

Your Comprehensive Guide to Breast Cancer Screening in Canada



Why a guide?

There is a lot of confusing and conflicting information about breast cancer screening. There is also misinformation being provided to health care providers and women about screening. We hope to empower women by offering accurate and current information so that they can take charge of their breast health and receive optimal breast screening.

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Disclaimer: *The material in this guide is meant to provide information only. It is not a substitute for a professional medical opinion. Readers are encouraged to confirm the information in this guide with other sources, including their health care provider. If you have a medical problem, please contact a qualified health care professional. You should never ignore professional advice or delay seeking treatment based on the information contained in this booklet. The content of this guide is based on scientific research available at the time of production.*

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Section 1

Signs of Breast Cancer and Risk Factors

1.1 Who gets breast cancer?

Anyone. Anyone can get breast cancer.

The two highest risk factors for breast cancer are being female and getting older.

Women are often surprised to learn that 75% of breast cancers occur in women with **NO** family history or known risk factors.ⁱ

1.2 What is breast cancer?

Breast cancer is a disease where a group of cells loses normal control. These abnormal cancer cells form in the tissues of the breast. They grow, usually into a lump, and invade and damage the adjacent normal tissue. Most breast cancers begin either in the glands for milk production, called lobules, or in the ducts that connect the lobules to the nipple. Breast cancer is not life threatening when it is confined to the breast, but it can be if it spreads to other parts of the body. Many cancers can be found before spreading to other organs and these can be more easily treated.

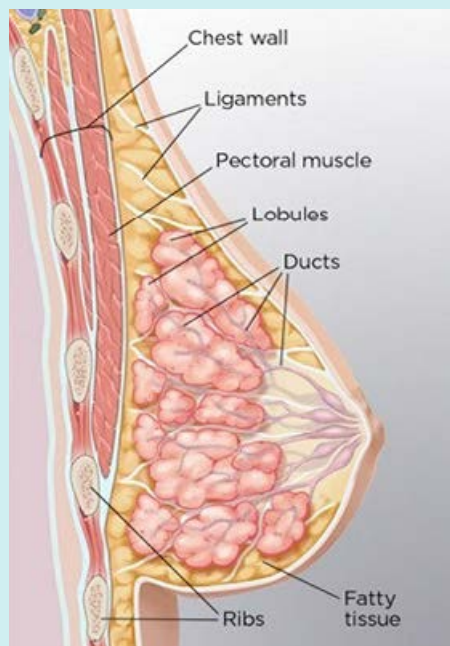


Image Source: MSK

1.3 Types of breast cancer

There are many types of breast cancer, but since this guide focuses on breast screening, this section will only briefly discuss the two most common types of breast cancer. As mentioned above, breast cancer can begin in different areas — the ducts, the lobules, or in some cases, the tissue in between. It can be non-invasive or invasive.

Invasive ductal carcinoma (IDC) is the most common type of breast cancer and makes up about 80% of all breast cancers. It begins in the milk ducts and is called invasive because it spreads to the surrounding breast tissues.ⁱⁱ

The second most common type of breast cancer is called Invasive lobular carcinoma (ILC) and makes up about 10% of breast cancers.ⁱⁱⁱ It begins in the milk-producing lobules, which empty out into the ducts that carry milk to the nipple. The cancer has broken through the wall of the lobule and begun to invade the tissues of the breast. Lobular cancer is more difficult to detect on a mammogram because instead of clustering together, lobular cells spread out single file like tree branches or spider webs.^{iv} As well, since the cells don't stick together well, there's often no lump, making it harder for women to find during self-exam.

Over time, both invasive ductal and lobular cancer can spread to the lymph nodes and possibly to other areas of the body. Visit www.breastcancer.org for more information.

1.4 Signs of breast cancer



Image Source: Knowyourlemons.com

Breast cancer can show up as a lump or in a number of other ways:

- a thickening (an area that feels firmer than the tissue around it)
- dimpling of the skin: cancer can attach to the overlying skin and pull it in, so it looks puckered
- crust on nipple
- warmth or redness: some cancers show up as a swollen, warm, red breast, and can look just like an infection. If the issue does not resolve on antibiotics, testing is recommended.
- discharge from the nipple: discharge is normal if it's white, yellow, or green. It is worrisome if it's completely clear like water, or bloody and if it comes out without squeezing.
- sores on skin
- if a vein under the skin gets bigger, it can rarely be a sign of cancer
- sometimes a breast can change in shape or size
- nipple retraction can be normal if it's longstanding, but if it's new, it should be checked

Most lumps in the breast are **not** cancer. Some lumps are fluid-filled sacs, called cysts. However, any new lump should be thoroughly investigated. Please see your health care provider if you discover any of the above changes and request imaging.

1.5 Risk Factors

A risk factor is any condition that makes a woman more likely to develop breast cancer. Some risk factors can be changed while others cannot. Since anyone can get breast cancer, it's important to be proactive about your breast health.

Please note the lists below do not cover all of the risk factors.

Factors beyond your control that can increase your risk of getting breast cancer:

- breast cancer genes - up to 10% of breast cancers are inherited, most commonly from mutations in the BRCA 1 and 2 genes
- age
- previous chest radiation for Hodgkin's disease
- dense breast tissue
- family history of breast cancer, especially a mother, father, sister, brother, or daughter
- previous biopsy that showed atypical cells
- starting periods early
- going through menopause later
- not having children

Risk factors you can control:

1. Taking hormones (estrogen and progestin)

Long-term use (over 5 years) of combined menopause hormone therapy (MHT) can increase breast cancer risk.^v

2. Alcohol consumption

There is no "safe limit" of alcohol consumption when it comes to breast cancer: even drinking small amounts of alcohol can increase risk. There is evidence suggesting that alcohol increases the level of estrogen in the blood, which can stimulate the growth of some tumours. As well, the ethanol in alcohol may damage the DNA of cells and alcohol can also decrease essential nutrient levels.^{vi} Alcohol is also a risk for development of other cancers.

3. Weight & diet

Obesity increases the risk of breast cancer because extra fat tissue stores estrogen which can cause breast cancers to develop. Those who have a BMI of >31.1 are 2.5 times more at risk than those with BMI <22.6.^{vii}

4. Exercise

Walking 30 minutes per day can lower breast cancer risk by 10%.^{viii}

5. Smoking

Both smoking and second-hand smoke increase the risk of breast cancer.

6. Sleep

Multiple studies show that those who work at night have increased cancer risks.

7. Chemical exposure

Some chemicals are hormone disruptors that affect estrogen

levels and can trigger hormone-receptor-positive breast cancer. Examples include: pesticides, lead, phthalates, BPA.

1.6 What is the probability of developing invasive breast cancer in the next 10 years?

A Canadian woman has a 12.4%, or a 1-in-8 chance of being diagnosed with breast cancer in her **lifetime** – if she lives till at least 85.^{ix}

Breast cancer is very uncommon in the 20's and 30's, but still occurs. The incidence jumps dramatically in the forties and keeps rising.^x

- A 20-year-old has a 1 in 1732 chance of developing breast cancer in the next 10 years.
- A 30-year-old has a 1 in 228 chance in the next 10 years
- A 40-year-old has a 1 in 69 chance in the next 10 years
- A 50-year-old has a 1 in 43 chance in the next 10 years
- A 60-year-old has a 1 in 29 chance in the next 10 years
- A 70-year-old has a 1 in 26 chance in the next 10 years

The lifetime risk has increased over the past decades and some possible reasons are: longer life expectancy, changes in reproductive patterns, menopausal hormone use, environmental factors, rising obesity, and increased detection through screening.

