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Effectiveness of magnetic resonance  
imaging (MRI) screening for women  
at high risk of breast cancer



*Supporting Informed Decisions*

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CADTH  
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**Canadian Agency for Drugs and Technologies in Health**

**Effectiveness of magnetic resonance imaging (MRI)  
screening for women at high risk of breast cancer**

Lesley Dunfield, PhD<sup>1</sup>  
Melissa Severn, MSt<sup>1</sup>

October 2007

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<sup>1</sup> Canadian Agency for Drugs and Technologies in Health



Canadian Agency for  
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HTA

HEALTH TECHNOLOGY INQUIRY SERVICE (HTIS)

Health technology assessment (HTA) agencies face the challenge of providing quality assessments of medical technologies in a timely manner to support decision making. Ideally, all important deliberations would be supported by comprehensive health technology assessment reports, but the urgency of some decisions often requires a more immediate response.

The Health Technology Inquiry Service (HTIS) provides Canadian health care decision makers with health technology assessment information, based on the best available evidence, in a quick and efficient manner. Inquiries related to the assessment of health care technologies (drugs, devices, diagnostic tests, and surgical procedures) are accepted by the service. Information provided by the HTIS is tailored to meet the needs of decision makers, taking into account the urgency, importance, and potential impact of the request.

Consultations with the requestor of this HTIS assessment indicated that a review of the literature would be beneficial. The research question and selection criteria were developed in consultation with the requestor. The literature search was carried out by an information specialist using a standardized search strategy. The review of evidence was conducted by one internal HTIS reviewer. The draft report was internally reviewed and externally peer-reviewed by two or more peer reviewers. All comments were reviewed internally to ensure that they were addressed appropriately.

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Pavel Crystal, MD  
Assistant Professor, Department of Medical Imaging  
University of Toronto  
Toronto ON

Susan F. Dent, BSc, MD, FRCPC  
Medical Oncologist  
The Ottawa Hospital Regional Cancer Center  
Associate Professor, University of Ottawa  
Ottawa ON

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# EXECUTIVE SUMMARY

## Context and Policy Issues

In 2007, there will be an estimated 22,300 Canadian women diagnosed with breast cancer, and approximately 5,300 deaths. The risk factors for breast cancer include reproductive and hormonal factors, lifestyle factors, a family history of breast cancer, and mutation in the tumour suppression genes *BRCA1* or *BRCA2*.

Women at high risk for breast cancer usually develop the disease at a younger age, when breast tissue has a higher density. This high-density breast tissue makes mammography less sensitive. In addition, women with mutations in *BRCA1/2* may be more susceptible to DNA damage, so that exposure to the ionizing radiation of mammography may be contraindicated. As a result, magnetic resonance imaging (MRI) is proposed as an alternative screening modality for these women.

While mammography is the most commonly used technology for breast cancer screening, the American Cancer Society recommends annual MRI screening for individuals with *BRCA1/2* mutations, those having a first-degree relative with a *BRCA1/2* mutation, or those with a lifetime risk for breast cancer of 20% to 25%.

## Research Questions

1. What is the clinical effectiveness of MRI screening compared to film mammography in women with a high risk of breast cancer?
2. What is the cost-effectiveness of MRI screening compared to film mammography in women with a high risk of breast cancer?
3. What is the strength of evidence used to support the American Cancer Society's guidelines regarding MRI screening for woman at high risk of breast cancer?

## Methods

A limited literature search was conducted on health technology assessment resources, including PubMed, EMBASE, CINAHL,

BIOSIS, The Cochrane Library (Issue 3, 2007), the University of York Centre for Reviews and Dissemination (CRD) databases, ECRI's HTAIS, EuroScan, international HTA agencies, and a focused Internet search. Results include articles published between 2002 and June 2007, and are limited to English-language publications.

## Summary of Findings

### *Clinical Effectiveness*

Evidence on the clinical effectiveness of MRI screening for breast cancer detection in high-risk women contained in systematic reviews, health technology assessments, and observational studies were included in this report. One health technology assessment, two systematic reviews, and 10 observational studies were found. No randomized controlled trials were found.

MRI was reported to be more sensitive than mammography for the detection of breast cancer in high-risk women. The information in the health technology assessment on MRI for breast cancer screening was limited, however, it was suggested that MRI was more sensitive than mammography for the detection of breast cancer in high risk women. One systematic review reported that the sensitivity of MRI for breast cancer screening ranged from 71% to 100%, compared to 13% to 40% for mammography. The sensitivity was reported to be 100% for MRI screening, compared to 33% to 46% for mammography in another systematic review. The specificity was reported to be 91% to 95% for MRI (false-positive rate of 5% to 9%), compared to 93% to 99% for mammography (false-positive rate of 1% to 7%). The evidence was reviewed in a horizon scanning report, which stated that the sensitivity ranged from 96% to 100% for MRI and 33% to 44% for mammography. The specificity was reported to be 91% to 95% for MRI and 92% to 99.5% for mammography.

