Introduction

Breast cancer is a disease that touches many Canadians. It is the most common cancer and the second leading cause of cancer-related death among Canadian women [1]. In 2024, it is estimated that 30,500 women will be diagnosed with breast cancer, representing 25.4% of all new cancers diagnosed (excluding non-melanotic skin cancers) [2]It is also estimated that 5,500 will die from the disease, representing 13.5% of all cancer deaths among this group in 2024. The treatments for breast cancer are improving and offer more and more hope for women with breast cancer. Mortality from breast cancer is declining, from 41.7 deaths per 100,000 in 1989 to an estimated rate of 21.8 deaths per 100,000 in 2024 [2].

We all want to find ways to continue to reduce the burden of this disease. That's why the Canadian Task Force on Preventive Health Care (Task Force) conducted a comprehensive evidence review on breast cancer screening, including recent observational trials, randomized controlled trials, and modelling. These were considered along with data from Statistics Canada and other sources to make sure we had the best, most recent and fulsome evidence for these draft recommendations.

The draft recommendations for breast cancer screening are for women* at average risk or at moderately increased risk**. They do not apply to those with a personal or extensive family history of breast cancer, genetic mutations that would increase breast cancer risk, or symptoms suggestive of breast cancer.

> *Cisgendered women, transgender men and nonbinary or other individuals assigned female at birth (who did not have bilateral mastectomy)
> **Moderately increased risk is defined in here as 12-20% lifetime risk which comprise women with dense breast category C or D or women with a moderate family history defined as one first degree relative or two second degree diagnosed after age 50. Any more extensive family history or multiple risk factors (e.g., high breast density and a family history of breast cancer) may put an individual at high lifetime risk. *(for more detail see https://www.cdc.gov/genomics/disease/breast_ovarian_cancer/risk_categories.htm)*

Draft recommendations

Recommendations

Breast cancer screening is a personal choice.

Women[1] aged 40 to 74 should be provided information about the benefits and harms of screening to make a screening decision that aligns with their values and preferences. If someone in this age range is aware of this information and wants to be screened, they should be offered mammography screening every 2 to 3 years.

[1] Cisgendered women, transgender men and nonbinary or other individuals assigned female at birth (who did not have bilateral mastectomy)

This information should be accessible and shared in absolute numbers[2]. It should include how age, family history, race and ethnicity, and breast density (if known) may impact benefits and harms of screening. Tools are available on the Task Force website to support decision making and discussions with healthcare providers.

For women aged 40 to 49, based on the current evidence (trials, observational studies, modelling and a review on values and preferences), we suggest not to systematically screen with mammography. Because individual values and preferences may differ, those who want to be screened after being informed of the benefits and harms should be offered screening every 2 to 3 years (conditional recommendation, very low certainty).

Benefits and harms: In ages 40 to 49, we found that the harms may outweigh the benefits.

Patient values and preferences: Our systematic review on values and preferences showed that a majority of patients aged 40 to 49 may not weigh the benefits as greater than the harms. However, all sources of information, including patient partners/clinical expert feedback, demonstrated variability in patient values and preferences.

Race and ethnicity: There are data showing variability in incidence, mortality, subtype and stage at diagnosis (e.g., higher mortality in Black women for this age group, even if lower incidence compared to White women). But there is a lack of data on the benefits and harms and on values and preferences from racial and ethnically diverse populations.

For women aged 50 to 74, based on the current evidence (trials, observational studies modelling and a review on values and preferences), we suggest screening with mammography every 2 to 3 years. Because individual values and preferences may differ, it is important that women aged 50 to 74 have information about the benefits and harms of screening to make their decision (conditional recommendation, very low certainty).

Benefits and harms: In ages 50 to 74, we found that the benefits may outweigh the harms.

Patient values and preferences: Our systematic review on values and preferences showed that a majority of patients aged 50 to 74 may weigh the benefit as greater than the harms. However, all sources of information, including patient partners/clinical expert feedback, demonstrated variability in patient values and preferences.

Race and ethnicity: There are data showing variability in incidence, mortality, subtype and stage at diagnosis (e.g., higher mortality in First Nation and Métis women for ages 60 to 69, even with similar incidence to White women). But there is a lack of data on benefits and harms and on values and preferences from racial and ethnically diverse populations.

[2] Absolute numbers give you an understanding of the actual impact of an intervention in real numbers. It tells you how many people will benefit or be harmed from the intervention. Relative risk reduction can be misleading if the baseline risk in a population (the risk without the intervention) is very low. For example, if the risk of dying of a disease is 2% (or 2 out of 100 people) and the treatment reduces it to 1% (or to 1 out of 100 people), the relative risk reduction would be 50%, which sounds impressive. In absolute terms, however, this means 1 fewer people out of 100, which gives a better representation of the benefit.

For women aged 75 and above, based on the current evidence (observational studies and modelling; no trials available), we suggest not to screen with mammography (conditional recommendation, very low certainty).

Benefits and harms: In ages 75 and above, there is a lack of information. But there is concern that the harms outweigh the benefits if screening continues beyond age 74.
Patient values and preferences: Our systematic review on values and preferences showed that a majority of patients aged 75 and above may weigh the benefits as greater than the harms for continuing screening beyond age 74. However, all sources of information, including patient partners/clinical expert feedback, demonstrated variability in patient values and preferences.
Race and ethnicity: There was a lack of data on benefits and harms from racial and ethnically diverse populations.

Recommendations on supplemental screening

For women with moderately increased risk due to high breast density (Category C and D), we did not find any evidence on the benefits of supplemental screening for outcomes important to patients (e.g., stage at diagnosis, death). Therefore, we do not suggest the use of MRI or ultrasound as supplementary screening tests for people with dense breasts (conditional recommendation, very low certainty).

