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Breast cancer screening in BC: What we should be proud of and how to make it even better

Women in BC are welcome to self-refer for breast cancer screening starting at age 40; however, many family doctors do not know this because of the Canadian Task Force on Preventive Health Care guidelines.

ABSTRACT: Optimal screening for women at average risk of breast cancer consists of annual mammograms starting at age 40, continuing for as long as women are in good health and have a life expectancy of another 10 years. Additionally, women with dense breasts should have supplemental screening with ultrasound, MRI, or other emerging technologies.

Breast cancer is the second-leading cause of cancer death in women in Canada. Screening is done to find cancers early to reduce mortality and to allow for successful treatment with less aggressive therapy. There is a wealth of data on mammography screening dating to randomized controlled trials conducted from the 1960s through the early 1990s. These proved the efficacy of mammography in reducing mortality for women aged 40 to 74 years.[1] The trials were conducted in the era of X-ray film mammography, which is no longer used, having been replaced by a high-resolution digital format. The therapies available at the time of the trials were primitive compared with current treatments. For these reasons, the randomized controlled trials vastly underestimate the current potential for mortality reduction. Moreover, the only benefit studied in the trials was mortality reduction. The other benefits of early detection[2] that improve quality of life for women with breast cancer—less invasive breast and axillary surgery, and less aggressive (or no) chemotherapy—were not measured in the trials.

All randomized controlled trials underestimate benefits because of noncompliance and contamination, but the two performed in Canada, collectively known as the Canadian National Breast Screening Studies (CNBSS), were outliers. Not only did they not show mortality reduction; they showed mortality excess in women in the mammography study groups. When the results of the studies were first published in 1992, it was suspected that poor study design had resulted in women being assigned to the study or control group nonrandomly: the imbalance in the numbers of advanced cancers and deaths in the study and control groups was statistically significant[3] and was unlikely to have occurred by chance.[4] This has now been verified[5] by former staff[6] from the study sites.[7]

Because relatively few women aged 40 to 49 years were enrolled in most of the earlier randomized controlled trials, CNBSS-1 was planned to enroll 50 000 women aged 40 to 49 years. Because this study involved the greatest number of women in this age group, it continues to have significant influence on the meta-analyses of screening mammography that inform screening guidelines globally. With inclusion of the CNBSS, meta-analysis shows mortality reduction of only 15% to 20%. Although the studies have now been discredited, CNBSS-1 is still the basis for screening recommendations for women aged 40 to 49 years in Canada[8] and many other countries. The tainted data from the study, which exaggerated the harms and understated the benefits, was used to create the decision tool[9] supplied to family physicians and nurse practitioners across Canada to facilitate shared decision making.

Observational studies conducted after the randomized controlled trials provide a better measure of the magnitude of mortality reduction associated with the use of digital mammography and contemporary therapies, as well as proof that excellent outcomes can be achieved with less invasive treatment[2] when cancer is found early, especially before it has spread beyond the breast. The largest observational study was conducted in Canada.[10] It included 2.8 million women and showed mortality reduction of 40% overall and 44% in women aged 40 to 49 years. A long-term follow-up study of women aged 40 to 69 years in Sweden who died of breast cancer showed that women who had screening were 60% less likely to die of their cancer in the first 10 years after diagnosis and 47% less likely to die in the

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20 years after diagnosis than women who did not have screening.[11] It is now widely acknowledged, even by organizations that do not recommend it, that annual mammography screening beginning at age 40 saves the most lives.[12]

In Canada, the Canadian Task Force on Preventive Health Care issues breast cancer screening guidelines for women at average risk. The Task Force is a volunteer panel of primarily family physicians who receive funding from Health Canada via the Public Health Agency of Canada. Patients and experts on breast cancer were excluded from the guidelines panel in 2011,[13] and again in 2018.[8] In 2019, the Minister of Health stated that "[the Task Force's] guidelines are not official government guidelines."[14]