The included observational studies all reported similar results. The sensitivity of MRI was higher than that for mammography, and the specificity was generally higher for mammography compared to MRI. The sensitivity of MRI was

reported in five of the 10 included studies. The sensitivity ranged from 77% to 93.8% compared to 30% to 58.8% for mammography. The specificity of MRI ranged from 81% to 97.2% and that of mammography ranged from 93% to 96.8%.

### **Cost-effectiveness**

A limited number of studies (four) that described the costs associated with MRI screening for breast cancer were available. An Italian study found that it cost about €6,000 per MRI-detected breast cancer, which the authors deemed to be cost-effective. A UK study reported the additional cost per cancer detected was £28,284 for MRI and mammography combined, compared to mammography alone. The incremental cost per cancer detected was £11,731 for *BRCA1* carriers and £15,302 for *BRCA2* carriers. Another UK study found there was an 80% chance that MRI combined with mammography would be cost-effective for 40- to 49-year-old women assuming a £20,000 willingness-to-pay threshold. An American study reported a cost per QALY gained of \$88,651 for *BRCA1* carriers and \$188,034 for *BRCA2* carriers aged 25 years to 69 years. For women aged 35 to 54 years, the cost per QALY gained was \$55,420 and \$130,695 for *BRCA1* and *BRCA2* carriers respectively.

### **Quality Assessment of American Cancer Society's Guidelines**

Using the AGREE instrument (Appraisal of Guidelines Research and Evaluation), two

independent reviewers assessed the quality of the American Cancer Society's guidelines. The rigour of development was found to be low, because the inclusion and exclusion criteria, the external review process, and the process for updating the guidelines were not reported. The editorial independence from the funding body and the conflicts of interest were not reported, making the editorial independence score zero. The clarity and presentation were well done, because the recommendations were specific and easily identifiable.

### **Conclusions and Implications for Policy Making**

The cost-effectiveness studies suggest that MRI for breast cancer screening could be cost-effective, depending on the willingness to pay and the value attributed to one QALY. Overall, MRI has a higher sensitivity for breast cancer screening compared to mammography. In addition, the number of cancers detected by MRI alone was higher than that detected by mammography alone, although MRI also missed some cancers. These results indicate that some breast cancers would have been missed with mammography screening alone and the addition of MRI resulted in more cancers being detected. High-risk women, such as those with *BRCA1/2* mutations, those having a first-degree relative with a mutation, or those with a strong family history of breast cancer, seem to benefit most from the addition of MRI to the screening modality.

**Title:** Effectiveness of magnetic resonance imaging (MRI) screening for women at high risk of breast cancer

**Date:** August 14, 2007

# 1 CONTEXT AND POLICY ISSUES

In 2007, there will be an estimated 22,300 Canadian women diagnosed with breast cancer, and approximately 5,300 deaths.<sup>1</sup> The incidence of breast cancer in women is 104 per 100,000.<sup>1</sup> The five-year survival is between 87% and 89% for women 40 years old to >70 years old. In women <40 years old, the five-year survival is 79%.<sup>1</sup>

The risk factors for breast cancer include reproductive and hormonal factors (such as nulliparity, early menarche, irregular menses, and use of exogenous hormones), lifestyle factors, (obesity, physical inactivity, and alcohol consumption), and other factors such as a family history of breast cancer, exposure to ionizing radiation, age,<sup>1</sup> and breast density.<sup>2</sup> Women with a mutation in the tumour suppression genes *BRCA1*, *BRCA2*, or *Tp53* (demonstrated by genetic testing) are considered to be at high risk for breast cancer.<sup>1,3</sup>

One author reports that women with *BRCA1* mutations have a 85% lifetime risk and women with *BRCA2* mutations have a 70% lifetime risk of developing breast cancer,<sup>4</sup> while another reports that the risk of breast cancer ranges from 45% to 65% in *BRCA1* and *BRCA2* carriers.<sup>5</sup> Another study reports the lifetime risk of developing breast cancer to be 25% to 50% in *BRCA1*, *BRCA2*, or *Tp53* mutation carriers, compared to 11.5% to 25% in other high-risk women and 9% in the general population.<sup>3</sup> Five to 10 per cent of breast cancer cases are associated with mutations in *BRCA1* or *BRCA2*.<sup>6</sup>

Women who have a strong family history of breast cancer are considered to be at high risk for developing breast cancer. They include women with  $\geq 3$  first- or second-degree relatives with breast or ovarian cancer; women with  $\geq 2$

first- or second-degree relatives with breast or ovarian cancer plus cancer occurring in both breasts (bi-laterality), onset of breast cancer before 40 years old, onset of ovarian cancer before 50 years old, occurrence of breast and ovarian cancer, Jewish ancestry, or breast cancer in a male relative; one first- or second-degree relative with breast cancer diagnosed at age  $\leq 45$  years old, plus another relative with bone or soft tissue sarcoma at  $\leq 45$  years old.<sup>3</sup>