If interested in screening, women who are aware that they have moderately increased risk due to high breast density (Category C and D) should refer to the recommendation that corresponds to their age group.

For women with moderately increased risk due to a family history[3] of breast cancer, we did not find any evidence on the benefits of supplemental screening for outcomes important to patients (e.g., stage at diagnosis, death). Therefore, we do not suggest the use of MRI or ultrasound as supplementary screening tests for people at moderately increased risk due to a family history of breast cancer (conditional recommendation, very low certainty).

If interested in screening, women with moderately increased risk due to a family history of breast cancer should refer to the recommendation that corresponds to their age group.

[3]Moderately increased risk due to a family history of breast cancer is defined as one first-degree or two second-degree relatives diagnosed after age 50. Any more extensive family history or multiple risk factors (e.g., high breast density and a family history of breast cancer) may put an individual at high lifetime risk. (for more details see https://www.cdc.gov/genomics/disease/breast_ovarian_cancer/risk_categories.htm)

What do the recommendations mean?

If you are a patient	If you are a primary care provider	For breast cancer screening programs
Breast cancer screening is a personal choice. Make sure you have the information about the benefits and harms of screening in order to make a screening decision that aligns with your values and preferences. Tools are available on the Task Force website to help support decision-making or discussions with a healthcare provider. These recommendations are for people who are at average to moderate risk of breast cancer and do not have any breast symptoms. If you have symptoms suggestive of breast cancer (e.g., a lump), these recommendations do not apply to you. You should speak to a healthcare provider.	If a woman aged 40 to 74 is considering screening, provide information in absolute numbers, about the possible benefits and harms. When possible, this should be done through a process of shared decision-making to arrive at a decision that aligns with the woman's values and preferences. Although the recommendation is favourable to screening in people 50 to 74 years, providing information about benefits and harms is still important. Tools are available on the Task Force website to support shared decision-making discussions. If a woman aged 40 to 74 decides to participate in screening, offer them mammography screening.	Regardless of whether people access screening programs through self-referral, invitation, or a healthcare provider, clear information, in absolute numbers, about the possible benefits and harms should be provided. Tools are available on the Task Force website. Programs should use the number of women able to make an informed decision as a quality metric. Programs should gather data related to race and ethnicity.

Methods

The recommendations were informed by three systematic reviews (including one based on the findings from the recent United States Preventive Services Task Force (USPSTF) review[3]), a modelling study, Statistics Canada data, Canadian breast cancer screening program data from the Canadian Partnership Against Cancer, and consultation with patient partners and clinical experts engaged in the working group, and various other stakeholders through an online portal and a Knowledge Exchange Event.

The research plan[4] for this guideline update, which outlines the key questions and types of evidence being considered, was published in September 2023.

Systematic reviews

The task force commissioned three Evidence Review and Synthesis Centres (ERSCs) to conduct the systematic reviews for this guideline update. The Task Force breast cancer screening working group with input from patient partners, clinical experts, ERSC teams, and the Science team at the Public Health Agency of Canada (PHAC), developed three key questions (KQs) on 1) effectiveness, 2) comparative effectiveness, and 3) relative importance placed on the benefits and harms of different mammography-based breast cancer screening strategies. The working group considered reduction in breast cancer related mortality, all-cause mortality, treatment-related morbidity, and stage distribution of breast cancer as critical or important benefits, and overdiagnoses, additional testing (no cancer) rates (formerly referred to as 'false positives'), and interval cancers as critical or important harms outcomes in this guideline. Thresholds for minimally important differences for these outcomes over 10 years (since most data was for this time frame) were established by the working group, patients, and experts according to Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology.

The evidence review for KQ1 was an update of the 2017 evidence review[5] on the effectiveness of different mammography-based breast cancer screening strategies, with changes to incorporate observational studies that include a comparator group, analyses for different ethnic groups, and studies where all participants have dense breasts. For KQ1, the Task Force also commissioned a second independent research group to conduct a systematic review on observational studies only, following the same research plan without direction from the working group. This was done as a verification step to ensure results did not vary due to working group choices or interpretation of the inclusion criteria. Despite minor differences in the interpretations of the eligibility criteria, the results of the two systematic reviews were very similar. For the deliberation purposes, the Task Force focused on the Ottawa ERSC KQ1 review.
The evidence review for KQ2 summarized the findings from the recent USPSTF review[3] on the comparative effects of different mammography-based screening strategies. The review for KQ3 was an update to the 2018 review[6] evaluating values and preferences for breast cancer screening, with the addition of examining health-state utility values (HSUVs) from health states related to screening, stage at cancer diagnosis, and curative treatments.

For more information about review methods, please see the linked documents.

Modelling

The Task Force commissioned a modelling analysis of different breast cancer screening scenarios in the average risk Canadian population using the OncoSim-Breast microsimulation model [7] to inform the breast cancer screening guideline update. The analysis modeled the incremental benefits and harms, and the cost-effectiveness of breast cancer screening with

digital mammography according to different ages to start screening, ages to stop screening, and screening intervals (Table 1). The model population excluded women at high risk of breast cancer according to their family history, defined as having at least one family member with a history of breast cancer diagnosed before the age of 50. Analyses were conducted to model outcomes over a lifetime, and assumed that all of those eligible would participate in breast cancer screening (100% participation and adherence rates).

The modelling results are based on the OncoSimX-Breast model version 3.6.2.5. A new version, OncoSim-Breast version 3.6.3.9, was recently developed. Up to date results from this new version will be shared soon. The modelling report is forthcoming.