In 2011, the Task Force claimed to have considered the "harms" of screening, claimed that the harms outweighed the "benefits" for women aged 40 to 49 years, and recommended that these women not be routinely screened. The Task Force allowed only randomized controlled trials to be used to determine the benefits but allowed much less robust research to determine the harms. Since the Task Force continued to reject all observational data in 2018 and the randomized controlled trial outcomes had not changed, the recommendations made in 2018 were the same as those made in 2011, with the addition that "women should be supported to make an informed choice on screening that is congruent with their own values and preferences."[8]

In a follow-up interview with CTV News in 2018, vice-chair of the Task Force, Dr Ainsley Moore, said, "The new guidelines are intended for an empowered position, which puts the decision making in the hands of the individual woman in terms of what she prioritizes."[15] This is not always done, however. Even in BC, where self-referral is permitted, some women do not attend because their physician has discouraged them based on a misunderstanding of the Task Force's guidelines. As Dr Moore stated, "I think there was in the past a lot of confusion about how the recommendations were interpreted."[15]

Unsurprisingly, there is variation among provincial and territorial screening programs regarding what age to start screening, how often to screen, and whether to inform women about their breast density.[16]

Breast cancer risk increases with increasing age. Many provinces allow women to self-refer only until age 74, because that is the age studied in the randomized controlled trials. The American Cancer Society recommends that screening continue as long as a woman is in good health and is expected to live at least 10 more years.[17] In Canada, the average life expectancy for a woman aged 75 is 13 years. At age 80, it is 10 years.[18]

Significance of breast density

Mammography reduces breast cancer mortality but does not work equally well in all women. Mammography sensitivity decreases as breast density increases. Breast density describes the ratio of normal breast tissue (which appears radiodense/white on a mammogram) to fat (which appears radiolucent/black on a mammogram). Radiologists classify breast density into four categories: A through D **[Figure 1]**.

Approximately 13% of women have category A density: almost entirely fatty; 43% have category B: scattered areas of fibroglandular density; 36% have category C: heterogeneously dense, which may obscure small masses; and 7% have category D: extremely dense, which reduces the sensitivity of mammography. Categories C and D are regarded as dense, so 43% of women aged 40 to 74 years have dense breasts.[19] Because cancers are also white on mammograms, they are more easily seen in non-dense breasts and can be masked in dense tissue[20] **[Figures 2–4]**. Cancers containing calcifications can be seen in dense tissue, but approximately 45% of invasive cancers are noncalcified[21] and can be masked on mammograms in women with dense breasts.

