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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

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About the Medical Advisory Secretariat

The Medical Advisory Secretariat is part of the Ontario Ministry of Health and Long-Term Care. The mandate of the Medical Advisory Secretariat is to provide evidence-based policy advice on the coordinated uptake of health services and new health technologies in Ontario to the Ministry of Health and Long-Term Care and to the healthcare system. The aim is to ensure that residents of Ontario have access to the best available new health technologies that will improve patient outcomes.

The Medical Advisory Secretariat also provides a secretariat function and evidence-based health technology policy analysis for review by the Ontario Health Technology Advisory Committee (OHTAC).

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To conduct its comprehensive analyses, the Medical Advisory Secretariat systematically reviews available scientific literature, collaborates with partners across relevant government branches, and consults with clinical and other external experts and manufacturers, and solicits any necessary advice to gather information. The Medical Advisory Secretariat makes every effort to ensure that all relevant research, nationally and internationally, is included in the systematic literature reviews conducted.

The information gathered is the foundation of the evidence to determine if a technology is effective and safe for use in a particular clinical population or setting. Information is collected to understand how a new technology fits within current practice and treatment alternatives. Details of the technology's diffusion into current practice and input from practising medical experts and industry add important information to the review of the provision and delivery of the health technology in Ontario. Information concerning the health benefits; economic and human resources; and ethical, regulatory, social and legal issues relating to the technology assist policy makers to make timely and relevant decisions to optimize patient outcomes.

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List of Abbreviations

AUC	Area under the curve
CEA	Cost-effectiveness analysis
CI	Confidence interval
DCIS	Ductal carcinoma in situ
DM	Digital mammography
EBA	Evidence-based analysis
FM	Film mammography
GBP	Great British pounds
HTA	Health technology assessment
HTPA	Health technology policy analysis
ICER	Incremental cost-effectiveness ratio
MAS	Medical Advisory Secretariat
MRI	Magnetic resonance imaging
OR	Odds ratio
OHTAC	Ontario Health Technology Advisory Committee
PPV	Positive predictive value
QALY	Quality-adjusted life year
RCT	Randomized controlled trial
RR	Relative risk
SD	Standard deviation
SE	Standard error
SROC	Summary receiving operating characteristic
USD	United States dollars

Executive Summary

Objective

The purpose of this review is to determine the effectiveness of 2 separate modalities, digital mammography (DM) and magnetic resonance imaging (MRI), relative to film mammography (FM), in the screening of women asymptomatic for breast cancer. A third analysis assesses the effectiveness and safety of the combination of MRI plus mammography (MRI plus FM) in screening of women at high risk. An economic analysis was also conducted.

Research Questions

- How does the sensitivity and specificity of DM compare to FM?
- How does the sensitivity and specificity of MRI compare to FM?
- How do the recall rates compare among these screening modalities, and what effect might this have on radiation exposure? What are the risks associated with radiation exposure?
- How does the sensitivity and specificity of the combination of MRI plus FM compare to either MRI or FM alone?
- What are the economic considerations?

Clinical Need

The effectiveness of FM with respect to breast cancer mortality in the screening of asymptomatic average- risk women over the age of 50 has been established. However, based on a Medical Advisory Secretariat review completed in March 2006, screening is not recommended for women between the ages of 40 and 49 years. Guidelines published by the Canadian Task Force on Preventive Care recommend mammography screening every 1 to 2 years for women aged 50 years and over, hence, the inclusion of such women in organized breast cancer screening programs. In addition to the uncertainty of the effectiveness of mammography screening from the age of 40 years, there is concern over the risks associated with mammographic screening for the 10 years between the ages of 40 and 49 years.

The lack of effectiveness of mammography screening starting at the age of 40 years (with respect to breast cancer mortality) is based on the assumption that the ability to detect cancer decreases with increased breast tissue density. As breast density is highest in the premenopausal years (approximately 23% of postmenopausal and 53% of premenopausal women having at least 50% of the breast occupied by high density), mammography screening is not promoted in Canada nor in many other countries for women under the age of 50 at average risk for breast cancer. It is important to note, however, that screening of premenopausal women (i.e., younger than 50 years of age) at high risk for breast cancer by virtue of a family history of cancer or a known genetic predisposition (e.g., having tested positive for the breast cancer genes BRCA1 and/or BRCA2) is appropriate. Thus, this review will assess the effectiveness of breast cancer screening with modalities other than film mammography, specifically DM and MRI, for both pre/perimenopausal and postmenopausal age groups.

International estimates of the epidemiology of breast cancer show that the incidence of breast cancer is increasing for all ages combined whereas mortality is decreasing, though at a slower rate. The observed decreases in mortality rates may be attributable to screening, in addition to advances in breast cancer therapy over time. Decreases in mortality attributable to screening may be a result of the earlier detection and treatment of invasive cancers, in addition to the increased detection of ductal carcinoma in situ

(DCIS), of which certain subpathologies are less lethal. Evidence from the Surveillance, Epidemiology and End Results (better known as SEER) cancer registry in the United States, indicates that the age-adjusted incidence of DCIS has increased almost 10-fold over a 20 year period, from 2.7 to 25 per 100,000.

There is a 4-fold lower incidence of breast cancer in the 40 to 49 year age group than in the 50 to 69 year age group (approximately 140 per 100,000 versus 500 per 100,000 women, respectively). The sensitivity of FM is also lower among younger women (approximately 75%) than for women aged over 50 years (approximately 85%). Specificity is approximately 80% for younger women versus 90% for women over 50 years. The increased density of breast tissue in younger women is likely responsible for the decreased accuracy of FM.

Treatment options for breast cancer vary with the stage of disease (based on tumor size, involvement of surrounding tissue, and number of affected axillary lymph nodes) and its pathology, and may include a combination of surgery, chemotherapy and/or radiotherapy. Surgery is the first-line intervention for biopsy-confirmed tumors. The subsequent use of radiation, chemotherapy or hormonal treatments is dependent on the histopathologic characteristics of the tumor and the type of surgery. There is controversy regarding the optimal treatment of DCIS, which is considered a noninvasive tumour.

Women at high risk for breast cancer are defined as genetic carriers of the more commonly known breast cancer genes (BRCA1, BRCA2 TP53), first degree relatives of carriers, women with varying degrees of high risk family histories, and/or women with greater than 20% lifetime risk for breast cancer based on existing risk models. Genetic carriers for this disease, primarily women with BRCA1 or BRCA2 mutations, have a lifetime probability of approximately 85% of developing breast cancer. Preventive options for these women include surgical interventions such as prophylactic mastectomy and/or oophorectomy, i.e., removal of the breasts and/or ovaries. Therefore, it is important to evaluate the benefits and risks of different screening modalities, to identify additional options for these women.

This Medical Advisory Secretariat review is the second of 2 parts on breast cancer screening, and concentrates on the evaluation of both DM and MRI relative to FM, the standard of care. Part I of this review (March 2006) addressed the effectiveness of screening mammography in 40 to 49 year old average-risk women. The overall objective of the present review is to determine the optimal screening modality based on the evidence.

Evidence Review Strategy

The Medical Advisory Secretariat followed its standard procedures and searched the following electronic databases: Ovid MEDLINE, EMBASE, Ovid MEDLINE In-Process & Other Non-Indexed Citations, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews and The International Network of Agencies for Health Technology Assessment database. The subject headings and keywords searched included breast cancer, breast neoplasms, mass screening, digital mammography, magnetic resonance imaging. The detailed search strategies can be viewed in Appendix 1.

Included in this review are articles specific to screening and do not include evidence on diagnostic mammography. The search was further restricted to English-language articles published between January 1996 and April 2006. Excluded were case reports, comments, editorials, nonsystematic reviews, and letters.

Digital Mammography: In total, 224 articles specific to DM screening were identified. These were examined against the inclusion/exclusion criteria described below, resulting in the selection and review of 5 health technology assessments (HTAs) (plus 1 update) and 4 articles specific to screening with DM.

Magnetic Resonance Imaging: In total, 193 articles specific to MRI were identified. These were examined against the inclusion/exclusion criteria described below, resulting in the selection and review of 2 HTAs and 7 articles specific to screening with MRI.

The evaluation of the addition of FM to MRI in the screening of women at high risk for breast cancer was also conducted within the context of standard search procedures of the Medical Advisory Secretariat. as outlined above. The subject headings and keywords searched included the concepts of breast cancer, magnetic resonance imaging, mass screening, and high risk/predisposition to breast cancer.
The search was further restricted to English-language articles published between September 2007 and January 15, 2010. Case reports, comments, editorials, nonsystematic reviews, and letters were not excluded.

MRI plus mammography: In total, 243 articles specific to MRI plus FM screening were identified. These were examined against the inclusion/exclusion criteria described below, resulting in the selection and review of 2 previous HTAs, and 1 systematic review of 11 paired design studies.

Inclusion Criteria

- English-language articles, and English or French-language HTAs published from January 1996 to April 2006, inclusive.
- Articles specific to screening of women with no personal history of breast cancer.
- Studies in which DM or MRI were compared with FM, and where the specific outcomes of interest were reported.
- Randomized controlled trials (RCTs) or paired studies only for assessment of DM.
- Prospective, paired studies only for assessment of MRI.

Exclusion Criteria

- Studies in which outcomes were not specific to those of interest in this report.
- Studies in which women had been previously diagnosed with breast cancer.
- Studies in which the intervention (DM or MRI) was not compared with FM.
- Studies assessing DM with a sample size of less than 500.

Intervention

- Digital mammography.
- Magnetic resonance imaging.

Comparator

- Screening with film mammography.

Outcomes of Interest

- Breast cancer mortality (although no studies were found with such long follow-up).
- Sensitivity.
- Specificity.
- Recall rates.

Summary of Findings

Digital Mammography

There is moderate quality evidence that DM is significantly more sensitive than FM in the screening of asymptomatic women aged less than 50 years, those who are premenopausal or perimenopausal, and those with heterogeneously or extremely dense breast tissue (regardless of age).

It is not known what effect these differences in sensitivity will have on the more important effectiveness outcome measure of breast cancer mortality, as there was no evidence of such an assessment.

Other factors have been set out to promote DM, for example, issues of recall rates and reading and examination times. Our analysis did not show that recall rates were necessarily improved in DM, though examination times were lower than for FM. Other factors including storage and retrieval of screens were not the subject of this analysis.

Magnetic Resonance Imaging

There is moderate quality evidence that the sensitivity of MRI is significantly higher than that of FM in the screening of women at high risk for breast cancer based on genetic or familial factors, regardless of age.

Radiation Risk Review

Cancer Care Ontario conducted a review of the evidence on radiation risk in screening with mammography women at high risk for breast cancer. From this review of recent literature and risk assessment that considered the potential impact of screening mammography in cohorts of women who start screening at an earlier age or who are at increased risk of developing breast cancer due to genetic susceptibility, the following conclusions can be drawn:

For women over 50 years of age, the benefits of mammography greatly outweigh the risk of radiation-induced breast cancer irrespective of the level of a woman's inherent breast cancer risk.

Annual mammography for women aged 30 – 39 years who carry a breast cancer susceptibility gene or who have a strong family breast cancer history (defined as a first degree relative diagnosed in their thirties) has a favourable benefit:risk ratio. Mammography is estimated to detect 16 to 18 breast cancer cases for every one induced by radiation (Table 1). Initiation of screening at age 35 for this same group would increase the benefit:risk ratio to an even more favourable level of 34-50 cases detected for each one potentially induced.

Mammography for women under 30 years of age has an unfavourable benefit:risk ratio due to the challenges of detecting cancer in younger breasts, the aggressiveness of cancers at this age, the potential for radiation susceptibility at younger ages and a greater cumulative radiation exposure.

Mammography when used in combination with MRI for women who carry a strong breast cancer susceptibility (e.g., BRCA1/2 carriers), which if begun at age 35 and continued for 35 years, may confer greatly improved benefit:risk ratios which were estimated to be about 220 to one.

While there is considerable uncertainty in the risk of radiation-induced breast cancer, the risk expressed in published studies is almost certainly conservative as the radiation dose absorbed by women receiving mammography recently has been substantially reduced by newer technology.

A CCO update of the mammography radiation risk literature for 2008 and 2009 gave rise to one article by Barrington de Gonzales et al. published in 2009 (Barrington de Gonzales et al., 2009, JNCI, vol. 101: 205-209). This article focuses on estimating the risk of radiation-induced breast cancer for mammographic screening of young women at high risk for breast cancer (with BRCA gene mutations). Based on an assumption of a 15% to 25% or less reduction in mortality from mammography in these high risk women, the authors conclude that such a reduction is not substantially greater than the risk of radiation-induced breast cancer mortality when screening before the age of 34 years. That is, there would be no net benefit from annual mammographic screening of BRCA mutation carriers at ages 25-29 years; the net benefit would be zero or small if screening occurs in 30-34 year olds, and there would be some net benefit at age 35 years or older.

The Addition of Mammography to Magnetic Resonance Imaging

The effects of the addition of FM to MRI screening of high risk women was also assessed, with inclusion and exclusion criteria as follows:

Inclusion Criteria

- English-language articles and English or French-language HTAs published from September 2007 to January 15, 2010.
- Articles specific to screening of women at high risk for breast cancer, regardless of the definition of high risk.
- Studies in which accuracy data for the combination of MRI plus FM are available to be compared to that of MRI and FM alone.
- RCTs or prospective, paired studies only.
- Studies in which women were previously diagnosed with breast cancer were also included.