The National Cancer Institute Gail and BRCAPRO are validated models to assess five-year breast cancer risk.<sup>7</sup> Age, race, incidence of breast cancer in first-degree relatives, number of times that a woman has given birth (parity), age at menarche, number of breast biopsies, and atypical hyperplasia are taken into account when assessing risk with the Gail model. The BRCAPRO model estimates risk using *BRCA1* and *BRCA2* mutation probabilities (based on family history of breast and ovarian cancer), age of the individual, and yearly incidence of breast cancer in a *BRCA1/2* carrier.<sup>7</sup>

Women at high risk for breast cancer are typically younger when they develop breast cancer than the general population.<sup>3,7,8</sup> They likely have a higher breast density, which makes mammography less sensitive because dense tissue looks similar to breast lesions.<sup>3,7,8</sup> In addition, MRI may be safer for women with *BRCA1/2* mutations because it does not use ionizing radiation and *BRCA1/2* play a role in DNA repair caused by ionizing radiation.<sup>3,7</sup> Mammography may be of limited usefulness in this high-risk population, so MRI is proposed as an alternative screening modality. MRI was first used in the early 1980s for breast imaging. Later in the 1980s, contrast imaging was introduced to enhance the MRI images.<sup>3</sup>

The American Cancer Society (ACS) has published guidelines regarding MRI screening in addition to mammography for breast cancer screening.<sup>9</sup> An expert panel was formed by the ACS to review the evidence on MRI screening for breast cancer. The data that were identified in the literature search were reviewed and discussed by panel members. The recommendations were approved by the ACS's

Breast Cancer Advisory Group and National Board of Directors.

The recommendations based on evidence include annual MRI screening for individuals with *BRCA1/2* mutations, for those having a first-degree relative with a *BRCA1/2* mutation, or for those with a lifetime risk of approximately 20% to 25% (defined by BRCAPRO or other similar models). The recommendations based on experts' consensus opinion include annual MRI screening for individuals who received radiation to the chest between 10 to 30 years of age, individuals with Li-Fraumeni syndrome and their first-degree relatives, and individuals with Cowden and Bannayan-Riley-Ruvalcaba syndromes and their first-degree relatives. MRI screening is not recommended by the ACS guidelines, for women with a <15% lifetime risk of breast cancer. In addition, there was insufficient evidence for the ACS to recommend screening for individuals with a lifetime risk of 15% to 20%; individuals with lobular carcinoma in situ or atypical lobular hyperplasia, atypical ductal hyperplasia, dense breast tissue on mammography; or women with a personal history of breast cancer.

## 2 RESEARCH QUESTIONS

1. What is the clinical effectiveness of MRI screening compared to film mammography in women with a high risk of breast cancer?
2. What is the cost-effectiveness of MRI screening compared to film mammography in women with a high risk of breast cancer?
3. What is the strength of evidence used to support the American Cancer Society's guidelines regarding MRI screening for women at high risk of breast cancer?

## 3 METHODS

Published literature was obtained by cross-searching BIOSIS Previews, EMBASE, MEDLINE, and CINAHL. Results include articles published from 2002 and are limited to English language publications only. Regular

alerts were established on BIOSIS, EMBASE, MEDLINE, and CINAHL, and information retrieved via alerts is current to June 2007. Parallel searches were performed on PubMed and the Cochrane Library (Issue 3, 2007) databases. Filters were applied to limit the retrieval to health technology assessments, meta-analysis, systematic reviews, clinical studies, clinical guidelines, observational studies, and economic studies.

The web sites of regulatory agencies, and health technology assessment and related agencies were searched, as were specialized databases such as those of the University of York Centre for Reviews and Dissemination. The Google™ search engine was used to search for information on the Internet.

## 4 SUMMARY OF FINDINGS

### 4.1 Clinical Effectiveness

Evidence on the clinical effectiveness of MRI screening for breast cancer detection in high-risk women contained in systematic reviews, health technology assessments, and observational studies was included in this report. One health technology assessment, two systematic reviews, 10 observational studies, and no randomized controlled trials were found.

#### 4.1.1 Health technology assessments and systematic reviews

A health technology assessment from Belgium investigated the effectiveness of MRI for a variety of indications.<sup>8</sup> A short section was specific to the use of MRI in breast cancer screening. Two systematic reviews were included in the section of this HTA that described MRI for breast cancer screening. The report found MRI to be more sensitive (i.e., higher true-positive rate) than mammography in the detection of breast cancer in high-risk women, but noted that it should not be used for screening the general population. In this

instance, high-risk women were defined as those with confirmed *BRCA1* or *BRCA2* mutations, those having known relatives with mutations, or those having first-degree relatives with a breast cancer history at a young age.<sup>8</sup>

