This sample included medical oncologists, radiation oncologists, radiologists, and genetics specialists. The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. The survey was mailed out on January 24, 2007. Follow-up reminders were sent at two weeks (post card). The Working Group reviewed the results of the survey.

In addition to the survey, the draft document was submitted to a number of other stakeholders for comment, including the radiology departments of Ontario hospitals, the Canadian College of Medical Geneticists, and other practitioners in Ontario that the authors believed would provide valuable feedback. Also, the draft document was provided to the members of the Breast Cancer Disease Site Group of the PEBC for comment.

Results

Seventeen responses were received out of the 57 surveys sent (29.8% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the practitioners who responded, 13 practitioners indicated that the report was relevant to their clinical practice and completed the survey. Key results of the practitioner feedback survey are summarized in Table 1.

Table 1. Responses to eight items on the practitioner feedback survey.

Item	Number (%)		
	Strongly agree or agree	**Neither agree nor disagree**	**Strongly disagree or disagree**
The rationale for developing a guideline, as stated in the "Introduction" section of the report, is clear.	12 (92.3%)	0	1 (7.7%)
There is a need for a guideline on this topic.	12 (92.3%)	0	1 (7.7%)
The literature search is relevant and complete.	12 (92.3%)	0	1 (7.7%)
The results of the trials described in the report are interpreted according to my understanding of the data.	11 (84.6%)	1 (7.7%)	1 (7.7%)
The draft recommendations in the report are clear.	12 (92.3%)	0	1 (7.7%)
I agree with the draft recommendations as stated.	11 (84.6%)	0	2 (15.4%)
This report should be approved as a practice guideline.	7 (69.2%)	2 (15.4%)	2 (15.4%)
If this report were to become a practice guideline, how likely would you be to make use of it in your own practice?	**Very likely or likely**	**Unsure**	**Not at all likely or unlikely**
	13 (100%)	0	0

Summary of Written Comments

Two respondents (15.4%) provided written comments that required a response. In addition, five other practitioners provided written comments. The main points contained in the written comments, with the author's response, were:

1. One respondent was concerned that the implication of the guideline is that MRI is not indicated for medium-risk women. This respondent was concerned that this would lead to lower risk patients being excluded from MRI screening due to lack of funding. The respondent pointed out that the benefits in these patients of MRI are unknown at this time, as opposed to there being evidence of no benefit, and suggested that an explicit statement regarding the need for further research be made. RESPONSE: The Working Group did not believe there were any implications for or against the use of

MRI screening in that population in this report, and that it was not the intent of this guideline to address medium risk women, nor were they included in the target population. No changes were made.

2. One respondent questioned the inclusion of patients with family history consistent with a hereditary breast cancer syndrome and estimated personal lifetime cancer risk >25%, and felt there was an absence of strong data to support this group having routine MRI over other imaging modalities. RESPONSE: The Working Group felt that the evidence for the use of MRI screening in this population was as strong as it was for the other groups included in the recommendation, as at least five of the included studies included women at high risk due to familial history. No changes were made.

3. One respondent indicated that they felt a recommendation should be made for the aggressive screening of patients who had received radiation therapy to the chest (before age 30 and at least 8 years previous), particularly patients who had received radiotherapy to the thorax for lymphoma. RESPONSE: The Working Group felt that as no studies were identified that addressed this population as part of the systematic review, there was no evidence to support a recommendation for this population. However, the opinion of the Working Group, as expressed in the clinical practice guideline, is that these women should be screened using MRI. No changes were made.

4. One respondent pointed out that while the recommendation indicated screening until age 69, in the discussion the authors suggest that it would be reasonable to halt screening after age 65, or to screen after two years after age 60. The respondent suggested that the recommendation be altered to say annual screening until age 60 and screening at clinicians discretion after that age. RESPONSE: The Working Group did not make a recommendation regarding the age range within which women should be screened. Rather, it expressed the opinion that screening should continue until age 69. The systematic review discussion pointed out that clinicians may reasonably differ on this issue. However, the respondent's comment made it clear that more needed to be done to differentiate the actual recommendations and the opinion-based advice of the Working Group in the clinical practice guideline. The clinical practice guideline was reformatted and rewritten to make this difference plain and to include the reasoning behind all expert opinions.

5. One respondent asked whether the authors recommended staggering of MRI and mammography or performing the screenings at the same time, or whether the authors were recommending this be left to the discretion of the clinician. RESPONSE: The Working Group did address this issue in the systematic review discussion, indicating there was simply no data as yet on which to base a recommendation or even an opinion on this subject. No changes made.

6. One respondent asked whether the recommendation should specify that women who had received radiotherapy to the chest should begin screening at 25 or eight years after that treatment. The respondent also asked if this recommendation specifically applied to patients who had received treatment for Hodgkin's disease or whether there are other frequent conditions at issue. RESPONSE: The Working Group agreed that, for this category, it was appropriate to begin screening at age 30 or eight years after the treatment, although this is an opinion, not a recommendation. The clinical practice guideline was altered to reflect this change.

7. One respondent asked that the authors specify frequency in the second recommendation. RESPONSE: The reformatted clinical practice guideline made it clear that the screening frequency opinion applies to the entire target population.

8. One respondent asked that the authors specify a starting age of screening for those with a high-risk marker on prior biopsy, and suggested this would be beginning with

diagnosis. RESPONSE: The Working Group agreed that in the rare cases where a high-risk marker is identified in a woman younger than age 30, screening should be considered. The qualifying statements were changed.

9. One respondent felt that the question of MRI screening for women with a prior history of breast cancer, particularly mammographically occult cancer and in whom the sensitivity of mammography is reduced (e.g., very dense breasts) should have been addressed. This respondent suggested there was some limited data available to address this question. RESPONSE: Unfortunately, given the time and effort necessary to address even the questions found within the current document, the Working Group felt that addressing this additional population would not be feasible. No changes were made.

10. One respondent expressed concern that the level of detail provided regarding the studies in the results section distracted from the overall message of the document. RESPONSE: The Working Group felt that the overall evidence-based series meets two goals: a complete systematic review of all the available evidence and a clinical practice guideline based on that evidence. The level of detail provided is appropriate given the complexity of the evidence. No changes were made.

11. One respondent found the discussion of sensitivities from the analysis of Warner A by period (3) was unclear and difficult to interpret. RESPONSE: This section was edited for clarity.

12. One respondent expressed concern regarding the validity of the meta-analytical techniques being used and suggested they be reviewed by an experienced biostatistician. RESPONSE: Comment on the methods used for the meta-analysis in this paper had been solicited prior to submission to external review by a biostatistician, Dr. Steve Hanna, with experience in this area; his comments were very helpful, and the Working Group was confident in the analysis. However, this respondent's comment pointed out that Dr. Hanna's name was left out of the acknowledgements section of the document, and it was added there.

Changes after Report Approval Panel and Practitioner Feedback

After the completion of both the Report Approval Panel review and practitioner feedback, a systematic review of the cost-effectiveness literature was incorporated into the document as Section 2-A. This section was originally intended to be part of a separate document but was included in this evidence-based series in order to ensure its rapid dissemination to clinicians and policy makers.

Policy Review

This document will be submitted to the Ontario Breast Screening Program, Cancer Care Ontario, and the Ontario Ministry of Health and Long-Term Care for their review regarding the funding and implementation of organized MRI screening for women at high risk of breast cancer in Ontario.

Conclusion

This report reflects the integration of feedback obtained through the external review process with final approval given by the Working Group and the Report Approval Panel of the PEBC. Updates of the report will be conducted as new evidence informing the question of interest emerges.

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2. Browman GP, Newman TE, Mohide EA, Graham ID, Levine MN, Pritchard KI, et al. Progress of clinical oncology guidelines development using the practice guidelines development cycle: the role of practitioner feedback. J Clin Oncol. 1998;16(3):1226-31.
3. Warner E, Causer PA, Hill KA, Ramsay E, Jong RA, Wong JW, et al. MRI surveillance downstages invasive cancer (IC) to DCIS in women at high risk for hereditary cancer [abstract]. Breast Cancer Res Treat. 2005;94 Suppl 1:A5001.