Exclusion Criteria

- Studies in which outcomes were not specific to those of interest in this report.
- Studies in which there was insufficient data on the accuracy of MRI plus FM.

Intervention

- Both MRI and FM.

Comparators

- Screening with MRI alone and FM alone.

Outcomes of Interest

- Sensitivity.
- Specificity.

Summary of Findings

Magnetic Resonance Imaging Plus Mammography

Moderate GRADE Level Evidence that the sensitivity of MRI plus mammography is significantly higher than that of MRI or FM alone, although the specificity remains either unchanged or decreases in the screening of women at high risk for breast cancer based on genetic/familial factors, regardless of age.

1. These studies include women at high risk defined as BRCA1/2 or TP53 carriers, first degree relatives of carriers, women with varying degrees of high risk family histories, and/or >20% lifetime risk based on existing risk models. This definition of high risk accounts for approximately 2% of the female adult population in Ontario.

Background

Issue

The Ontario Breast Screening Program (OBSP), under the auspices of Cancer Care Ontario, presently targets mammography screening in women 50 to 69 years of age. Cancer Care Ontario was interested in expanding its program to include average-risk women 40 to 49 years of age, and had requested a review of Ministry policy. This issue was addressed in a review completed by the Medical Advisory Secretariat in March 2006, in which screening mammography of average-risk women aged 40 to 49 years was not recommended (based on evidence published to April 2006). These findings were consistent with present provincial and national guidelines indicating that women 40 to 49 years of age should not be screened systematically. The present review examines the effectiveness of 2 screening modalities, namely digital mammography (DM) and magnetic resonance imaging (MRI), as possible alternatives to film mammography (FM).

Breast Cancer

Breast cancer is diagnosed mainly in the epithelial tissue of the breast (i.e., within the milk ducts). It is considered to be a hormone-related cancer, and thus, risk increases with increasing age (partly a result of increased lifetime hormonal exposure). While most cancers are sporadic (not of an inherited predisposition), approximately 15% of all breast cancer diagnoses in Canada are attributable to genetic factors. Approximately half of these are attributable to the 2 main breast cancer genes, BRCA1 and BRCA2, whereas the remaining half are attributable to a combination of other breast cancer genes and the aggregation of cancer in families. The population prevalence of BRCA1 and BRCA2 combined is approximately 0.50%; this is the proportion of the general population that may be carriers of these genes.

The mean change in age-standardized incidence rates of breast cancer in Canada has been increasing at 0.2% per year (from 1992 to 2001), whereas the mean change in age-standardized mortality rate has been decreasing at a rate of 2.8% per year (from 1993–2002). (1) This translates to an estimated 21,600 new cases of breast cancer annually in Canada. Of these, 8,200 are expected in Ontario, of which 1,368 are estimated to occur in women aged 40 to 49 years at diagnosis. The death rate for all stages of breast cancer combined is about 25%, for an estimated 2,000 deaths expected in Ontario in 2005, of which about 400 will occur in women aged 40 to 49 years.

Women at high risk for breast cancer are defined as genetic carriers of the more commonly known breast cancer genes (BRCA1, BRCA2 TP53), first degree relatives of carriers, women with varying degrees of high risk family histories, and/or women with greater than 20% lifetime risk for breast cancer based on existing risk models. Genetic carriers for this disease, primarily women with BRCA1 or BRCA2 mutations, have a lifetime probability of approximately 85% of developing breast cancer. Preventive options for these women include surgical interventions such as prophylactic mastectomy and/or oophorectomy, i.e., removal of the breasts and/or ovaries. Therefore, it is important to evaluate the benefits and risks of different screening modalities, to identify additional options for these women.

Mammography Screening

Screening mammography is effective in women aged 50 years or over. It is not recommended for average risk women under the age of 50 years. The lack of effectiveness of screening mammography in women 40-49 years of age was the subject of the Medical Advisory Secretariat review completed in March 2006, and was based on all randomized controlled trials (RCTs) conducted on this issue. The standard of care for screening has been FM, but evidence suggests that the accuracy of a screening test may vary with breast density and other factors. This may be the reason for the lack of effectiveness of screening

mammography in younger women. Therefore, screening modalities other than mammography require assessment, particularly as there may be alternative screening options for certain subgroups of women.

Other Technologies

Breast cancer screening technologies other than FM to be reviewed in this health technology policy assessment (HTPA) include DM and MRI. This HTPA assesses the effectiveness of DM, and MRI, as compared with FM.

Technology Being Reviewed: DM and MRI

Digital Mammography

DM is similar to FM, with the exception of a shortened procedure time (5 minutes with DM compared to 20 minutes with FM: Personal Communication, Industry, August 2006). The main difference is that images for DM, once taken, are electronic, and thus, can be altered for contrast and resolution, whereas FM images are not adjustable. In addition, the DM systems allow for the adjustment of radiation dose, whereas FM systems do not. Industry claims that screening with DM also gives rise to lower radiation exposure for women, partly attributable to a lower recall rate than FM (i.e., as women are less likely to be subject to repeat exams), and the ability of DM to produce images of similar quality to FM at lower dosages. The main DM system manufacturers in Canada are Hologic/Lorad and Fuji (distributed by The Christi Group), General Electric, and Siemens.

Magnetic Resonance Imaging

MRI is a screening modality that involves no radiation exposure. Nevertheless, the procedure time is estimated at approximately 40 minutes compared with 20 minutes required for FM (Personal communication, Industry, August 2006). It is not considered a feasible screening tool for average risk women. This is partly due to the lower specificity relative to FM, and mainly due to the lack of resources available for screening large numbers of women. MRI is a more invasive test than mammography in that it involves the administration of a contrast agent.

Evidence Based Analysis

Objectives

- To determine the effectiveness of DM, relative to FM, in the screening of asymptomatic women for breast cancer.
- To determine the effectiveness of MRI, relative to FM, in the screening of asymptomatic women for breast cancer.
- To conduct an economic analysis.

Research Questions

- How does the sensitivity and specificity of DM compare to FM in the screening of asymptomatic women for breast cancer?
- How does the sensitivity and specificity of MRI compare to FM in the screening of asymptomatic women for breast cancer?
- How do the recall rates compare among these screening modalities, and what effect may this have on radiation exposure. What are the risks associated with radiation exposure?
- What are the economic considerations?

Methods

The Medical Advisory Secretariat followed its standard search procedures and searched the following electronic databases: Ovid MEDLINE, EMBASE, Ovid MEDLINE In-Process & Other Non-Indexed Citations, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews and The International Network of Agencies for Health Technology Assessment database. The subject headings and keywords searched included breast cancer, breast neoplasms, mass screening, digital mammography, and magnetic resonance imaging. The detailed search strategy can be viewed in Appendix 1.

Included in this review are articles specific to screening and do not include evidence on diagnostic mammography. The search was further restricted to English-language articles published between January 1996 and April 2006. Excluded were case reports, comments, editorials, nonsystematic reviews, and letters.

Digital Mammography: In total, 224 articles specific to DM screening were identified. These were examined against the inclusion/exclusion criteria described below, resulting in the selection and review of 5 previous HTAs (plus 1 update), 2 RCTs and 2 paired studies comparing DM to FM.

Magnetic Resonance Imaging: In total, 193 articles specific to MRI were identified. These were examined against the inclusion/exclusion criteria described below, resulting in of the selection and review of 2 HTAs and 7 paired studies comparing MRI to FM.

Inclusion Criteria

- English-language articles and English or French-language HTAs published from January 1996 to April 2006.
- Articles specific to screening of women with no personal history of breast cancer.

- Studies in which DM or MRI were compared with FM, and the specific outcomes of interest were reported.
- RCTs or paired studies only for assessment of DM.
- Prospective, paired studies only for assessment of MRI.

Exclusion Criteria

- Studies in which outcomes were not specific to those of interest in this report.
- Studies in which women had been previously diagnosed with breast cancer.
- Studies in which the intervention (DM or MRI) was not compared with FM.
- Studies assessing DM with a sample size less than 500.

Intervention

- Digital mammography.
- Magnetic resonance imaging.

Comparators

- Screening with film mammography.

Outcomes of Interest

- Breast cancer mortality, although no studies were found with such long follow-up.
- Sensitivity.
- Specificity.
- Recall rates.

Results of Literature Review

Digital Mammography

Included in this review are 5 HTAs (and 1 update), 2 RCTs and 2 paired studies that evaluate DM compared with FM in the screening of asymptomatic women for breast cancer. The earliest of the HTAs included in this review was conducted by the Agence Nationale d'Accréditation et d'Evaluation en Santé(ANAES) in 2000. (2) The most recent, a 2006 update by the Blue Cross and Blue Shield Technology Evaluation Center (TEC) (3)**,** includes articles published to December 2005. Of note, the Digital Mammographic Imaging Screening Trial (DMIST) trial was published in October 2005 (4), and the 2006 update by TEC is the only HTPA to date that includes results of this trial.

It is important to note that the effectiveness of a screening modality should be based on longer-term outcomes such as breast cancer mortality. However, studies conducted on the effectiveness of either DM or MRI relative to FM are based on measures of accuracy only, that is, sensitivity, specificity, and positive predictive values (PPV). The underlying assumption for such comparisons is that improved accuracy (relative to FM in each study) will give rise to improved long- term outcomes, such as reduced breast cancer mortality. However, it is unclear as to whether this assumption is valid or not.

Summary of Existing Health Technology Assessments

The authors and focus of the HTAs for DM are outlined in Table 1.

Table 1: Summary and Focus of Previous Health Technology Assessments on Digital Mammography*

Year	Author	Focus of Assessment
2006, 2002	Blue Cross and Blue Shield Association (3;5;5)	●To determine the effectiveness of DM compared with FM in the screening for or diagnosis of breast cancer. The outcomes of interest are cancer detection, recall and biopsy rates. ●To update the 2002 recommendations on this issue.
2004	NHS Quality Improvement Scotland (6)	●To determine the costs and benefits of DM.
2002	Canadian Coordinating Office for Health Technology Assessment (CCOHTA) (7)	●To compare the technical, clinical and potential costs of DM and FM within the context of the Canadian health care system.
2002	Comite d'Evaluation et de Diffusion des Innovations Technologiques (CEDIT) (8)	●To appraise full-field DM, i.e., technical, medical, economic and financial aspects.
2000	Agence Nationale d'Accréditation et d'Evaluation en Santé (ANAES) (2)	●To conduct a clinical evaluation of DM in breast cancer diagnosis and screening.

* DM refers to digital mammography; FM, film mammography.

The most recent assessment was published in 2006 by TEC (3), an update of their 2002 report (5), to include results of the DMIST trial (4). The DMIST trial was conducted by the American College of Radiology Imaging Network, and published in October 2005.

Blue Cross Blue Shield Association, Technology Evaluation Center, United States, 2006 (update of 2002 report)

TEC (3;5), published the following report:

Full-Field Digital Mammography

Objective: To update the 2002 assessment on full-field DM, and to compare cancer detection, recall, and biopsy rates for full-field DM versus FM.

Search Date: June 2002 through December 2005.

Studies Included	Comments	Conclusions
DMIST trial, in addition to the 2002 report	➢ DM may be at radiation doses no higher and may be lower than FM.	➢ DM is as accurate as FM, but more sensitive in cases where FM is less sensitive. ➢ Support DM for subgroups of the DMIST trial.

This HTA included the DMIST trial and accounted for studies in the 2002 report. The first report, published in July 2002 (5), focused its review on (i) a screening population, and (ii) the population of patients referred to diagnostic mammography based on initial suspicious findings. The outcomes of interest were primarily radiation exposure, recall rates, biopsy and cancer detection rates. The details pertaining to this report are as follows:

Objective: To compare DM and FM for use in both the screening and the diagnostic populations, comparing radiation exposure, recall rates, biopsy and cancer detection rates.

Search Date: January 1966 and June 2002.

Studies Included	Comments	Conclusions
2 main studies	➢ Whether DM improves net health outcomes or is as beneficial as FM not yet established. ➢ Whether DM improves outcomes compared with FM has not yet been established. ➢ Radiation dose in DM reduced by 20-35%, yet additional evidence required to determine actual radiation exposure.	➢ Insufficient evidence to conclude on effects of DM relative to FM in screening for breast cancer.

The authors indicate that 2 main studies comprise the available data to date. These were the studies conducted by Lewin et al. (9) in the United States, and Skaane et al. (10) in Norway, the latter having been reported in a proceedings paper and 2 conference abstracts. Results of the Lewin et al. article and the work by Skaane et al., as reported in subsequent publications, will be discussed further in the Medical Advisory Secretariat section of this HTPA. Overall, this TEC report concluded there was insufficient evidence on which to base recommendations on the effectiveness of DM relative to FM.