Table 1: Screening Scenarios under comparison

Interval	**Age group**	**Outputs**
Annual	Age to start screening: 50-74 45-74 40-74 Age to stop screening: 50-79 45-79 40-79	Number of Mammograms performed Number of Cancers detected (DCIS / Invasive) Number of Biopsies performed QALYs (total/gained) Life years gained Breast Cancer Mortality Stage at Diagnosis Exposure to treatment (mastectomy/ lumpectomy) False Positives Overdiagnosis* Interval Cancers Incremental Cost Effectiveness Ratio (ΔCost/ΔQALY)
Biennial	Age to start screening: 50-74 45-74 40-74 Age to stop screening: 50-79 45-79 40-79	
Hybrid (annual to age 49 followed by biennial)	Age to start screening: 40-74 45-74 Age to stop screening: 40-79 45-79	

*Novel approach was derived to be able to obtain an estimate of overdiagnosis from OncoSim.

A Grading of Recommendations, Assessment, Development and Evaluation (GRADE) assessment was conducted by the Science team at PHAC.

Screening program data

To calculate the rates of screening mammography requiring additional imaging in those without breast cancer (formerly referred to as “false positives”), we used the CPAC 2011-2012 report[8]. This report is the most recent publicly available Canadian data on recall, cancer detection, and non-malignant biopsy rates stratified by initial versus subsequent screens and by age decade that could be used for these calculations. Additional data was received from CPAC from two provinces for the 2019 screening year, and additional searches for provincial and territorial

screening program data were performed to confirm the validity of using the 2011/12 CPAC data (see Appendix 20 in the systematic review on effectiveness).

Statistics Canada data
Statistics Canada provided new Canadian data on breast cancer incidence, subtypes, stage and mortality based on race/ ethnicity and age. Comparisons for screened versus non-screened individuals were not available for these data.

A recently published paper analyzed breast cancer incidence trends in younger women using Statistics Canada data[9].

Additional data on race and ethnicity
PHAC conducted a search in Medline, Embase, Global Health, and Scopus databases for publications from 2010 to July 23, 2023 to identify any other published Canadian data related to disparities that may exist on breast cancer risk and mortality based on race and ethnicity.

Patient engagement
The Knowledge Translation group at St. Michael's Hospital (Toronto) recruited three patient partners to support the working group (two with lived experience) via advertisement on public websites (i.e., Craigslist and Kijiji). These patient partners received training, attended regular working group meetings, and reviewed key documents during the research planning and evidence synthesis phases. Their perspectives, based on their values and preferences, were incorporated in the development of the research plan, outcome rating, and interpretation of research findings.

Patient input was also sought via the Task Force Public Advisory Network (TF-PAN) in two phases[10]. In phase 1, TF-PAN members attended a virtual education session on this guideline on April 26, 2024. In a subsequent session (May, 3, 2024), they provided feedback on the draft recommendations and key messages.

External and content expert review
Four clinical and content experts, including a medical oncologist, a surgical oncologist, a radiologist, and a radiation oncologist, were involved in the breast cancer screening working group, attending working group meetings, and contributing to the development of the research plan, outcome rating, and interpretation of evidence. As per the Task Force methods, they did not vote on the direction or strength of the evidence but did provide input on the wording of the recommendations.

In addition, through the external stakeholders' review process, coordinated by the Task Force Office and the Science team, 24 organizational reviewers from 17 organizations, and two individuals reviewed the research plan and provided input.

A summary of the public comments received on this draft and how they were addressed will be included in the final guideline.

Online Public Portal
The Task Force hosted an online portal during the month of August 2023 through which Canadians could provide information to be considered for the guideline update. We received 145 documents from 19 individuals and 9 organizations which were considered by the evidence centres for inclusion in the systematic reviews for the guideline.

Knowledge Exchange Event
Task Force representatives attended a two-day virtual knowledge exchange event hosted by PHAC in September 2023. People with lived experience, Canadian and international experts, health professionals, academics and researchers, representatives from patient advocacy groups, Indigenous and racialized communities, non-governmental organizations, provinces and territories, among other shared their perspectives on various topics related to breast cancer screening. The shared perspectives (also published in a report[11]) were considered in the development of this guideline.

Knowledge translation tools
The Knowledge Translation Program at St. Michael's Hospital (Toronto) developed draft knowledge translation tools for clinicians and patients that accompany the draft recommendations. The tools were informed by feedback from clinicians and patients and can help women make evidence-informed screening decisions aligned with their priorities.

Results

Benefits of mammography screening

Women aged 40-49 years at average risk for breast cancer

1. All-cause mortality

RCTs: Using a minimally important difference (MID) threshold of 1.0 per 1,000, a meta-analysis of seven RCTs [12–17] found that compared to no screening, screening may result in little to no difference in all-cause mortality over 10 years, (absolute risk difference (ARD): 0.13 fewer per 1,000, 95% confidence interval (CI): 0 fewer to 0.25 fewer) (low certainty evidence).

Observational studies and mathematical model: No data.

2. Mortality from breast cancer

Summary: Using a MID threshold of 1.0 per 1,000, screening may result in little to no difference in breast cancer mortality over 10 years (low to very low certainty evidence). Using a lower MID threshold of 0.5 per 1,000, the impact of screening women age 40 to 49 on breast cancer mortality ranged from little to no difference to a benefit depending on study type (low to very low certainty evidence).