Evidence-Based Series 15-11 Version 3: Section 4

Magnetic Resonance Imaging Screening
of Women at High Risk for Breast Cancer

Guideline Review Summary

E. Warner, C. Agbassi, and the Expert Panel on MRI Screening of Women at High Risk for Breast Cancer

January 24, 2018

+---+
| *The 2007 guideline recommendations are* |
| |
| *ENDORSED* |
| |
| *This means that the recommendations are still current and* |
| *relevant for decision making* |
+---+

OVERVIEW

      The original version of this guidance document was released by the Program in Evidence-based Care (PEBC), Cancer Care Ontario, in 2007. In 2011, this document was assessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist (CA) conducted an updated search of the literature from 2006 to 2011 and the data supported the 2007 recommendations. Please see Appendix A for this document summary and review table.

      In February 2017, this document was assessed again in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist (CA) conducted an updated search of the literature. A clinical expert (EW) reviewed and interpreted the new eligible evidence and proposed the existing recommendations could be endorsed. An Expert Panel was convened in October 2017 to discuss the new evidence and the proposal to endorse the recommendations. The Expert Panel suggested some modifications to the recommendations and qualifying statements with respect to patients in risk category 5 because the evidence has changed for this group. On January 19, 2018 the recommendations, with modifications, found in Section 1 (Clinical Practice Guideline) were endorsed.

DOCUMENT ASSESSMENT AND REVIEW RESULTS
Questions Considered

- What is the effectiveness of adding breast magnetic resonance imaging (MRI) to standard screening (mammography) compared to screening mammography alone?
- Does the addition of breast MRI to standard screening detect breast cancer at an earlier stage?
- What is the optimal frequency of MRI screening?
- Are there subgroups (risk category, age, or breast density) that benefit more from MRI screening than do others?
- What harms are associated with MRI screening, and are there any relative or absolute contraindications to its use?
- In the presence of an abnormal finding seen only on MRI imaging, what is the optimal workup and follow-up after screening?

Literature Search and New Evidence

The new search (January 2012 to April 2017) yielded 13 relevant new publications representing two guidelines/recommendations, two pooled/meta-analysis, and nine prospective non-randomized studies. Brief results of these publications are shown in the Document Review Tool below.

Impact on the Guideline and Its Recommendations

The original guideline concluded that screening MRI in addition to mammography is recommended for women in target population risk categories 1, 2, 3; and that there was insufficient evidence to recommend for or against the addition of MRI for categories 4 and 5. The literature search updated to April 2017 provided new data that support the addition of MRI to mammography in women in risk category 5. For women in risk category 4, there is insufficient evidence to make definitive recommendations for or against screening MRI in addition to mammography. The ESMO recommendations [1] suggest that mammography should not be done before age 35 but there is insufficient evidence supporting this statement.

In 2011, the Ontario Breast Screening Program (OBSP) expanded screening services to include women at high risk for breast cancer, aged 30 to 69 years. During the development of the high risk OBSP, the clinical expert panel weighed evidence and expert opinion to make decisions about program design and delivery. The expert panel opted to include risk category 5 (women with radiation therapy to the chest) along with categories 1, 2, and 3 in the high risk screening eligibility criteria because the group is small, distinct, and easily recognizable. Preliminary program data suggest that this group makes up only 6% of the total high risk clients screened within the first eight months of the program's existence. Of note, the American Cancer Society's (ACS) high risk breast cancer screening guidelines also recommend screening MRI and mammography for this group of women (14).

Document Review Tool

Number and Title of Document under Review	15-11 Magnetic Resonance Imaging Screening of Women at High Risk for Breast Cancer
Current Report Date	August 20, 2012
Clinical Expert	Ellen Warner
Research Coordinator	Chika Agbassi
Date Assessed	February 7, 2017
Approval Date and Review Outcome (once completed)	January 19, 2018 ENDORSED

Original Question(s):

- What is the effectiveness of adding breast magnetic resonance imaging (MRI) to standard screening (mammography) compared to screening mammography alone?
- Does the addition of breast MRI to standard screening detect breast cancer at an earlier stage?
- What is the optimal frequency of MRI screening?
- Are there subgroups (risk category, age, or breast density) that benefit more from MRI screening than do others?
- What harms are associated with MRI screening, and are there any relative or absolute contraindications to its use?
- In the presence of an abnormal finding seen only on MRI imaging, what is the optimal workup and follow-up after screening?

Target Population:

Women at very high risk for breast cancer, 'very high risk' being defined as:
1. Known mutation in BRCA1, BRCA2 or other gene predisposing to a markedly elevated breast cancer risk.
2. Untested first-degree relative of a carrier of such a gene mutation
3. Family history consistent with a hereditary breast cancer syndrome and estimated personal lifetime cancer risk >25%.
4. High-risk marker on prior biopsy (atypical ductal hyperplasia, atypical lobular hyperplasia, lobular carcinoma in situ [LCIS])
5. Radiation therapy to chest (before age 30 and at least eight years previous).

Study Selection Criteria:

Inclusion criteria:
- Systematic reviews, meta-analyses, and clinical practice guidelines that addressed the use of MRI in the screening of women at high-risk breast cancer were included.
- Randomized studies or prospective non-randomized studies of MRI compared to mammography with or without ultrasound and clinical breast examination for the screening of women at very high risk for breast cancer are included. Studies had to report at least one relevant measure of effectiveness/benefit, including sensitivity, specificity, positive or negative predictive value, accuracy, time to diagnosis, tumour stage information (size, proportion DCIS, etc.), or improvement in patient outcome (response or survival).
- The studies had to be relevant to the target population, that is, women at very high risk for breast cancer. 'Very high risk' was defined as:
1. Known mutation in BRCA1, BRCA2 or other gene predisposing to a markedly elevated breast cancer risk.
2. Untested first degree relative of a carrier of such a gene mutation
3. Family history consistent with a hereditary breast cancer syndrome and estimated personal lifetime cancer risk >25%.
4. High risk marker on prior biopsy (atypia, LCIS)
5. Radiation therapy to chest (before age 30 and at least 8 years previous).

Exclusion criteria:
- Due to the lack of translation resources, non-English language reports were excluded.
- Because of changes in both mammographic and MRI technology, publications prior to 1995 were considered out-of-date and excluded.

Search Details:

- January 2012 to April 2017 (MEDLINE, EMBASE)
- January 2012 to April 2017 (ASCO Annual Meeting San Antonio Breast Cancer Symposia and Clinicaltrials.gov))

Summary of new evidence:

Of 706 total hits from MEDLINE and EMBASE; 194 total hits from ASCO and San Antonio Breast Cancer Symposia abstract searches, 13 references representing two guidelines/recommendations, two pooled/meta-analysis, 1 systematic review without meta-analysis, and 12 prospective non-randomized studies were found comparing MRI + Mammography vs. Mammography or MRI or ultrasound(US) alone. Two ongoing trials were identified. Details from the included trials are summarized in the tables below.

Guidelines		
Reference	**Title**	**Recommendations**
Cardoso et al 2012 [1]	The European Society of Breast Cancer Specialists recommendations for the management of young women with breast cancer	• **Annual** MRI screening should be available starting at age 30. Starting annual screening before age 30 may be discussed, such as in BRCA1 or BRCA2 mutation carriers (starting between age 25 and 29 years) andTP53 mutation carriers (starting at age 20). • **Annual** MRI screening should be offered to:

						o BRCA1, BRCA2 and TP53 mutation carriers.