National Health Service Quality Improvement Scotland, 2004

The National Health Service (NHS) Quality Improvement Scotland (6) published the following report:

Comparison of Digital Mammography and Film Screen Mammography :Issues for Health Service Planners and Practitioners

This is a summary bulletin of FM and DM in Scotland outlining findings of previous HTAs, namely that by the Canadian Coordinating Office for Health Technology Assessment (CCOHTA, (7) and the 2002 report by TEC (5). In Scotland, breast screening is offered every 3 years to women between 50 and 64 years of age, extended to the age of 70. An outline of the costs and benefits includes discussion of the possible reduction in radiation exposure with reduced retake and recall rates with DM, although the clinical significance of this reduced exposure is not clear. The authors comment on the 2 screening studies included in the CCHOTA report that suggest there is no difference in diagnostic accuracy between DM and FM. Of the 3 studies included in the TEC assessment, the results differed in that the Lewin et al. study reported lower recall and biopsy rates in the DM group, whereas for Skaane et al., recall rates were higher for DM. The recall rate for the DMIST trial was similar in both study arms, but this was expected as the intent of the study was to ensure similar image quality between the 2 screening modalities. However, none of the studies reported significant differences in detection rates between DM and FM.

Canadian Coordinating Office for Health Technology Assessment, Canada, 2002

The Canadian review published in October 2002 was conducted by CCOHTA (7). They concluded that despite the promise of advantages with DM, it was not clear that this technology was better than conventional FM for the early detection of breast cancer.

Digital Mammography versus Film-Screen Mammography: Technical, Clinical and Economic Assessments

Objectives: In the context of an assessment of the technical, clinical and economic aspects of DM, this review addressed the specific issues of whether DM is more expensive, and more clinically effective than FM.

Search: All published and conference literature comparing the technical, clinical, and economic aspects of DM and FM up to April 2002.

Studies Included	Comments	Conclusions
37 relevant articles on technical review, 7 on clinical review, 17 on economic analysis.	➢ A significant benefit is shorter examination times; Potential for reduced radiation dose, but the significance of this is unclear. ➢ Advantages include removal of procedural burdens of dealing with FM, e.g., archiving, computer-assisted diagnosis. However, DM systems also require technical improvements to achieve full benefit.	➢ Economic: DM has significantly higher annualized costs than FM. ➢ Technical: Potential benefits (improved diagnostic accuracy, shorter examination time, lower radiation dose) for patients, institutions and payers not demonstrated in clinical setting. Clinical: Ability to detect cancer comparable for both procedures. ➢ Assuming clinical equivalence, minimum-cost system is preferred; therefore, FM preferable to DM at this time.

The assessment by CCOHTA addressed the technical, clinical and potential costs of DM in Canada. At the time of publication of this report, results of the more recent DMSIT trial were not available. As such, it was concluded that the ability of DM to detect cancer was comparable to FM. Furthermore, assuming at best, clinical equivalence between DM and FM, the minimum cost system is preferred. As DM has significantly higher annualized costs than FM, the preference was for FM over DM at that time.

Comite d'Evaluation et de Diffusion des Innovations Technologiques, France, 2002

The Comite d'Evaluation et de Diffusion des Innovations Technologiques (CEDIT) published the following report: (8)

Full Field Digital Mammography

This is a summary of recommendations for DM given its advantages with regards to image acquisition, processing and interpretation. A review of existing evidence is not provided. The authors report that the anticipated reduction in direct radiation dose of 15% to 30% with DM has not yet been demonstrated. They also mention that the investment costs of DM are abut 4 times the cost of FM, and conclude that CEDIT does not currently recommend the generalized use of DM.

Agence Nationale d'Accréditation et d'Evaluation en Santé , France, 2000

ANAES (2) published the following report:

Clinical Evaluation of Digital Mammography in Breast Cancer Diagnosis and Screening

This summary reports on the evidence of DM systems, concluding that further clinical trials are required to confirm the equivalence of DM relative to FM in both screening and diagnostic populations. There is mention of the DMIST and Norwegian studies that were ongoing at the time of the ANAES report.

Summary of Findings on Effectiveness of Digital Mammography

Prior to the publication of the DMIST study results, the consensus was that DM should not be made readily available due to the absence of evidence of its effectiveness relative to FM, and the larger investment costs. All HTAs prior to publication of the DMIST study results reached this conclusion. The 2006 TEC update of their 2002 report, however, included the DMIST study results, and found that DM was significantly more accurate than FM for women with heterogeneously (defined as 50% to 74% of breast tissue being dense) or extremely dense breasts (defined as 75% or more of the breast tissue being dense), those who are premenopausal or perimenopausal, as well as for women younger than 50 years of age.

Magnetic Resonance Imaging (MRI)

The search for HTAs on MRI screening for breast cancer gave rise to 2 reports, both published in December 2003; 1 by the Institute for Clinical Systems Improvement (ICSI)(11), and the other by the TEC. (12) Whereas the former assessed MRI for the detection of abnormalities in all women, the report by TEC focused on screening of women at high genetic risk for breast cancer.

Institute for Clinical Systems Improvement, United States, 2003

The ICSI (11) report included a review of MRI as a second-line, i.e., after mammography or ultrasound, as well as a first-line screening modality, the latter comparison being of interest in this Medical Advisory Secretariat assessment. Evidence for MRI screening of women at average risk for breast cancer was not found, as published studies were specific to women at high risk for breast cancer based on genetic or familial factors. Evidence for MRI in the evaluation of treatment outcomes and the resolving of difficult cases from FM screens was also presented (i.e., as a second-line screen), but being outside of the scope of this review, these results are not reported here.

Magnetic Resonance Imaging (MRI) for the Detection of Breast Abnormalities

Objectives: To determine the potential uses, contraindications, and efficacy of MRI for local staging, monitoring of treatment response, and problem-solving situations.

Studies Included	Comments	Conclusions
5 studies specific to women at high genetic risk.	➢ MRI uses include local staging, response to treatment, and problem solving of difficult situations. ➢ Contraindications discussed below.	➢ MRI screening for general population not studied, hence, not to be performed at this time. ➢ Invasive breast cancer: reported sensitivities of 93%-100%, specificity from 37% -96%. DCIS: sensitivity from 45%-100%. ➢ Studies of MRI screening of high- risk patients underway.

The section on MRI screening included 5 studies on effectiveness for women at high risk, defined as a personal or strong family history of breast cancer or carriers of a breast cancer susceptibility gene. As no RCTs were found in the screening literature, and the reviewed studies were of varying quality, a specific recommendation was not made with respect to this group of women; there was mention of ongoing multi-center studies. With respect to MRI as a screening tool, the authors found no published evidence for average-risk women and given the absence of any evidence, concluded that MRI screening for the general population should not be performed at this time.

Blue Cross and Blue Shield Association, Technology Evaluation Center, United States, 2003

TEC (12) published the following report:

Magnetic Resonance Imaging of the Breast in Screening Women Considered to be at High Genetic Risk of Breast Cancer

Objectives: To evaluate the effectiveness of MRI of the breast for screening asymptomatic women thought to be at high risk of breast cancer due to genetic risk.

Studies Included	Comments	Conclusions*
5 studies, all restricted to women at high genetic risk.	➢ Evidence on long-term clinical outcomes not available. ➢ Hence, sensitivity and specificity are limited outcome measures.	➢ MRI screening of women at high risk is recommended. ➢ High-risk is defined as confirmed presence of BRCA1/2 mutation, or known mutation in relatives, or multiple affected 1st degree relatives, often at young ages and with bilateral disease.

* BRCA1/2 indicates the presence of either a BRCA1 and/or BRCA2 gene mutation.

This assessment concludes that current evidence is limited as only studies comparing the sensitivity and specificity of MRI and FM screening are available. The limitation to this evidence is that it is not known whether improvements in sensitivity and specificity give rise to improved patient outcomes.

Based on the 5 studies of the effectiveness of MRI, this assessment recommends the use of this screening modality for women at high risk. High-risk is defined as the confirmed presence of the BRCA1/2 (major breast cancer genes) mutation, such a known mutation in a relative, or the presence of multiple first-degree relatives affected with breast cancer, often occurring at an early age, and with bilateral disease.

On the basis of these 2 reports, MRI screening is recommended for women at high risk based on genetic or familial factors, but not for use in the population of average-risk women.

Summary of Medical Advisory Secretariat Review

As 2 separate technologies are being examined in this Medical Advisory Secretariat report, each relative to FM, the evidence will be presented first for DM and then for MRI. A summary of findings for both modalities together will be presented at the end of this section.

Digital Mammography

Table 2 outlines the quality of the evidence, as defined by the Medical Advisory Secretariat, for screening with DM compared with FM.

Table 2: Quality of Evidence for Screening with Digital Mammography*

Study Design	Level of Evidence	Number of Eligible Studies
Systematic reviews of RCT	1a	0
Large RCT	1b	2 + 2
Large RCT unpublished but reported to an international scientific meeting	1(g)	0
Small RCT	2	0
Small RCT unpublished but reported to an international scientific meeting	2(g)	0
Non-RCT with contemporaneous controls	3a	0
Non-RCT with historical controls	3b	0
Non-RCT presented at international conference	3(g)	0
Surveillance (database or register)	4a	0
Case series (multisite)	4b	0
Case series (single site)	4c	0
Retrospective review, modeling	4d	0
Case series presented at international conference	4(g)	0

*RCT refers to randomized controlled trial; g, grey literature.

Randomized Clinical Trials

Two RCTs on screening with digital mammography met the inclusion and exclusion criteria for this assessment. The most recently published (2005) is the DMIST trial (4) and involved the randomization of 49,528 asymptomatic women (regardless of menopausal status) to screening with either DM or FM first, and the other modality second; a total of 42,760 women for whom complete data were available were included in the final analysis. The objective of this study was to compare the accuracy, by way of the sensitivity, specificity, and positive predictive values (PPV), of DM relative to FM. This was a multicenter trial with women screened between October 2001 and November 2003 at 33 sites in Canada and the United States. Results were presented for all participants combined, as well as for subgroups of patients determined a priori.

Women presenting at study sites were eligible for randomization if they had not undergone mammography in the previous 11 months, reported no symptoms, had not had breast implants, were not likely to be pregnant, and had no history of breast cancer treated with both lumpectomy and radiation. For each woman, the digital and film examinations were read independently by 2 radiologists, 1 for each examination. A workup, including a biopsy or aspiration of a suspicious-appearing lesion, was performed

if either radiologist recommended it (occurring for 14.0% of women). Women were recorded as positive for breast cancer if a pathology confirmation was made within 455 days after the initial study mammogram, and negative if their 1 year follow-up mammogram was normal, if pathology results of a biopsy specimen were negative, or if both criteria were met. The period of 455 days was selected to allow for all study participants to have a minimum follow-up of 365 days from their first screen.

Within 455 days after study entry, a total of 335 breast cancers were diagnosed. Of these, 254 (75.8 %) were diagnosed within 365 days of study entry, whereas the remaining 81 (24.2 %) were diagnosed between days 366 and 455 of study entry. The call-back rate was 8.4% for both groups. Although other studies have found differences in the call-back rates between the 2 screening groups, the similarity of proportions in the DMIST study is likely attributable to the fact that the intent of the study was to equate the quality of the screens in both groups. Under such circumstances, assuming that the recall rate is associated with the quality of the screens, a similar recall rate between the 2 groups was anticipated. Therefore, this data is not useful in determining the actual recall rates expected in the field.

In the DMIST trial, Pisano et al. (4) report the diagnostic accuracy of the 2 procedures to be similar for all subjects combined (difference between 2 procedures area under curve [AUC]=0.03, 95% confidence interval [CI]: -0.02 to 0.08, $P = 0.18$). Therefore, on the basis of this study, DM could not be recommended for average-risk women. In addition to comparisons based on the receiver operating characteristics (ROC) curve, it is important to review the measures of accuracy for each of the procedures. For all subjects combined, the sensitivity, specificity, and the PPV were not significantly different for DM relative to FM within 365 days of the initial mammogram (Table 3).

However, the diagnostic accuracy of DM was significantly higher than FM for 3 subgroups of women: those aged less than 50 years (difference in AUC=0.15, 95%CI: 0.05-0.25, $P = 0.002$), those with heterogeneously dense or extremely dense breasts (difference in AUC=0.11, 95%CI=0.04-0.18, $P = 0.003$), and those who are premenopausal or perimenopausal (difference in AUC=0.15, 95%CI: 0.05-0.24, $P = 0.002$).

These findings are consistent with data reported in Table 3, where the sensitivity of FM is between 51% and 55%, and 70% to 78% for DM across the 3 reported subgroups at 365 days follow-up. The specificity and PPV were similar for both procedures.

Table 3: Measures of Accuracy Within DMIST Trial at 365 Days from Initial Screen*

Subjects	Measure of Accuracy	Digital Mammography (mean ±SE)	Film Mammography (mean ±SE)
All women	Sensitivity	0.70 ±0.030	0.66 ±0.030
	Specificity	0.92 ±0.001	0.92 ±0.001
	PPV	0.05 ±0.004	0.05 ±0.003
Less than 50 years	Sensitivity	0.78 ±0.050	0.51 ±0.070
	Specificity	0.90 ±0.003	0.90 ±0.003
	PPV	0.03 ±0.005	0.02 ±0.004
Pre- or peri-menopausal	Sensitivity	0.72 ±0.050	0.51 ±0.060
	Specificity	0.90 ±0.002	0.90 ±0.002
	PPV	0.04 ±0.005	0.03 ±0.004
Heterogeneous or extremely dense breasts	Sensitivity	0.70 ±0.040	0.55 ±0.040
	Specificity	0.91 ±0.002	0.90 ±0.002
	PPV	0.04 ±0.005	0.03 ±0.004

*; PPV refers to positive predictive value; SE, standard error.

