Introduction:

Individuals at high risk for developing hereditary breast cancer related to genetic mutations may benefit from various interventions such as genetic counselling, as well as preventative therapy (i.e., tamoxifen) and enhanced screening, or risk-reducing surgery (i.e., prophylactic mastectomy) (1). Enhanced breast screening for women at high risk has been previously established to include both the use of magnetic resonance imaging (MRI) and mammography. An initial thorough clinical history and family history by the healthcare provider is necessary. The addition of an on-line risk-assessment tool, such as B-RST, IBIS, and the Gail model, may be useful in guiding the healthcare provider to determine whether the individual is suitable for intervention (2-4).

The Eastern Health Breast Disease Site Group deems any individual, who has been previously assessed by a genetic counsellor as having a 20% to 25% personal lifetime risk of breast cancer (using either of the risk assessment tools as mentioned above) or meets either of the following criteria, to be “high risk” for developing hereditary breast cancer:

1. a known mutation in the breast cancer susceptibility gene 1 or 2 (i.e., known as BRCA1, BRCA2), CDH1 (Hereditary Diffuse Gastric Cancer), or other genes predisposing to a markedly elevated breast cancer risk;

2. an untested first- or second-degree relative of a carrier of such a genetic mutation;

3. a family history consistent with a hereditary breast cancer syndrome, mutation unknown. Individuals eligible for MRI in such families would be first- (mother, daughter, sister) and second-degree (grandmother, aunt, niece, or half-sister) relatives of individuals with breast and ovarian cancer, where there are:
a) Four or more relatives with breast* or ovarian** cancer at any age on the same side of the family, who are all first- or second-degree relatives of one another or in a pattern suggestive of a hereditary cancer predisposition;

b) Three first- or second-degree relatives with breast* or ovarian** cancer, on the same side of the family, with one or more of the following:
   - One person affected < 50 years of age,
   - Breast and ovarian cancer in the same individual, bilateral or multifocal breast cancer in one individual,
   - Male breast cancer.

If the healthcare provider establishes that the individual qualifies as being high risk, a referral for genetic counselling is warranted. If the individual also meets the Eastern Health Breast Disease Site Group’s “high risk” criteria, enhanced screening may be an option. This would include annual breast MRI screening, with or without mammography, dependent upon the age of the individual and at the request of the referring physician, and reported by a radiologist with specific training in breast MRI.

**Question:**
What is the recommended breast screening protocol for “high risk” patients?

**Target Population:**
These recommendations apply to all patients who are deemed to be at high risk for the development of hereditary breast cancer, as per the criteria outlined by the Eastern Health Breast Disease Site Group.

**Supporting Evidence:**
Magnetic resonance imaging (MRI) is a noninvasive imaging technique that does not involve exposure to radiation. The primary goal of providing breast MRI to high risk women is to reduce subsequent breast cancer mortality through early detection. Studies have shown breast MRI to be superior in sensitivity to mammography, and subsequently has been recommended for use in screening those individuals deemed to be at high risk of developing hereditary breast cancer (5-9). However, breast MRI has also been found to have significantly lower specificity, which carries the potential risk of false-positive and false-negative findings. False-positives result in anxiety, further testing and possible biopsy for the patient, while false-negatives will miss a true cancer at a potentially curable stage. Breast MRI should be scheduled during the second week of the menstrual cycle (days 5 to 13) in premenopausal women. Occasionally, areas of normal hormonally sensitive breast tissue may enhance intensely on MRI which may cause a false positive reading. Therefore, examination is best performed in mid-menstrual cycle (10). The interpretation of breast MRI also presents a unique challenge in pregnant and lactating women due to the related physiological changes in the breast. Furthermore, gadolinium-based contrast

* includes ductal carcinoma in-situ (DCIS), but not lobular carcinoma in-situ (LCIS).
** refers to invasive non-mucinous epithelial ovarian cancer, includes cancer of the fallopian tubes or primary peritoneal cancer; excludes borderline ovarian tumors.
agents have been classified as pregnancy category C by the U.S. Food and Drug Administration, due to animal reproduction studies which have shown adverse effects on the fetus. Although there are no reports of teratogenic effects of gadolinium-based contrast agents in humans, there have also been no prospective controlled studies evaluating its effects on human fetuses. Therefore, contrast-enhanced MRI screening of the breast is not recommended during pregnancy, and can be postponed in women, who are breastfeeding until after cessation of lactation (11).