The evidence regarding breast cancer screening modalities was systematically reviewed in a report published in *JAMA*.<sup>10</sup> MRI, mammography, ultrasound, clinical breast examination (CBE), and self-examination were included in this report. Systematic reviews, meta-analyses, randomized controlled trials, and observational studies were eligible for inclusion in this review. Six observational studies that were included, screened 105 to 1,909 women. Five prospective studies and one retrospective study reported the sensitivity of MRI screening for breast cancer. It ranged from 71% to 100%, compared to 13% to 40% for mammography and 13% to 33% for ultrasound. Three of the prospective studies and the one retrospective study reported a sensitivity of 100%, whereas the other two prospective studies reported 71% and 77%. This report discussed specificity (i.e., true-negative rate) on the basis of one study that found the specificity of MRI to be 89.8% compared to 95% for mammography and 98.1% for clinical breast examination.<sup>10</sup>

A second systematic review investigated the accuracy of mammography, CBE, ultrasound, and MRI for breast cancer screening.<sup>11</sup> Studies that examined MRI screening among asymptomatic women in the general population, including those at high risk for breast cancer, were included. Of the four observational studies that were included, three studies reported sensitivity. For MRI, the sensitivity was 100%, which was higher than the sensitivity of the comparators: mammography (33% to 46%), CBE (33%), and ultrasound (33% to 60%). The false-positive rate was 5% to 9% for MRI (specificity of 91% to 95%) compared to 1% to 7% for mammography (specificity of 93% to 99%) and 7% to 20% for ultrasound (specificity of 80% to 93%). One study reported the false-positive rate for CBE, which was 1%.<sup>11</sup>

#### 4.1.2 Horizon scanning reports

A horizon scanning report from the Australia and New Zealand Horizon Scanning Network (ANZHSN) reviewed the evidence for MRI screening in high-risk breast cancer.<sup>3</sup> One study that ANZHSN summarized found that the sensitivity of MRI was 71% and the specificity 88% for women with no prior history of breast cancer. The sensitivity was higher for MRI than for mammography and clinical examination (36% and 16% respectively), but the specificity was lower, with mammography and clinical examination having a specificity of 95% and 97% respectively. The sensitivities and specificities for MRI screening in women who may have a personal history of breast cancer were discussed in various studies that were included in this report. Similar results were reported in all studies, with the MRI sensitivity ranging from 96% to 100% and the specificity ranging from 91% to 95%. The sensitivity and specificity of mammography were 33% to 44% and 92% to 99.5% respectively. One study was included that looked at women at high risk of developing breast cancer. This study conducted the MRI for screening six months after mammography. Therefore, the results may not reflect the accuracy of MRI screening. The cancers detected could have been missed by mammography or they could be cancers that developed during the six months between mammography and MRI. Three cancers were detected in 109 women (2.8%).<sup>3</sup>

#### 4.1.3 Observational studies

The data from the observational studies appear in Appendix 1. Table 1 describes the sensitivity and specificity of MRI and mammography. Because the research questions focus on MRI and mammography, only data from these types of examinations appear in Table 1. In addition, only the studies with a calculated sensitivity and specificity are included. Table 2 describes the number of detected breast cancers and the number of these cancers that were detected by MRI only.

A prospective cohort study examined the MRI screening of high-risk women.<sup>7</sup> Thirty women

(average age of 41.1 years) who had a high risk of breast cancer and dense breasts were included in the study. All women had a risk of breast cancer of at least 3.5%, or a *BRCA1* or *BRCA2* mutation. The average risk was 4.8% as calculated using the Gail model and the BRCAPRO model. All women underwent a mammogram or physical examination within three months of being enrolled in the study, and none were found to have breast cancer at that time. Of the 30 women in this study, 22 were classified as “negative” or “benign,” and eight were classified as “probably benign.” These eight patients underwent follow-up by ultrasound, cyst aspiration, fine needle aspiration, or core biopsy, and one patient was diagnosed with breast cancer.<sup>7</sup>

A prospective trial compared mammography, ultrasound, and MRI for breast cancer screening in high-risk women.<sup>12</sup> Women were considered to be high risk if they had a proven mutation in *BRCA1* or *BRCA2*, or had a first-degree relative with a proven *BRCA1* or *BRCA2* mutation. Women with a history of breast cancer were included if one breast was unaffected. One hundred and five patients (average age 46 years) were screened by mammography, MRI, and ultrasound. Overall, eight patients were diagnosed with breast cancer, and five previously had breast cancer. Seven cases were diagnosed using MRI only (and not by mammography or ultrasound), and the remaining case was detected by mammography and by ultrasound. The false-positive case was detected using MRI.<sup>12</sup>