Data in Table 3 demonstrate that the sensitivity of FM was lower than that of DM, whereas the specificity and PPV are similar between the 2 modalities. The cancer detection rates, as calculated from data reported in Table 2 of the article, include 122 cancers detected by both DM and FM, 52 detected by FM alone, and 63 detected by DM alone. Thus, the cancer detection rate for FM was 0.41% (from 122+52/42,760) and 0.43% (from 122+63/42,760) for FM. These figures are similar to those reported by Lewin et al. (2001) in his paired study, which will be reviewed below. Nevertheless, a striking observation was that 29.3% of cancers reported in the DMIST trial (73 invasive cancers and 25 cases of DCIS out of the 335 cancers diagnosed) were not detected by either modality.

The second RCT was the Oslo II Study published in 2004 by Skaane et al. (10) This trial involved the randomization of 25,263 women aged 45 to 69 years to undergo only one screening procedure, either FM or DM. Independent double reading was performed. In 17,911 women screened with FM, 73 cancers were detected (detection rate=0.41%) compared with 41 cancers in 6,997 women screened with DM (detection rate=0.59%, $P = 0.06$). These detection rates are similar to those of the DMIST trial (4) and the Lewin et al. study (9) to be discussed below.

Recall rates, positive predictive values and cancer detection rates were also reported separately by age group. Among women aged 50 to 69 years, the cancer detection rate was 0.54% for FM and 0.83% for DM (difference, $P = 0.53$), whereas among those aged 40 to 49 years, the detection rate was lower at 0.22% for FM and 0.27% for DM. Recall rates for both age groups were significantly higher ($P < 0.05$) for DM (3.8% for those over 50 years, 3.7% for those 45-49 years) than for FM (2.5% for those over 50 years, 3.0% for those 45-49 years), but the positive predictive value was not significantly different (about 22% for both modalities for those over 50 years, and 7.3% for those under 50 years).

Lewin et al. published one article in 2001 (9) and one article in 2002 (13), both paired designs. Both studies intended to compare DM with FM in a screening population in the United States. In the study published in 2001 (9), 4,945 women aged 40 years and over who presented to either of 2 screening clinics for FM also underwent DM; 2 views were obtained for each modality, and images from each modality were interpreted independently. The cancer detection rate was not significantly different between the 2 groups, with 22 cancers detected by FM (0.44%) and 21 with DM (0.42%). Four interval cancers that became palpable within 1 year of initial screening were designated as false-negatives for both modalities. The recall rate, however, was significantly different between the 2 groups, with a rate of 11.5% for DM and 13.8% for FM (difference, $P < 0.03$). The rate of positive biopsies was higher for DM (30%, 21 of 69 biopsies were positive) than for FM (19%, 22 of 114 biopsies were positive), though the difference was not significant.

The Lewin et al. publication of 2002 (based on 6,736 examinations) is a follow-up of the 2001 publication (based on 4,945 examinations). Similar to the 2001 article, the results of the 2002 publication (13) reveal no significant difference in cancer detection rates between DM and FM, and a significantly lower recall rate for DM (11.9%) than for FM (14.9%).

Magnetic Resonance Imaging

Table 4 outlines the quality of the evidence, as defined by the Medical Advisory Secretariat, for screening with MRI compared with FM.

Table 4: Quality of Evidence for Screening with Magnetic Resonance Imaging*

Study Design	Level of Evidence	Number of Eligible Studies
Systematic reviews of RCT	1a	0
Large RCT	1b	0 + 7
Large RCT unpublished but reported to an international scientific meeting	1(g)	0
Small RCT	2	0
Small RCT unpublished but reported to an international scientific meeting	2(g)	0
Non-RCT with contemporaneous controls	3a	0
Non-RCT with historical controls	3b	0
Non-RCT presented at international conference	3(g)	0
Surveillance (database or register)	4a	0
Case series (multisite)	4b	0
Case series (single site)	4c	0
Retrospective review, modeling	4d	0
Case series presented at international conference	4(g)	0

*RCT refers to randomized controlled trial; g, grey literature.

Non-Randomized Clinical Trials

No RCTs were found which assessed the effectiveness of MRI for breast cancer screening. However, 7 prospective studies in which all study subjects had received both MRI and FM screening (considered paired designs), were identified. The paired aspect of the design, in which each woman is her own control, was deemed to be of superior quality to a non-RCT with contemporaneous controls, and thus, has been included in Table 4 as Level 1 evidence. All studies identified focused on asymptomatic women at high risk for breast cancer by virtue of their genetic predisposition or a family history of cancer. No studies were identified for MRI screening of average-risk women.

All 7 studies reported results for all women combined, not stratified by age group; therefore, conclusions were specific to high-risk women, regardless of age.

Two of the 7 studies were conducted in Toronto, Ontario, Canada (14;15). However, the 2001 results are of the first round of screening for the first 196 patients, and will be discussed within the context of the 2004 publication of 236 Canadian women who were BRCA1/2 positive or had a strong family history of either breast or ovarian cancer on recruitment. Though current recommendations for women who are BRCA1- or BRCA2 positive include screening from age 25 with FM annually and clinical breast examination every 6 months, the authors reported that many tumours are detected at advanced stages. Therefore, the objective of this study was to compare the sensitivity and specificity of MRI and ultrasound with FM and clinical breast examination in women with genetic predisposition to breast cancer. All screens were conducted in one day. In total, 22 cancers were detected (16 invasive cancers and 6 DCIS) in 21 women, with an average age at diagnosis of 47.4 years (33.4-63.0 years).

The reported sensitivity and specificity, based on biopsy rates, was 36% and 99.8% for FM, 33% and 96% for ultrasound, 9.1% and 99.3% for clinical breast examination, and 77% and 95.4% for MRI. Furthermore, the sensitivity of MRI was significantly higher than either mammography ($P = 0.02$) or

ultrasound ($P = 0.006$).

The remaining 5 studies were conducted in Europe: 2 each in the Netherlands (16;17) and Germany (18;19); and 1 in the United Kingdom (20). The 2 publications by Kriege et al. (16;17) were based on a total of 1,909 women (including 358 carriers of germline mutations) with a familial or genetic predisposition screened by both MRI and FM. The median follow-up was 2.9 years, within which 51 tumours (44 invasive cancers, 6 DCIS and 1 lymphoma) were diagnosed. The sensitivity for the detection of invasive cancer by clinical breast examination, FM and MRI was 17.9%, 33.3%, and 79.5%, respectively. The specificity for invasive cancer by clinical breast examination, FM and MRI was 98.1%, 95.0%, and 89.8%, respectively.

A comparison of sensitivities and specificities for MRI screening of high-risk women, relative to FM, is presented in Table 5.

Table 5: Measures of Accuracy for MRI and FM Screening in Women at High Risk for Breast Cancer*†

Author, Year N, Country	Measure of Accuracy	MRI	Film Mammography
MARIBS Study, 2005 N=649, UK (20)	Sensitivity	77.0%	40.0%
	Specificity	81.0%	93.0%
Kuhl et al. 2005 N=529, Germany (18;19)	Sensitivity	91.0%	33.0%
	Specificity	97.2%	96.8%
Warner et al. 2004 N=236, Canada (14;15)	Sensitivity	77.0%	36.0%
	Specificity	95.4%	99.8%
Kriege et al. 2004 N=1909, Netherlands (16;17)	Sensitivity	79.5%	33.3%
	Specificity	89.8%	95.0%

*High risk is based on genetic or familial factors.
† FM refers to film mammography; MRI, magnetic resonance imaging; UK, United Kingdom.

Of 4 reports in Table 5, the sensitivity of MRI was significantly higher than that of FM, yet the specificity was lower for MRI across all studies except 1 (19), which reported a similar value for MRI (97.2%) and FM (96.8%). These results are specific to women at increased risk for breast cancer based on genetic/familial factors, and include both premenopausal and postmenopausal women. Results for both studies are not presented stratified by menopausal status or by age.

Policy Development

Radiation Risks and Screening for Breast Cancer

Based on the Medical Advisory Secretariat review completed in March 2006, screening mammography was not recommended for women 40 to 49 years of age who are at average risk of breast cancer. This decision was based on a lack of effectiveness with respect to breast cancer mortality and the presence of risks associated with screening mammography in this age group. Nevertheless, for women at high risk for breast cancer based on genetic/familial factors, it is appropriate to screen at younger ages. The full Cancer Care Ontario analysis is available in Appendix 2.

To address radiation risk in women under 50 years of age at high risk for breast cancer, Cancer Care Ontario (CCO) conducted a review of this issue. From this review of recent literature and risk assessment that considered the potential impact of screening mammography in cohorts of women who start screening at an earlier age or who are at increased risk of developing breast cancer due to genetic susceptibility, the following conclusions can be drawn:

For women over 50 years of age, the benefits of mammography greatly outweigh the risk of radiation-induced breast cancer irrespective of the level of a woman's inherent breast cancer risk.

Annual mammography for women aged 30 – 39 years who carry a breast cancer susceptibility gene or who have a strong family breast cancer history (defined as a first degree relative diagnosed in their thirties) has a favourable benefit:risk ratio. Mammography is estimated to detect 16 to 18 breast cancer cases for every one induced by radiation (Table 1). Initiation of screening at age 35 for this same group would increase the benefit:risk ratio to an even more favourable level of 34-50 cases detected for each one potentially induced.

Mammography for women under 30 years of age has an unfavourable benefit:risk ratio due to the challenges of detecting cancer in younger breasts, the aggressiveness of cancers at this age, the potential for radiation susceptibility at younger ages and a greater cumulative radiation exposure. Mammography when used in combination with MRI for women who carry a strong breast cancer susceptibility (e.g., BRCA1/2 carriers), which if begun at age 35 and continued for 35 years, may confer greatly improved benefit:risk ratios which were estimated to be about 220 to one.

While there is considerable uncertainty in the risk of radiation-induced breast cancer, the risk expressed in published studies is almost certainly conservative as the radiation dose absorbed by women receiving mammography recently has been substantially reduced by newer technology.

A CCO update of the mammography radiation risk literature for 2008 and 2009 gave rise to one article by Barrington de Gonzales et al. published in 2009 (Barrington de Gonzales et al., 2009, JNCI, vol. 101: 205-209). This article focuses on estimating the risk of radiation-induced breast cancer for mammographic screening of young women at high risk for breast cancer (with BRCA gene mutations). Based on an assumption of a 15% to 25% or less reduction in mortality from mammography in these high risk women, the authors conclude that such a reduction is not substantially greater than the risk of radiation-induced breast cancer mortality when screening before the age of 34 years. That is, there would be no net benefit from annual mammographic screening of BRCA mutation carriers at ages 25-29 years; the net benefit would be zero or small if screening occurs in 30-34 year olds, and there would be some net benefit at age 35 years or older.

Magnetic Resonance Imaging Plus Mammography (MRI plus FM)

Objectives

- To determine the effectiveness of adding FM to MRI screening of asymptomatic women who are at high risk for breast cancer.
- To conduct an economic analysis.

Questions Asked

- How does the sensitivity and specificity of MRI plus FM compare to either MRI or FM alone in the screening of asymptomatic women for breast cancer?
- What are the economic considerations?

Methods

The Medical Advisory Secretariat followed its standard search procedures and searched the following electronic databases: Ovid MEDLINE, EMBASE, Ovid MEDLINE In-Process & Other Non-Indexed Citations, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews and The International Network of Agencies for Health Technology Assessment database.

The subject headings and keywords searched included the concepts of breast cancer, magnetic resonance imaging, mass screening, and high risk/predisposition to breast cancer. The detailed search strategy can be viewed in Appendix 1.

Included in this review are articles specific to screening and do not include evidence on diagnostic mammography. The search was further restricted to English-language articles published between September 2007 and January 15, 2010. Case reports, comments, editorials, nonsystematic reviews, and letters have not been excluded.

MRI plus mammography: In total, 243 articles specific to MRI plus FM screening were identified. These were examined against the inclusion/exclusion criteria described below, resulting in the selection and review of 2 previous HTAs, and 1 systematic review of 11 paired design studies.

Inclusion Criteria

- English-language articles and English or French-language HTAs published from September 2007 to January 15, 2010.
- Articles specific to screening of women at high risk for breast cancer, regardless of the definition of high risk.
- Studies in which accuracy data for the combination of MRI plus FM are available to be compared to that of MRI and FM alone.
- RCTs or prospective, paired studies only.
- Studies in which women were previously diagnosed with breast cancer were also included.

Exclusion Criteria

- Studies in which outcomes were not specific to those of interest in this report.
- Studies in which there was insufficient data on the accuracy of MRI plus FM.

Intervention

- Both MRI and FM.

Comparators

- Screening with MRI alone and FM alone.

Outcomes of Interest

- Sensitivity.
- Specificity.