The benefits of enhanced screening for high-risk individuals, according to a recent Dutch prospective cohort study include a higher likelihood to detect smaller breast tumors (<T2) which are more likely to be node negative, and almost three times less likely to have developed metastases compared to the control arm (12). Numerous cost analysis and cost effectiveness studies have been performed by various countries. Many, if not all, support the use of the combination of MRI and mammography for those at high risk for hereditary breast cancer.

There is no national or international standardized approach regarding the appropriate starting age for breast screening of high risk groups. Inconsistencies in sample characteristics and limitations in previous studies have often made interpretation of the results difficult. As a result, the age recommended to begin screening varies between countries and even provinces, and frequently is based on expert opinion. In the general population, exposure to ionizing radiation in children and adolescents has been an established risk factor for breast cancer for several years, with speculation that BRCA1 and BRCA2 mutation carriers would be at even greater risk. However, a recent retrospective analysis of a large European cohort study found that any exposure to diagnostic radiation, such as mammography, for BRCA1/2 mutation carriers before the age of 30 was associated with an increased risk of breast cancer [hazard ratio 1.90, 95% confidence interval (1.20 to 3.00)], in a dose-response pattern (13). A joint Dutch and U.K. study also found that age of screening onset is also determined by family history, where screening should ideally begin 5 to 10 years before the age of the youngest affected relative (14).

There is insufficient evidence to recommend at what age enhanced breast screening can safely be reduced for those deemed to be high risk. A recent international high-risk screening meta-analysis indicated that similar screening sensitivity and significantly better screening specificity exists for MRI plus mammography for those females ≥ 50 age group, compared to the < 50 age group (15); while a Dutch study found a continuing benefit for screening high-risk BRCA1/2 mutation carriers in the ≥ 60 age group (16). Cancer Care Ontario recommends that by age 70, annual mammography alone is sufficient (23). Their reasoning is that the relative risk of developing hereditary breast cancer decreases with age, and the sensitivity of mammography increases as breast density decreases with age. Few participants older than 69 years have been included in the arms of any screening study cohorts. Furthermore, there is a lack of evidence for a mortality reduction from screening women older than 70. Therefore, the Breast Disease Site Group recommends enhanced screening to continue until age 69 as long as individuals are in good health. The decision to discontinue screening due to multiple comorbidities or deteriorating health status should be at the discretion of both patient and physician.

For optimal screening of individuals at high risk for developing breast cancer, annual breast MRI and annual mammography should begin at age 30, beginning with an initial mammogram, followed by breast MRI alternately, until age 69. Mammography may be performed annually from age 70 onward as long as the individual maintains good health.
Screening by breast MRI alone is appropriate for high risk individuals from 25 to 29 years of age, when the youngest affected relative’s age at diagnosis is < 40 years. Mammography can assist in breast MRI interpretation, therefore a baseline mammogram will be performed prior to the initial breast MRI only. MRI screening alone may commence at ten years prior to age of youngest affected relative, beginning no earlier than 25 years of age.

A recent international meta-analysis concluded that the addition of mammography to breast MRI did not significantly increase screening sensitivity for all ages of BRCA1/2 mutation carriers (17). However, mammography alone detected 34.5% of breast cancers for BRCA2 mutation carriers, who were ≤ 40 years of age, but provided limited contribution in detecting breast cancers in BRCA1 mutation carriers. Though this evidence may support the use of a differential screening schedule based on BRCA status, at present the limited availability to genetic counselling services and testing would inhibit the feasibility of its initiation.

There is insufficient evidence to recommend the use of breast MRI screening for those patients who have dense breasts or pathological findings of lobular carcinoma in situ (LCIS), atypical ductal hyperplasia (ADH), or atypical lobular hyperplasia (ALH), on a previous breast biopsy, in the absence of any indication of known/unknown genetic mutation or increased familial risk (23, 25, 26). The utilization of an on-line risk-assessment tool, as described previously (i.e., B-RST, IBIS, the Gail model), may be useful in guiding decision-making regarding suitability of appropriate imaging modality (2-4). There is also no evidence to support a role for breast MRI screening in the high risk male population.