1.7 What is the percentage of breast cancer by decade?

An often-used reason not to screen women 40-49 years of age is that most breast cancers occur in women more than 50 years of age. However, there is no abrupt increase that occurs at the age of 50.^{xi} A significant number of cancers occur in the 40s.

Age	Percentage of Breast Cancers
Under 40	5%
40-49	18%
50-59	23%
60-69	26%
70+	28%

1.8 Assessing your risk with a risk calculator

A breast cancer risk calculator is a tool that can help you and your doctor better understand your risk and make informed decisions. We're suggesting the Tyrer Cuzik 8 model because it includes breast density as a risk factor, is a well-studied and is a widely used model that is easy and quick. Just click Imperial Units and if you know your density click BIRADS. If you don't know your density, you can still use it and retry it when you find out your density. The model calculates 10-year risk and lifetime risk. Here is the tool <https://ibis.ikonopedia.com/>

Section 2

How We Screen for Breast Cancer

2.1 Why do we screen for breast cancer?

- to detect cancer as early as possible
- to save lives by finding and treating the disease earlier
- to allow for treatment with less aggressive therapy and surgery which is possible when cancers are found early

2.2 What do we see in women who get screened?

- less likely to die from breast cancer
- less likely to need more extensive surgery, like mastectomy
- less likely to have breast cancer spread to lymph nodes
- less likely to have more extensive treatment, i.e., chemotherapy

2.3 How can we screen for breast cancer?

- Breast self-examination
- Clinical breast examination
- Mammography (2D and 3D)
- Ultrasound (handheld and automated)
- MRI and Abbreviated MRI
- Contrast-Enhanced Mammography
- Molecular Breast Imaging

2.4 What is a mammogram?

A mammogram is a low-dose X-ray of the breast that can show breast cancer. It is the only test shown to reduce breast cancer deaths, because it is the only test that has been studied for mortality reduction. Other methods for screening, used in select populations, like Ultrasound, MRI, and MBI have not been studied in a randomized control trial for mortality reduction. That doesn't mean they don't save lives.

Mammograms can detect cancer early, when it is most treatable and long before it can be felt. This improves the odds of survival and can help avoid more extensive treatment. However, mammography is not a perfect test, as discussed in the section on dense breasts.



Image source: Mammatone.com

2.5 What happens during mammography screening?

A specially trained technologist will perform your mammogram. To get a high-quality picture, your breast must be compressed. The technologist will place your breast on the machine. The plastic upper plate is lowered to compress your breast while the technologist takes a picture.

Compression is used to spread out the tissue, so radiologists can see better, and that includes seeing cancers. The actual breast compression only lasts a few seconds. A top to bottom image and a side view of each breast is taken for a screening mammogram.

All mammography machines have a release switch, so the compression releases as soon as the exposure is made.

The most common complaint about mammography is the uncomfortable feeling when the breast is temporarily compressed. To alleviate some of the discomfort these tips can be considered:

- Premenopausal woman can schedule the exam 5 to ten days after the beginning of their period when the breasts are less tender.
- Consider taking ibuprofen an hour before.
- Tell the technologist about your previous experience.

This video shows how compression makes a difference.

<https://youtu.be/q1PIZfmdtHw>

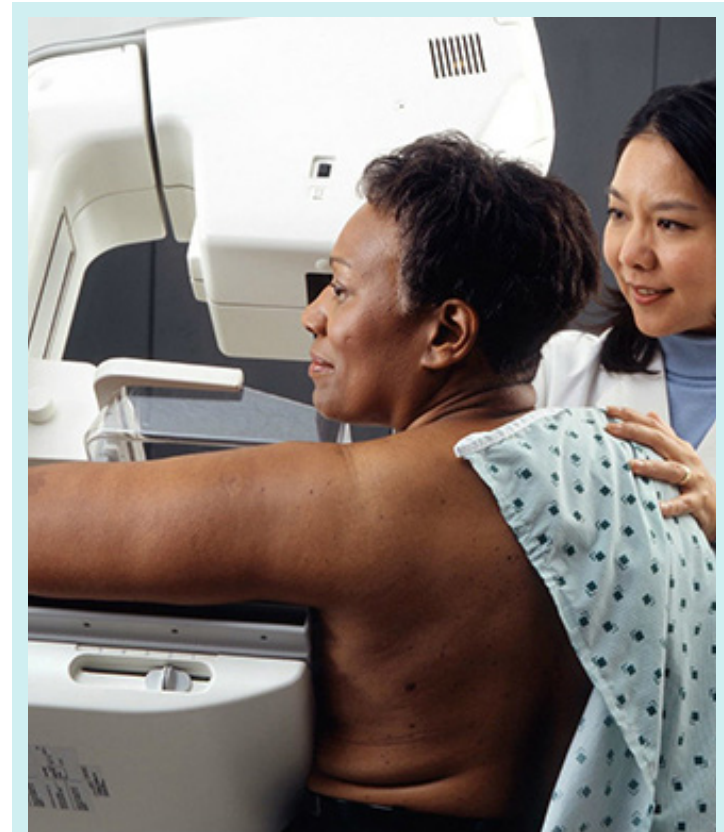


Image Source: bassmedicalgroup.com

2.6 What is the difference between a screening mammogram and a diagnostic mammogram?

A screening mammogram is used to look for breast cancer in a woman who has no signs or symptoms of breast cancer. Screening mammograms do not prevent breast cancer. Their purpose is to detect breast cancer as early as possible and before it is large enough to be felt or cause symptoms.

A diagnostic mammogram is used for women with symptoms. Diagnostic mammography is also performed for women with an abnormal screening mammogram.

2.7 Mammograms for women with implants

Women with breast implants still need regular mammograms. In most provinces, women with implants require a requisition for a diagnostic mammogram. Only in Alberta and Quebec are women with implants included in the screening program and can self-refer after age 50. There are four images taken of each breast, two including the implant and two with the implant pushed back out of the way.

The “usual” views (the compression vertically, and the compression angled side-to-side) are obtained on each side. These include the implant and allow inclusion of tissue as far back as possible in each image.

In addition, similar angles are used, but with the implant pushed back so only the breast tissue is included in the images. These allow better compression and visualization of the breast tissue, but can't include as much of the tissue at the back of the breast.

2.8 What happens if my mammogram is abnormal?

If your mammogram is abnormal, you will be asked to schedule an appointment to have more tests to help diagnose any potential problems. Some women need more mammogram pictures, some will need a breast ultrasound, or both. Just because there is an abnormality does not mean you have breast cancer. There are many reasons the radiologist is asking for more information. Less than 10% of women who are called back for more tests are found to have breast cancer.^{xii}

2.9 Benefits of Mammograms

1. Mammograms can find cancer early

Mammograms can find cancerous tumours 2-3 years before they can be felt.^{xiii} Finding breast cancer early can increase survival and also reduce the need for harsher treatments like chemotherapy and mastectomy.