Results of Literature Review

Magnetic Resonance Imaging Plus Film Mammography

Included in this review are 2 HTAs and 1 systematic review with 11 paired-design studies. A paired-design study is one in which the same woman is screening with more than one screening modality. Both HTAs were published in 2007, one having been conducted in Canada by the Canadian Agency for Drugs and Technologies in Health (CADTH) (21) and the other in New Zealand conducted by the New Zealand Health Technology Assessment (NZHTA) group. (22)

As previously noted, the effectiveness of a screening modality should be based on longer-term outcomes such as breast cancer mortality. However, studies conducted on high risk women for MRI plus FM are also based on measures of accuracy only, as were the studies of DM and MRI alone earlier in this report.

Summary of Existing Health Technology Assessments

The authors and focus of the HTAs for MRI plus FM are outlined in Table 6.

Table 6: Summary and Focus of Previous Health Technology Assessments on Magnetic Resonance Imaging plus Film Mammography

Year	Author	Focus of Assessment
2007	Canadian Agency for Drugs and Technologies in Health (21)	●To determine the clinical and cost-effectiveness of MRI screening compared to FM in women at high risk.
2007	New Zealand Health Technology Assessment (22)	●To determine the accuracy and health outcomes of several screening modalities for women at high risk, including MRI and FM.

Canadian Agency for Drugs and Technologies in Health (CADTH), 2007

CADTH published the following report in 2007 (21):

Effectiveness of Magnetic Resonance Imaging (MRI) Screening for Women at High Risk of Breast Cancer

Objectives: To determine the clinical and cost-effectiveness of MRI screening compared to FM, and to determine the strength of evidence used to support the American Cancer Society's guidelines regarding MRI screening for women at high risk for breast cancer.

Search period: 2002 and June 2007.

Studies Included	Comments	Conclusions
Two systematic reviews and 10 observational studies specific to women at high risk.	➢ All studies were observational; no evidence from randomized clinical trials. ➢ Outcomes were accuracy of MRI and FM as screening modalities in high risk women. No evidence assessing effects on mortality.	➢ Lack of high level evidence (RCTs) regarding effectiveness of MRI screening for breast cancer detection. ➢ Based on observational studies, MRI screening has higher sensitivity but lower specificity than FM, resulting in lower false negatives and higher false positives for MRI. ➢ MRI detected more breast cancers in high risk women than FM, that would have otherwise been missed if MRI was not used. ➢ High risk women seem to benefit most from the addition of MRI to FM as a screening modality.

RCTs: randomized clinical trials.

This HTA included 10 observational studies on the effectiveness of MRI screening in women at high risk. As no RCTs were found in the literature, the extent of the evidence is based on these observational studies in which women serve as their own controls. The main focus of this HTA was to compare the accuracy of MRI to FM: MRI sensitivity was higher than that of FM with the number of cancers detected by MRI alone also being higher, although some cancer were also missed by MRI that were detected by FM. The issue of the combined effectiveness of these two modalities was assessed in relation to the American Cancer Society guidelines which recommend screening with both MRI and FM. Based on low quality evidence, including expert opinion, the authors conclude that 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 FM.

New Zealand Health Technology Assessment (NZHTA), 2007

NZHTA published the following report in 2007 (22):

Surveillance of Women at High Risk of Breast Cancer

Objectives: To evaluate the international evidence for surveillance of women at high risk for breast cancer.

Search period: 1996 to June 2006.

Studies Included	Comments	Conclusions*
Two systematic reviews and 10 observations studies for MRI plus FM in the screening of women at high risk.	➢ Evidence on survival outcomes not available. ➢ Hence, sensitivity and specificity are limited outcome measures.	➢ Results for combined modality based on two studies: there may be an increase in sensitivity but little difference in specificity. ➢ Not clear whether combined modality offers any additional benefit compared with MRI alone.

* BRCA1/2 indicates the presence of either a BRCA1 and/or BRCA2 gene mutation.

Based on 10 observational studies of the effectiveness of MRI, this review supports this screening modality for women at high risk. However, in determining the effectiveness of the combined screening of MRI plus FM, only two studies were included, Kuhl et al. (19) and Leach et al. (20). From these two studies, Kuhl et al. showed little change in sensitivity although Leach et al. report a significant improvement with the combined modality of MRI plus FM compared to MRI alone; specificity was unchanged in either study. Based on these two studies, authors conclude that it is not clear whether MRI plus FM offers any additional benefit over MRI alone in the screening of women at high risk.

Summary of Medical Advisory Secretariat Review

Table 7 outlines the quality of the evidence, as defined by the Medical Advisory Secretariat, for screening with MRI plus FM compared with FM and MRI alone.

Table 7: Quality of Evidence for Screening with Magnetic Resonance Imaging and Film Mammography *

Study Design	Level of Evidence	Number of Eligible Studies
Systematic reviews of RCT	1a	0
Large RCT	1b	0
Large RCT unpublished but reported to an international scientific meeting	1(g)	0
Small RCT	2	0
Small RCT unpublished but reported to an international scientific meeting	2(g)	0
Non-RCT with contemporaneous controls	3a	11
Non-RCT with historical controls	3b	0
Non-RCT presented at international conference	3(g)	0
Surveillance (database or register)	4a	0
Case series (multisite)	4b	0
Case series (single site)	4c	0
Retrospective review, modeling	4d	0
Case series presented at international conference	4(g)	0

*RCT refers to randomized controlled trial; g, grey literature.

Non-Randomized Clinical Trials

No RCTs assessing the effectiveness of MRI plus FM for breast cancer screening were found. However, a systematic review by Warner et al. published in 2008 (23) included 11 prospective studies published within the search period of 1996 to September 2007. Study results as presented in the systematic review are listed in Table 8.

This MAS review uses the Warner et al. 2008 systematic review as a basis for its analysis, from which estimates of sensitivity and specificity for the combined modality of MRI plus FM were obtained. An attempt by MAS to update this systematic review did not give rise to any additional studies for inclusion in this EBA.

Of the 11 studies outlined in Table 8, five studies (14;16;24-26) did not provide sufficient information on the accuracy of the combination of MRI plus FM, and were therefore excluded from further review in this EBA. .

Results in Tables 8 – 10 are presented stratified by the American College of Radiology Breast Imaging Reporting and Data System (or BIRADS) classification system. The BIRADS score is a radiologic measure of the presence or absence of a suspicious breast lesion with scores defined as follows: 0=indeterminate; 1=negative; 2=benign finding; 3=short follow-up interval required; 4=suspicious abnormality, biopsy should be considered; and 5=highly suspicious for malignancy. Biopsies are generally performed on suspicious lesions, for example, those classified as a BIRADS 4 or 5 lesion, and possibly BIRADS 3 lesions.

Of the 11 studies in Table 8, the six with sufficient data on which to base a decision for the combination screening modality of MRI plus mammography compared to FM or MRI alone are as follows: Warner et al. (15), Kuhl et al.(19), Leach et al.(20), Lehman et al. (27), and Lehman et al. (28).

In the 2004 surveillance study by Warner et al (15), 236 Canadian women aged 25 to 64 years of age underwent 1 to 3 annual screening examinations with MRI, ultrasound (US), FM and clinical breast exam (CBE). All women were BRCA1 or BRCA2 carriers with either no personal history or with a past history of unilateral breast cancer. For a BIRADS score of 4 or 5, the sensitivity was 36%, 77%, and 86% and the specificity was 100%, 95% and 95% for FM alone, MRI alone and for MRI plus FM, respectively. The differences were more clear for women classified as either a BIRADS 0, 3, 4 or 5, with sensitivity being 36%, 82%, and 90% and the specificity was 99%, 81% and 80% for FM alone, MRI alone and for MRI plus FM, respectively.

Similar improvements in sensitivity were observed by Kuhl et al. (19)in a German surveillance cohort of 529 asymptomatic women at high risk for breast cancer followed for an average of 5.3 years. Women ages ranged from 25 to 59 years and were defined as high risk if they had a lifetime risk for breast cancer of at least 20%. Surveillance included FM, US, and MRI. Results for all women revealed a sensitivity of 33% for FM, 91% for MRI and 93% for both MRI and FM. Specificity was similar across the three modalities at approximately 97%. When stratified by risk categories, the sensitivity for FM alone decreased to 25% and that for MRI alone and for MRI plus FM increased to 100% for women with a 21% to 40% lifetime risk and/or mutation carriers. Specificity remained at approximately 97%.

Two prospective multicenter studies conducted in the US and Canada (Toronto) by the International Breast MRI Consortium Working Group were published in 2005 (27) and 2007 (28). The study by Lehman et al. (27) included 367 asymptomatic women ≥25 years of age with at least a 25% lifetime risk of breast cancer based on family history or genetic test confirmation. All exams (MRI, US, and CBE) were performed within 90 days of each other. Based on women classified as BIRADS 4 or 5, the sensitivity was 25% for FM and 100% for MRI alone or MRI plus FM. The specificity decreased from

98% to 93% and 91% for FM and MRI alone, followed by MRI plus FM. Similar results were observed for their 2007 publication (28) in which 171 high risk women (defined as BRCA1/2 carriers or with at least a 20% probability of carrying such a mutation) aged 25 to 72 years were screened with MRI, FM and US. For BIRADS scores of 3, 4 or 5, the sensitivity was 33%, 100% and 100% for FM alone, MRI alone and MRI plus FM; the specificity was 91%, 79% and 73%, respectively.

The publication by Trecate et al. (29) was of an Italian multicenter study of 116 women aged 23 to 81 years who were either BRCA1 or BRCA2 carriers or had a strong family history of breast cancer and who underwent annual exams by FM, MRI, US and CBE. Similar to the Lehman et al. publications above, their sensitivity results (BIRADS scores of 4 or 5) were 33%, 100% and 100% for FM alone, MRI alone and MRI plus FM; the specificity, however was 100% for FM alone and 97% for both MRI alone and for MRI plus FM.

The MARIBS study published by Leach et al. (20) is the only one of the six studies that screened women with MRI and FM (without US and/or CBE). In this prospective cohort study of 649 women aged 35 to 49 years of age with a high probability of a BRCA1, BRCA2, or TP53 mutation, or a strong family history of breast cancer, the sensitivity for FM alone was 40%, for MRI alone it was 77% and for both modalities together, it was 94%. Specificity decreased from 93% to 81% to 77% for FM, MRI and MRI plus FM, respectively.

Table 8: Summary of Findings for Studies Reported in Systematic Review by Warner et al. 2008 (23)

Author, year	BIRADS score	Measure	FM	MRI	MRI plus FM
Warner et al., 2001	4 or 5	Sensitivity	43.0%	86.0%	100.0%
		Specificity	99.0%	91.0%	NR
Warner et al., 2004	0, 3-5	Sensitivity	36.0%	82.0%	90%
		Specificity	99.0%	81.0%	80%
	4 or 5	Sensitivity	36.0%	77.0%	86.0%
		Specificity	100.0%	95.0%	95.0%
Kriege et al, 2004	0, 3-5	Sensitivity	40.0%	71.0%	89.0%
		Specificity	95.0%	90.0%	NR
	4 or 5	Sensitivity	33.0%	64.0%	NR
		Specificity	99.0%	96.0%	NR
Hartman et al, 2004	4 or 5	Sensitivity	0.0%	100.0%	100.0%
		Specificity	NR	75.0%	NR
Leach et al., 2005	0, 3-5	Sensitivity	40.0%	77.0%	94%
		Specificity	93.0%	81.0%	77%
	4 or 5	Sensitivity	14.0%	51.0%	60.0%
		Specificity	98.0%	96.0%	95.0%
Kuhl et al., 2005	4 or 5	Sensitivity	32.0%	91.0%	93%
		Specificity	97.0%	97.0%	96%
Trecate et al., 2006	4 or 5	Sensitivity	33.3%	100.0%	100.0%
		Specificity	100.0%	97.0%	97.0%
Lehman et al., 2005	4 or 5	Sensitivity	25.0%	100.0%	100.0%
		Specificity	98.0%	93.0%	91.0%
Lehman et al., 2007	3, 4, 5	Sensitivity	33.0%	100.0%	100.0%
		Specificity	91.0%	79.0%	73.0%
Sardenelli et al., 2007	4 or 5	Sensitivity	59.0%	94.0%	100.0%
		Specificity	99.0%	98.0%	NR
Hagen et al., 2007	3, 4, 5	Sensitivity	32.0%	68.0%	80.0
		Specificity	NR	NR	NR

NR not reported; MRI magnetic resonance imaging; FM film mammography.

Source*: Warner E, Messersmith H, Causer P, Eisen A, Shumak R, Plewes D. 2008. Systematic review: using magnetic resonance imaging to screen women at high risk for breast cancer. Annals of Internal Medicine, vol. 148. Used with permission from The American College of Physicians.*

A meta-analysis utilizing all available data from the 11 studies in Table 8 was also reported by Warner et al. (23) Results of this meta-analysis (Table 9), stratified by BIRADS scores of 3 or more and 4 or more, reveal an improvement in sensitivity for the combination modality of MRI plus FM compared to MRI and FM alone, more so for the BIRADS 3 or more group of studies than the 4 or more, whereas the specificity was either unchanged (for BIRADS 4 or more) or decreased (for BIRADS 3 or more studies).