Despite the lack of evidence to suggest that breast self-exam (BSE) improves survival, the Breast Disease Site Group agrees with other national and international guidelines, which deem it prudent to promote women’s recognition of early changes in breast texture and appearance, especially in the high risk population (26-28).

Future Trends:

An abbreviated MRI screening protocol (ABMRI) is under study which may detect cancers that enhance rapidly while decreasing the time required for the scanning process (18-20).

Recommendations:

The Eastern Health Breast Disease Site Group recommends screening for all women at risk of developing hereditary breast cancer in the form of:

- Developing breast awareness by performing periodic self-breast exam,
- Clinical breast exam once or twice a year,
- An initial mammogram starting at the age of 30, followed by annual mammography screening as long as the individual remains in good health. Discontinuation of breast screening should be at the discretion of a joint patient/physician decision,
- An annual MRI from age 30 years to age 69 years. Breast screening by MRI alone, following an initial baseline mammogram, is also appropriate for high risk individuals from 25 to 29 years of age, when the youngest affected relative’s age at diagnosis is < 40 years. Hence, MRI screening may commence at ten years prior to age of the youngest affected relative, beginning no earlier than 25 years of age,
Breast MRI should be scheduled during the second week of the menstrual cycle (days 5 to 13) in premenopausal women. Contrast-enhanced MRI screening is not performed during pregnancy, and can be postponed in lactating women until after cessation.

Insufficient evidence exists to recommend breast MRI screening for those with dense breasts or previous pathological findings of LCIS, ADH, or ALH in a breast biopsy, in the absence of any indication of genetic mutation or a history of familial risk.

Search Strategy:
Literature searches for this guideline were conducted in Pubmed and the Cochrane Library, using keywords “magnetic resonance imaging” and “breast” and “neoplasms” and “screening” and “high risk” and also “guidelines”. Guideline searches were also carried out on the websites of the world’s most highly respected cancer organizations and agencies. The initial search selected literature articles and source guidelines in English and dated after the year 2000, (unless the selection was an earlier landmark study) up to March 2011. The new search incorporated new study articles and source guidelines in English and dated from the year 2011, up to and including March 2016. The inclusion/exclusion process consisted of selecting guidelines from reputable international cancer organizations, with preference given to those from Canadian sources where possible. Seven source guidelines were identified initially in the first search which conformed to our search criteria, of which the Alberta Health Services (AHS) “risk reduction and surveillance strategies for individuals at high genetic risk for breast and ovarian cancer” guideline had been chosen to be adapted (21). Seven recent source guidelines were identified in the new search and were selected due to currency of content and/or were Canadian in origin (22-28).

The seven identified source guidelines (22-28) were put through the ADAPTE process (29) (including an AGREE II assessment)(30), and Cancer Care Ontario’s (CCO) “Magnetic Resonance Imaging Screening of Women at High Risk for Breast Cancer “ guideline was chosen to be adapted for our guideline (23). The CCO guideline was selected as the optimal choice due to its applicability, quality and currency of content.

There has been much debate but no consensus on the ‘grading of evidence’ in Canada. Presently, Canadian experts in the field of guideline development are involved in an ongoing in-depth analysis of the functionality of grading. Until such time as a report is released of their findings, and a consensus reached on whether to assign a grade of recommendation to a guideline, this group has decided to forgo the use of grading.

No competing or conflicts of interest were declared.

Disclaimer:
These guidelines are a statement of consensus of the Breast Disease Site Group regarding their views of currently accepted approaches to diagnosis and treatment. Any clinician seeking to apply or consult the guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient’s care or treatment.
Literature Support:


2. B-RST. [www.breastcancergenescreen.org](http://www.breastcancergenescreen.org)

3. IBIS. [www.ems-trials.org/riskevaluator](http://www.ems-trials.org/riskevaluator)