2. A mammogram can save your life

Multiple studies have found that routine screening from age 40-74 substantially reduces deaths from breast cancer. Current evidence shows women aged 40-49 who have mammograms are 44% less

likely to die of breast cancer.^{xiv} Women aged 50-74 are 40% less likely to die of breast cancer.^{xv}

3. Mammograms help you find out your breast density

It's important to know if you have dense breasts, which can increase your risk. Your breast density can only be assessed by the radiologist from looking at your mammogram.

2.10 Limitations of Mammograms

Current evidence shows that the benefits of mammograms outweigh the limitations for women aged 40-74.

1. Mammograms may lead to more tests which can create anxiety

You may be told that mammograms can result in “false positives”, but this term is a misnomer. A better term would be “false alarm.” Any time the mammogram shows something unclear that has any possibility of being cancer, you will be recalled for extra images to see the area more clearly. About 10% of women are recalled and over 95% of these women do not have cancer.^{xvi} Waiting for the extra tests and the results can be stressful. However, evidence shows that the anxiety is short lived and does not harm women psychologically in the long term.^{xvii}

2. Over detection/Over diagnosis

You may be told that there is a theoretical possibility that you could be diagnosed and treated for a cancer that would never threaten your life, even if it was not treated. It's not that there are “harmless cancers,” it's just that some cancers are more aggressive, and some grow so slowly that you might die of something else (another cancer, a heart attack, etc.) before the breast cancer becomes deadly. Since doctors can't predict perfectly which cancers can be left untreated, all cancers are treated. But there is ongoing research to determine if some cancers can be treated less aggressively.

You may be told that the estimated rate of over detection is 41 percent of breast cancers.^{xviii} Current evidence estimates the rate is actually between 1-10%,^{xix} and is lowest in younger women, since they are less likely to have other serious illnesses than older women.

3. Not all breast cancers can be detected by mammograms

Cancer may not be visible on the mammogram or may develop between two mammograms. A woman's age, the location of the cancer, and a woman's breast density can make cancers more or less difficult to see.

4. Not all women whose cancers have been found by mammograms will survive

Treatment does not always lead to survival, even when cancer is detected at an early stage.

5. Mammograms use low doses of radiation

A mammogram is an X-ray and uses a low dose of radiation, slightly higher than a chest X-ray. The risk of breast cancer due to

radiation from a mammogram is very low, and probably negligible after age 40.^{xx} The benefit of early diagnosis and treatment for breast cancer far outweighs the risk of the small amount of radiation received during a mammogram.

Watch Dr. Paula Gordon on the benefits and limitations of mammograms <https://youtu.be/7ncVqT6fuNM>

2.11 Screening for minority women

One size does not fit all when it comes to screening. Canadian breast screening guidelines do not recognize that minority women are underserved by screening starting at age 50. Here are the latest statistics.^{xxi}

Minority women are:

- 72% more likely to be diagnosed with breast cancer before age 50
- 58% more likely to be diagnosed with advanced stage disease prior to age 50
- 127% more likely to die of breast cancer before age 50 compared to white women

2.12 Screening for transgender people

Current evidence shows that females transitioning to male who do not undergo mastectomies maintain their previous risk for breast cancer.^{xxii} Males transitioning to female are at increased risk for breast cancer due to hormone use.^{xxiii} The American College of Radiology recommends annual screening starting at age 40 in male-to-female patients who have used hormones for 5 years or more, and for female-to-male patients who have not had mastectomy. Please check your provincial screening program for policies.

2.13 Screening for high-risk women

Please check with your provincial screening program for its policies regarding high-risk women. In Ontario, women deemed as high risk must meet the following criteria,^{xxiv} but your province may have different criteria.

- Have a gene mutation that increases their risk for breast cancer (e.g., BRCA1, BRCA2, TP53, PTEN, CDH1)
- Have a first-degree relative (parent, brother, sister, or child) who has a gene mutation
- Have been assessed by a genetics clinic as having a 25% or greater lifetime risk of breast cancer based on personal family history
- Have had radiation therapy to the chest to treat another cancer or condition (e.g., Hodgkin lymphoma) before age 30 and at least 8 years ago

2.14 Radiation and mammograms

Mammograms use a low dose of radiation to detect tumors, including ones that may be too small to feel. The dose of radiation from a mammogram is 0.4 mSv (millisieverts). It is slightly above that of a chest X-ray.^{xxv}

The dose from a mammogram is similar to going for a walk outside every day for 7 weeks at sea level or 3-4 weeks living in Colorado.

2.15 What are the other types of breast screening?

This section briefly discusses a variety of technology used for screening. More information about each technology can be found at www.densebreast-info.org

2.16 Ultrasound

- **What it is:** Ultrasound uses high frequency sound waves to image the breast.
- Ultrasound is used frequently to investigate lumps, either those that are felt, or those seen on screening mammograms
- **Positives:** When used for screening in addition to mammography in women with dense breasts, ultrasound increases the rate of cancer detection.^{xxvi} There is observational data from multiple studies showing ultrasound finds an additional 2-7 cancers per 1000 women.^{xxvii} It is quick, safe, and non-invasive. No ionizing radiation is involved.
- **Limitations:** Like mammograms, ultrasound can cause false alarms that require additional investigation
- **Accessibility:** A requisition for ultrasound is not usually given unless there has been a suspicious finding on a mammogram, MRI, or a clinical breast exam. There may be a private clinic in your city where you do not need a requisition and can pay directly. In BC: Screening ultrasound is now covered by MSP for women with dense breasts, with a requisition.



Image Source: Caperay.com

2.17 Automated Breast Ultrasound (ABUS, 3D Ultrasound)

- **Positives:** Like handheld ultrasound, ABUS can find small, invasive, node-negative cancers missed by mammography.
- **Limitations:** Like hand-held ultrasound, ABUS may identify non-cancerous abnormalities (false alarms) that may require additional ultrasound or biopsy.
- **Accessibility:** Currently, ABUS can be found in Ontario and Alberta
- In Ontario, patients can pay out of pocket for ABUS, but some private/group insurance plans may cover part of the cost. ABUS can be found in two locations in downtown Toronto and also in Barrie. In Alberta, ABUS is covered under the provincial health insurance plan (AHIC) for women with dense breasts who qualify. A number of clinics offer ABUS.

2.18 Tomosynthesis/3D Mammography

- **What it is:** Also known as 3D mammography, it creates multiple thin slices of images so that overlapping tissue is less likely to hide a cancerous tumour. The patient is positioned exactly the same way as for a standard mammography but is in compression for several seconds longer.
- **Positives:** Tomosynthesis increases the detection of invasive tumours over digital mammogram by an additional 1-2 cancers per 1000 women. It decreases the false positive rate of mammography.^{xxviii}
- **Limitations:** Does not detect as many cancers in dense breasts compared to an ultrasound. The radiation dose may be slightly higher than regular mammography depending on the technique used.
- **Accessibility:** Currently, tomosynthesis is mostly being used for diagnostic testing after an abnormality is found with screening. However, in Alberta, patients visiting certain clinics are screened with tomosynthesis. A large study is taking place including sites in Canada to evaluate the role of tomosynthesis in screening for breast cancer.



