SCREEN THIS

Research mounts that magnetic resonance imaging is the best way to detect breast cancer in women at high risk of the disease

For years, mammography has been the standard screening method for tumours in the breast. However, this technique may be failing young women with a family history of breast cancer, many of whom carry the BRCA1 or BRCA2 gene mutation. This is partly due to denser breast tissue common among young women, which makes it harder for mammograms to find cancers early. By the time a tumour is detected, it is highly likely that the cancer has advanced. Therefore, these women, who have a lifetime risk of up to 75% of developing breast cancer, often face a difficult choice: continue annual screening with an ineffective technique, or surgically remove both breasts.

"You're 35 years old and find out that you have a gene mutation. One of the factors that goes into that [decision] is if I don't remove my breasts and just do screening, what's my chance of dying of breast cancer?" says Dr. Ellen Warner, a researcher at Sunnybrook Research Institute (SRI) and an oncologist at the Odette Cancer Centre at Sunnybrook Health Sciences Centre.

An estimated one in nine Canadian women will be diagnosed with breast cancer. Most of these cancers will be diagnosed after age 60, detected by mammography. However, women with a BRCA mutation or who have close relatives who developed breast cancer at an early age, often develop breast cancer before age 50.

In an effort to detect this disease at the earliest possible stage in these high-risk women, researchers at SRI have spent more than a decade comparing the use of magnetic resonance imaging (MRI) with the "traditional" screening methods of mammography and clinical breast examination, and with ultrasound, a modality shown to have greater sensitivity (the ability to detect a disease when it is there) than mammography in women with dense breasts.

Since 1997, Warner and her team have been exploring the role of MRI in screening women with a BRCA1 or BRCA2 mutation. In 2004, she authored a landmark study published in *The Journal of the American Medical Association* that analyzed five years of data on 236 Canadian women aged 25 to 65 years with the BRCA gene mutations. The study compared the sensitivity and specificity (the rate of detecting suspicious abnormalities that turn out not to be cancer, known as false positives) of four imaging methods—mammography, ultrasound, MRI and clinical breast exam—for detecting breast cancer in these high-risk women. The researchers found MRI detected lesions with much higher sensitivity than did mammography, ultrasound or clinical breast exam. There were more false positives with MRI, but the rate was acceptable, and there were far fewer after the first year of screening.

It was the largest such single-centre study. Results showed MRI detected breast cancer tumours with 77% sensitivity, compared to 36% for mammography, 33% for ultrasound and 9% for clinical breast exam. When all four methods were combined, sensitivity increased to 95%.

"We found all these small cancers with MRI that mammography missed, and it was incredibly exciting," says Warner, who is also a professor in the department of medicine at the University of Toronto. "MRI is the best method we have for high-risk women and the most sensitive to pick up cancers at a very early stage."

It was logical to believe that had the women not been screened with MRI, their cancers would have eventually been detected, but at a significantly more advanced stage. However, this remained to be proven. Building on her earlier research, Warner and colleagues published a cohort study in 2011 in the *Journal of Clinical Oncology*. They followed 1,275 women (including those from the previous study) aged 25 to 65 years with the BRCA1 and BRCA2 mutations. Of these, 445 received MRI screening in Toronto, and 830 had conventional screening

DR. ELLEN WARNER

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elsewhere in Canada and the U.S. Researchers compared the incidence of early- and late-stage breast cancer between the two groups. At the end of the three-year trial, there were 41 cases of breast cancer in the MRI-screened cohort and 76 cases in the comparison group.

The researchers found there was a 70% reduction in the risk of advanced breast cancer in the MRI group. They concluded that annual MRI screening is associated with reduced rates of advanced-stage breast cancer compared to conventional screening. This was the first study to compare an MRI-screened cohort of BRCA gene mutation carriers with a control group.

Warner and her colleagues aim to follow women in both cohorts to determine whether annual MRI screening reduces mortality rates in high-risk women. "Our results have been quite impressive and successful since we started the first study," she says. "Now, we just have to sit and watch these women long enough to be fairly confident that we're not going to see substantial numbers dying from breast cancer." Warner adds it will take at least 10 more years to see significant survival differences. "So far, the results are very reassuring, as there hasn't been a single breast cancer death in women getting yearly MRI screening," says Warner.

The group's research has also helped make annual MRI screening the standard of care for women at high risk in Ontario.

The Ontario Ministry of Health and Long-Term Care puts the five-year survival rate for breast cancer in the province at 88%. In July 2011, the province expanded the Ontario Breast Screening Program to provide women at high risk for breast cancer aged 30 to 69 years with greater access to specialized screening centres. These sites will provide patients with referrals for genetic testing, and offer breast screening MRI and mammography, plus diagnostic services for any abnormality detected.

The screening program is designed for women aged over 50 years who are at average risk of developing breast cancer. The expansion is part of a $15-million investment over three years to conduct 90,000 more breast cancer tests based on clinical evidence and recommendations from Cancer Care Ontario.

The ministry estimates 34,000 women in Ontario are at high risk of developing breast cancer. By providing women with annual breast MRI and mammography screening, doctors will be able to detect about 17 cancers per year in every 1,000 women screened. The hope is that through this initiative more breast lesions will be detected at earlier stages, thereby increasing women's chance of survival, and, moreover, with less invasive treatments.

In spite of its improved sensitivity, one of the drawbacks of MRI screening is the high number of false positives it detects. For this reason, it is not for everyone, says Warner. "If your chance of having breast cancer in the first place is small, then you're more likely to have a false positive than to have a real cancer, and that's annoying and stressful for the patient."

Although regular mammograms are still a good method for detecting breast cancer in average-risk women, the age at which women should be tested has recently sparked a debate among medical experts.

In November 2011, the Canadian Task Force on Preventive Health Care released new screening guidelines for women who are at average risk of developing breast cancer. They recommend that women aged under 50 years should not have regular mammograms; rather, only those women considered higher risk within this age group should be screened.

"There is a lot of controversy around what age to start, and part of the problem with the new guidelines is how they are expressed and interpreted," Warner says. "Women were told by the task force in 2001 to consider going every year to 18 months for a mammogram between the ages of 40 to 49, and now the task force says don't have your breasts examined."

In response to media coverage on the topic, Warner published a commentary in *The Globe and Mail*. In it, she says the new recommendations are based on data from outdated mammography and that "digital mammography today is better than film mammography and more likely to find cancers in women with dense breasts."

As researchers continue to improve screening techniques and advance breast cancer treatments, prevention is the most important piece of the puzzle.

"We want to find out why so many women are getting breast cancer and learn how to reduce the risk of breast cancer for all women," Warner says. "The ideal thing for women with BRCA mutations and other very high-risk women would be to have excellent prevention methods, other than surgical prevention, and to use MRI screening as a back-up plan."—Eleni Kanavas

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