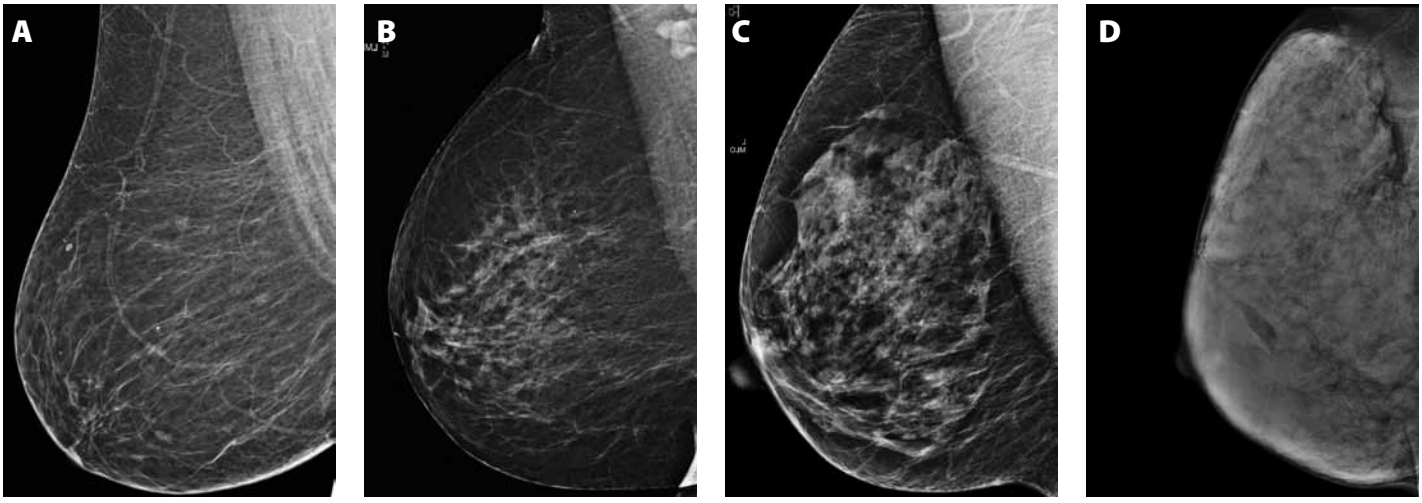

FIGURE 1. Right mediolateral oblique views from mammograms of four women, showing the four density categories: **A**: almost entirely fatty; **B**: scattered fibroglandular densities; **C**: heterogeneously dense, which may obscure small masses; **D**: extremely dense, which limits the sensitivity of mammography.

Cancers not seen on mammograms continue to grow and potentially spread; they may present weeks to years after a normal screening mammogram, usually as a lump. They are referred to as interval cancers, which tend to be larger than screen-detected cancer, are more often higher grade, and more often spread to lymph nodes and beyond. They have a poorer prognosis than screen-detected cancers.[22] Interval cancers are 13 to 18 times[20,23] more common in women with category D breast density than category A. An important goal of screening is to detect more cancers earlier, before they become interval cancers, when they can be treated with less aggressive therapy and have better outcomes.[24]

Most Canadian screening programs screen average-risk women biennially; some screen women annually if they have dense breasts. Seely and colleagues compared the interval cancer rates in jurisdictions with a policy of annual screening versus those with biennial screening for women with dense breasts. In provinces that conducted biennial screening for women with dense breasts, interval cancer rates were 63% higher than in jurisdictions that screened annually.[25]

When mammography alone is used for breast cancer screening, mortality reduction is significantly less for women with dense breasts. Van der Waal and colleagues showed a 41% mortality reduction in women with category A breast density but only a 13% reduction in women with categories B, C, and D density.[26] Chiu and colleagues showed that women with dense breasts had almost double the breast cancer mortality after adjusting for other risk factors.[27]

Modalities such as screening ultrasound[28] and MRI[29] have been shown to detect cancers missed on mammograms and to reduce interval cancers. And most of those cancers are small, invasive, and node negative.

In addition to the risk of masking cancer, dense breasts are an independent risk factor for developing breast cancer. Risk increases as density increases: women in category D have approximately a 5 times higher risk than women in category A.[20] Since only 13% of women have category

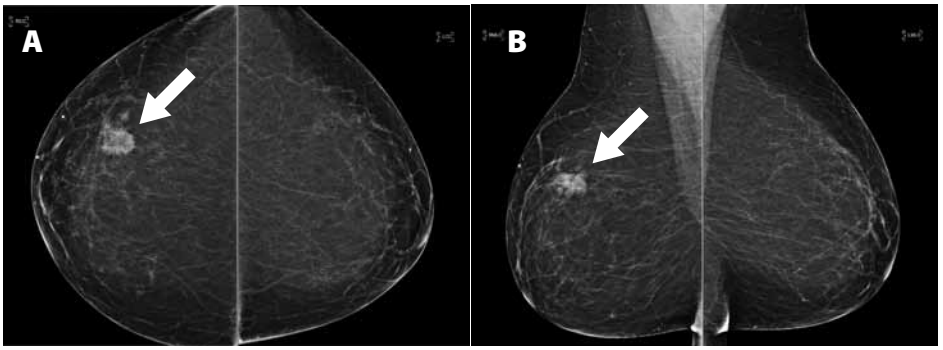

FIGURE 2. Screening mammogram in a woman aged 57 years. Right and left craniocaudal (A) and mediolateral (B) views. The small cancer (arrows) in the right upper outer quadrant is easily seen in her category A density breast tissue.