Image Source: Medgadget.com

2.19 MRI

- **What it is:** It uses magnetic fields, radio frequency pulses, and a computer to produce detailed images of the breast.
- **Positives:** It is an effective screening tool for women with dense breasts and detects 18 or more additional cancers per 1000 women.^{xxix} No ionizing radiation is involved. MRI is generally recommended for women with the highest cancer risk (those who carry the breast cancer gene, women who have had chest wall radiation for treatment of lymphoma, and some with rare genetic diseases)
- **Limitations:** MRI is likely to generate more false positives requiring biopsy. It requires intravenous contrast injection called Gadolinium. The FDA has released statements on the use of Gadolinium.
- **Accessibility:** MRI is available across Canada, but it is not used as a screening tool for average risk women. It is currently used along with mammography for high-risk patients. In some locations it is used for women with dense breasts and breast cancer. There are some private pay MRI locations. A referral is required.



Image Source: Hopkinsmedicine.com

2.20 Abbreviated MRI

- **What it is:** The shorter version of the standard Breast MRI exam that takes fewer images and takes less time to read.
- **Positives:** Takes less than 10 minutes (so more tolerable for women with claustrophobia), is less costly than an MRI, is more accurate than a mammogram and an ultrasound, and is not limited by breast density.
- **Limitations:** Since the tests use shorter MRI protocols, it may be difficult to get the kinetic information needed to detect whether the tumor is malignant or benign, leading to possible false positives. It requires an intravenous contrast injection called Gadolinium. The FDA has released statements on Gadolinium use.
- **Accessibility:** Abbreviated MRI is performed in Ottawa. Longer version MRIs are currently used along with a mammogram for high-risk patients (BRCA gene, a strong family history, or history of radiation to chest).

2.21 Contrast Enhanced Mammography

- **What it is:** A standard iodinated contrast agent is used; the same contrast used for CT scans. Cancer cells take up the contrast agent, which absorbs X-rays, so the cancer appears white on the mammogram.
- **Positives:** Is lower cost than MRI and can detect cancers that are not visible on a standard mammogram.
- **Limitations:** Uses slightly more radiation than a standard mammogram. Women with poor kidney function or who have had a previous allergic reaction to contrast agents might be advised to avoid this test.
- **Accessibility:** Is available in a few locations across Canada, such as London, Ontario, Hamilton, and Quebec.

2.22 Molecular Breast Imaging (MBI)

- **What it is:** A small amount of radioactive material is injected and accumulates in cancer cells. A gamma camera is used to detect the tracer.
- **Positives:** Detects additional cancers after mammography and can be used by patients who cannot use contrast-enhanced MRIs.
- **Limitations:** MBI requires a greater dose of radiation than mammograms.
- **Accessibility:** Currently, MBI at a low dose is being tested in a trial in Toronto, Ontario.



Image Source: dotmed.com

2.23 What about Thermography?

Due to misunderstanding about the risks of radiation, and misinformation from health care providers, some women turn to thermography. This procedure uses an infrared camera to produce images that show the pattern of heat and blood flow on or near the surface of the breast. It is based on the theory that a temperature change in the breast reflects increased blood

flow in the underlying tissues, allowing detection of cancer and precancerous changes.^{xxx}

Thermography has been around since the 1950s and has been well-studied. There is not a single scientific study that has shown thermography to be an effective tool for detecting breast cancer.

Thermography was discredited in the 1970s. It can find big cancers that are palpable, but also shows up benign masses like fibroadenomas, resulting in many false alarms. Even normal tissue can look abnormal and result in false alarms, and it misses small cancers that are seen on mammograms or ultrasounds.

Thermography is not a useful screening modality and both Health Canada and the FDA in the United States have posted alerts that thermography should not be used for screening.

The FDA commissioner stated, "People who substitute thermography for mammography may miss the chance to detect breast cancer in its earliest and most treatable stages."^{xxxi}

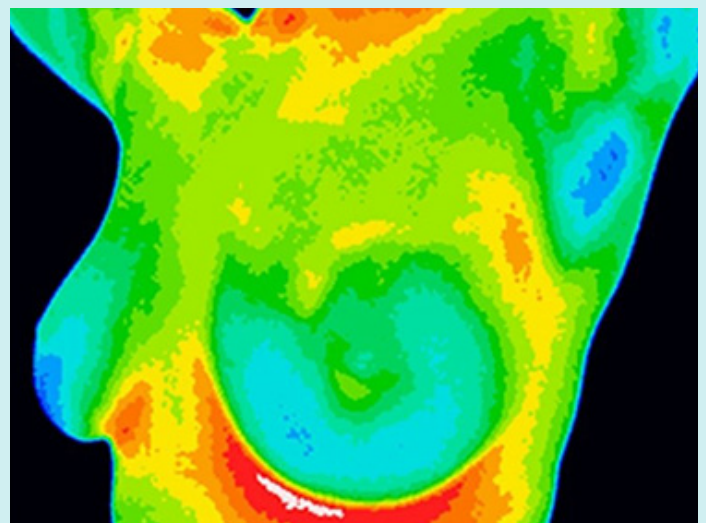


Image Source: news-medical.net

2.24 How do I do a breast self-examination?

- The term you'll hear now is that women should be "breast aware," which means pay attention to how your breasts look and feel.
- You should be familiar with the shape of your breasts and know what your normal breast texture feels like.
- Puckering is sometimes more visible if you look in the mirror with your arms raised. You can check your breasts lying in bed or in the shower. Soapy hands make it easier to slide your hand along the skin and make it easier to notice normal texture or a lump.
- Some cancers are not detectable on mammograms, so breast self-exams are worth doing, especially if your mammograms are done less than once per year. By getting to know what your normal breast feels like, you'll know if there's a change. Check out www.knowyourlemons.com

Section 3

Breast Density

3.1 Why is breast density important?

Mammograms find 81-93% of cancers in women with fatty breasts, but miss up to 43% in women with the densest breasts, even with modern digital mammography.^{xxxii} Even tomosynthesis (3D mammograms) does not find all cancers in dense breasts. Radiologists say that looking for cancer in a dense breast is like looking for a snowball in a snowstorm. A small cancer, easily seen in a fatty breast, can be hidden in normal dense breast tissue.

It's important for women with dense breasts to know their breast density because if they're told that their mammogram is negative, it can give them a false sense of security.

Radiologists divide breast density into 4 categories A to D using the Breast Imaging Reporting and Data system, or BIRADS. Categories C and D are regarded as dense. In Newfoundland and NWT, density is divided into 4 categories using percentages. Breasts with over 50% dense tissue are considered dense breasts. Breast density can decline with age but doesn't always.

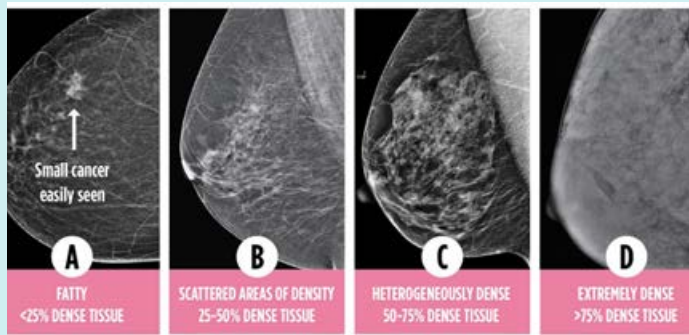


Image source: densebreastscanada.ca

3.2 Dense breasts are normal and common

Breast density refers to the composition of tissues in the breast. Dense breasts contain a higher proportion of glandular and fibrous tissue compared to fat. Breasts that have more than 50% glandular and fibrous tissue are called dense breasts.^{xxxiii} Categories C and D are regarded as dense breasts.