<table>
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○ BRCA1, BRCA2 and TP53 mutation carriers.
○ Women at 50% risk to be carriers of BRCA1, BRCA2 or TP53 mutation (first-degree relatives of mutation carriers)
○ Women from families not tested or inconclusively tested for BRCA mutation with a 20-30% lifetime risk or greater.
○ Women with prior mantle radiotherapy before age 30 (e.g. for Hodgkin disease), starting 8 years after their treatment.
○ Women at high risk and who were already diagnosed and treated for breast cancer should be included in screening programs including MRI

Women of any age undergoing prophylactic mastectomy should have a MRI examination within the 3 months before surgery to screen for occult breast cancer
Screening mammography should not be performed in high-risk women below 35 years as there is no evidence that the benefits outweigh the risks in this young age group
In TP53 mutation carriers of any age, annual mammography can be avoided based on the discussion of risks and benefits from radiation exposure
Annual mammography may be considered for high risk women starting at age 35 years
If annual MRI is performed, additional screening with breast ultrasound (US) and clinical breast examination (CBE) are not necessary as there is no evidence of any benefit added to MRI. They are however recommended in women under 35 years who do not tolerate or have contraindications to MRI or gadolinium-based contrast administration.
Cases requiring workup after MRI should be initially assessed with conventional imaging – re-evaluation of mammography and targeted US. In cases of suspicious findings solely detected by MRI, MR guided biopsy localization should be performed
Risk factors such as prior diagnosis of invasive breast cancer or Ductal Carcinoma In Situ (DCIS), atypical ductal hyperplasia, lobular intraepithelial neoplasia, heterogeneous or dense breasts on mammography, if not associated with other risk factors, do not confer an increased risk justifying the use of screening MRI

</td></tr>
<tr><td>Mulder et al 2013[2]</td><td>Recommendations for breast cancer surveillance for female survivors of childhood, adolescent, and young adult cancer given chest radiation: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group</td><td colspan="5">

Strong recommendation: mammography, breast MRI, or both is recommended. Evidence is insufficient to recommend the ideal imaging method
Weak recommendation: clinical breast examination might be reasonable for CAYA cancer survivors returning for follow-up medical assessments in countries where access to breast cancer surveillance is through clinical referral

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Pooled/Meta-analysis

Author, year, reference	Population	N	Median Follow-up	Intervention / Comparison	Criteria for a positive test result	Brief results

Phi et al 2015[3] Phi et al 2016[4]	Women with *BRCA1/2* mutations who had completed at least one screening round with both MRI and mammography. Age ≥50yr	1514	NR	MRI + MMG vs. MMG alone
				
				Included Studies: 6
					BI-RADS score 0,3,4,or 5	• Overall, MRI detected 145 (78.8%) of 184 breast cancers, and mammography detected 71 (38.6%) of 184 tumors.
						• **Sensitivity:** Compared to MMG
						  ○ **MMG:** 39.6% (95% CI: 30.1 to 49.9)
						  ○ **MRI:** 85.3% (95% CI: 69.1 to 93.8) p<0.001
						  ○ **MRI + MMG:** 93.4% (95% CI 80.2 to 98.0) p<0.001

						• **Specificity:** Compared to MMG
						  ○ **MMG:** 93.6% (95% CI: 88.8 to 96.5)
						  ○ **MRI:** 84.7% (95% CI: 79.0 to 89.1) p=0.010
						  ○ **MRI + MMG:** 80.3% (95% CI: 72.5 to 86.2) p=0.0016
						• **In Women age ≥50yr**
						  ○ **The** sensitivity of MRI alone or in combination with MMG was not significantly different from that in women <50yrs:
						  ○ **MRI + MMG:** 94.1 (95% CI: 77.7 to 98.7) vs. 93.2 %(95% CI, 79.3 to 98), p= 0 .79).
						  ○ The specificity of MRI alone or in combination with MMG was significantly different from that in women < 50yr: 85.3% (95% CI, 78.5 to 90.2) vs.78.7% (95% CI, 70.6 to 85.0), p < 0.001

Gareth et al 2014[5]	**MRI Group**
	Asymptomatic women aged 35–55 years were selected to receive annual MRI screening based on the presence of a proven or likely BRCA1, BRCA2, or TP53 mutation.
	
	MMG group
	Women who were BRCA1/2 mutation carriers (usually identified after the breast cancer diagnosis) and/or were at equivalent risk (40 % lifetime risk) of developing breast cancer who had received mammography screening only were selected as controls.
	
	Unscreened group
	Women with BRCA1/2 mutations who were identified from the Manchester genetic database as having been diagnosed with breast cancer after 1990 aged ≤55 years and who had not undergone intensive surveillance.
	
	Mean age: 40.2yr
	(range = 29 to 51)
		959	10 yr	MRI + MMG vs. MMG alone or unscreened
				
				Included Studies: 2
					NR	• MRI screen detected tumors were significantly more likely to be smaller, noninvasive, and lymph node negative than unscreened tumors (p<0.0001) but not the mammography-only detected tumors.
						• In the MRI-screened group, the axillary lymph node status was negative in 83 % of cases compared to 70 % in the mammography-screened group (p = 0.2) and 65 % in the unscreened group (p<0.0001).
						• **Survival**
						  ○ There were no differences in 10-year survival between the MRI + MMG and MMG alone groups,
						  ○ Survival was significantly higher in the MRI-screened group (95.3 %) compared to no intensive screening (73.7 %; p = 0.002).
						• **5yr OS**
						  ○ **MMG+MRI vs. MMG:** 95.3 (95% CI: 89.3 to 100.0) vs.90.7 (95% CI: 82.4 to 99.8), p = 0.075
						  ○ **MMG+MRI vs. no Screening:** 95.3 (95% CI: 89.3 to 100.0) vs. 86.7 (95% CI: 83.6 to 90.0) p = 0.002
						• **10yr OS**
						  ○ **MMG+MRI vs. MMG:** 95.3 (95% CI: 89.3 to 100.0) vs.87.7 (95% CI: 78.0 to 98.5), p = 0.075
						  ○ **MMG+MRI vs. no Screening:** 95.3 (95% CI: 89.3 to 100.0) vs. 73.7 (95% CI: 69.3 to 78.4) p = 0.002

Systematic review

Author, year, reference	Population	Number of studies	Brief results
Koo et al, 2015 [15]	Broad review of women with second cancers of the breast	138 studies	Recommends annual mammography and MRI for women treated with 20 Gy chest irradiation before the age of 30 years, beginning 8 years after the RT or age 25 years (whichever occurs later)

Published Non-Randomized Controlled Trials

Author, year, reference	Population	N	Median Follow-up	Intervention/ Comparison	Criteria for a positive test result	Brief results
Saadatmand et al 2015[6]	**MRI group:** Women with a familial or hereditary predisposition for breast	186	10 yr (range 4-14)	MRI + MMG vs. MGG	NR	• MRI screened patients had smaller (87% vs. 52% < 0.001) and node negative (69% vs. 44%, p=0.001) tumor.

	cancer. **Control group:** with breast cancer who received no screening if younger than 50 years of age, or were screened with biennial MMG if 50 years or older Median follow-up: 9 yrs (range 0-14)				• MRI screened patients received less chemotherapy (39% vs. 77%, p=0.001) and hormonal therapy (14% vs. 47%, p < 0.001) than the controls. • Metastasis was significantly less in the MRI group (9% vs. 23% p=0.009) • MFS was better in the MRI group; HR 0.36HR (95% CI 0.16-0.80), p=0.008, Overall survival was non-significantly better in MRI group HR 0.51, (CI 0.24-1.06) p=0.064,