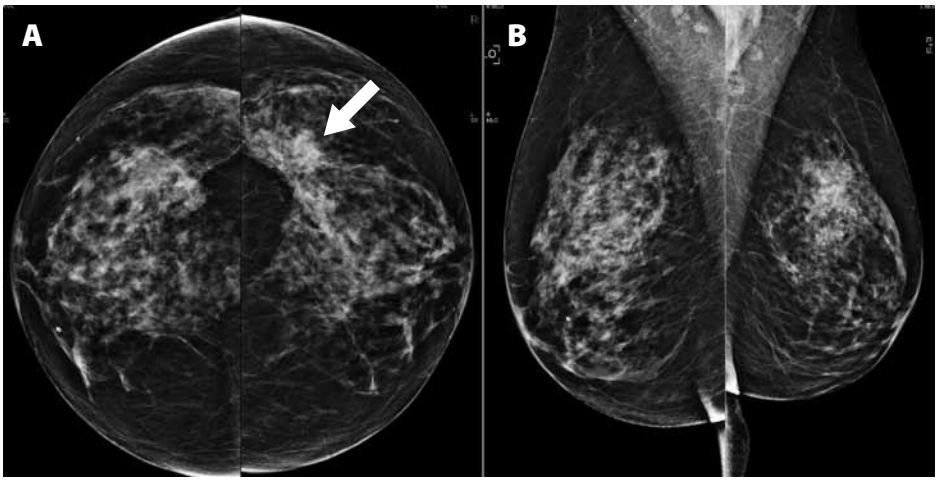

FIGURE 3. Screening mammogram in a woman aged 62 years. Right and left craniocaudal (A) and mediolateral (B) views. The 1.5 cm cancer (arrow) in the left upper outer quadrant is subtle but visible on the craniocaudal view because its anterior margin is adjacent to fat, but it is masked on the mediolateral view because it is surrounded by normal dense tissue in her category C density breast tissue.

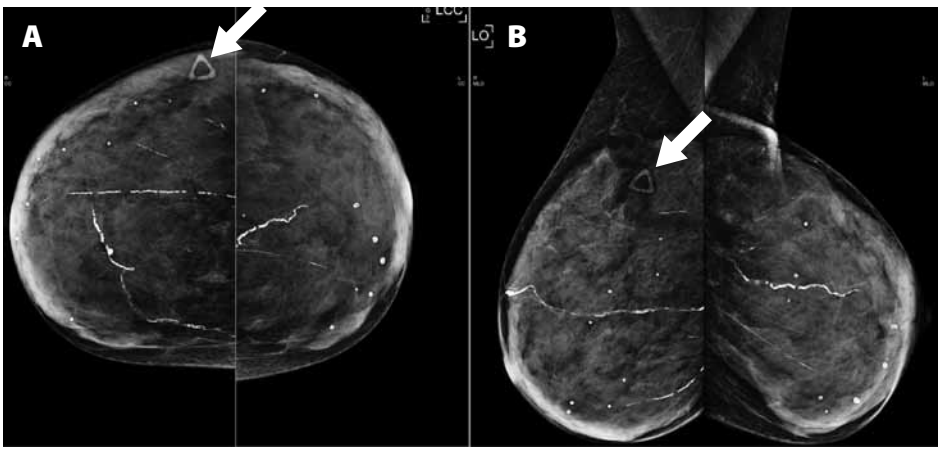

FIGURE 4. Diagnostic mammogram in a woman aged 78 years who presented with a palpable lump in her right upper outer quadrant. Right and left craniocaudal (A) and mediolateral (B) views. The technologist taped a radiopaque triangular skin marker over the site of the palpable lump (arrows), but the 1.3 cm cancer is not seen; it is completely masked in her category D density breast tissue. Up to 50% of cancers are missed on mammograms in women with category D breast tissue.

A breast density, risks have also been calculated relative to women with category B density, who are more "average." Women with heterogeneously dense breasts (category C) have a 1.2 to 1.5 times higher risk than women with scattered densities (category B), and women with extremely dense breasts (category D) have a 2.1 to 2.3 times higher risk.[30]

Because of the two risks associated with breast density, in Austria and France, screening breast ultrasound is offered to all women with categories C and D breast density.[31] Women in the United States began being notified of their breast density and the associated risks in 2009. Supplemental screening with ultrasound or MRI (depending on a woman's calculated risk) is now increasingly used and is covered by health insurance in many states.[32] The European Society of Breast Imaging now recommends that all women aged 50 to 70 years with category D breast density have screening breast MRI every 2 to 3 years, but no less often than every 4 years. The Society states that mammography and ultrasound may be used if MRI is not available and acknowledges that MRI might also be valuable for women with less dense breast tissue but that more research is needed.[33]

Mammograms find approximately 5 cancers per 1000 screens. Ultrasound is reported to find an additional 2 to 7 cancers per 1000 (cancers missed on mammograms). MRI finds an additional 16 cancers per 1000.