> RCTs: Among average risk women aged 40 to 49 years, a meta-analysis of eight RCTs[12,13,18–21] found (using a MID threshold of 1.0 or 0.5 per 1000) that compared to no screening, screening for breast cancer with mammography may make little to no difference in reducing breast cancer mortality over 10 years (ARD: 0.27 fewer breast cancer deaths per 1,000, 95% CI: 0.13 fewer to 0.40 fewer) (low certainty evidence).
>
> Observational studies: There was very low certainty evidence from observational studies ranging from little to no difference to a reduction (using a MID threshold of 1.0 and 0.5 per 1000 respectively) in breast cancer mortality over 10 years (7 case-control studies[22–28], ARD: 0.79 fewer per 1,000, 95% CI: 0.65 fewer to 0.92 fewer; 4 cohort studies[29–32], ARD:0.94 fewer per 1,000, 95% CI: 0.77 fewer to 1.06 fewer). Additional findings from observational studies (n = 3) include 0.03 fewer breast cancer deaths per 1,000 person-

years (i.e., 0.3 deaths for 1,000 among women over 10 years) age 40 to 49 following the implementation of breast cancer screening programs[33,34] and lower breast cancer mortality in provinces where individuals aged 40 to 49 years are included in mammography screening programs[35] (incidence based mortality rate ratio: 0.92, 95% CI: 0.85 to 0.99), but the evidence from all studies was very uncertain (very low certainty evidence).

Mathematical model: Estimated from the mathematical model, biennial screening starting at age 40 and continuing to age 74 may result in fewer breast cancer deaths when compared to biennial screening from age 50 to 74 years (0.52 fewer per 1,000), but the evidence was very uncertain (very low certainty evidence).

3. Stage at diagnosis

RCTs: Compared to no screening, findings from a single RCT[36] suggest that screening may make little to no difference in the number of women with breast cancer diagnosed at Stage II or higher based on a minimally important threshold of 3 per 1,000 (ARD:1 more per 1,000, 95% CI: 1 more to 3 more), but the evidence was very uncertain (very low certainty evidence).

Observational studies: No data.

Mathematical model: Model-based estimates suggest that biennial screening from age 40 to 74 may make little to no difference in stage at diagnosis when compared to biennial screening from age 50 to 74 (Stage II or higher using a MID threshold of 3.0 per 1,000: 1.68 fewer per 1,000; Stage III or higher using a MID threshold of 2.0 per 1,000: 0.83 fewer per 1,000; Stage IV using a MID threshold of 1.0 per 1,000: 0.25 per 1,000) (low certainty evidence for all outcomes).

4. Treatment outcomes

RCTs and Observational studies: Regarding treatment outcomes, there was no available evidence from RCTs or observational studies comparing screened versus unscreened women.

Mathematical model: Using a MID threshold of 5.0 per 1,000 for radiation and 2.0 per 1,000 for chemotherapy and breast surgery, the model found that when compared to starting at age 50, biennial screening starting at age 40 and continuing to age 74 may make little to no difference on breast cancers requiring radiation (ARD: 0.89 fewer per 1,000) or any breast surgery (i.e., mastectomy or breast conserving surgery) (ARD: 0.04 more per 1,000) but may result in fewer requiring chemotherapy (ARD: 2.23 fewer per 1,000) (low certainty evidence for all outcomes).

There was no evidence from any source (RCTs, observational studies, model) regarding the effect of screening (versus no screening) on surgical management of axilla.

5. Life-years gained

RCTs and Observational studies: No data.

Mathematical model: Model estimates suggest that screening biennially from age 40-74 may result in 16.13 more life-years gained and 11.22 more health-adjusted life-years per 1,000 compared to starting screening at age 50 (very low to low certainty evidence across outcomes). Life-years gained measures the total added years of life within a specific screening cohort (e.g., screening age 40-49) over a lifetime. However, it should not be divided to provide an 'average life-years gained' as the gains are not equally distributed and probably only realized by those with breast cancer.

6. Other benefit outcomes

RCTs, observational studies, mathematical model: No data for breast cancer morbidity (as measured by a tool) or health-related quality of life.

7. CNBSS

Including or excluding the Canadian National Breast Screening Study (CNBSS) (or other high risk of bias RCTs) did not meaningfully change the outcomes estimates for ages 40-49 (e.g., Including all RCTs: Breast cancer mortality RR=0.85 (95% CI: 0.78 to 0.93) vs without CNBSS and other high risk of bias RCTs: RR=0.87 (95% CI:0.74-1.01).

Women aged 50-59 years at average risk for breast cancer

1. All-cause mortality

RCTs: Using the same MID thresholds as described above (i.e., 1.0 per 1,000) for all-cause mortality over 10 years, screening may result in little to no difference when compared to no screening (3 RCTs[14,37], 0.31 fewer per 1,000, 95 % CI: 0 fewer to 0.61 fewer) (low certainty evidence).

Observational studies and mathematical model: No data.

2. Mortality from breast cancer

Summary: Using a MID threshold of 1.0 per 1,000, the impact of screening women age 50 to 59 on breast cancer mortality over 10 years ranged from little to no difference to a benefit depending on study type (low to very low certainty evidence). Using a MID threshold of 0.5 fewer deaths per 1,000, compared to no screening, screening may reduce breast cancer mortality over 10 years in women aged 50 to 59 years but results were very uncertain (very low certainty evidence).

RCTs: Using a MID threshold of 1.0 per 1,000, screening may result in little to no difference when compared to no screening (n = 6 studies[18,20,21,38], ARD: 0.50 fewer breast cancer deaths per 1,000, 95% CI: 0.23 fewer to 0.73 fewer (low certainty evidence). Using a MID threshold of 0.5 fewer per 1,000, on the above evidence, screening may reduce breast cancer mortality over 10 years in women aged 50 to 59 years when compared to no screening but the evidence was very uncertain (very low certainty)

Observational studies: Evidence from observational studies (n = 7 case control[22–25] and 4 cohort studies[29–32]) was very uncertain. Using a MID threshold of either 1.0 or 0.5 per 1,000, screening may reduce breast cancer mortality over 10 years in women aged 50-59 years (case control: ARD: 1.45 fewer per 1,000, 95% CI: 1.19 fewer to 1.68 fewer; cohort: ARD: 1.72 fewer per 1,000, 95% CI: 1.42 fewer to 1.95 fewer (very low certainty evidence). Two observational studies[33,34] reported a range of 1.3 fewer to 0.2 more deaths from breast cancer per 1,000 over 10 years among women 50 to 59 years of age following the implementation of breast cancer screening programs (very low certainty).