More than 40% of women, between the ages of 40-74 have dense breasts.^{xxxiv} Over 1/2 of women in their 40s have dense breasts, and almost 1/3 of women in their 60's have dense breasts.^{xxxv}

While it is normal to have dense breasts, women need to know if they have dense breasts so that they can understand the implications. By our calculations, using demographic figures from the 2016 Census, there are ~3.4 million women in Canada over age 40 with dense breasts. Over 800,000 women in Canada are in the highest density category (D).

3.3 Why it's important to know if you have dense breasts

1. Women in Category D have 4-6x higher risk of developing breast cancer than women with fatty breasts.^{xxxvi} Dense tissue and cancer both appear white on a mammogram, so cancer can hide in dense tissue. Cancers in women with dense breasts are, on average, larger and more often node positive than in women with fatty breasts.
2. Women with dense breasts have an 18x higher risk of an interval cancer (which is a cancer discovered between screenings, usually as a lump).^{xxxvii} These cancers have a worse prognosis than those found in a screen-detected cancer.

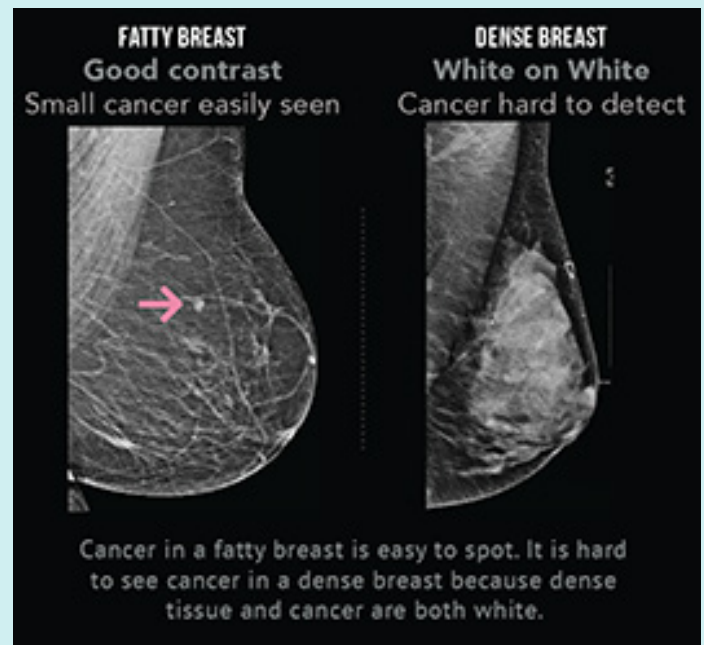


Image source: densebreastscanada.ca

3.4 How do you know if you have dense breasts?

Breast density can only be determined by the radiologist when viewing a mammogram and not by breast size or touch. Your health care provider cannot tell by a physical exam. Lumpy breasts are not the same as dense breasts. Both fatty and dense breasts can feel soft, firm, or lumpy.

The Nova Scotia Breast Screening Program and some clinics in Alberta use software to measure the level of density.

3.5 Your health care provider may be unaware of the following:

- the greater risk of getting breast cancer when breasts are dense
- having dense breasts is a more prevalent risk factor than a family history

- the greater likelihood of a cancer being missed on a mammogram when breasts are dense because of the camouflage effect: dense tissue and cancer both appear white on a mammogram
- up to 43% of cancers are missed in women with the highest density
- the ability of ultrasound to find the cancers missed on a mammogram when breasts are dense, even if 3D mammogram is used.

It is important to know your breast density and understand the implications so you can consider advocating for yourself.

3.6 What should you do if you have dense breasts?

- Continue having mammograms because they can detect cancer not visible on an ultrasound.
- Perform regular self-exams, ideally every month. If you're still menstruating, do the exam just after your period. If you notice any change, see your health care provider. Even if you just had a negative mammogram.
- Consider modifying your lifestyle factors to decrease cancer risk, such as: getting to and staying at a healthy weight, doing moderate exercise, decreasing alcohol intake, and decreasing menopausal hormone use, if using combined estrogen and progesterone.
- Consider requesting a screening breast ultrasound, in addition to your mammogram.
- Consider requesting an annual mammogram. This lowers the risk of interval cancer.

3.7 Breast ultrasound for women with dense breasts

The Canadian Task Force on Preventive Health Care says there's insufficient evidence to recommend supplementary screening for women with dense breasts. This statement is a result of the Task Force's insistence on Randomized Control Trials (RCT). An RCT of screening ultrasound is underway in Japan but it will take at least 7-10 years before it can prove mortality reduction. It's already showing that they're finding more early cancers in women having both mammography and ultrasound, and that those women have fewer interval cancers.^{xxxviii} There is observational data from multiple studies starting in 1995 showing that ultrasound finds an additional 3-7 cancers per thousand women.^{xxxix} Finding these cancers earlier will allow less aggressive treatment AND reduce mortality.

3.8 Screening for women with dense breasts and breast cancer

Women who have breast cancer are at higher risk of getting a second cancer in the same breast or the opposite breast. Women who have breast cancer and have dense tissue are at higher risk of getting breast cancer in the other breast than a woman

with non-dense breasts.^{xi} Patients with high density have a much greater risk of local recurrence compared with women with the least dense breasts (21% compared with 5%).^{xii}

The American College of Radiology now recommends screening with mammography and MRI for women who've had cancer, who have dense breasts, or for women who were diagnosed with cancer before age 50, with all breast densities. These recommendations are not routine in Canada, but experts recommend you advocate for yourself.

3.9 Breast Density Notification in Canada

Currently all women having a screening mammogram in BC, AB, MB, NS, PEI, NB, ON, YT, NWT are directly informed of their breast density in the mammogram results letter mailed to them. Women in SK and QC can check their online health portal for their breast density category. In six jurisdictions, women with the highest category of density are asked to return annually for a mammogram. There are fewer interval cancers in provinces where women with dense breasts have annual mammograms.^{xiii}

3.10 Provincial comparison chart

Province	Density		
	All women are told breast density in letter	Only women in Category D are told their density	Women in Category D offered annual mammograms
BC	X		
NS	X		X
PEI	X		X
YT	X		X
AB	X		
MB	X		
NB	X		
SK	X		X
ON	X		X
NL		X	X
QC	X		
NWT	X		

Legend:

- provinces that directly inform all women after their mammogram.
- provinces that only inform women with Category D.
- provinces where women with Category D are asked to return for an annual mammogram.

Watch Dr. Paula Gordon: What women with dense breasts need to know <https://youtu.be/kqFrEvlI3H4>

Section 4

Breast Screening Practices in Canada

4.1 Optimal breast screening practices

Is optimal breast screening provided in your province?

Although current evidence shows there are significant benefits to annual screening starting at 40, there are variations among provinces in what age to start, how often women can be screened and what age to stop. Here's what experts would like to see versus what we have in practice.