Riedl et al 2016 [7]	BRCA mutation carriers and women with a high familial risk (> 20% lifetime risk) for breast cancer
	Med Age = 44yr
	(Range 22-83)
		599	NR	MRI vs. MMG or US vs. combinations of the 3	BI-RADS score 4 or 5	• **Sensitivity:**
						  ○ The sensitivity of MRI was significantly higher than that of US (p<0.001), MMG (p<0.001), and US + MMG (P< 0.001)
						  ○ DCIS detection was 100% for MRI and 36% for US or MMG
						  ○ MRI: 90.0% (95% CI: 76.9 to 96.0)
						  ○ **US:** 37.5% (**95%CI: 35.2** to **64.8**)
						  ○ **MMG:** 37.5% (95%CI: 24.2 to 53.0)
						  ○ **US + MMG:** 50% (95%CI: 35.2 to 64.8)
						  ○ **US + MRI:** 90% (**95%CI: 76.9 to 96.0**)
						  ○ **MMG + MRI:** 95% (**83.5 to 98.6**)
						  ○ **US + MMG + MRI:** 95% (95%CI: 83.5 to 98.6)
						• **Specificity:**
						  ○ MRI had a significantly lower specificity than mammography or ultrasound (p<0.001)
						  ○ **MRI:** 88.9 (95%CI: 87.1 to 90.5)
						  ○ **US:** 96.9 (95%CI: 95.8 to 97.7)
						  ○ **MMG:** 97.1 (95%CI: 96.1 to 97.9)
						  ○ **US + MMG:** 95.7 (95%CI: 94.5 to 96.7)
						  ○ **US + MRI:** 87.8 (95%CI: 83.5 to 98.6)
						  ○ **MMG + MRI:** 88.2 (95%CI: 86.3 to 89.8)
						  ○ **US + MMG + MRI:** 87.5 (95%CI: 83.5 to 98.6)
						• **NPV:**
						  ○ **MRI:** 99.7 (95%CI: 99.1 to 99.9)
						  ○ **US:** 98.1 (95%CI: 97.2 to 98.7)
						  ○ **MMG:** 98.1 (95%CI: 97.2 to 98.7)
						  ○ **US + MMG:** 98.4 (95%CI: 97.6 to 99.0)
						  ○ **US + MRI:** 99.7 (95%CI: 99.1 to 99.9)
						  ○ **MMG + MRI:** 99.8 (95%CI: 99.4 to 100.0)
						  ○ **US + MMG + MRI:** 99.8 (95%CI: 99.4 to 100.0)
						• **PPV:**
						  ○ **MRI:** 19.7 (95%CI: 14.6 to 26.0)
						  ○ **US:** 26.8 (95%CI: 1.70 to 3.96)
						  ○ **MMG:** 28.3 (95%CI: 18.0 to 41.6)
						  ○ **US + MMG:** 26.0 (95%CI: 17.5 to 36.7)
						  ○ **US + MRI:** 18.2 (95%CI: 13.4 to 24.1)
						  ○ **MMG + MRI:** 19.5 (95%CI: 14.5 to 25.6)
						  ○ **US + MMG + MRI:** 18.6 (95%CI: 13.9 to 24.5)

Berg et al 2012[8]	Asymptomatic women with heterogeneously dense or extremely dense breast tissue and at least one other risk factor for breast cancer
	Median age: 55yr
	
	(range 25 to 91)
		612	NR	MRI + MMG + US vs. US + MMG	BI-RADS score 3, 4, or 5	• Of the 111 breast cancers detected, 33 were detected on mammography only, 32 on US only, 26 on both mammography and US, and 9 on MRI after mammography and US
						• Number of screens needed to detect one cancer was 127(95%CI 99 to 167) for mammography; 234(95%CI 173 to 345) for supplemental ultrasound and 68 (95%CI 39 to 286) for MRI after negative M+US
						• **Yield, per 1000:**
						  ○ **US + MMG:** 11.4% (95%CI: 19.8 to 70.1)
						  ○ **US+ MMG + MRI:** 26.1%(95%CI: 15.0 to 42.1) p=0.004
						• **Sensitivity:**
						  ○ **US + MMG:** 43.8% (95%CI: 4.6 to 23.4)
						  ○ **US+ MMG + MRI:** 100%(95%CI: 61.5 to 100.0), p<0.001
						• **Specificity:**
						  ○ **US + MMG:** 84.4% (95%CI: 81.2 to 87.2)

					o **US+ MMG + MRI:** 65.4(95%CI: 61.5 to 69.3), p<0.001 • **Recall rate:** o US + MMG: 16.3% (95%CI: 13.5 to 19.5) o US+ MMG + MRI: 36.3%(95%CI: 32.5 to 40.2), p<0.001 • **PPV:** o **US + MMG:** 18.4% (95%CI: 7.7 to 34.3) o **US+ MMG + MRI:** 26.1%(95%CI: 15.0 to 42.1), p=0.983
Bosse et al 2014[9]	BRCA1 and BRCA2 mutation carrier **Median age:** 42 yr **Median F/U:** 5 screenings (range 1 to 22)	221	30 m (five semi-annual screenings)	US vs. MMG vs. MRI vs. US + MMG	RI-RADS score 4 or 5	• 27 BRCA-associated breast cancers were detected in 25 patients. • **Sensitivity:** o **US:** 77% (95%CI: 4.6 to 23.4) o **MMG :** 27%(95%CI: 61.5 to 100.0), p<0.001 o **MRI:** 100% o US + MMG 77% • **Specificity:** o **US:** 84.2% o **MMG :** 82.3% o **MRI:** 55.5%
Mokhtar et al 2014[10]	High risk patients coming for regular annual screening	30	NR	MRI vs. MMG	BI-RADS score 3, 4, or 5	• **Sensitivity:** o MRI: 87.0% o MMG: 60.0% • **Specificity:** o **MRI:** 87.0% o **MMG:** 27.0% • **Accuracy:** o **MRI:** 87.0% o **MMG:** 43.0% • **NPV:** o **MRI:** 87.0% o **MMG:** 45.0% • **PPV:** o **MRI:** 87.0% o **MMG:** 40.0% (p=nr)
Ng et al 2013[11]	Women treated with chest irradiation for Hodgkin's lymphoma at age ≤35 yr who were more than 8 yr post treatment	148	33 mo (range 0 to 67)	MRI vs. MMG vs. MRI + MG	BI-RADS score 4 or 5	• Breast MRI was not more sensitive than MMG for breast cancer detection. *P*=1.0 • **Sensitivity:** o **MRI:** 67.0% o **MMG:** 68.0% o **MMG+MRI:** 94% • **Specificity:** o **MRI:** 93.0% o **MMG:** 94.0% o **MMG+MRI:** 90% • **NPV:** o **MRI:** 99.0% o **MMG:** 100.0% o **MMG+MRI:** 100% • **PPV:** o **MRI:** 60.0% o **MMG:** 36.0% o **MMG+MRI:** 31%
Tieu et al 2014 [12]	Female survivors of childhood HL treated with chest radiotherapy Med age = 30 yr	96	NR	MRI vs. MMG vs. MRI + MMG	Histologically proven invasive breast cancer or DCIS	• **Sensitivity:** o MRI: 80.0% o MMG: 70.0% o MMG+MRI: 100% • **Specificity:** o MRI: 93.5% o MMG: 95.0% o MMG+MRI: 88.6%
Passaperuma et al 2012[13]	Women with a known BRCA1/2 mutation, of whom 380 had no previous cancer history.	380	8.4 yr	MRI vs. MMG vs. MRI + MMG	BI-RADS score 4 or 5	• **Distant disease-free survival of 28 previously unaffected women with screen-detected invasive breast cancer was 96% at median follow-up of 8.4 years**

Study	Population	n	Follow-up	Intervention/Comparison	Outcome	Results

	Age range 25 to 65					• **Sensitivity:**
						  o **MRI:** 86.0% vs.
						  o **MMG:** 19.0%. **p <0.0001**
						  o **MRI + MMG 89.5%**
						• **The** relative sensitivities of MRI and mammography did not differ by mutation, age, or invasive vs. non-invasive disease.
						  o **BRCA 1:** 90% vs. 19%; p<0.0001
						  o **BRCA 2:** 80% vs. 20%; p <0.0001
						• **Specificity:**
						  o **MRI:** 90.0% vs.
						  o **MMG:** 97.0%; p=nr

Sung et al 2011 [16]	Women with a history of chest irradiation for Hodgkin disease or non-Hodgkin lymphoma. Median age 24 yr at primary cancer diagnosis; median age 40 yr at first MRI screening.	91	NR	MRI vs. MMG	BI-RADS score 4 or 5	• 10 breast cancers diagnosed in 9 patients.
						• Sensitivity:
						  o MRI: 66.7% vs.
						  o MMG: 66.7%
						• Specificity
						  o MRI: 81.7% vs.
						  o MMG: 93.2%
						• Addition of MRI resulted in an incremental detection rate of 4.4%

Freitas et al 2013 [17]	Women with a history of chest irradiation Hodgkin lymphoma or non-Hodgkin lymphoma. Mean age 37 yr.	98	1 yr	MRI vs MMG	BI-RADS score 4 or 5	• Breast cancer diagnosed in 13 patients (14%)
						• Sensitivity:
						  o MRI: 92% vs.
						  o MMG: 69%
						• Specificity
						  o MRI: 94% vs.
						  o MMG: 98%
						o Addition of MRI resulted in an incremental detection rate of 4.1%