Mathematical model: Model findings on breast cancer mortality for women 50 to 74 years of age, when compared to no screening, are described below (see benefits for 'women of all ages at average risk for breast cancer').

3. Stage at diagnosis

RCTs: Using a MID threshold of 3.0 per 1,000, screening (versus no screening) may make little to no difference in the number of women with breast cancer diagnosed at Stage II or higher (1 RCT[36], ARD: 0 fewer per 1,000, 95% CI: 1 fewer to 2 more), but the evidence was very uncertain (very low certainty evidence).

There was no evidence from RCTs on cancers diagnosed at Stage III or higher or at Stage IV.

Observational studies: No data.

Mathematical model: Model findings on stage at diagnosis for women 50 to 74 years of age, when compared to no screening, are described below (see benefits for 'women of all ages at average risk for breast cancer').

4. Treatment outcomes, life-years gained, other benefit outcomes

RCTs and Observational studies: There was no evidence from RCTs or observational studies comparing screened vs unscreened women on treatment outcomes (including surgical management of axilla), life-years gained, or other benefit outcomes for women aged 50 to 59 years (see benefits for 'women of all ages at average risk for breast cancer').

Mathematical model: Model findings on treatment-related outcomes (i.e., chemotherapy and radiation) for women 50 to 74 years of age, when compared to no screening, are described below (see benefits for 'women of all ages at average risk for breast cancer').

5. CNBSS:

Excluding the Canadian National Breast Screening Study (CNBSS) and other high risk of bias RCTs resulted in only one applicable trial for ages 50-59 showing no effect of screening. Including all RCTs: Breast cancer mortality RR=0.81 (95% CI: 0.67 to 0.98) vs without CNBSS and other high risk of bias RCTs: RR=1.00 (95% CI:0.72 to 1.38).

Women aged 60-69 years at average risk for breast cancer

1. All-cause mortality

RCTs: Using a MID threshold of 1.0 per 1,000 for all-cause mortality, screening in women aged 60 to 69 years may result in little to no difference when compared to no screening but the evidence was very uncertain (2 RCTs[14], ARD: 0.71 fewer per 1,000, 95% CI: 0 fewer to 1.43 fewer) (very low certainty evidence).

Observational studies and mathematical model: No data.

2. Mortality from breast cancer

Summary: Using a MID threshold of 1.0 per 1,000, the impact of screening in women aged 60 to 69 years ranged from little to no difference to a benefit depending on study design (low to very low certainty evidence). Using a MID threshold of 0.5 per 1,000, screening may reduce breast cancer mortality over 10 years in women aged 60 to 69 years but results were very uncertain (very low certainty).

RCTs: Using a MID threshold of 1.0 per 1,000, screening in women aged 60 to 69 years may result in little to no difference in breast cancer mortality when compared to no screening (4 RCTs[13,18,19,21], ARD: 0.65 fewer per 1,000, 95% CI: 0.30 fewer to 0.95 fewer) (low certainty evidence). Using a MID threshold of 0.5 per 1,000, screening in this age group may reduce breast cancer mortality over 10 years when compared to no screening but the evidence was very uncertain (very low certainty evidence).

Observational studies: Using both MID thresholds for breast cancer mortality (i.e.,1.0 per 1,000 and 0.5 per 1,000), evidence from observational studies (n = 7 case-control[22–25,27,28] and 4 cohort studies[29–32]) suggests that compared to no screening, screening women aged 60 to 69 years may reduce breast cancer mortality over 10 years (case control: ARD: 1.89 fewer per 1,000, 95% CI: 1.55 fewer to 2.19 fewer; cohort: ARD: 2.24 fewer per 1,000, 95% CI: 1.85 fewer to 2.54 fewer (very low certainty evidence)) but the evidence was very uncertain (very low certainty evidence). Across two observational studies[33,34], there was very low certainty evidence of 0.17 fewer to 0.21 more deaths per 1,000 person-years among women aged 60 to 69 years and 60 to 74 years, respectively, following the implementation of breast cancer screening programs (or 1.7 fewer to 2.1 more for 1,000 women over 10 years).

Mathematical model: Model findings on breast cancer mortality for women 50 to 74 years of age, when compared to no screening, are described below (see benefits for ‘women of all ages at average risk for breast cancer’).

3. Other benefit outcomes:

RCTs and observational studies: No data (for stage at diagnosis, breast cancer morbidity (as measured by a tool), treatment outcomes (including surgical management of axilla), life-years gained, and health-related quality of life).

Mathematical model: Model findings on stage at diagnosis and treatment-related outcomes (i.e., chemotherapy and radiation) for women 50 to 74 years of age, when compared to no screening, are described below (see benefits for 'women of all ages at average risk for breast cancer').

Women aged 70-74 years at average risk for breast cancer

1. Mortality from any cause

RCTs: Using a MID threshold of 1.0 per 1,000, breast cancer screening in women aged 70 to 74 years may reduce all-cause mortality over 10 years when compared to no screening, but the evidence was very uncertain (2 RCTs[14], ARD: 1.41 fewer per 1,000, 95% CI: 0 to 2.81 fewer) (very low certainty evidence).

Observational studies and mathematical model: No data.

2. Mortality from breast cancer

Summary: Using a MID threshold of 1.0 per 1,000, the impact of screening women aged 70 to 74 on breast cancer mortality is very uncertain and ranged from little to no difference to a benefit depending on study design (very low certainty evidence). Using a MID threshold of 0.5 per 1,000, screening may reduce breast cancer mortality over 10 years in women age 70 to 74 years but results were very uncertain (very low certainty evidence).