- 1. Screening starting at age 40:** This saves the most lives, but only four jurisdictions allow women to self-refer for a mammogram at 40: BC, PEI, YT, NS; in AB and NWT it is 45. In AB and in NWT, a requisition from a doctor is required for the first screen from 40-44 and then self-referral is allowed after the first screen.
- 2. Annual screening starting at age 40:** Cancers in the 40s can grow aggressively, but only in these 3 jurisdictions can women self-refer for mammograms annually: PEI, NS, YT (and AB and NWT after first screen 40-44).
- 3. Breast density notification:** Only in these provinces are all women directly informed of their breast density: BC, NS, AB, MB, PEI, NB, ON, NWT and YT. In SK and QC, women can check their online portal for their breast density category.
- 4. Annual mammograms for women in Category D density:** These are the only jurisdictions where women with the highest category of density are asked to return for a mammogram every year instead of every two years: ON, PEI, NL, SK, NWT, YT and NS.
- 5. Supplemental screening depends on where you live:** Please check out our Breast Screening Advocacy Toolkit.
- 6. Risk Assessment for women starting at age 25:** Experts recommend assessment between age 25-30.
- 7. Screening should continue after age 75:** Experts recommend screening continues if a woman is in good health.
- 8. If you have a first degree relative with breast cancer,** annual mammography is recommended.

4.2 The 40s

There is a general consensus amongst experts that starting screening at age 40 saves lives.

4.3 What age to start screening and how to start

Each provincial screening program chooses the age at which to start screening and the screening interval. We have a mishmash of screening policies across the country.

The Canadian Task Force on Preventive Health Care says that the decision to have a mammogram is a woman's, based on her values and preferences. However, getting a mammogram at age 40 may not be so easy and depends on where a woman lives.

In Nova Scotia, British Columbia, Prince Edward Island, and Yukon women may self-refer for a mammogram, starting at age 40. In Alberta, and NWT at 45. Women can go annually in NS, PEI, and YT.

Although some jurisdictions do not offer self-referral in the 40s, it is important to note that women in their 40s are able to have a mammogram **IF** they can get a doctor's requisition. In some provinces, this mammogram will be performed outside of the organized screening program at a diagnostic centre. When mammograms are not done through an organized screening program there are no reminder letters sent, no results letter sent, and women are not informed of their density even if their province has implemented notification.

All women in Canada should be able to access a mammogram in their 40s if they choose to do so. Visit mybreastscreening.ca for more information about your province.

4.4 Why is it important to start screening in the 40s?

1. Saves Lives

Annual mammograms starting at age 40 save the most lives and offer the best chance of detecting cancer early. Recent observational studies show 44-60% mortality reduction in screened women starting at age 40, far higher than shown in the randomized trials done from the 1960s to early 1990s.^{xiii}

The Pan Canadian study compared women who had mammography to those that didn't. They obtained data on almost 3 million women attending screening programs in Canada. It's the largest study of this type ever published. They showed that women who attend screening are overall 40% less likely to die of breast cancer, than those who don't. And for women in their 40's, they're 44% less likely to die.^{xiv}

2. Cancer happens in the 40s

There is no scientific or biological reason to delay screening until the age of 50. There are no sudden jumps at 50. Rather, breast cancer incidence increases substantially around age 40. 1 in 6 breast cancers (17%) are detected in women aged 40-49.^{xiv}

3. Increase years of life saved

27% of the years of life lost to breast cancer are in women diagnosed in their 40s.^{xvi}

4. At age 40 the risks of radiation from a mammogram are negligible

5. Cancers in the 40s can be more aggressive

Half of the more aggressive and lethal breast cancers occur in women diagnosed before age 50. The growth rate is faster

in this age group given the presence of ovarian estrogens in younger women.^{xvii}

6. Reduces need for mastectomy

Women ages 40–49 years who do not get screened frequently are 3.4 times more likely to need a mastectomy.^{xviii}

7. Reduces need for chemotherapy treatments

Women between the ages of 40–49 years who do not get screened frequently are 2.5 times more likely to need chemotherapy if they get breast cancer.^{xix}

8. Minority women

Minority women are more likely to have breast cancer at a younger age than white women. Minority women are 72% more likely to be diagnosed with breast cancer before age 50, are 58% more likely to be diagnosed with advanced-stage disease under the age of 50 and are 127% more likely to die of breast cancer under age 50, as compared to non-Hispanic white women.ⁱ As stated by the American College of Radiology, “waiting until age 50 to be screened is detrimental to all women, but disadvantages minority women in particular.”ⁱⁱ

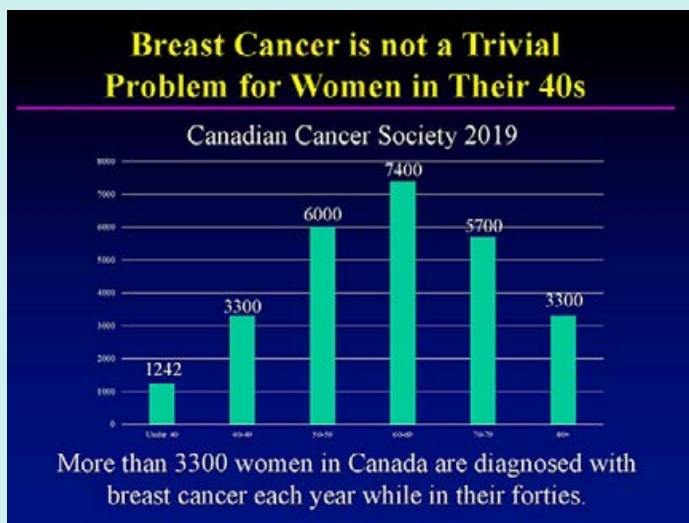


Image Source: Canadian Cancer Society

4.5 Who recommends beginning mammograms at age 40?

Many major Canadian and US organizations recommend mammograms starting at 40: Canadian Society of Breast Imaging, Canadian Association of Radiologists, the American Medical Association, the American College of Obstetricians and Gynecologists, the American College of Radiology, the National Cancer Institute, the National Comprehensive Cancer Network, Society of Breast Imaging, World Health Organization, American Society of Breast Surgeons. The American Cancer Society recommends that women aged 40 to 44 should have the choice to start annual mammograms and women 45-54 should get mammograms every year.

4.6 Annual Screening vs Biennial Screening

Annual screening between ages 40-79 years for average risk women results in a 37% reduction in breast cancer mortality.ⁱⁱⁱ Biennial screening between ages 50-74 years results in a 26% reduction in breast cancer mortality.ⁱⁱⁱ

4.7 Comparison Chart: Screening program practices for women in 40s

Province	Practice		
	Can self-refer at age 40	Can self-refer annually in 40s	Need a requisition from age 40-49
BC	X		
NS	X	X	
PEI	X	X	
YT	X	X	
AB	X Age 45		X 1st Screen Only Age 40-45
MB			X
NB	X 2024		X
SK	X Jan. 2025		X
ON	X Fall 2024		X
NL			X
QC			X
NWT	X Age 45		X 1st Screen Only Age 40-45

4.8 Provincial screening program practices for women 50-74

In MB, SK, ON, QC, NL, NB, women become eligible to be a part of the screening program at age 50. In the other jurisdictions, the age is 40 (AB and NWT is 45). Provincial programs recommend screening every two years unless a woman has a family history. Some recommend annual screening for women with Category D density.

4.9 When should women stop screening?

Canadian guidelines recommend screening till age 74. However, women today are living longer. According to Statistics Canada, the average life expectancy for a 75-year-old woman is 13 years. At age 80, it's 10 years.^{iv} So, when to stop screening?

According to Canadian breast screening experts, women over age 74 should continue to screen every 1-2 years with mammography as long as they are in good health, with a life expectancy of at least 7 years, and as long as they are willing to have treatment if a cancer is found. Treatment is often modified for older women. If a woman is frail, she can often still have cancer removed with local anesthetic, and probably wouldn't need radiation or chemotherapy.