A prospective multicentre study compared mammography to MRI for the detection of breast cancer in women with *BRCA1*, *BRCA2*, or *TP53* mutations; or women with a first-degree relative with *BRCA1*, *BRCA2*, or *TP53* mutations; or women with a strong family history of breast or ovarian cancer.<sup>13</sup> The criteria for defining a strong family history were not reported. Most of the women underwent MRI and mammography screening on the same day (76%), and most of the remaining cases were screened within the same month. The sensitivity was 77% for MRI, 40% for mammography (p=0.01 MRI versus mammography), and 94%

when MRI and mammography were used. The specificity was 81% for MRI, 93% for mammography (p< 0.0001 MRI versus mammography), and 77% for both. Of the 649 women included in the study (median age 40 years), 35 cancers were detected, with 19 being detected using MRI only, six by mammography only, and eight detected by both methods. Two interval cancers were suspicious based on mammography or MRI results, but were not diagnosed. They were discovered using a follow-up questionnaire.<sup>13</sup>

A prospective multicentre study used mammography and MRI screening for women at high risk for breast cancer.<sup>14</sup> Women who had a proven genetic mutation in *BRCA1* or *BRCA2*, or a lifetime risk of breast cancer of at least 25% (as defined by established models such as the Gail model) were included. In addition, women with a prior history of breast cancer were included, and the contralateral breast was screened. Data from 367 women with an average age of 45 years are included in the study, with 38 cancers detected. Using MRI only led to positive results in 30 women, mammography only led to positive results in seven women, and both MRI and mammography led to positive results in one woman. Of these, four women were diagnosed as having malignant lesions. Of the four cancers that were diagnosed, 4/4 were detected using MRI, and 1/4 was also detected using mammography.<sup>14</sup>

A prospective study investigated the use of CBE, mammography, and MRI for screening women at high risk of breast cancer.<sup>15</sup> Overall, 1,909 women who had a proven gene mutation or a family history of breast cancer were included, and 50 cancers were detected. CBE and mammography were conducted twice a year, whereas MRI was conducted once a year. In the first round of imaging of women who had had a previous mammography, there was a significant difference in sensitivity between MRI (93.3%) compared to mammography (30%) (p= 0.003). This difference was maintained in subsequent screening rounds, with the sensitivity of MRI being 76.5% and that of mammography 29.4% (p=0.02). The specificity was higher with mammography at 94.5%, compared to MRI at

86% ( $p < 0.001$ ).<sup>15</sup> A follow-up study included 45 of the 50 detected cancers.<sup>16</sup> The cancers that are excluded were detected using a method that did not follow the protocol, occurred in pregnant women, or occurred in one woman who refused MRI. Of the included cancers, 20 were detected using MRI only, and six were detected by mammography only.<sup>16</sup>

The sensitivity and specificity of MRI were compared to those of CBE, mammography, and ultrasound in 236 women who have *BRCA1* or *BRCA2* mutations.<sup>17</sup> Women with a previous history of breast cancer were allowed to participate in this study provided the contralateral breast was unaffected. The average age was 46.6 years, and each woman was screened using all four methods on the same day. Twenty-one women were diagnosed with breast cancer (one woman had bilateral cancer). The mean age of these women was 47.4 years. MRI detected 17 of the 22 cancers, whereas mammography detected eight, ultrasound detected seven, and CBE detected two. The sensitivity of a combined screening modality of all four methods was 95%. Seven cancers were detected using MRI only, compared to two detected by mammography only and two by ultrasound only. The sensitivity was 77% for MRI compared to 33% for mammography ( $p=0.02$ ) and 9.1% for CBE ( $p=0.006$ ), and the specificity was 95.4% for MRI, 96% for mammography, and 99.3% for CBE.<sup>17</sup>

A multicentre study screened 116 women aged 35 years to 61 years who were *BRCA1* or *BRCA2* mutation carriers, had a first-degree relative with a proven gene mutation, or had a family history of breast cancer.<sup>18</sup> A family history was defined as at least three cases of breast cancer in first- or second-degree relatives under the age of 60 years, or at least three cases of breast cancer in first- or second-degree relatives under the age of 60 years plus a relative with ovarian cancer or male breast cancer. Over a five-year period, participants were screened using CBE, mammography, ultrasound, and MRI once a year, and 12 cancers were detected. All four detection methods were used in these 12 cases, except one patient who refused to undergo MRI. Of the 12 detected breast cancers, six were

detected only by using MRI, and none were missed by using MRI screening.<sup>18</sup>

A prospective cohort study of women at high risk for breast cancer examined four methods for screening.<sup>19</sup> Women were to be considered high risk if they had at least two cases of breast cancer occurring in relatives under the age of 50 years old or had relatives with both breast and ovarian cancer; or at least three cases of breast cancer in relatives; or one case diagnosed in a relative under the age of 35 years; or a male relative with breast cancer. CBE, ultrasound, mammography, and MRI were conducted within an eight-week period. Out of the 529 women involved in the study, 41 were diagnosed with breast cancer (total of 43 cancers). Of these 43 cancers, 40 were detected using the imaging studies and three using CBE. Thirty-nine cancers were detected using MRI, and all 40 were detected when MRI was combined with mammography. The one case that was detected using mammography was identified as “probably benign” using MRI. Fourteen were detected by mammography, and 17 by ultrasound. MRI alone detected 19 cancers. The sensitivity was significantly higher for MRI at 90.7% compared to mammography at 32.6% and ultrasound at 39.5% ( $p<0.001$ ). The sensitivity was increased to 93% when MRI was combined with mammography. The specificity was similar for MRI (97.2%) and mammography (96.8%).<sup>19</sup>