Nadler et al 2017 [18]	Women with a previous diagnosis of a high-risk lesion or invasive breast cancer and dense breasts (>50% density). Mean age 46 yr at initial breast cancer or high risk lesion.	198	1 yr	MRI	BI-RADS score 4 or 5	• 15 breast cancers diagnosed in 14 patients. All but 1 were mammographically occult.
						• Sensitivity:
						  o MRI: 100%
						• Specificity
						  o MRI: 80.5%
						• The overall cancer detection rate was 5.26%

BI-RADS, Breast Imaging Reporting and Data System; CAYA, childhood, adolescent and young adults; DCIS, ductal carcinoma in situ; MFS, metastasis free survival; MMG, mammography; MRI, magnetic resonance imaging; MRT, Mean reading time; US, ultrasound; PPV, positive predictive value; n, number enrolled; NPV, Negative predictive value; NR, Not Reported; OS, overall survival; vs, versus;

Ongoing trials

Protocol ID	Official Title	Intervention/ Comparison	Status	Estimated Study Completion Date	Last Updated
NCT02324894	Initial Evaluation of Ultra-FAST Breast Magnetic Resonance in Breast Cancer Screening: Comparative Study With Mammography and Ultrasound.	MRI+MMG	Recruiting	February 2017	June 15, 2016
NCT02275871	Dual-energy Contrast-enhanced Digital Subtraction Mammography (CESM) as a Tool to Screen High Risk Women for Breast Cancer: a Comparison to Screening Breast MRI	MRI vs. MMG	Active not recruiting	January 2019	August 1, 2016

Clinical Expert Interest Declaration:

Dr. Warner wrote a chapter (MRI Screening of and surveillance in managing BRCA mutation carriers) in Chagpar et al 2017 [14]. She is also a member of the Ontario Breast Screening Program. She is also Principal investigator of the Toronto MRI screening study [13].

| 1. Does any of the newly identified evidence contradict the current recommendations? (i.e., the current recommendations may cause harm or lead to unnecessary or improper treatment if followed) | The ESMO recommendations [1] suggest that mammography should not be done before age 35 as it doesn't add anything. There is insufficient evidence supporting this statement to change our current recommendations. However, the incremental sensitivity of MMG over MRI in various age and risk subgroups in the High Risk OBSP's data needs to be studied; this would be an invaluable contribution to the literature. |

2. Does the newly identified evidence support the existing recommendations?	Yes	
3. Do the current recommendations cover all relevant subjects addressed by the evidence? (i.e., no new recommendations are necessary)	Yes	
Review Outcome as recommended by the Clinical Expert	ENDORSE Slight modifications to current recommendations.	
DSG/GDG Commentary	The Expert Panel agreed with ENDORSING the recommendations with modifications made with respect to risk category 5.	

New References Identified:

1. Cardoso F, Loibl S, Pagani O, Graziottin A, Panizza P, Martincich L, et al. The European Society of Breast Cancer Specialists recommendations for the management of young women with breast cancer. Eur J Cancer. 2012;48(18):3355-77.
2. Mulder RL, Kremer LC, Hudson MM, Bhatia S, Landier W, Levitt G, et al. Recommendations for breast cancer surveillance for female survivors of childhood, adolescent, and young adult cancer given chest radiation: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. Lancet Oncol. 2013;14(13):e621-9.
3. Phi XA, Houssami N, Obdeijn IM, Warner E, Sardanelli F, Leach MO, et al. Magnetic resonance imaging improves breast screening sensitivity in BRCA mutation carriers age > 50 years: evidence from an individual patient data meta-analysis. J Clin Oncol. 2015;33(4):349-56.
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10. Mokhtar O, Mahmoud S. Does dynamic post contrast MRI of the breast have a role in screening of high risk patients? Egyptian Journal of Radiology and Nuclear Medicine. 2014;45(3):1029-41.

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12. Tieu MT, Cigsar C, Ahmed S, Ng A, Diller L, Millar BA, et al. Breast cancer detection among young survivors of pediatric Hodgkin lymphoma with screening magnetic resonance imaging. Cancer. 2014;120(16):2507-13.

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14. Saslow D, Boetes C, Burke W, Harms S, Leach MO, Lehman CD, et al. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography.[Erratum appears in CA Cancer J Clin. 2007 May-Jun;57(3):185]. CA: a Cancer Journal for Clinicians. 2007;57(2):75-89.

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18. Nadler M, Al-Attar H, Warner E, Martel AL, Balasingham S, Zhang L, Lipton JH, Curpen B. MRI surveillance for women with dense breasts and a previous breast cancer and/or high risk lesion. Breast. 2017 Aug;34:77-82.

Members of the Expert Panel

Name	Affiliation	Declarations of Interest
June Carroll	Family Physician, Mount Siani Hospital	Published on the objects of study in this document: 1. Chiarelli AM, Prummel MV, Muradali D, et al. Effectiveness of screening with annual magnetic resonance imaging and mammography: Results of the initial screen from the Ontario High Risk Breast Screening Program. J Clin Oncol. 2014 Jun 16;32(21):2224-30. 2. Warner E, Heisey R, Carroll JC. Applying the 2011 Canadian guidelines for breast cancer screening in practice. CMAJ. 2012 Nov 6;184(16):1803-7. 3. Carroll JC, Heisey R, Warner E. Family history and breast cancer. CMAJ. 2012 Sep 4;184(12):1391. Provided advice or guidance regarding the objects of study in a public capacity: Expert Panel member, High Risk OBSP Working Group; various presentations regarding management of women at high risk of breast cancer to physicians at continuing education conferences - Point of care tools and educational materials on management of women at

		increased risk of breast cancer on the GECKO web site www.geneticseducation.ca. Health Quality Ontario 2017 - present: Vice-Chair, Ontario Genetics Advisory Committee (not currently involved in any projects with COI)
Petrina Causer	Clinical Director of Mammography and Division Head of Breast Imaging, North York General Hospital	No conflict declared
Anna Chiarelli	Provincial Scientific Lead, Ontario Breast Screening Program	Published on the objects of study in this document: Co-authored chapter in text book: Phi XA, Chiarelli AM, de Bock G. Screening women with known or suspected cancer genes mutations. In: Houssami N, Miglioretti DL, eds. Breast Cancer Screening: An examination of Scientific Evidence. London, UK: Elsevier, pp 265-294, 2016. Provided advice or guidance regarding the objects of study in a public capacity: Expert Panel member, High Risk OBSP Working Group
Susan Done	Pathologist, University Health Network	Provided advice or guidance regarding the objects of study in a public capacity: Expert Panel member, High Risk OBSP Working Group
Andrea Eisen	Ontario Breast Cancer Lead, Disease Pathway Management	Provided advice or guidance regarding the objects of study in a public capacity: Expert Panel member, High Risk OBSP Working Group
Joan Glazier	Provincial Medical Radiation Technologist Lead, Ontario Breast Screening Program	No conflict declared.
Wendy Meschino	Geneticist, North York General Hospital	Consulting: Member of AstraZeneca National Advisory Board for Lynparza 2015-2016; Ownership: Meschino Medicine Professional Corporation, outreach clinic in Timmins, Ontario; Annual stipend from the Porcupine Health Unit in Timmins to supervise the genetics nurses/counsellors, as well as a per diem to attend clinics. Provided advice or guidance regarding the objects of study in a public capacity: Expert Panel member, High Risk OBSP Working Group
Derek Muradali	Radiologist-in-Chief, Ontario Breast Screening Program	Provided advice or guidance regarding the objects of study in a public capacity: Expert Panel member, High Risk OBSP Working Group; Asked to comment to news or public media on screening of high risk women with breast MRI

Medline

#	Searches	Results
1	exp Magnetic Resonance Imaging/	376128
2	magnetic resonance imaging.ti.	41285
3	MRI.ti.	49869
4	1 or 2 or 3	390137
5	breast neoplasms/ or carcinoma, ductal, breast/	255711
6	(breast or mammary).tw.	410323
7	(cancer or carcinoma or neoplasm).tw.	1734845
8	5 or (6 and 7)	350779
9	screening.mp.	489591
10	high risk.mp.	227160
11	hereditary.mp.	82295
12	brca.mp.	3602
13	(familial or family history).mp.	155131
14	(prior or previous).mp.	1200597
15	(radiotherapy or radiation).mp.	582565
16	10 or 11 or 12 or 13 or 14 or 15	2143447
17	exp Mass Screening/	114831
18	9 or 17	497998
19	8 and 16 and 18	7001
20	limit 19 to english language	6513
21	limit 20 to humans	5816
22	exp Health Education/	154084
23	exp health promotion/	66940
24	exp Retrospective Studies/	645883
25	case reports.pt.	1880180
26	(letter or editorial or comment or news).pt.	1748324
27	review.pt. not systematic.mp.	2186435
28	questionnaires/ or health surveys/	425303
29	22 or 23 or 24 or 25 or 26 or 27 or 28	6608858
30	21 not 29	3609
31	4 and 30	184
32	(201201$ or 2013$ or 2014$ or 2015$ or 2016$ or 201704$).ed.	4231837
33	31 and 32	62