For our purposes, these findings were considered indirect comparisons of the accuracy of the screening modalities as different subgroups of the studies (or patients) were compared. To determine if these estimates of accuracy were affected by study or patient characteristics across the studies, MAS conducted an additional meta-analysis based on the six studies with complete data for all 3 screening modalities (FM alone, MRI alone, MRI plus FM). Considering a direct comparison across screening modalities, results of the meta-analysis conducted by MAS (Table 10) show similar findings to that of the Warner et al. 2008 report.

Table 9: Meta-Analysis of 11 Studies in Warner et al. (23)

Screening Modality by BIRADS Cut-off	No. studies/ screens/ tumors	Sensitivity (95%CI)	Specificity (95%CI)
FM			
≥3	4 / 6678/ 108	39.0 (37.0-41.0)	94.7 (93.0-96.5) *
≥4	7 / 8818/ 178	32.0 (23.0-41.0) *	98.5 (97.8-99.2) *
MRI			
≥3	5 / 6719/ 109	77.0 (70.0-84.0)	86.3 (80.9-91.7) *
≥4	8 / 8857/ 178	75.0 (62.0-88.0) *	96.1 (94.8-97.4) *
MRI plus FM			
≥3	3 / 2509/ 63	94.0 (90.0-97.0)	77.2 (74.7-79.7) *
≥4	5 / 4272/ 115	84.0 (70.0-97.0)*	95.2 (93.7-96.6) *

* Significant statistical heterogeneity (chi-square p <0.10); MRI magnetic resonance imaging; FM film mammography.

Source: *Warner E, Messersmith H, Causer P, Eisen A, Shumak R, Plewes D. 2008. Systematic review: using magnetic resonance imaging to screen women at high risk for breast cancer. Annals of Internal Medicine, vol. 148. Used with permission from The American College of Physicians.*

Table 10: Medical Advisory Secretariat Meta-Analysis of 6 Studies with Complete Data

Screening Modality by BIRADS Cut-off	No. studies/ screens/ tumors	Sensitivity (95%CI)	Specificity (95%CI)
FM			
≥3	3 / 2509/ 63	38.0 (26.0-51.0)	94.4 (93.4-95.2) *
≥4	5 / 4272 / 115	28.0 (20.0-37.0)	98.0 (97.5-98.4) *
MRI			
≥3	3 / 2509/ 63	81.0 (69.0-90.0)	81.1 (79.5-82.6)
≥4	5 / 4272/ 115	77.0 (68.0-84.0) *	95.9 (95.3-96.5) *
MRI plus FM			
≥3	3 / 2509/ 63	94.0 (85.0-98.0)	77.2 (75.5-78.8) *
≥4	5 / 4272/ 115	84.0 (75.0-90.0)*	95.2 (94.5-95.8) *

* Significant statistical heterogeneity (chi-square p <0.10); MRI magnetic resonance imaging; FM film mammography.

Summary of Findings of Literature Review for MRI Plus Mammography

Moderate GRADE Level Evidence that the sensitivity of MRI plus mammography is significantly higher than that of MRI or FM alone, although the specificity remains either unchanged or decreases in the screening of women at high risk for breast cancer based on genetic/familial factors, regardless of age.

These studies include women at high risk defined as BRCA1/2 or TP53 carriers, first degree relatives of carriers, women with varying degrees of high risk family histories, and/or >20% lifetime risk based on existing risk models. This definition of high risk accounts for approximately 2% of the female adult population in Ontario.

Quality of Evidence

The quality of the body of evidence was assessed as high, moderate, low, or very low according to the GRADE Working Group criteria (30) as presented below.

- Quality refers to the criteria such as the adequacy of allocation concealment, blinding and follow-up.
- Consistency refers to the similarity of estimates of effect across studies. If there are important and unexplained inconsistencies in the results, our confidence in the estimate of effect for that outcome decreases. Differences in the direction of effect, the magnitude of the difference in effect, and the significance of the differences guide the decision about whether important inconsistency exists.
- Directness refers to the extent to which the interventions and outcome measures are similar to those of interest.

As stated by the GRADE Working Group, the following definitions of quality were used in grading the quality of the evidence:

High Further research is very unlikely to change confidence in the estimate of effect.

Moderate Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.

Low Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.

Very Low Any estimate of effect is very uncertain

Table 11: GRADE Quality of Evidence for the Accuracy of Magnetic Resonance Imaging Plus Mammography in the Screening of Women at High Risk for Breast Cancer

Outcome	Explanation	GRADE
Design	11 non-randomize clinical trials (observational studies)	High
Quality	All subjects exposed to both MRI and FMand CA; heterogeneity in both summary estimates of sensitivity and specificity	High → Moderate
Consistency	Consistent for sensitivity and specificity	Unchanged
Directness	Direct comparisons of MRI plus FM to either MRI or FM alone.	Unchanged
Quality of evidence		**Moderate**

Table 12: Factors Affecting GRADE Quality of Evidence

Factor	Explanation	Effect on GRADE
Risk of Bias		
Study design	▪ 11 non-randomized clinical trials (observational studies)	High
Limitations	▪ Same woman exposed to both MRI and FM, therefore, estimates of accuracy for one test not necessarily independent of the other test.	Unchanged
Indirectness		
Outcomes	▪ Estimates of accuracy are considered as proxy measures for the more important outcome of mortality. No evidence exists in the literature for effects on mortality based on screening of women at high risk with MRI (or MRI plus FM).	High → Moderate
Patient populations, diagnostic test, comparison test, and indirect comparisons	▪ Direct comparisons of MRI plus FM to either MRI or FM alone.	Unchanged
Important inconsistency in study results	▪ No inconsistency	Unchanged
Imprecise evidence	▪ Confidence intervals for sensitivity, specificity were sufficiently precise.	Unchanged
Publication bias	▪ No obvious publication bias.	Unchanged
Quality of evidence		**Moderate**

Economic Analysis

DISCLAIMER: The Medical Advisory Secretariat uses a standardized costing method for its economic analyses of interventions. The main cost categories and the associated methods from the province's perspective are as follows:

Hospital: Ontario Case Costing Initiative cost data are used for in-hospital stay, emergency visit and day procedure costs for the designated International Classification of Diseases (ICD) diagnosis codes and Canadian Classification of Health Interventions procedure codes. Adjustments may be required to reflect accuracy in estimated costs of the diagnoses and procedures under consideration. Due to the difficulties of estimating indirect costs in hospitals associated with a particular diagnosis or procedure, the secretariat normally defaults to considering direct treatment costs only.

Nonhospital: These include physician services costs obtained from the Ontario Schedule of Benefits, laboratory fees from the Ontario Schedule of Laboratory Fees, drug costs from the Ontario Drug Benefit Formulary, and device costs from the perspective of local health care institutions whenever possible or its manufacturer.

Discounting: For cost-effectiveness analyses, a discount rate of 5% is applied as recommended by economic guidelines.

Downstream costs: All numbers reported are based on assumptions on population trends (i.e. incidence, prevalence and mortality rates), time horizon, resource utilization, patient compliance, healthcare patterns, market trends (i.e. rates of intervention uptake or trends in current programs in place in the Province), and estimates on funding and prices. These may or may not be realized by the system or individual institutions and are often based on evidence from the medical literature, standard listing references and educated hypotheses from expert panels. In cases where a deviation from this standard is used, an explanation is offered as to the reasons, the assumptions, and the revised approach. The economic analysis represents ***an estimate only***, based on the assumptions and costing methods that have been explicitly stated above. These estimates will change if different assumptions and costing methods are applied to the analysis.

Study Question

The objective of this economic analysis was to report costs associated with annual screening of high risk women between the ages of 35 and 70 with breast MRI and annual screening of high risk women between the ages of 35 and 49 with mammography.

Economic Analysis Method

An Excel spreadsheet was built to simulate a screening program whereby high risk women would be screened once a year with breast MRI or mammography. The women drop out of the model due to all-cause mortality as they age as they are being screened over time. Currently the province does not pay for MRIs to screen women between the ages of 35 and 70 or mammography to screen women between the ages of 35 and 49 at high risk for breast cancer. Ontario pays for screening of women at high risk for breast cancer between the ages of 50 and 70 with mammography. Since this cost is already being absorbed by the provincial system, it was not included in this analysis and only an incremental cost to the current Ontario system is being reported.

A cost impact analysis for the MRI screening of a cohort of asymptomatic women at high risk for breast cancer between the ages of 35 and 70 until age 70 and for the mammography screening of the same cohort of asymptomatic women at high risk for breast cancer between the ages of 35 and 49 until age 49 was conducted in the province of Ontario.

Age-specific population (31) and mortality (32) data were obtained from Statistics Canada and estimates associated with women at high risk for breast cancer were obtained from clinical expert opinion (personal communication, clinical expert opinion, September 2009). Additionally, it was assumed that the eligible population (of 35-70 year old women at high risk for breast cancer) was screened with breast MRI or mammography annually until the age of 70 and 49 respectively, irrespective of whether the women had been previously diagnosed with breast cancer.

Economic Literature Review

A literature search was performed on January 15th, 2010 using OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, Wiley Cochrane, Centre for Reviews and Dissemination/International Agency for Health Technology Assessment, and EconLit for studies published from 1950 (MEDLINE) to week 01, 2010 (EMBASE, MEDLINE). Included studies were those with full economic evaluations describing both costs and consequences of performing breast magnetic resonance imaging (MRI), with or without film (x-ray) mammography, in women at high-risk of developing breast cancer.

The primary outcome of interest for the present review was the incremental cost-effectiveness ratio (ICER) using quality-adjusted life years (QALYs). A secondary outcome was the cost per additional cancer detected. Study data extracted for purposes of comparison included: first author, year of publication, comparator strategy, "usual care" or base strategy, type of economic analysis, reported costs and outcomes, ICERs, currency, and patient characteristics.

Search Strategy Results

There were 5 studies identified that compared annual screening in high-risk women using breast MRI with either film mammography alone, or in combination with breast MRI.(33-37) The results of the literature search are summarized in Table 13. Of the 5 studies, 3 were done in the USA and 2 were done in the UK. As a result, the currencies reported in Table 13 are United States dollars (USD) and Great Britain pounds (GBP). All studies discounted both costs and benefits in the cost-effectiveness analysis (CEA) by the same amount, which ranged from 3% to 5% annually; 1 study did not apply discounting (36).

Most of the 5 studies identified high-risk women as carriers of the BRCA1 or BRCA2 gene mutation, or those with a strong family history of breast or ovarian cancer. One study measured "high risk" as a cumulative lifetime risk of breast cancer of greater-than-or-equal to 15% based on Claus tables.(34) Another study also included women with the gene mutation TP53.(36) The base case or population used in the CEAs varied: women aged 40 years with no previously detected breast cancer or previous bilateral mastectomy (33); women aged 35-49 years (36), 30-39 or 40-49 years (35), all with high genetic risk of breast cancer; women aged 25 years or older with BRCA1 or BRCA2 (37). The length of screening using either breast MRI or film mammography alone, or in combination, also varied by study: a 1-time screening for women aged 40 years with a lifetime follow up (33), annual screening over 10 or 25 years (34;35), annual screening between 2-7 years (36), and annual screening for women aged 25-69 years with an additional annual breast MRI for women in specific age groups (37).

Several types of economic models were used in the CEAs reviewed. Markov models were used in 2 studies (34;35), a decision analytic model was used in 1 study (33), a net benefit analysis with Bayesian Monte Carlo methods was used in 1 study (36), and a continuous-time Monte Carlo simulation model was used in the remaining study (37). The analytic perspectives of the CEAs followed the jurisdiction of evaluation: a payer perspective was taken for 2 US studies (33;34), a health system perspective was taken for the 2 UK studies (35;36); 1 US study used a societal perspective for the economic analysis (37).

In terms of sensitivity analyses, all studies reported changes in the ICERs based on different scenarios and parameter ranges. Three studies performed probabilistic sensitivity analyses and reported the likelihood of breast MRI, film mammography, or a combination of the two being cost-effective.(34-36) In general, the cost-effectiveness of strategies was sensitive to the following factors: rate of breast cancer (e.g. developing breast cancer by the age of 70), cost of MRI tests, rate of true negatives (test specificity), prevalence of undiagnosed breast cancer, and discounting of costs and benefits.

Conclusion of Literature Review

Cancer screening using breast MRI (with or without contrast enhancement) was cost-effective for women at high risk of developing breast cancer. MRI was generally more cost-effective for women with the BRCA1 gene mutation when compared to women with the BRCA2 gene mutation. However, when only breast MRI or film mammography was compared to screening using both MRI and film mammography together, the combination strategy was frequently found to be the cost-effective option. One study did not find the combination of MRI and film mammography to be cost effective when compared against the other two performed separately, but only in the case of women aged 35-49 years with the BRCA1 gene mutation; the cost-effective strategy here was breast MRI alone. Note that a strategy was considered cost-effective in the current context if the willingness-to-pay was reported as $50,000 USD or £20,000 GBP; some authors used a willingness-to-pay of £30,000 GBP.