RCTs: Using a MID threshold of 1.0 per 1,000, when compared to no screening, screening may result in little to no difference in breast cancer mortality over 10 years in women age 70 to 74 years, but the evidence was very uncertain (2 RCTs[13,19], ARD: 0.92 fewer per 1,000, 95% CI: 0.43 fewer to 1.43 fewer) (very low certainty evidence). However, using a MID threshold of 0.5 per 1,000, screening (versus no screening) may reduce breast cancer mortality over 10 years in this age group, but the evidence was very uncertain.

Observational studies: Using both MID thresholds (i.e.,1.0 per 1,000 and 0.5 per 1,000), evidence from observational studies (n = 7 case-control[22–25,27,28] and 4 cohort studies[29–32]) suggests that compared to no screening, screening women aged 70 to 74 years may reduce breast cancer mortality over 10 years (case control: ARD: 2.68 fewer per 1,000, 95% CI: 2.20 fewer to 3.11 fewer; cohort: ARD: 3.17 fewer per 1,000, 95% CI: 2.62 fewer to 3.60 fewer (very low certainty evidence)) but the evidence was very uncertain (very low certainty evidence). One observational study[33] reported 0.02 more breast cancer deaths per 1,000 person-years among women aged 70 to 79 years following implementation of breast cancer screening programs, but the evidence was very uncertain (very low certainty evidence). There was also very low certainty evidence from a single observational study[39] suggesting that continued annual screening from age 70

to 74 years may reduce breast cancer death when compared to stopping at age 69, (0.81 fewer per 1,000 over 10 years, 95% CI: 0.19 fewer to 1.37 fewer).

Mathematical model: Model findings on breast cancer mortality for women 50 to 74 years of age, when compared to no screening, are described below (see benefits for 'women of all ages at average risk for breast cancer').

3. Stage at diagnosis

RCTs: No data.

Observational studies: One observational study[40] reported a range of 0.7 fewer to 1.3 fewer stage III+ cancers per 1,000 over 10 years among women 70 to 75 years of age following the implementation of breast cancer screening programs (very low certainty evidence).

Mathematical model: Findings on stage at diagnosis for women 50 to 74 years of age, when compared to no screening, are described below (see benefits for 'individuals of all ages at average risk for breast cancer').

4. Treatment outcomes

RCTs: No data.

Observational studies: No observational studies reported on treatment outcomes reported within the screening population.

One observational study[41] reported that among women diagnosed with breast cancer who had continued annual screening from 70 to 74 years, fewer received chemotherapy (59 fewer per 1,000 women with breast cancer) and radical mastectomy (43 fewer per 1,000 people with breast cancer) but more received radiation (111 more per 1,000 women with breast cancer) and simple mastectomy (9 more per 1,000 women with breast cancer) as compared to those who stopped screening at age 69 (low certainty for all outcomes). MID thresholds do not apply to this population as they measure per 1000 screens (not per women diagnosed with breast cancer).

There was no data on the surgical management of axilla.

Mathematical model: Findings on treatment-related outcomes (i.e., chemotherapy and radiation) for women 50 to 74 years of age, when compared to no screening, are described below (see benefits for 'individuals of all ages at average risk for breast cancer').

5. Other benefit outcomes

RCTs and observational studies: No data (for breast cancer morbidity (as measured by a tool), life-years gained, or health-related quality of life).

Table 2: Summary of findings for breast cancer screening by outcome and risk category per 1,000 women over 10 years in a general population

	BrCa Mortality RCT Per 1000 screens *RR: 0.85 (0.78 to 0.93)*		**BrCa Mortality Obs. ATSA Per 1000 screens** *RR: 0.48 (0.41 to 0.57)*		**BrCa Mortality Obs. CC Per 1000 screens** *OR: 0.56 (0.49 to 0.64)*		**ACM RCT Per 1000 screens** *RR: 0.99 (0.98 to 1.00)*	**Stage II or higher RCT Per 1000 screens**	**ODX (Invasive + In situ)**	**i) Additional testing (no cancer) ii). With biopsy Per 1000 screens**
Clinical decision threshold	0.5 fewer	1 fewer	0.5 fewer	1 fewer	0.5 fewer	1 fewer	1 fewer	3 fewer	5 more	150 (additional testing) 15 (biopsy)
40-49 years	0.27 fewer (0.13 fewer to 0.40 fewer)		0.94 fewer (0.77 fewer to 1.06 fewer)		0.79 fewer (0.65 fewer to 0.92 fewer)		0.13 fewer (0 to 0.25 fewer)	1 more (1 more to 3 more) [a]	RCT: 1.95 (0.89 to 3.01) [b]	i) 367.5 ii) 54.7
	⊕⊕◯◯	⊕⊕◯◯	⊕◯◯◯	⊕◯◯◯	⊕◯◯◯	⊕◯◯◯	⊕⊕◯◯	⊕◯◯◯	⊕◯◯◯	⊕⊕⊕◯
50-59 years	0.50 fewer (0.23 fewer to 0.73 fewer)		1.72 fewer (1.42 fewer to 1.95 fewer)		1.45 fewer (1.19 fewer to 1.68 fewer)		0.31 fewer (0 to 0.61 fewer)	0 (1 fewer to 2 more) [c]	RCT: 1.93 (0.24 to 3.86) [d]	i) 286.4[e]-365.5[f] ii) 34.0[e]-46.2[f]
	⊕◯◯◯	⊕⊕◯◯	⊕◯◯◯	⊕◯◯◯	⊕◯◯◯	⊕◯◯◯	⊕⊕◯◯	⊕◯◯◯	⊕⊕◯◯	⊕⊕⊕◯
60-69 years	0.65 fewer (0.30 fewer to 0.95 fewer)		2.24 fewer (1.85 fewer to 2.54 fewer)		1.89 fewer (1.55 fewer to 2.19 fewer)		0.71 fewer (0 to 1.43 fewer)	no evidence	Obs: 1.5 (CI not available)	i) 257.2 ii) 32.8
	⊕◯◯◯	⊕⊕◯◯	⊕◯◯◯	⊕◯◯◯	⊕◯◯◯	⊕◯◯◯	⊕◯◯◯		⊕◯◯◯	⊕⊕⊕◯
70-74 years	0.92 fewer (0.43 fewer to 1.34 fewer)		3.17 fewer (2.62 fewer to 3.60 fewer)		2.68 fewer (2.20 fewer to 3.11 fewer)		1.41 fewer (0 to 2.81 fewer)	no evidence	Obs: 20 (CI not available)	(70+) i) 220.4 ii) 30.4
	⊕◯◯◯	⊕◯◯◯	⊕◯◯◯	⊕◯◯◯	⊕◯◯◯	⊕◯◯◯	⊕◯◯◯		⊕⊕◯◯	⊕⊕⊕◯