Embase

#	Searches	Results
1	exp Magnetic Resonance Imaging/	676332
2	magnetic resonance imaging.ti.	39494
3	MRI.ti.	64323
4	1 or 2 or 3	678672
5	breast neoplasms/ or carcinoma, ductal, breast/	5294
6	(breast or mammary).tw.	409646
7	(cancer or carcinoma or neoplasm).tw.	1835228
8	5 or (6 and 7)	323203
9	screening.mp.	672656
10	high risk.mp.	401562

11 hereditary.mp.	71986
12 brca.mp.	6769
13 (familial or family history).mp.	194322
14 (prior or previous).mp.	1310957
15 (radiotherapy or radiation).mp.	710566
16 10 or 11 or 12 or 13 or 14 or 15	2502722
17 exp Mass Screening/	164603
18 9 or 17	672870
19 8 and 16 and 18	11548
20 limit 19 to english language	10917
21 limit 20 to humans	10050
22 exp Health Education/	215036
23 exp health promotion/	70968
24 exp Retrospective Studies/	489131
25 case reports.pt.	0
26 (letter or editorial or comment or news).pt.	1107617
27 review.pt. not systematic.mp.	1667423
28 questionnaires/ or health surveys/	470421
29 22 or 23 or 24 or 25 or 26 or 27 or 28	3798020
30 21 not 29	7222
31 4 and 30	728
32 (201201$ or 2013$ or 2014$ or 2015$ or 2016$ or 201716$).ew.	17733048
33 31 and 32	644

ASCO Annual Meeting - searched   http://www.ascopubs.org/search with keywords: MRI AND (Breast cancer)
San Antonio Breast Cancer Symposia - searched http://www.sabcs.org/search with keywords: "MRI"
Clinicaltrials.gov – searched http://clinicaltrials.gov/ct2/home with keywords: MRI AND (Breast cancer)

DEFINITIONS OF REVIEW OUTCOMES

1. **EDUCATION AND INFORMATION** – EDUCATION AND INFORMATION means that a Clinical Expert and/or Expert Panel has reviewed new evidence pertaining to the guideline topic and determined that the guideline is out of date or has become less relevant. The document will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of our website and each page is watermarked with the words "EDUCATION AND INFORMATION."

2. **ENDORSE** – ENDORSE means that a Clinical Expert and/or Expert Panel has reviewed new evidence pertaining to the guideline topic and determined that the guideline is still useful as guidance for clinical decision making. A document may be endorsed because the Expert Panel feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. **UPDATE** – UPDATE means the Clinical Expert and/or Expert Panel recognizes that the new evidence pertaining to the guideline topic makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The Expert Panel advises that an update of the document be initiated. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making, unless the recommendations are considered harmful.

APPENDIX A: DOCUMENT SUMMARY AND REVIEW CONDUCTED IN 2012

Evidence-Based Series #15-11 Version 2: Section 4

Magnetic Resonance Imaging Screening of Women at High Risk for Breast Cancer: Document Review Summary and Tool

E. Warner, F. Perera, C. Agbassi, N, Ismailia, and the Expert Panel on MRI Screening of Women at High Risk for Breast Cancer

August 8, 2012

The 2007 guideline recommendations are

ENDORSED

This means that the recommendations are still current and relevant for decision making.

OVERVIEW

The original version of this guidance document was released by Cancer Care Ontario's Program in Evidence-based Care in 2007. In September 2011, this document was assessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist conducted an updated search of the literature. Two clinical experts (FP, EW) reviewed and interpreted the new eligible evidence and proposed the existing recommendations could be endorsed. An expert panel was convened and in August 2012 endorsed the recommendations found in Section 1 (Clinical Practice Guideline).

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Questions Considered
- What is the effectiveness of adding breast magnetic resonance imaging (MRI) to standard screening (mammography) compared to screening mammography alone?
- Does the addition of breast MRI to standard screening detect breast cancer at an earlier stage?
- What is the optimal frequency of MRI screening?
- Are there subgroups (risk category, age, or breast density) that benefit more from MRI screening than do others?

- What harms are associated with MRI screening, and are there any relative or absolute contraindications to its use?
- In the presence of an abnormal finding seen only on MRI imaging, what is the optimal workup and follow-up after screening?

Literature Search and New Evidence

The new search (May 2006 to Dec 2011) yielded 15 relevant new publications representing seven guidelines/recommendations, one meta-analysis and seven prospective non-randomized studies were found. Brief results of these publications are shown in Section 6: Document Review Tool at the end of this report.

Impact on Guidelines and Its Recommendations

The original guideline concluded that screening MRI in addition to mammography is recommended for women in target population subgroups 1, 2, 3; and the new data support the recommendations with no contradictory evidence identified. These recommendations are therefore **ENDORSED** in their entirety.

For women in target populations 4 and 5, there is insufficient evidence to make definitive recommendations for or against screening MRI in addition to mammography. Since the new evidence does not contradict the Expert Opinion and Qualifying Statements regarding frequency of screening, age of initiation and cessation of screening in Section 1, these statements are also **ENDORSED** in their entirety.

In 2011, the Ontario Breast Screening Program (OBSP) expanded to include screening services for women at high risk for breast cancer, aged 30 to 69. During the development of the OBSP's high risk screening program, the clinical expert panel weighed evidence and expert opinion to make decisions about program design and delivery. The expert panel opted to include population 5 (women with radiation therapy to the chest) along with populations 1, 2, and 3 in the OBSP's high risk screening eligibility criteria because the group is small, distinct, and easily recognizable. Preliminary program data suggest that this group makes up only 6% of the total high risk clients screened within the first eight months of the program's existence. Of note, the American Cancer Society (ACS)'s high risk breast cancer screening guidelines also recommend screening MRI and mammography for this group of women (15).

A study with long-term follow-up is due to be published soon (16). This study will likely provide valuable data on the questions addressed by the guideline, but there is no expectation that it will do anything but support the existing recommendations, so the expert panel believes an endorsement of these recommendations prior to it's publication is appropriate and prudent.

In 2007, a cost-effectiveness systematic review was conducted (included as Section 2-A in this document) for the purpose of informing decisions by Cancer Care Ontario and the Ministry of Health and Long Term Care regarding the provision of MRI services for screening women at high risk of breast cancer in Ontario. This review has not been updated since the requirement for this information was met in the earlier version.

Document Review Tool

Number and title of document under review	15-11 Magnetic Resonance Imaging Screening of Women at High Risk for Breast Cancer
Current Report Date	April 2007
Clinical Expert	Francisco Perera and Ellen Warner
Research Coordinator	Chika Agbassi and Nofisat Ismaila

Date Assessed	Sept 2011
Approval Date and Review Outcome (once completed)	8 Aug 2012 [ENDORSED]

Original Question(s):
- What is the effectiveness of adding breast magnetic resonance imaging (MRI) to standard screening (mammography) compared to screening mammography alone?
- Does the addition of breast MRI to standard screening detect breast cancer at an earlier stage?
- What is the optimal frequency of MRI screening?
- Are there subgroups (risk category, age, or breast density) that benefit more from MRI screening than do others?
- What harms are associated with MRI screening, and are there any relative or absolute contraindications to its use?
- In the presence of an abnormal finding seen only on MRI imaging, what is the optimal workup and follow-up after screening?

Target Population:
Women at very high risk for breast cancer, 'very high risk' being defined as:
6. Known mutation in BRCA1, BRCA2 or other gene predisposing to a markedly elevated breast cancer risk.
7. Untested first-degree relative of a carrier of such a gene mutation
8. Family history consistent with a hereditary breast cancer syndrome and estimated personal lifetime cancer risk >25%.
9. High-risk marker on prior biopsy (atypical ductal hyperplasia, atypical lobular hyperplasia, lobular carcinoma in situ [LCIS])
10. Radiation therapy to chest (before age 30 and at least eight years previous).