Breast cancer screening in BC

BC had the first organized mammography screening program in North America. Thanks to the foresight of its founder, Dr Linda Warren, the Screening Mammography Program of BC accepted its first patient in 1988. From the beginning, women were able to self-refer starting at age 40, and initially all women could attend annually. This is the ideal, because it is known to be associated with earlier stage of diagnosis, fewer interval cancers, and the most lives saved.[12] In BC, women may continue to self-refer after age 75.[34]

Although breast cancer is less common in younger women and increases in incidence with increasing age, it grows faster in younger, premenopausal women because of the presence of ovarian hormones. This also applies to hormone receptor–positive cancers in postmenopausal women on hormone therapy.[35] This explains why 27% of years lost to breast cancer occur in women diagnosed at ages 40 to 49 years.[36] Moreover, 85% of women diagnosed with breast cancer have no family history or other known risk factors.[37]

In 1997, the screening interval was changed: women aged 40 to 49 years could still attend annually, but women aged 50 to 74 years could attend only biennially unless they had a first-degree family history of breast cancer. Interval cancers are much more common when screening is biennial (2.1 cancers per 1000 screens) rather than annual (0.8 cancers per 1000 screens).[38,39] In 2015, the screening interval for women aged 40 to 49 years was also increased to biennial unless they had a first-degree family history of breast cancer.

BC is one of only four provinces that allow women to self-refer for screening mammography starting at age 40. A recent review by Wilkinson and colleagues, in conjunction with Statistics Canada, showed the negative consequences of not screening women until age 50, as is the case in most other Canadian jurisdictions.[40] The authors compared the stage of diagnosis of breast cancer in women aged 40 to 49 years and 50 to 59 years in provinces that allow screening starting at age 40 with that in provinces that do not screen until age 50. Women aged 40 to 49 years in provinces that do not screen that age group had higher proportions of cancers diagnosed at stages II, III, and IV than those in provinces that do screen that age group. Women aged 50 to 59 years in provinces that do not screen women aged 40 to 49 years had higher proportions of cancers diagnosed at stages II and III than those in provinces that do screen women aged 40 to 49 years. Hence, screening women aged 40 to 49 years benefits women from age 40 to 59 years. Given that only 25% of eligible women aged 40 to 49 years attend screening in BC,[41] these results probably underestimate the benefits of screening women in this age group.

In October 2018, BC became the first province in Canada to notify all women of their breast density; in early 2019, supplemental breast ultrasound became covered by MSP for women with categories C and D breast density, but it requires a requisition and is not widely available. In the first year that supplemental breast ultrasound was covered, an audit of a Vancouver practice showed that 7 cancers were detected per 1000 screens.[42] These had been missed on the mammograms. Notably, 40% were in women with no family history of breast cancer, and 60% were in women with category C breast density. Screening breast ultrasound has shown a low specificity, but when radiologists and technologists receive adequate training and gain experience, recall and biopsy rates decrease, and the positive predictive value of biopsies increases.[43] In the Vancouver study, the average tumor size was 9 mm, all were node negative, the biopsy rate was 1.3%, and the positive predictive value was 42%.[42]

Women at high risk, generally with at least a calculated lifetime risk of 20% to 25%, may be eligible for screening with MRI. Typically, these are women with genetic mutations such as *BRCA* or those who had mantle radiation for lymphoma prior to age 30. Many risk calculators are available online.