Table 13: Summary of ICERs and selected characteristics of studies evaluating breast MRI and film mammography

Comparator strategy	Base strategy	Study	Population for annual screening	ICER (discounted)
Film mammography	No screening	Norman et al. 2007 (35)	Women aged between 30 and 39 years (BRCA1 gene mutation)	£5,240
			Women aged between 40 and 49 years (BRCA1 gene mutation)	£2,913
MRI	Film mammography	Norman et al. 2007 (35)	Women aged between 30 and 39 years (BRCA1 gene mutation)	***£13,080***
			Women aged between 40 and 49 years (BRCA1 gene mutation)	***£8,175***
		Moore et al. 2009 (34)	Young women with ≥ 15% cumulative lifetime risk of breast cancer (Claus tables)	***$179,599***
MRI + Film mammography	Film mammography	Norman et al. 2007 (35)	Women aged between 30 and 39 years (BRCA1 gene mutation)	£13,449
			Women aged between 40 and 49 years (BRCA1 gene mutation)	£7,785
Contrast enhanced MRI	Film mammography	Taneja et al. 2009 (33)	Women aged 40 years (BRCA1 or BRCA2 gene mutations)	$25,340
			Other high-risk characteristics- 3.0% undiagnosed breast cancer prevalence	$46,686
		Griebsch et al. 2006 (36)	Women aged 35–49 years, screening for 7 years (high genetic risk)	***£35,255***
			Women aged 35–49 years, screening for 7 years (only BRCA1 gene mutation)	£11,735
			Women aged 35–49 years, screening for 7 years (only BRCA2 gene mutation)	***£63,854***
Contrast enhanced MRI + Film mammography	Film mammography	Taneja et al. 2009 (33)	Women aged 40 years with BRCA1 or BRCA2 gene mutations	$25,277
			Other high-risk characteristics- 3.0% undiagnosed breast cancer prevalence	$45,566
		Griebsch et al. 2006 (36)	Women aged 35–49 years, screening for 7 years (high genetic risk)	£28,288
			Women aged 35–49 years, screening for 7 years (only BRCA1 gene mutation)	***£13,340***
			Women aged 35–49 years, screening for 7 years (only BRCA2 gene mutation)	£15,305
		Plevritis et al. 2006 (37)	Women aged 35–54 years (BRCA1 gene mutation)	$55,420
			Women aged 25–69 years (BRCA1 gene mutation)	***$88,651***
			Women aged 25–69 years, MRI screening only for ages 40–49 (BRCA1)	$43,484
			Women aged 25–69 years, MRI screening only for ages 35–49 years (BRCA1)	***$71,401***
			Women aged 35–54 years (BRCA2 gene mutation)	***$130,695***
			Women aged 25–69 years (BRCA2 gene mutation)	***$188,034***
			Women aged 25–69 years, MRI screening only for ages 40–49 years (BRCA2)	***$111,600***
			Women aged 25–69 years, MRI screening only for ages 40–54 years (BRCA2)	***$154,876***

Note: Griebsch 2006 used cost per additional cancer detected and did not discount costs and benefits; all other studies used cost per QALY; Bold-italicized figures were not reported as cost-effective by the authors.

Target Population

The target population of this cost impact analysis was asymptomatic women at high risk for breast cancer entering a screening program to be screened annually with MRI if between the ages of 35 and 70 and to be screened annually with mammography between the ages of 35 and 49 in Ontario.

Perspective

The primary analytic perspective was that of the Ministry of Health and Long-Term Care (MOHLTC).

Resource Use and Costs

The physician fee to perform a multi-slice sequence bilateral MRI of the breast was obtained from the Ontario Schedule of Benefits (OSB) (38) and is valued at $75.55. The average hospital outpatient cost of MRI is $377.00 ($118.00-$664.00) and was obtained from the Ontario Case Costing Initiative (OCCI) database (39). The professional fee and technical fee to perform mammography is $25.25 and $38.10 respectively, obtained from OSB (38).

The proportion of women considered at high risk for breast cancer based on genetic and/or familial factors is 2% (personal communication, clinical expert opinion, September 2009).

Table 14: Resources and costs associated with screening high risk women for breast cancer.

Parameter	Value	Assumptions	Reference
Proportion of women eligible for breast screening because they are considered high risk	2%	Assumed high-risk for breast cancer. There are currently approximately 1500 women with a BRCA1 or BRCA2 mutation in Ontario that know their mutation status; there may be 500 first degree relatives that are untested. It is reasonable to require that they be tested/screened; approximately 1% of women have a family history that puts them at 25% lifetime risk of cancer. Depending on the model used and how strongly you stick to the model estimate to determine eligibility; In summary, at most 2% of women should be considered at high risk, but fewer than this will be identified as such.	Based on clinical expert opinion
Cost of physician fee to perform bilateral MRI	$75.55		X446 – multi-slice sequence (38)
Cost of physician fee to perform bilateral Mam	$25.25		X185 – bilateral mammogram (P) (38)
Cost of technician fee to perform bilateral Mam	$38.10		X185 – bilateral mammogram (H) (38)
Average cost of outpatient MRI	$377.00	assumed direct cost only	UHN case costing - accessed January 2010 (39)
Minimum cost of outpatient MRI	$118.00	assumed direct cost only	UHN case costing - accessed January 2010 (39)
Maximum cost of outpatient MRI	$664.00	assumed direct cost only	UHN case costing - accessed January 2010 (39)

Ontario-Based Cost Impact Analysis

Table 15 reports costs (in millions of Canadian dollars, or M) associated with breast screening of women between the ages of 35 and 70, depending on the technology, at high risk based on genetic and/or familial factors, with differences in costs reflected in the varying rates of screening uptake.

Table 15. Costs associated with breast MRI in screening high risk women aged 30-70 years.

Uptake	Annual average cost of MRI alone	Range	Annual average cost of MRI + FM	Range
100%	25.2M	11-41M	26.9M	13-43M
75%	18.9M	8-31M	20.2M	9-32M
50%	**12.6M**	**5-21M**	**13.5M**	**6-21M**
25%	6.3M	3-10M	6.7M	3-11M

FM = film mammography

*Assumed 30% of high risk women are already being screened with mammography and the cost is already being absorbed by the current provincial system.

Assuming that a 50% uptake rate is a reasonable rate for the introduction in the province of a screening program for women at high risk for breast cancer, the annual average expenditure can be estimated at $13.5M with a range of $6 - $21M, if women are screened with both MRI and mammography. These women may already be screened in the province with mammography, therefore cost will be lower.

There were several limitations to this analysis. This analysis only included direct costs to the MOHLTC that were incurred by screening women annually. These costs were physician fees and hospital procedural costs on an outpatient basis. Capital costs of screening machines were not factored into the analysis. Furthermore this analysis did not include downstream costs such as those associated with surgery or cancer treatment that can be a great burden to the province. Further analyses are required to estimate these costs and project more accurate outcomes over time.

Conclusion

Breast MRI plus mammography is a cost-effective strategy for high risk women and the budget impact is estimated at $7- $27M annually, predicated by the uptake rate.

Appendices

Appendix 1: Literature Search Strategies

Search Strategy – Digital Mammography 2006

Search date: May 8, 2006
Databases searched: OVID Medline, Medline In-Process and Other Non-Indexed Citations, Embase, Cochrane Library, and INAHTA

Database: Ovid MEDLINE(R) <1966 to April Week 4 2006>
Search Strategy

1 *breast neoplasms/ (103597)
2 exp mass screening/ (74813)
3 screen$.au,fa,ti. (61620)
4 2 or 3 (105228)
5 digital mammography.mp. (378)
6 exp Radiographic Image Enhancement/ or exp Image Processing, Computer-Assisted/ or exp Radiographic Image Interpretation, Computer-Assisted/ (235102)
7 exp Mammography/ (16275)
8 5 or (6 and 7) (1677)
9 1 and 4 and 8 (139)
10 limit 9 to (humans and english language and yr="1995 - 2006") (90)
11 (systematic$ review$ or meta-analysis or metaanalysis).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (28362)
12 10 and 11 (3)
13 10 (90)
14 limit 13 to (case reports or comment or editorial or letter or news or newspaper article or "review") (23)
15 13 not 14 (67)
16 12 or 15 (70)

Database: EMBASE <1980 to 2006 Week 18>
Search Strategy

1 exp Breast Tumor/ (122698)
2 exp MASS SCREENING/ or exp CANCER SCREENING/ (47003)
3 screen$.au,ti. (47594)
4 2 or 3 (77544)
5 digital mammography.mp. (388)
6 exp Computer Assisted Diagnosis/ (224705)
7 exp MAMMOGRAPHY/ (15924)
8 6 and 7 (1107)
9 5 or 8 (1406)
10 1 and 4 and 9 (241)
11 limit 10 to (human and english language and yr="1995 - 2006") (177)
12 (systematic$ review$ or meta-analysis or metaanalysis).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (38680)
13 11 and 12 (8)
14 11 (177)
15 limit 14 to (editorial or letter or note or "review") (66)
16 Case Report/ (884233)
17 14 not (15 or 16) (109)
18 13 or 17 (114)

Search Strategy – Magnetic Resonance Imaging 2006

Search date: May 9, 2006
Databases searched: OVID Medline, Medline In-Process and Other Non-Indexed Citations, Embase, Cochrane Library

Database: Ovid MEDLINE(R) <1966 to April Week 4 2006>
Search Strategy
1 *Breast Neoplasms/ (103597)
2 exp Magnetic Resonance Imaging/ (149103)
3 (magnetic resonance imaging or mri).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (166349)
4 1 and (2 or 3) (1788)
5 exp Mass Screening/ (74813)
6 screen$.au,fa,ti. (61620)
7 4 and (5 or 6) (128)
8 limit 7 to (humans and english language and yr="1995-2006") (102)
9 (systematic$ review$ or meta-analysis or metaanalysis).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (28362)
10 8 and 9 (3)
11 8 (102)
12 limit 11 to (case reports or comment or editorial or letter or "review") (45)
13 11 not 12 (57)
14 10 or 13 (60)

Database: EMBASE <1980 to 2006 Week 18>
Search Strategy
1 exp Breast Tumor/ (122698)
2 exp Nuclear Magnetic Resonance Imaging/ (162897)
3 (mri or magnetic resonance imaging).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (171377)
4 1 and (2 or 3) (2718)
5 exp Mass Screening/ or exp Cancer Screening/ (47003)
6 screen$.au,ti. (47594)
7 4 and (5 or 6) (329)
8 limit 7 to (human and english language and yr="1995 - 2006") (262)
9 (systematic$ review$ or meta-analysis or metaanalysis).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (38680)
10 8 and 9 (10)
11 8 (262)
12 limit 11 to (editorial or letter or note or "review") (152)
13 Case Report/ (884233)
14 11 not (12 or 13) (105)
15 10 or 14 (114)

Final Search Strategy – MRI Plus Mammography

Search date: January 15, 2010
Databases searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, Wiley Cochrane, Centre for Reviews and Dissemination/International Agency for Health Technology Assessment

Database: Ovid MEDLINE(R) <1950 to January Week 1 2010>
Search Strategy
1 exp Breast Neoplasms/ (167374)
2 exp Carcinoma, Ductal, Breast/ (8135)
3 ((breast* or mammar*) adj2 (cancer* or neoplas* or tumo?r* or carcinoma*)).ti,ab. (150193)
4 (ductal carcinoma* or DCIS).ti,ab. (6857)
5 or/1-4 (202585)
6 exp Magnetic Resonance Imaging/ (215971)
7 (magnetic resonance or mr or mri).ti,ab. (240299)
8 6 or 7 (315047)
9 exp Genetic Predisposition to Disease/ (53061)
10 (high risk or increase* risk or bcra* or hereditary or (genetic* adj2 predispos*) or family history).ti,ab. (258833)
11 exp Radiation Injuries/ (48664)
12 "Genes, BRCA1"/ (3452)
13 exp BRCA2 Protein/ or exp Genes, BRCA2/ (3355)
14 exp Genes, BRCA1/ (3452)
15 exp BRCA1 Protein/ (2197)
16 or/9-15 (350746)
17 exp Mass Screening/ (78822)
18 screen*.mp. (341764)
19 17 or 18 (347121)
20 5 and 8 and 16 and 19 (226)
21 limit 20 to (english language and humans and yr="2008 -Current") (62)
22 ("200709*" or "200710*" or "200711*" or "200712*").ed. (247743)
23 20 and (21 or 22) (70)

Database: EMBASE <1980 to 2010 Week 01>
Search Strategy
1 exp breast cancer/ (161836)
2 exp intraductal carcinoma/ (2597)
3 ((breast* or mammar*) adj2 (cancer* or neoplas* or tumo?r* or carcinoma*)).ti,ab. (130818)
4 (ductal carcinoma* or DCIS).ti,ab. (6519)
5 or/1-4 (182463)
6 exp nuclear magnetic resonance imaging/ (257781)
7 (magnetic resonance or mr or mri).ti,ab. (209194)
8 6 or 7 (311957)
9 exp genetic predisposition/ (43619)
10 exp family history/ (29528)
11 exp radiation injury/ (21105)
12 exp BRCA2 protein/ or exp BRCA1 protein/ (5960)
13 (high risk or increase* risk or bcra* or hereditary or (genetic* adj2 predispos*) or family history).ti,ab. (233435)
14 exp familial cancer/ (6878)
15 exp high risk patient/ or exp high risk population/ (87458)
16 or/9-15 (351693)
17 exp cancer screening/ (31302)
18 screen.ti,ab. (44686)
19 17 or 18 (74170)
20 5 and 8 and 16 and 19 (326)
21 limit 20 to (human and english language and yr="2007 -Current") (132)

Appendix 2: Radiation Risk Review

Cancer – A Review of Current Evidence

Prepared for the Division of Preventive Oncology, Cancer Care Ontario (February 19, 2009)

Introduction: It has been known and clearly established for many years that the benefits of mammographic screening for breast cancer greatly exceed any risks associated with the procedure itself. Even so, with the development of new technologies and procedures, one aspect of the review undertaken in assessing whether new strategies should be adopted is consideration of the risks and benefits of a new intervention. In particular, advances in cancer genetics make it possible to now identify women who carry a cancer susceptibility allele (e.g., a BRCA1 or BRCA2 mutation) such that they have an increased likelihood of developing breast cancer. In addition, advances in imaging technologies have resulted in improvements in the detection of small lesions, such as by using magnetic resonance imaging (MRI) in contrast to conventional mammography. Before a recommendation could be made to provide more intensive screening to women who are at elevated risk, it is important to ensure that the screening procedure itself would not further increase their risk.