Women ( $n=278$ ) with known *BRCA1/2* mutations, with a relative with a mutation, or with a family history ( $\geq 3$  cases in first- or second-degree relatives) of breast or ovarian cancer were included in a prospective study in which women were screened using CBE, ultrasound, mammography, and MRI.<sup>20</sup> Women with previous breast cancers were included if one breast was incompletely excised. The average age of women who were included in the study was 46 years. During the first round of screening, 11 women were detected with cancer. In the second screening round, seven patients were detected with cancer. The sensitivity was higher for MRI (93.8%) compared to mammography (58.8%), ultrasound (64.7%) and CBE (50%). Six of the 18 cancers were detected

using MRI only. None were detected using the other detection methods alone.<sup>20</sup>

The reliability of MRI screening for women at risk of breast cancer was studied in 23 women with a proven or suspected *BRCA1/2* mutation.<sup>21</sup> Women were included if they had a proven *BRCA1/2* mutation, a relative with a *BRCA1/2* mutation, or a family history of breast cancer ( $\geq 3$  cases of breast cancer in relatives under the age of 60 years; ovarian cancer and male breast cancer). Four cases of cancer were identified in these 23 women, and three of these cases were identified only by using MRI and not by using mammography.<sup>21</sup>

There are differences in the observational studies, such as the timing of the screening using mammography and MRI, and the inclusion criteria. Some studies specified that the screening done by different methods be conducted on the same day, whereas others did not specify the timing of screening or were unclear. All studies used both MRI and mammography to screen for breast cancer, and some also screened using CBE or ultrasound. Some studies included women with proven *BRCA1/2* mutations only, whereas others included those with relatives with mutations or relatives with a history of breast cancer. In addition, four studies included women with a previous personal history of breast cancer, whereas these women were excluded in other studies. Only five of the 10 studies measured the sensitivity and specificity of the screening tests. Overall, the observational studies suggest that MRI screening is effective at diagnosing breast cancer that could otherwise be missed when other methods are used.

## 4.2 Cost-effectiveness of MRI screening for breast cancer

Four studies addressed the economic issues surrounding MRI screening for breast cancer. An Italian report<sup>12</sup> focused on the clinical effectiveness but did discuss the additional costs associated with MRI screening for women at high risk for breast cancer.<sup>12</sup> The addition of MRI to mammography and ultrasound costs

about €41,000 in this study (for 119 MRI examinations). Considering that the addition of MRI led to the detection of seven cases of breast cancer that were not detected using the other methods, the authors deemed MRI to be cost-effective at about €6,000 per MRI-detected breast cancer.<sup>12</sup>

A UK economic analysis examined the cost-effectiveness of MRI breast cancer screening compared to mammography in a high-risk population.<sup>22</sup> Women were considered to be high risk if they had a confirmed mutation in *BRCA1*, *BRCA2*, or *TP53*; if they had a first-degree relative with one of these mutations; or if they had a strong family history of breast or ovarian cancer. The UK National Health Service perspective was used in this analysis. The cost of mammography was found to be £33.50, and the cost of MRI was found to be £249.60 in the clinical setting and £405.10 in the research setting. For mammography combined with MRI, the additional cost per cancer detected was £28,284 compared to mammography alone. In the patients with *BRCA1* mutations, the incremental cost per cancer detected was £11,731 for MRI compared to mammography. In those with *BRCA2* mutations, the incremental cost per cancer detected was £15,302 for the combined MRI and mammography, relative to mammography alone. The sensitivity analysis found that the cost associated with the MRI test was the factor that most affected the cost-effectiveness. Recall rates and the frequency of additional MRI tests were also found to affect the results. Treatment-related costs were not considered in this economic analysis, and the value of a cancer detected is unknown.<sup>22</sup>

An American report examined the cost-effectiveness of MRI for the screening of *BRCA1/2* mutation carriers compared to mammography.<sup>23</sup> This report used a computer model to simulate a *BRCA1/2* mutation carrier population and the societal perspective to analyze cost-effectiveness. The cost per quality-adjusted life-year (QALY) gained was US\$88,651 to add MRI screening for *BRCA1* mutation carriers and US\$188,034 for *BRCA2* mutation carriers from the age of 25 years to 69 years. The sensitivity analysis revealed that the

cost per QALY was affected by the age of the patients and the cost of MRI. The lowest cost per QALY was US\$43,484 for *BRCA1* mutation carriers between 40 to 49 years old. In addition, MRI is more cost-effective with an increased risk of breast cancer. The cost per QALY gained was \$41,183 for *BRCA1* carriers and \$98,454 for *BRCA2* carriers with the addition of MRI screening for women under 50 years old with extremely dense breasts. The cost per QALY gained was \$55,420 for *BRCA1* and \$130,695 for *BRCA2* mutation carriers ages 35 years to 54 years.<sup>23</sup>