Potential future directions

Mammograms are not 100% sensitive or specific. Digital breast tomosynthesis was approved by Health Canada in 2012, and several sites in BC acquired the technology. It is quasi-3-D but is often described as 3-D mammography. It increases sensitivity (finds more cancers) and specificity (reduces false alarms). However, the technology is expensive to purchase, the large file sizes are expensive to archive, and the exams take twice as long to read compared with standard 2-D mammograms. It is widely used for screening in the United States. As of March 2022, 82% of American facilities had

digital breast tomosynthesis units, and 45% of all accredited units were digital breast tomosynthesis.[44] Although digital breast tomosynthesis is available at multiple screening sites in Alberta, it is not used by any Canadian screening program other than those participating in a National Institutes of Health–sponsored randomized trial, one of which is in Vancouver. Although digital breast tomosynthesis finds more cancers than 2-D mammography, it does not obviate the need for supplemental screening for women with dense breasts. Ultrasound finds 5 times as many additional cancers as digital breast tomosynthesis, compared with 2-D mammography.[45]

MRI is the most sensitive screening test for breast cancer. It requires IV contrast and may be contraindicated in women with pacemakers or other metallic implants. The conventional scan takes approximately 45 minutes and may not be tolerated by women with claustrophobia. MRI is by far the most expensive modality. In Canada, it is used only for screening women at very high risk of breast cancer, such as those with *BRCA* and other genetic mutations or women who had mantle radiation for Hodgkin lymphoma. The European Society of Breast Imaging now recommends that all women aged 50 to 70 years with category D breast density undergo MRI no less than every 4 years, but ideally every 2 to 3 years.[33] An abbreviated MRI protocol that takes approximately 10 minutes in the magnet is showing accuracy almost equal to that of the longer scan, which will reduce the cost and make it more tolerable for women with claustrophobia.[46]

Like MRI, contrast-enhanced dual-energy mammography is a functional modality that exploits the visibility of abnormal "leaky" neovessels in cancers. It gives results similar to those of MRI but uses iodinated contrast (as in CT scans) rather than gadolinium-based contrast (as in MRI). It is done on a modified mammogram machine, so claustrophobia is not an issue, and it is a fraction of the cost of MRI. However, it is not yet widely available in BC.[47]

Molecular breast imaging is a nuclear medicine test that uses radioactive IV contrast. It also shows promise in screening dense breast tissue, but the dose is to the whole body (unlike mammography, where the dose is just to the breast), and it uses a higher dose than that used in mammography.[48] This test is not available anywhere in Canada.

Artificial intelligence

Artificial intelligence will inevitably play a significant role in breast cancer screening. It has shown tremendous promise in mammography and digital breast tomosynthesis; studies have shown that it could be used to preread screening mammograms and would be reliable at discerning those that do not need to be seen by a radiologist (i.e., mammograms that are reliably negative).[49,50] The remaining mammograms would be triaged by artificial intelligence to prioritize faster interpretation of the most suspicious cases by the radiologist. Artificial intelligence can also be used to determine risk and to objectively determine breast density. Artificial intelligence applications in ultrasound have been shown to improve inter-reader agreement and diagnostic accuracy and specificity, particularly for inexperienced readers, and to reduce interpretation time for automated examinations.[51] Artificial intelligence is also used in MRI.[52]

Summary

Breast cancer screening reduces morbidity and mortality by finding cancers early, ideally when cancer is confined to the breast. All women are at risk, risk increases with age, and 85% of women who develop breast cancer have no family history or other known risk factors, so all women should be screened.

Annual mammograms starting at age 40 save the most lives. In BC, women can self-refer starting at age 40. Although the incidence of interval cancers is much higher in programs that screen biennially, women in BC may get screened annually only if they have a first-degree family history or previous atypical ductal hyperplasia or lobular neoplasia. Overall, only 50% of eligible women in BC participate in the provincial mammography screening program, and participation is only 25% in women aged 40 to 49 years, who potentially have the most years of life to lose.[40] It is important that family doctors encourage women to have screening mammograms because seeing a family doctor in the past 12 months more than doubles the odds of having had a screening mammogram in the past 2 years.[53]

Women with dense breast tissue deserve the same opportunity for early detection of breast cancer as women with nondense breasts. They should be encouraged to have supplemental screening, usually with ultrasound. As with mammography, they should be informed, in advance, that false alarms are common (i.e., women are recalled for more tests to determine whether a finding is suspicious), especially on a woman's first visit when no priors are available.

Competing interests

Dr Gordon is a practising breast radiologist in Vancouver and works in a practice that offers screening and diagnostic breast imaging and ultrasound-guided breast needle biopsies.

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