Question to address: The establishment of a provincial program to screen high risk women for breast cancer (e.g. women positive for BRCA1/2 gene mutations) with an annual MRI scan and mammogram may increase their cumulative lifetime radiation exposure. To assess whether such a screening program is justified, a question to address is whether the risk of radiation-induced breast cancer is small compared with the benefits of breast screening.

Method: Recent scientific literature was reviewed, in order to summarize the potential risks and benefits of breast screening, based primarily on the literature that applies statistical dose-response models of the relationship between ionizing radiation exposure and breast cancer risk. Particular attention was given to the age-related patterns of exposure and outcome, since one implication of screening those who are genetically susceptible is that screening would commence at an earlier age than is standard in organized screening programs. The review and interpretation were aided by consultation with experts in radiation physics who reviewed and whose work contributed to this report, including Dr. Martin Yaffe, Physics Consultant to the Ontario Breast Screening Program, and Dr. Douglas Chambers, an expert in radiation risk assessment and a Canadian representative and advisor to the United Nations Scientific Committee on the Effects of Atomic Radiation. Initial articles for this review were identified in a letter written on this topic by Dr. Yaffe (referred to below). Using these articles and the PUBMED search engine (search terms: "radiation, breast screening, mammography, radiation risk;" http://www.ncbi.nlm.nih.gov/sites/entrez/) key articles that quantified the risk to women from repeated screening mammography were collected and reviewed, and their implications regarding the above research question were considered.

Summary of Findings: In a letter dated 17 February 2007, Dr. Yaffe commented on the risk of radiation induced breast cancer in women between age 40 and 49 years, in response to an Ontario Health Technology Assessment Committee report on breast cancer screening for women in this age group. Based on the statistical dose-response model that was derived from women exposed to ionizing radiation and that is the international standard for risk assessment,[6] Dr. Yaffe showed that the breast cancer risk posed by radiation from annual mammography in women from age 40 was "negligible compared to the benefit of reduced mortality offered by annual mammography even if that benefit of reduced mortality (of breast cancer) was as little as 10%".

In a further correspondence (November 22, 2007) that provided a more indepth analysis, Dr. Yaffe estimated statistically that while assuming a dose of 3.6 mGy per mammographic screen, six breast cancer

cases would be expected to be induced by annual screening from age 40 to 69 years in a hypothetical cohort of 10,000 women who live to age 90, and that one of these cases would be fatal. Based on estimates that in the absence of screening, 650 breast cancer cases would emerge in these 10,000 women during the 30 year period (which is conservative as compared to national data[1]), that there would be a breast cancer case fatality rate of 22%, and that screening would result in a mortality reduction of 25% (as reported in BC2), this cohort would have 36 fewer deaths (= 650x22%x25%) from breast cancer due to screening. This can be compared to the number of deaths expected among radiation-induced cases where the presence of screening still confers a mortality reduction [6 cases x 22% x (1-25%) = 0.99], resulting in a benefit:risk ratio of 36:1 (breast cancer deaths saved vs. caused) in this hypothetical cohort living until age 90.

In that correspondence, Dr. Yaffe repeated the calculation for high risk women (e.g., those with BRCA1/2 mutations), whereby the number of cancers that might be induced by radiation must be considered in the context of cancer being more common in this cohort, and of mammography being potentially more effective in a higher risk group. It was estimated that screening beginning at age 35 years would induce nine breast cancer cases (i.e., for the same number of person-years as above, but assuming a greater susceptibility). Modeling assumptions for this high risk cohort were similar to those in the previous paragraph, except that cancer risk was assumed to be 10 times higher than in the general population (e.g., the number of cancers expected in 10,000 high-risk women in the 35 year period from 35-69 in the absence of screening = 6700). Also, screening has been shown to have considerably greater sensitivity when MRI is combined with mammography (sensitivity = 94%, versus 85% for MRI alone). Direct evaluations of mortality benefits in high risk cohorts have not been reported, however there is indirect evidence that mortality benefits should be similar to those reported for older cohorts of average risk women (~25%).3 In particular, evaluations of the contribution of MRI plus mammography have reported that the majority of cancers were detected when lymph nodes were negative,[4-6] which is associated with improved survival rates. Assuming a 25% reduction in mortality due to screening, and that 10% of the sensitivity derives from mammography (vs. MRI), it can be estimated that 10% of the mortality benefit can be ascribed to mammography. As above, assuming a case fatality rate of 22% and that screening would result in a mortality reduction of 25%, the high-risk cohort would have 369 fewer deaths (= 6700x22%x25%) from breast cancer due to screening. Of this, 332 (90%) can be ascribed to MRI, and 37 (10%) to mammography. This can be compared to the number of deaths expected among radiation-induced cases where the presence of screening still confers a mortality reduction, which can be estimated to be 1-2 deaths in the 350,000 examinations of these 10,000 women over 35 years [9 cases x 22% x (1-25%) = 1.5]. This results in a benefit:risk ratio for mammography alone of 25 to one (37 breast cancer deaths saved vs. 1.5 caused), and for and mammography (when used in combination with MRI) of 221 to one (332 deaths averted vs. 1.5 caused).

In recent related scientific literature, Mattson and Rutquvist (2000)[7] similarly calculated two estimates of the increased incidence and deaths due to screening using an 18 month screening interval from 40 to 49 years followed by biannual screening from 50 to 69 years. An increase in cumulative breast cancer incidence of 0.2% to 0.9% (from a baseline of 9.29% to either 9.31% or 9.37%, respectively) was found depending on the underlying radiation dose-response model used. This translated into an estimated increase of 7 to 31 deaths compared to the 674 deaths averted (or a benefit:risk ratio of 22-96 to one) by screening a cohort of 100,000 women. This study's range of ratio estimates included the value estimated by Dr. Yaffe, but also suggested under their assumptions that the benefits may be greater than those estimated above.

Law et al. (2007)[8] used the same standard dose-response models as applied by Dr. Yaffe, and estimated the detection/induction ratios for annual screening by age for those with and without a family history of breast cancer (Table 1). Table 1 summarizes the results from these papers, showing a substantial improvement in the benefit:risk ratio by initiating screening after 35 years of age for women with a positive family history and after age 40 years for those without. The report by Law et al. is an extension

of earlier estimations published in 2001,[9] and then in 2002 the authors incorporated an adjustment factor to convert from a detection:induction ratio to a benefit:risk ratio.[10] Using a number of methods the authors calculated this conversion factor as 0.82 to 1.62, which means that the benefit:risk could be much higher or slightly lower than the detection:induction ratios in Table 1. The conversion ratio was influenced by the upper age of screening, as more benefit of screening could be expected if women who were exposed to mammography in their 50's were still actively screened into their late 60's when radiation induced cancers would most likely occur. Although there is uncertainty in the conversion factors, its impact on the interpretation of benefit:risk ratios must also be considered in the context of there also being substantial uncertainty in the estimation of the potential number of radiation-induced cancers.

Table 1: Detection/Induction Ratios for Breast Cancer Incidence by Age Group (from Law et al. 2007)

	No Family History		Positive Family History (index patient diagnosed between 30 and 39 years of age)	
Age at Exposure (years)	EAR (Preston)	NRPB-2003	EAR (Preston)	NRPB-2003
25-29			4.2	4.4
30-34	3.3	2.9	18	16
35-39	10	7.0	50	34
40-44	25	13	87	46
45-49	56	24	124	53

Assumptions: Based on 4.5 mGy mean glandular dose, two views, annual screening. Abbreviations and references: EAR – excess absolute risk model (as apposed to the ERR – excess relative risk); NRPB – National Radiation Protection Board[11]; Preston – from an international pooled analysis by Preston et al.[12]

Another British study[13] that applied risk assessment models to estimate breast cancer deaths caused by and averted by mammography came to slightly different conclusions. For women undergoing yearly screening for a decade at age 30 years or younger, it was estimated that more deaths could be caused by mammography than averted. For women age 40 to 50 years, the situation was reversed, as screening was projected to avert a modest two-times as many deaths than mammography could cause (although there was uncertainty due to the underlying assumptions).

Several recent epidemiological studies assessed whether those who are genetically susceptible to develop breast cancer, also have an increased radiation-related risk. Narod et al (2006)[14] reported on a Canadian case-control study and showed that for women carrying a BRCA1/2 mutation, mammography was not associated with increased breast cancer risk, which in this cohort had a mean initiation of screening at age 35 years. Within this cohort, women who initiated mammography screening between 31 and 40 years of age had a statistically significantly increased risk of breast cancer before age 40 years; however, it is important to note that this was due to screen detection since there was no association after breast cancers detected by mammography were removed from analysis.

In contrast, a retrospective cohort study[15] of the relationship between breast cancer incidence and chest x-ray history in BRCA1/2 carriers showed a hazard ratio of 1.5 ($p = 0.007$) for the entire cohort and 4.6 (95% CI = 2.2–10.9, $p < 0.001$) for carriers less than 20 years of age when exposed. The effect was dose-dependent and radiation from each chest x-ray, at approximately 0.5 mGy is lower than the 3.5 mGy exposure level from recent mammography technology.

The biology of the breast heavily influences the risk of radiation induced cancer. It is known that the developing breast tissue is vulnerable to the effects of radiation and that risk per unit of dose decreases substantially as a woman ages, as illustrated in Table 2 from the atomic bomb survivors study. Also, the

risk of breast cancer incidence in any year after the exposure was estimated to decline by 5% per year after the exposure so, for example, the excess relative risk of breast cancer at age 34 (exposure at age 20) is 14 (4.4 – 63.9) but declines to only 1.8 (0.1 – 6.2) by age 64.

Table 2: Variation in relative risk due to ionizing radiation (from the Atomic Bomb Survivors Study)[16]

Age At Exposure	Excess Relative Risk of Breast Cancer per Sv Exposure
< 10 Years	2.41 (1.63 – 3.44)
10 – 29 Years	1.25 (0.77 – 1.87)
30 – 50 Years	0.48 (0.002 – 1.28)

Conclusions: Even though the biological effects and the role in cancer etiology are well established for ionizing radiation, the literature makes it clear that there remains substantial uncertainty in efforts to estimate the potential frequency of radiation-induced cancers (e.g., due partly to the challenge of translating risks from knowledge about the effects of very large doses down to the much smaller exposures from mammography). Even so, for the purpose of risk assessment, well established models based on the combined results of large international studies provide a solid base on which potential impacts can be estimated. The detection:induction ratios and the benefit:risk ratios derived from the risk assessment models provide estimates, albeit with considerable uncertainty, and demonstrate that mammography has benefits after age 40 years for women without a family history, and above age 30 years, and even more so above 35 years, for "high-risk" women. The favourable benefit:risk ratio is strengthened even further if screening extends beyond age 65 for women initiating screening at age 50 years.

From this review of recent literature and risk assessment that considered the potential impact of screening mammography in cohorts of women who start screening at an earlier age or who are at increased risk of developing breast cancer due to genetic susceptibility, the following conclusions can be drawn:

- For women over 50 years of age, the benefits of mammography greatly outweigh the risk of radiation-induced breast cancer irrespective of the level of a woman's inherent breast cancer risk.
- Annual mammography for women aged 30 – 39 years who carry a breast cancer susceptibility gene or who have a strong family breast cancer history (defined as a first degree relative diagnosed in their thirties) has a favourable benefit:risk ratio. Mammography is estimated to detect 16 to 18 breast cancer cases for every one induced by radiation (Table 1). Initiation of screening at age 35 for this same group would increase the benefit:risk ratio to an even more favourable level of 34-50 cases detected for each one potentially induced.
- Mammography for women under 30 years of age has an unfavourable benefit:risk ratio due to the challenges of detecting cancer in younger breasts, the aggressiveness of cancers at this age, the potential for radiation susceptibility at younger ages and a greater cumulative radiation exposure.
- Mammography when used in combination with MRI for women who carry a strong breast cancer susceptibility (e.g., BRCA1/2 carriers), which if begun at age 35 and continued for 35 years, may confer greatly improved benefit:risk ratios which were estimated to be about 220 to one.
- While there is considerable uncertainty in the risk of radiation-induced breast cancer, the risk expressed in published studies is almost certainly conservative as the radiation dose absorbed by women receiving mammography recently has been substantially reduced by newer technology.

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