Inclusion criteria:
- Systematic reviews, meta-analyses, and clinical practice guidelines that addressed the use of MRI in the screening of women at high-risk breast cancer were included.
- Randomized studies or prospective non-randomized studies of MRI compared to mammography with or without ultrasound and clinical breast examination for the screening of women at very high risk for breast cancer are included. Studies had to report at least one relevant measure of effectiveness/benefit, including sensitivity, specificity, positive or negative predictive value, accuracy, time to diagnosis, tumour stage information (size, proportion DCIS, etc.), or improvement in patient outcome (response or survival).
- The studies had to be relevant to the target population, that is, women at very high risk for breast cancer. 'Very high risk' was defined as:

6. Known mutation in BRCA1, BRCA2 or other gene predisposing to a markedly elevated breast cancer risk.
7. Untested first degree relative of a carrier of such a gene mutation
8. Family history consistent with a hereditary breast cancer syndrome and estimated personal lifetime cancer risk >25%.
9. High risk marker on prior biopsy (atypia, LCIS)
10. Radiation therapy to chest (before age 30 and at least 8 years previous).

Exclusion criteria:
- Due to the lack of translation resources, non-English language reports were excluded.
- Because of changes in both mammographic and MRI technology, publications prior to 1995

were considered out-of-date and excluded.

Search Details:
- May 2006 to Dec 2011 (Medline wk 4 + wk 52 Embase)
- May 2006 to March 2012 (ASCO Annual Meeting)
- 2009 to 2011 (San Antonio Breast Cancer Symposia)
- May 2006 to March 2012 (Clinicaltrials.gov)

Brief Summary/Discussion of New Evidence:
Of 440 total hits from Medline + Embase and 31 total hits from ASCO + 130 total hits from San Antonio Breast Cancer Symposia abstract searches + 116 total hits from Clinicaltrials.gov. 15 references representing 7 guidelines/recommendations, one meta-analysis and 7 prospective non-randomized studies were found comparing MRI + Mammography vs. Mammography or MRI or US alone. 7 prospective non-randomized studies are potentially new studies, of which 6 had full text publications and one is in abstract form.

Meta-analysis						
Imaging technique	BI-RADS cut off	Studies (n)	Population	Screening examinations/ Tumors (n)	Brief results	References
MRI + Mammography Vs. Mammography Or MRI	≥3 or ≥4	10	Women at high risk of breast cancer. Age ≥19 yrs (n 4492)	9227/193	• The negative LR for the combination of MRI plus mammography was 0.14 (CI, 0.05 to 0.42), compared with 0.7 (CI, 0.59 to 0.82) for mammography alone, and the probability after a negative test result for the combination was 0.3% (CI, 0.1% to 0.8%), compared with 1.4% (CI, 1.2% to 1.6%) for mammography alone. • The positive LR and probability after a positive test result for MRI plus mammography were 16.4 (CI, 11.1 to 24.1) and 25.0% (CI, 18.4% to 33.0%), respectively, compared with 24.8 (CI, 11.6 to 53.0) and 33.6% (CI, 10.1% to 51.9%) for mammography alone.	Warner et al 2008[15]

Prospective non-randomized studies				
Imaging technique	BI-RADS cut off (# of screening)	Population	Brief results	References
MRI Vs. FSM or DM or US	0, 3, 4 or 5 (1168)	Women with CLTR ≥ 25% +ve BRCA 1 or 2 Age ≥ 25yrs (n= 609)	• The cancer yield by modality was 1.0% for FSM (six of 597 women), 1.2% for DM (seven of 569 women), 0.53% for WBUS (three of 567 women), and 2.1% for MRI (12 of 571 women). • Of the 20 cancers detected, some were only detected on one imaging modality (FSM, n =1; DM, n= 3; WBUS, n =1; and MRI, n=8). • MRI was the most sensitive (71% among the other modalities (FSM=33%, DM=39%, WBUS=17%) though with no statistical significance, while the specificities ranged from 79% to 94%.	Weinstein et al 2009[16]
MRI Vs. MG or US	≥4 (758)	Women with known BRCA 1 or 2 30% risk of being a carrier Age ≥ 21yrs (n=184)	• Of the 12 cancers diagnosed, MRI detected 10, and MG, 7. • The overall recall rate after MRI was 21.8%, as compared with 16.1% for MG. • All tests displayed high specificity (93.6%-95.9%). • The sensitivities of MRI and MG (83% vs. 58%, p = 0.37) and of MRI and US (83% vs. 42%, p = 0.09) were not statistically different.	Trop et al 2010[17]
MRI +MG Vs. MRI or MG	≥4 (1592)	Women with known BRCA 1 or 2	• Of the 52 cancers diagnosed, 16 (31%) were diagnosed only by MRI but no detail on how many were diagnosed by MRI and MG	Sardanelli et al, 2011[18]

or CBE or US alone		50% risk of being a carrier Age ≥ 25yrs (n= 01)	• The sensitivity of MRI plus MG (93%), of MRI plus US (93%), or of MRI plus MG plus US (93%) was not significantly higher than that of MRI alone (91%) • The negative LR of MRI (0.09) was significantly lower than that of ultrasonography (0.49), mammography (0.50), or CBE (0.83) (P < 0.05). • An ROC analysis showed the area under the curve of MRI (0.97) was significantly higher than that of mammography (0.83) or ultrasonography (0.82) and not significantly increased when MRI was combined with mammography and/or ultrasonography.	

MRI +MG Vs. MRI or MG or CBE alone	0, 3, 4 or 5 (3085)	Women with CLTR 30-50% Age ≥ 27yrs (n=1 69)	• Of the 27 cancers detected, 8 were detected by MRI + MG, 9 by MRI alone and 2 by MG alone.
			• Overall, the difference in sensitivity between MRI (70.7%) and mammography (41.3%) was significant (p=.0016).
			  ○ In patients with invasive CIS, MRI was more sensitive than mammography (p<0.0005)
			  ○ In DCIS mammography (69.2%) was more sensitive than MRI (38.5%). However this difference was not significant (p=0.388)
			• Cumulative distant metastasis-free and overall survival at 6 years in all 42 BRCA1/2 mutation carriers with invasive breast cancer were 83.9% (95% CI, 64.1% to 93.3%) and 92.7% (95% CI, 79.0% to 97.6%), respectively, and 100% in the familial groups (n=43)
				Rijnsburger et al 2009[19]

MRI +MG vs. MG or US	NR (867)	Women with known *BRCA 1* or *2* Age ≥ 18yrs (n=491)	• Sensitivity to detect cancer was 19/22(86%) for MRI and 12/24(50%) for XMR. • Among 21 cancers that were examined by both methods, 19 were in BRCA1 mutation carriers and 2 in BRCA2 mutation carriers. • MRI detected 18/21(86%) compared to 10/21(48%) for XRM (p=0:02). • For BRCA1 mutation carriers alone, the sensitivities were 16/19 (84%) and 10/19(53%), respectively (p= 0:04).	Hagen et al 2007[20]
MRI Vs. MG	≥3 (561)	Women with known *BRCA 1* or *2* (n=173)	• Of the 13 cancers detected, 3 were prevalent, 5 interval and 5 screen-detected carcinomas. • The screen-detected and prevalent carcinomas were all diagnosed in stage I/II. Of the 5 interval carcinomas 1 was in stage III. • The sensitivities of mammography and MRI were 67% and 71%, respectively. • The PPV of mammography and MRI was 60% and 12%, respectively. The NPV was 99% for both tests.	De Bock et al 2010 (abstract)[21]
MRI +MG vs. MRI +US or MRI	4 or 5 (1679)	Asymptomatic women with elevated familial risk ≥20% LTR Age ≥ 25yrs (n=687)	• MRI alone was significantly more sensitive (93%) than mammography or ultrasound alone (P=.0001) or combined (P=.005). • Adding mammography to MRI did not allow a statistically significant increase of sensitivity (P=.5). • The positive predictive value was highest for MRI (48.0%), followed by mammography (39.1%) and ultrasound (35.7%). • Diagnostic accuracy (area under the ROC curve) of MRI was significantly higher than that of mammography or ultrasound or the combined use of both methods, and the accuracy did not change significantly with the added use of ultrasound or mammography or both to MRI	Kuhl et al 2010[22]