A UK study analyzed the cost utility of MRI for *BRCA1* mutation carriers.<sup>24</sup> Markov modelling and a societal perspective were used to determine the cost per QALY of a hypothetical cohort of 1,000 women. The cost per QALY of MRI in addition to mammography was £13,486 for women aged 30 to 39 years and £7,781 for women aged 40 to 49 years. The cost per QALY of MRI alone was not calculated for either age group because it was considered to be subject to extended dominance, and the combined screening approach would offer more QALYs at a lower cost per QALY. The sensitivity analysis revealed that the five-year survival rates affected the results. One limitation to this study was that the frequency of screening was not taken into account. The cost-effectiveness depends on the willingness to pay, and this analysis assumed a willingness-to-pay threshold of £20,000 per QALY. Overall, this study found that there is an 80% and a 63% chance that the combined MRI and mammography screening would be cost-effective in 40- to 49-year-olds and 30- to 39-year-olds respectively, at a £20,000 willingness-to-pay threshold.<sup>24</sup>

### 4.3 Limitations

Although many reports were identified that compared MRI to mammography for breast cancer screening in high-risk women, none of the studies were randomized controlled trials. Observational studies do not control for potential bias. MRI was compared to mammography in the observational studies, and most patients underwent screening using both methods. This report excluded studies in which

women were already diagnosed with breast cancer. Annual MRI screening was studied in the observational reports, and there is a lack of data for shorter or longer screening intervals.

Different models for assessing risk estimates may vary. This would complicate the use of quantitative risk thresholds when making recommendations for screening. Models of risk assessment have been used in some of the included studies, whereas some studies assess risk based on family history or *BRCA* status (proven or suspected). No Canadian cost-effectiveness studies were identified. Of the four economic studies included, two measured cost per QALY – an American study and a UK study.<sup>23,24</sup> It is unknown whether these costs could be translated to a Canadian context.

### 4.4 Quality assessment of American Cancer Society's guidelines

The AGREE instrument (Appraisal of Guidelines Research and Evaluation) was used by two independent reviewers to evaluate the quality of the American Cancer Society's (ACS) guidelines.<sup>25</sup> The scope, purpose, stakeholders' involvement, rigour of development, clarity, presentation, applicability, and editorial independence are assessed in the instrument. The standardized domain scores appear in Appendix 2. The inclusion and exclusion criteria for selecting evidence, the external review process, and the process for updating the guidelines were not reported. Therefore, the score for the rigour of development was low. In addition, the editorial independence score was zero because the editorial independence from the funding body and the conflicts of interest were not reported. The clarity and presentation of the guidelines were well done, because the recommendations were specific and easily identifiable. The authors of the guideline recognize that some of the recommendations are not based on solid evidence because of the lack of outcome data. Because of the deficiency in the quality of evidence, parts of the guidelines are based on a consensus opinion.<sup>9</sup>

## 4.5 Conclusions and implications for decision or policy making

The ACS recommends annual MRI screening in addition to mammography for women at high risk of breast cancer.<sup>9</sup> Some of these recommendations are not based on high-quality evidence because of the lack of high-level evidence, such as randomized controlled trials, and are based on consensus opinion. MRI screening was shown to be more sensitive than mammography for the detection of breast cancer. The sensitivity of MRI in the included studies that reported sensitivity ranged from 77% to 93.8%, compared to a sensitivity of 30% to 58.8% for mammography. Therefore, the false-negative rate would be lower for MRI compared to mammography. The specificity of MRI ranged from 81% to 97.2%, which was lower than that of mammography, which ranged from 93% to 96.8%. This indicates that the number of false-positive test results with MRI would be higher than the number of false-positive results with mammography. Although the cancers detected by MRI only in high-risk women ranged from 33.3% to 87.5%, these numbers were consistently higher than the numbers detected by mammography only. Overall, MRI detected more breast cancers in high-risk women than mammography and there were a high number of cancers that would have been missed if MRI screening had not been used.

The cost-effectiveness studies suggest that MRI for breast screening can be cost-effective if it is limited to women at high risk of breast cancer.<sup>22</sup> This depends on the willingness to pay and the value attributed to one QALY. MRI screening conducted in addition to mammography was found to be cost-effective for *BRCA1/2* mutation carriers between the ages of 35 years to 54 years, but not in women <34 years old or in women >55 years old.<sup>23</sup> It is suggested that the extra costs of MRI screening for breast cancer is reasonable in those patients with a very high risk of breast cancer, such as those with *BRCA1/2* mutations.<sup>12</sup> Therefore, MRI screening may not be cost-effective for the general population and those without *BRCA1/2* mutations.