- Breast cancer incidence and death rates generally increase with age. Women 75 years and up receive the same benefits of early detection from screening as younger women: more lives saved through less invasive treatment.
- In these provinces women 75 years and over can call to book their own mammogram: BC, NS, MB, SK, NL, YT, NWT
- In these provinces, women 75 years and over need a requisition: PEI, AB, NB, ON. In QC, the age a requisition is required is 70 years and up.

4.10 Comparison Chart Screening in Canada age 75 and over

Province	Age	
	75+ need a requisition	75 can self refer
BC		X
NS		X
PEI	X	
YT		X
AB	X	
MB		X
NB	X	
SK		X
ON	X	
NL		X
QC	70+	
NWT		

4.11 Is optimal breast cancer screening accessible in your province/territory?

Screening in the 40s can be lifesaving, but only 4 provinces allow women to self-refer for a mammogram at 40: BC, PEI, YT, NS. In AB and NWT, self-referral is allowed after the first screen in AB, refer begins at 45.

Cancers in the 40s can grow aggressively, but only in PEI, NS, YT, and AB can women self-refer for mammograms annually.

Only in these provinces are all women directly informed of their breast density: BC, NS, AB, MB, PEI, NB, ON, YT. In SK and QC women can find their breast density in their online portal.

These are the only provinces where women with the highest category of density are asked to return for a mammogram every year instead of every two years: ON, PEI, NL, SK, NWT, NS, YT.

Breast Screening Practices in Canada

Province/ Territory	At age 40 can self-refer for a mammogram	Age 40-49 annual screening offered	Breast Density Category mailed to all women having a screening mammogram	Annual Mammogram for women with Category D density	After age 74 can self-refer (others need req)
BC	Yes		Yes		Yes
NS	Yes	Yes	Yes	Yes	Yes
PEI	Yes	Yes	Yes	Yes	
YT	Yes	Yes	Yes	Yes	Yes
AB	After 1st screen or age 45		Yes		
MB			Yes		Yes
NB	Starting early 2024		Yes		
SK	Starting Jan.2025		Online Portal	Yes	Yes
ON	Coming Fall 2024		Yes	Yes	
NL				Yes	Yes
QC			Online Portal		
NWT	After 1st screen or age 45	Age 40-44	Yes	Yes	

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Section 5

Canadian Breast Cancer Screening Guidelines

5.1 Who makes the guidelines on breast screening for average risk Canadian women aged 50-74?

The guidelines for Canadian breast cancer screening were made by a panel of 14 members selected by the Public Health Agency of Canada and the College of Family Physicians of Canada. The panel is called the Canadian Task Force on Preventive Health Care (CTF). The panel **did not** include any experts in breast cancer screening. The panel included a psychologist, an occupational therapist, and a nephrologist (kidney specialist), family doctors, nurses, a chiropractor, and an emergency room doctor. The guidelines ignored the input of experts in breast cancer diagnosis and treatment.

5.2 What does the Canadian Task Force recommend?

The CTF recommends **no** routine screening till age 50, and then only every 2-3 years. And they say that doctors should stop doing breast exams, and women shouldn't do breast self-exams. They recommend no supplemental screening for women with dense breasts. Updated guidelines are expected in Spring 2024.

<https://canadiantaskforce.ca/guidelines/published-guidelines/breast-cancer-update/>

5.3 How do the Task Force recommendations for average risk women differ from the recommendations of experts?

NON-EXPERTS: Canadian Task Force Recommendations	EXPERTS: Canadian Association of Radiologists/Canadian Society of Breast Imaging
Screening for women aged 40-49 is not recommended.	Women aged 40-49 should screen annually with mammography.
Women aged 50-74 should screen every 2-3 years with mammography	Women aged 50-74 should screen every 1-2 years with mammography.
There are no recommendations for screening women over age 74	Women over aged 74 should screen every 1-2 years with mammography as long as they are in good health with life expectancy of ~7+ years.
Supplemental screening is not recommended for women with dense breasts	Women with dense breasts can benefit from supplemental screening.
Risk assessment not recommended	Risk should be assessed by age 25-30 to determine if early screening is appropriate.
Clinical breast exam is not recommended	Mammography may miss breast cancers and clinical breast exam is complementary to mammography
Breast self-exam is not recommended.	Breast self-awareness is recommended

Update on Breast Cancer Screening Recommendations Inclusive of All Women at Average Risk

All women, should have a risk assessment by age 30

30

Especially minority women, to ensure that they are not in a higher risk category.

Annual mammography screening starting at age 40

40

Greatest breast cancer mortality reduction.

Diagnosis at earlier stage.

Better surgical options and more effective chemotherapy.

Screening should continue past age 74

75+

No upper age limit unless severe comorbidities limit life expectancy.

Benefits should be considered along with the possibility of

- Recall for additional imaging
- Benign biopsy
- Risks of anxiety and overdiagnosis.

The ACR and SBI affirm that weighing the benefits and risks of mammography should be done by women, not for women.

JACR VISUAL ABSTRACT

Image Source: Society of Breast Imaging

5.4 What are the issues with the evidence used by the Task Force?

The Task Force only used data from studies done from the 1960s to the early 1990s called Randomized Control Trials (RCTs) to determine the benefits of screening, and they ignored more recent studies using modern mammogram machines. The RCTs were designed to study only mortality reduction, which is why the CTF ignored the other benefits of early detection. Two of the RCTs done in Canada were poorly designed and poorly executed. They were not blindly randomized, and included women known to have breast lumps, so they were not really trials of screening.

A 2014 observational study of screening in Canada showed 40% fewer deaths among women who had screening mammograms than women who didn't, but the CTF deliberately chose to ignore this, and other observational studies done with modern mammography equipment, in favour of RCTs from the 1960's to 1990's, which show only a 15-20% mortality reduction. In doing so, they understated the benefits of screening.

Moreover, they looked not only at the lives saved by screening, but also what they regarded as the risks of screening (which they called "harms"). They exaggerated the harms and underestimated the benefits of early detection, so they concluded that the harms outweigh the benefits. The main risk of screening is the transient anxiety from a recall for more tests. This does not equate with the harm of a later stage diagnosis. The decision whether to participate in screening is up to individual women with input from their health care provider. For there to be true shared decision-making, both a woman and her physician need to have clear and accurate information on the benefits and harms of screening.

5.5 A summary of why these guidelines matter to you

These guidelines are to be used by 60,000 Canadian health care providers in their interactions with 9 million women aged 40-74.

- 1. The guidelines ignore expert advice:** There are no breast cancer experts on the Task Force.
- 2. The guidelines ignore the importance of screening for women in their 40s**
- 3. The guidelines advise against breast self-exams:** These exams are an important measure women can take to increase early detection of breast cancer, especially in women with dense breasts.
- 4. The guidelines exaggerate the harms of recalling women for additional testing after a mammogram:** About 10% of women are recalled for additional images and this may cause anxiety. The Task Force considers this anxiety a harm and uses it to dissuade women from screening. The anxiety is not long lasting. Better safe than sorry.

5. The guidelines ignore significant health benefits of early cancer detection: The Task Force does not acknowledge the benefits of avoiding chemotherapy, avoiding mastectomy, and avoiding lymphedema.