Abbreviations: ACM: all-cause mortality; ATSA: adherence to screen analysis; BrCa: breast cancer; CC: case-control study; OBS: Observational study; OR: odds ratio; RCT: randomized controlled trial; RR: Relative risk; ODX: Overdiagnosis. **Explanation:** Red values indicate an increase (rather than a reduction) in risk of outcome. Relative effects are presented in italics.

[a] RR 1.55 (1.23 to 2.11)
[b] RR 1.11 (1.05 to 1.17)
[c] RR 1.09 (0.82 to 1.45)
[d] RR 1.08 (1.01 to 1.16)
[e] Starting screening prior to age 50
[f] Starting screening at age 50

Very low certainty of evidence
Low certainty of evidence
Moderate certainty of evidence
No evidence

*Note: All absolute effect estimates are calculated using the relative effect for each outcome (pooled across included studies, when multiple studies were included for an outcome) and the reported baseline risk in the comparator group (averaged in the case of multiple studies).

Please refer to KT tools for modelling visuals.

Women aged 75 years and older at average risk for breast cancer

1. Mortality from any cause

RCTs, observational studies, mathematical model: No data.

2. Mortality from breast cancer

RCTs: No data.

Observational studies: Findings from one observational study[39] suggest that continued annual screening from 75 to 84 years of age may result in little to no difference in breast cancer mortality when compared to stopping at age 74, but the evidence was very uncertain (ARD: 0 fewer per 1,000 over 10 years, 95% CI: 0.63 fewer to 0.70 more) (very low certainty evidence).

Mathematical model: Data from the model showed that for biennial screening starting at 50 years, stopping screening at 79 compared to 74 years of age may result in similar breast cancer mortality (ARD: 0.16 fewer per 1,000) (low certainty evidence).

3. Stage at diagnosis

RCTs: No data.

Observational studies: One observational study[40] reported a range of 0.1 more to 0.3 more stage III+ cancers per 1,000 over 10 years among women 76 to 80 years of age following the implementation of breast cancer screening programs (very low certainty).

Mathematical model: Model estimates suggest that when compared to biennial screening from 50 to 74 years of age, biennial screening from age 50 to 79 years may make little to no difference on stage at diagnosis (Stage II or higher using a MID threshold of 3.0 per 1,000, ARD: 0.74 fewer per 1,0000; Stage III or higher using a MID threshold of 2.0 per 1,000, ARD: 0.38 fewer per 1,000; Stage IV or higher using a MID threshold of 1.0 per 1,000, ARD: 0.09 fewer per 1,000).

4. Treatment outcomes:

RCTs: No data.

Observational studies: One observational study[41] reported that among people diagnosed with breast cancer who had continued annual screening from 75 to 84 years of age, fewer received chemotherapy (29 fewer per 1,000 people with breast cancer) and radical mastectomy (28 fewer per 1,000 people with breast cancer) but more required radiation (93 more per 1,000 people with breast cancer) and simple mastectomy (7 more per 1,000 people with breast cancer) when compared to those who stopped screened at age 74 (low certainty for all outcomes). MID thresholds do not apply to this population as they measure per 1000 screens (not per women diagnosed with breast cancer).

Mathematical model: Using a MID threshold of 5.0 per 1,000 for radiation and 2.0 per 1,000 for chemotherapy, model estimates suggest that when compared to biennial screening from 50 to 74 years of age, biennial screening from age 50 to 79 years may make little to no difference on treatment outcomes (ARD estimates ranging from 0.19 fewer to 0.12 more per 1,000 across outcomes) (low certainty evidence for all outcomes).

5. Life-years gained:

RCTs and observational studies: No data.

Mathematical model: Compared to stopping at age 74, biennial screening from 50 to 79 years of age may result in 1.21 more life-years gained and 0.29 health-adjusted life-years per 1,000 according to the model (very low to low certainty evidence across outcomes).

6. Other benefit outcomes

RCTs, observational studies, mathematical model: No data.

Women aged ≥40 years (all ages) at average risk for breast cancer

1. Mortality from any cause

RCTs, observational studies, mathematical model: No data.

2. Mortality from breast cancer

RCTs: No data.

Observational studies: One observational study[42] examining the impact of breast cancer screening program implementation over two screening periods (1958-1975 and 1977-2015) reported 0.30 fewer to 0.37 fewer deaths per 1,000 person years from breast cancer within 10 years of diagnosis, but the evidence was very uncertain (very low certainty evidence).

Mathematical model: MID thresholds do not apply to the lifetime estimates from the model. Evidence on breast cancer mortality from the model found that compared to no screening, biennial screening from age 40 to 74 and from age 50 to 74 years may result in 6.97 fewer and 6.45 fewer breast cancer deaths per 1,000 women screened over a lifetime for all eligible women, respectively (low certainty evidence). Therefore, using the lifetime model estimation of 28 deaths per 1,000 without screening, there would be 21 and 21.5 deaths per 1,000 if screening started at 40 and 50 respectively.