Guidelines/Recommendations	
Title	**Reference**
Magnetic resonance imaging of the breast: recommendations from the EUSOMA working group	Sardanelli et al 2010[23]
Breast cancer screening: From science to recommendation	Pettiti et al 2010[24]
MRI and mammography surveillance of women at increased risk for breast cancer: recommendations using an evidence-based approach	Granader et al 2008[25]
Screening for breast cancer: U.S. Preventive Services Task Force recommendation statement.	U. S. Preventive Services Task

	Force[26]
Breast cancer screening with imaging: recommendations from the Society of Breast Imaging and the ACR on the use of mammography, breast MRI, breast ultrasound, and other technologies for the detection of clinically occult breast cancer	Lee et al 2010[27]
Cancer screening with digital mammography for women at average risk for breast cancer, Magnetic Resonance Imaging (MRI) for women at high risk: An evidence-based analysis	Medical Advisory Secretariat[28]
American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography	Saslow et al 2007[29]

Abbreviations: FSM, film screen mammography; DM, digital mammography; MG, mammography; CBE, clinical breast examination; MRI, magnetic resonance imaging; US, ultrasound; DCIS, ductal carcinoma in situ; PPV, positive predictive value; NPV, Negative predictive value; Bi-RADS, Breast Imaging Reporting and Data System; LR, Likelihood Ratio; CLTR, Cumulative Life Time Risk; +ve, Positive; NR, Not Reported

Instructions. These questions are answered by the Clinical Expert assigned by the DSG/GDG. Beginning at question 1 answer the questions in order, following the instructions in the black boxes as you go.

4. Does any of the newly identified evidence, on initial review, contradict the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed? Answer Yes or No, and explain if necessary, citing newly identified references:	1. No
	If Yes, the document will be immediately removed from the PEBC website, and a note as to its status put in its place. **Go to 2**.
5. On initial review, a. Does the newly identified evidence support the existing recommendations? b. Do the current recommendations cover all relevant subjects addressed by the evidence, such that no new recommendations are necessary? Answer Yes or No to each, and explain if necessary:	2. New evidence supports the existing recommendations but the existing recommendations do not cover all relevant areas. The updated search supports the original recommendations with some new but not practice-changing information. The Dutch MRISC study (ref 5 above), in particular, suggests that • Mammogram screening is much less sensitive vs MRI for BRCA1 patients. • BRCA1 patients in that study had larger and more interval cancers. However, the current guideline does not endorse MRI screening for target population #5 with history of chest radiation, as there are no published studies evaluating MRI screening in this group. The Saslow ACS guideline does recommend MRI for this group (in combination with mammography), as would most experts today based on their very high lifetime risk and consistent reports of higher sensitivity of the combination of MRI plus mammography compared to mammography alone in all screened populations. This is why the new OBSP

	program includes this group in their list of high risk women who qualify for MRI screening.
	With respect to MRI technique, there is one randomized double blind trial comparing Gadobenate vs. Gadopentate (DETECT trial; Martincich et al Radiology 258 (2): 396 2011 that found Gadobenate to have superior sensitivity, specificity. It may be necessary to consider the question of MRI technique in a future document.
	If both are Yes, the document can be ENDORSED. If either is No, go to 3.
6. Is there a good reason (e.g., new stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline? Answer Yes or No, and explain if necessary:	3. Not applicable
	If Yes, a final decision can be DELAYED up to one year. If No, go to 4.
7. Do the PEBC and the DSG/GDG responsible for this document have the resources available to write a full update of this document within the next year?	4. Not applicable
	If Yes, the document needs an UPDATE. It can be listed on the website as IN REVIEW for one year. If a full update is not started within the year, it will be automatically ARCHIVED. If NO, go to 5.

5. If Q2, Q3, and Q4 were all answered NO, this document should be **ARCHIVED** with no further action.

Review Outcome	Endorsed
DSG/GDG Approval Date	
DSG/GDG Commentary	There is an ongoing study with over 8 years follow-up that supports the existing guideline(16)

COMPOSITION OF EXPERT PANEL

1. Dr. Ellen Warner – REVIEWER
2. Dr. Derek Muradali
3. Dr. Don Plewes
4. Dr. Wendy Meschino
5. Dr. Andrea Eisen
6. Dr. Rene Shumak
7. Dr. June Carroll
8. Dr. Linda Rabeneck

New References Identified:

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<u>Literature Search Strategy</u>:

Medline
1. meta-Analysis as topic.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
2. meta analysis.pt.
3. (meta analy$ or metaanaly$).tw.
4. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or Quantitative synthes?s or quantitative overview?).tw.
5. (systematic adj (review$ or overview?)).tw.
6. (exp Review Literature as topic/ or review.pt. or exp review/) and systematic.tw.
7. or/1-6
8. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
9. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
10. (selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
11. (study adj selection).ab.
12. 10 or 11
13. review.pt.
14. 12 and 13
15. exp randomized controlled trials as topic/ or exp clinical trials, phase III as topic/ or exp clinical trials, phase IV as topic/
16. (randomized controlled trial or clinical trial, phase III or clinical trial, phase IV).pt.
17. random allocation/ or double blind method/ or single blind method/
18. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
19. or/15-18
20. (phase II or phase 2).tw. or exp clinical trial/ or exp clinical trial as topic/
21. (clinical trial or clinical trial, phase II or controlled clinical trial).pt.
22. (20 or 21) and random$.tw.

23. (clinic$ adj trial$1).tw.
24. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
25. placebos/
26. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
27. (allocated adj2 random).tw.
28. or/23-27
29. practice guidelines/
30. practice guideline?.tw.
31. practice guideline.pt.
32. or/29-31
33. 7 or 8 or 9 or 14 or 19 or 22 or 28 or 32
34. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
35. 33 not 34
36. limit 35 to english
37. limit 36 to human
38. exp breast neoplasms/
39. (cancer? or carcinoma? or neoplasm? or tumo?r).tw.
40. (breast? or mammary).tw.
41. 39 and 40
42. 38 or 41
43. screening.tw.
44. (MRI? or magnetic resonance imaging).tw.
45. 43 and 44
46. 42 and 45
47. (200604$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$).ed.
48. 46 and 47

Embase
1. exp meta analysis/ or exp systematic review/
2. (meta analy$ or metaanaly$).tw.
3. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview).tw.
4. (systematic adj (review$ or overview?)).tw.
5. exp review/ or review.pt.
6. (systematic or selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
7. (study adj selection).ab.
8. 5 and (6 or 7)
9. or/1-4,8
10. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
11. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
12. exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/
13. randomization/ or single blind procedure/ or double blind procedure/
14. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
15. or/12-14
16. (phase II or phase 2).tw. or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/
17. 16 and random$.tw.
18. (clinic$ adj trial$1).tw.
19. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
20. placebo/
21. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
22. (allocated adj2 random).tw.
23. or/18-22

24. practice guidelines/
25. practice guideline?.tw.
26. practice guideline.pt.
27. or/24-26
28. 9 or 10 or 11 or 15 or 17 or 23 or 27
29. (editorial or note or letter or erratum or short survey).pt. or abstract report/ or letter/ or case study/
30. 28 not 29
31. limit 30 to english
32. limit 31 to human
33. exp breast neoplasms/
34. (cancer? or carcinoma? or neoplasm? or tumo?r).tw.
35. (breast? or mammary).tw.
36. 34 and 35
37. 33 or 36
38. screening.tw.
39. (MRI? or magnetic resonance imaging).tw.
40. 38 and 39
41. 37 and 40
42. (200614$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$).ew.
43. 41 and 42

ASCO Annual Meeting - searched http://www.ascopubs.org/search with keywords: MRI AND (Breast cancer)
San Antonio Breast Cancer Symposia - searched http://www.sabcs.org/search with keywords: "MRI"
Clinicaltrials.gov – searched http://clinicaltrials.gov/ct2/home with keywords: MRI AND (Breast cancer)

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