There are several criteria to consider when assessing a screening test.<sup>26</sup> The test must be easy to administer and acceptable to the patients undergoing the test. In addition, the screening should be accurate. The cost and precision of the test should be taken into account. Sensitivity and specificity are important factors. MRI screening for breast cancer in high-risk women meets most of these criteria, in that it is an acceptable test with accurate results and has a high sensitivity. The sensitivity of MRI screening is significantly higher than that of mammography screening, although the specificity is lower.

There is a lack of high-level evidence regarding the effectiveness of MRI screening for breast cancer detection. Randomized controlled trials would aid in the evaluation of MRI screening and would provide better evidence for clinical effectiveness and cost-effectiveness. Existing observational studies show that MRI can be used to detect breast cancers that are not detected using other methods, such as CBE, mammography, or ultrasound. High-risk women (those with *BRCA1/2* mutations, a first degree relative with a mutation, or a strong family history of breast cancer) seem to benefit the most from the addition of MRI to the screening modality.

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# APPENDIX 1

Sensitivity and specificity of MRI compared to mammography from included observational studies on MRI for breast cancer screening

Table 1: Sensitivity and specificity of MRI and mammography*		
Study	Sensitivity of MRI Versus Mammography	Specificity of MRI Versus Mammography
MARIBS study group <sup>13</sup>	77% versus 40%, p = 0.01	81% versus 93%, p <0.0001
Kriege <i>et al.</i> <sup>15</sup>	93.3% versus 30%, p = 0.003	86% versus 94.5%, p <0.001
Warner <i>et al.</i> <sup>17</sup>	77% versus 33%, p = 0.02	95.4% versus 96%, NR
Kuhl <i>et al.</i> <sup>19</sup>	90.7% versus 32.6%, p <0.001	97.2% versus 96.8%, p >0.5
Sardanelli <i>et al.</i> <sup>20</sup>	93.8% versus 58.8%, NR	NR

NR = not reported. \* Studies included are those that reported sensitivity, specificity, or both.

Table 2: Number of breast cancers detected, and number detected by MRI only			
Study	Number of Patients	Number of Cancers Detected	Number Detected By MRI Only (%)
Sardanelli <i>et al.</i> <sup>12</sup>	105	8	7 (87.5)
MARIBS study group. <sup>13</sup>	649	35	19 (54.3)
Lehman <i>et al.</i> <sup>14</sup>	367	4	3 (75.0)
Warner <i>et al.</i> <sup>17</sup>	236	22	7 (33.3)
Trecate <i>et al.</i> <sup>18</sup>	116	12	6 (50.0)
Kuhl <i>et al.</i> <sup>19</sup>	529	43	19 (44.2)
Sardanelli <i>et al.</i> <sup>20</sup>	278	18	6 (33.3)
Trecate <i>et al.</i> <sup>21</sup>	23	4	3 (75.0)
Kriege <i>et al.</i> <sup>16</sup>	1,909	45	20 (44.4)

## APPENDIX 2

AGREE individual domain scores and standardized domain scores

Standardized domain score =  $\frac{\text{obtained score} - \text{minimum possible score}}{\text{maximum possible score} - \text{minimum possible score}}$

Table 1: Domain scores – scope and purpose*				
	Item 1	Item 2	Item 3	Total
Appraiser 1	4	4	4	12
Appraiser 2	3	2	2	7
				19

\*Standardized domain score =  $(19 - 6) / (24 - 6) = 72\%$

Table 2: Domain scores – stakeholder involvement*					
	Item 1	Item 2	Item 3	Item 4	Total
Appraiser 1	4	1	3	1	9
Appraiser 2	3	2	3	1	9
					18

\*Standardized domain score =  $(18 - 8) / (32 - 8) = 42\%$

Table 3: Domain scores – rigour of development*								
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Total
Appraiser 1	3	2	3	4	2	1	1	16
Appraiser 2	3	1	3	3	1	1	1	13
								29

\*Standardized domain score =  $(29 - 14) / (56 - 14) = 36\%$

Table 4: Domain scores – clarity and presentation*					
	Item 1	Item 2	Item 3	Item 4	Total
Appraiser 1	3	4	4	2	13
Appraiser 2	4	3	4	1	12
					25

\*Standardized domain score =  $(25 - 8) / (32 - 8) = 71\%$

Table 5: Domain scores – applicability*				
	Item 1	Item 2	Item 3	Total
Appraiser 1	3	3	2	8
Appraiser 2	1	2	1	4
				12

\*Standardized domain score =  $(12 - 6) / (24 - 6) = 33\%$

Table 6: Domain scores – editorial independence*			
	Item 1	Item 2	Total
Appraiser 1	1	1	2
Appraiser 2	1	1	2
			4

\*Standardized domain score =  $(4 - 4) / (16 - 4) = 0\%$