6. The guidelines ignore current data: The Task Force relies on outdated and flawed studies. The obsolete studies estimate that women are 15-20% less likely to die if they have breast screening. Current studies show that women who have mammograms are actually 40-44% less likely to die of breast cancer than those who do not.

7. The guidelines ignore the risks of breast density: The risks of dense breasts have been known for 40 years. Dense breasts increase the risk of developing breast cancer and increase the risk that cancer will be masked on a mammogram. The guidelines ignore the benefits of supplemental screening for women with dense breasts.

8. Women are being asked to make decisions about life-saving screening based on inaccurate information: Using the new guidelines women may make decisions that may ultimately lead to a late diagnosis, unnecessary suffering, and a poorer prognosis.

Canadian women and their healthcare practitioners deserve to have accurate information about the benefits of screening.

Please consider signing the advocacy letter for your province. It can be found in the footer of our website: densebreastscanada.ca

Watch Dr. Paula Gordon: What you need to know about the breast cancer screening guidelines
https://youtu.be/_8wf8IPWPVA



Section 6

Facts vs Myths

Here are some of the most persistent myths about breast cancer and screening, and the facts:

1. Myth: Your chance of getting breast cancer decreases with age

Fact: The older you get, the greater the risk of breast cancer. The biggest risk factor for breast cancer is being a woman. If you don't die of something else, the risk of getting breast cancer keeps climbing.

2. Myth: You can't get screened if you have breast implants

Fact: Women with breast implants should have regular mammograms. Please note in most provinces, you won't be able to make an appointment directly with the screening program as you will require special positioning and additional images. Contact your health care provider for a referral for a mammogram at a diagnostic facility. In Alberta and Quebec, you can book directly through the screening program.

3. Myth: All breast cancers can be detected on a mammogram

Fact: No screening test is perfect. Although mammography is the best early-detection tool we have, it doesn't always find breast cancer at an early stage. Some cancers grow rapidly, and though a cancer may not have been present at the time of the most recent mammogram, it can grow to be feelable before a woman's next mammogram, especially if she is having mammograms less frequently. It can also happen because a cancer may be hidden on the mammogram. A woman's age or breast density can make cancers more or less difficult to see.

It's harder to see cancers in dense tissue than in fatty tissue. Images can look normal even though cancer is present. For women with dense breasts or those at high risk for breast cancer, breast ultrasound or MRI may be beneficial in addition to mammography. It's also important to pay attention to any changes in your breasts and perform periodic breast self-exams. It is important to note that although mammograms are not perfect, women who have mammograms are 40% less likely to die of breast cancer than women who do not have mammograms.

4. Myth: Radiation exposure during a mammogram can cause cancer

Fact: Mammograms use a low dose of radiation to detect tumors, including cancers that may be too small to feel. There is background radiation all around us. This includes cosmic radiation from the sun and stars, radioactive material in rocks and in the ground, radon gas in the air, and radioactive substances in water and organic material. Natural radiation is greater at higher elevation because there's less shielding of cosmic radiation by the atmosphere.

The dose from a mammogram is similar to going for a walk outside every day for 7 weeks at sea level or 3-4 weeks living in Colorado.

The radiation risk of breast cancer from mammograms is primarily in women less than 20 years old.

5. Myth: All breast cancers are life-threatening

Fact: Not all breast cancers are life-threatening, but most cancers will grow if left untreated. Theoretically, some breast cancers detected by screening never cause any harm, but it is not possible to tell which cancers will or will not turn into a life-threatening cancer in the future.

6. Myth: Compression of the breasts causes cancer

Fact: There is no scientific evidence that compression of the breast causes cancer or causes cancer to spread. Compression of the breast during a mammogram assists in separating the breast tissue to reveal any abnormalities. It also helps to hold the breast in place which eliminates blur on the image.

7. Myth: If I don't have a family history of breast cancer, I won't get breast cancer

Fact: Women with a family history of breast cancer are at higher risk of getting breast cancer, but 75% of women who get breast cancer have **no** family history. The biggest risk factors are simply being a woman and growing older.

Newly diagnosed women, trying to understand how they got breast cancer will often ask, "I eat healthy, I'm at a healthy weight, I'm active, and I barely drink. So how did I end up with breast cancer?" The answer is that anyone can get breast cancer. It is important to manage the risk factors you can control, such as weight, diet, exercise, alcohol, and hormone use. Although reducing risk factors may help lower breast cancer risk, there are no guarantees. It's important to get regular screenings and pay attention to any unusual changes in your breasts.

8. Myth: Breast cancer always causes a lump you can feel

Fact: Breast cancer does not always cause a lump that can be felt during a self-exam. There are different symptoms of breast cancer. Although being breast aware is important, regular screening with mammography can detect cancer before symptoms appear.

9. Myth: Breast cancer only happens to middle-aged and older women.

Fact: Younger women can and do get breast cancer. In 2017, about 4% of invasive breast cancers were diagnosed in women under age 40, 17% were diagnosed in women in the 40s, 23% in women in their 50s and 27% in women ages 60 to 69. While 4% might sound small, it isn't zero. This percentage means that one in every 25 invasive breast cancer cases occurred in women under 40.^{iv}

Women of all ages need to pay attention to their breasts, perform self-exams, and report any unusual changes to their doctors — and insist that breast cancer be ruled out if there's a concerning symptom. Even some doctors don't realize that women in their 20s and 30s get breast cancer. Women with a strong family history of breast cancer, especially cancers diagnosed in relatives before age 50, should start screenings sooner.

Section 7: Suggested Additional Resources

www.densebreastscanada.ca

mybreastscreening.ca

www.densebreast-info.org

www.breastcancer.org

www.knowyourlemons.com

www.csbi.ca

www.40not50.org

<https://www.sbi-online.org/endtheconfusion/Home.aspx>

This guide was designed by Amanda Theyers, a graphic designer who graduated from the York University and Sheridan College Design program with a Bachelor of Design Honours Degree in 2016. She went to work at a number of companies afterwards; Metroland Media, Optimé International and SJC. Amanda believes that the biggest dreams are the ones we would like to make real. She became a graphic designer with the hope that one day all great dreams will become great realities. Learn more about her and her work on her portfolio site: adtdesign.myartsonline.com and on [her linkedin profile](#).

Section 8: Endnotes

- i. <https://www.acraccreditation.org/mammography-saves-lives>
- ii. <https://www.breastcancer.org/symptoms/types/idc>
- iii. <https://www.breastcancer.org/symptoms/types/ilc>
- iv. <https://lobularbreastcancer.org/ilc-fact-sheet/>
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- vi. <https://www.cancer.ca/en/cancer-information/cancer-type/breast/risks/?region=on#alcohol>
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- viii. <https://cebp.aacrjournals.org/content/23/9/1893.abstract>
- ix. <https://www.cancer.ca/en/cancer-information/cancer-type/breast/statistics/?region=on>
- x. https://www.breastcancer.org/symptoms/understand_bc/risk/understanding
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- xvii. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6381538/>
- xviii. <https://pubmed.ncbi.nlm.nih.gov/6802546/>
- xix. <https://pubmed.ncbi.nlm.nih.gov/22972810/>
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- xxi. [https://www.jacr.org/article/S1546-1440\(21\)00383-5/fulltext](https://www.jacr.org/article/S1546-1440(21)00383-5/fulltext)
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