3. Stage at diagnosis:

RCTs: Evidence from RCTs suggest that screening may result in fewer cancers diagnosed at stage II or higher when compared to no screening (5 RCTs reported in one publication[36], ARD: 3 fewer per 1,000, 95% CI: 5 fewer to 1 more) but the evidence was very uncertain. For stage III or higher evidence suggests that there was little to no difference from screening (3 RCTs reported in one publication[36], ARD: 1 fewer per 1000, 95% CI: 0 fewer to 1 fewer) but the evidence was very uncertain.

Observational studies: Results from one observational study[43] suggest that screening may make little to no difference on the number of women with Stage II or higher at diagnosis (ARD: 0.5 fewer per 1,000, 95% CI: 0.4 fewer to 0.6 fewer per 1,000), but the evidence was very uncertain (very low certainty evidence).

Mathematical model: MID thresholds do not apply to the lifetime estimates from the model. Model-based estimates suggest that biennial screening from age 50 to 74 years may result in

22.53 fewer breast cancers diagnosed at Stage II or higher, 11.39 fewer diagnosed at Stage III or higher, and 3.39 fewer diagnosed at Stage IV per 1,000 women screened over a lifetime for all eligible women, when compared to no screening (low certainty evidence for all outcomes). Starting screening at age 40 and continuing until age 74 would result in an additional benefit (compared to starting at 50) of 1.68 fewer breast cancers diagnosed at Stage II or higher, 0.83 fewer diagnosed at Stage III or higher, and 0.25 fewer diagnosed at Stage IV per 1,000 women screened over a lifetime for all eligible women, when compared to no screening (low certainty evidence for all outcomes).

4. Treatment outcomes:

RCTs: RCT data on all ages (≥40 years) suggests little to no difference in the number of breast cancers requiring radiotherapy (ARD: 2.85 more (95% CI: 1.42 more to 4.45 more per 1,000) and chemotherapy (ARD: 0.14 fewer (95% CI: 0.79 fewer to 0.68 more per 1,000)[44] (low certainty).

Observational studies: Observational data was very uncertain. One study suggests little to no difference in the number of breast cancers with breast conserving surgery (compared to full mastectomy (ARD: 0.9 more per 1,000, 95% CI 0.73 more to 1.10 more) (very low certainty).

Mathematical model: MID thresholds do not apply to the lifetime estimates from the model. Lifetime modelling data for ages 50 to 74 suggests that biennial screening, when compared to no screening, may result in 12.4 fewer breast cancers requiring chemotherapy, 6.35 more requiring breast surgery (i.e., mastectomy or breast conserving surgery), and 0.75 more requiring radiation per 1,000 women screened over a lifetime for all eligible women (low certainty evidence for all outcomes). Starting screening at age 40 and continuing until age 74 would result in an additional benefit (compared to starting at 50) of 2.23 fewer breast cancers requiring chemotherapy, 0.89 fewer requiring breast surgery (i.e., mastectomy or breast conserving surgery), and 0.75 more requiring radiation per 1,000 women screened over a lifetime among all eligible women (low certainty evidence for all outcomes).

5. Life-years gained and other benefit outcomes

RCTs and observational studies: No data.

Mathematical model: As estimated from the model, biennial screening from 50 to 74 years of age may result in 90.35 more life-years gained and 42.21 more health-adjusted life-years per 1,000 women screened over a lifetime for all eligible women, when compared to no screening (very low to low certainty evidence across outcomes). Starting screening at age 40 and continuing until age 74 would result in an additional benefit (compared to starting at 50) of 16.13 more life-years gained and 11.22 more health-adjusted life-years per 1,000.

Women at moderately increased risk for breast cancer

1. Mortality from any cause

RCTs, observational studies, mathematical model: No data.

2. Mortality from breast cancer

Summary: Direct evidence on the effect of screening for women with a moderately increased lifetime risk of breast cancer, due to family history or dense breasts, was unavailable. However, estimation of breast cancer mortality was possible using indirect methods. To calculate moderately increased risk group, we used an estimate from Engmann et al. [45] suggesting that having a first degree relative increases the lifetime risk by 1.6 times and multiplied the general population risk estimate by 1.6. To calculate a moderately increased risk group due to dense breasts, we used an estimate from the Swedish mammography trial which suggested those with high breast density have a relative increased lifetime risk of 1.9. These calculations have limitations as they are indirect and assume the same effect of screening [46]. We considered harms to be the same as they could not be estimated.

Using a MID threshold of 1.0 or 0.5 per 1,000 the impact of screening 40-49 year olds with moderate family history or dense breasts ranges from little to no difference to a benefit for breast cancer mortality depending on study design (low to very low certainty evidence). Using a MID threshold of 1.0 per 1,000 the impact of screening 50-59 year olds with moderate family history or dense breasts ranges from little to no difference to a benefit for breast cancer mortality depending on study design (low to very low certainty evidence). Using a MID threshold of 0.5 per 1,000 the impact of screening 50-59 year olds with moderate family history or dense breasts is very uncertain but shows a benefit for breast cancer mortality. For all other age groups (i.e., 60-69, and 70-74 years), extrapolated estimates from both RCTs and observational studies (using a MID threshold of 0.5 or 1.0 per 1000) suggest that screening may reduce breast cancer mortality among women with a moderately increased risk of breast cancer due to family history or dense breasts but the evidence was very uncertain. There was no evidence for women 75 years of age and older with moderately increased risk.

RCTs:

40-49: Using a MID threshold of 1.0 per 1,000, RCT evidence for ages 40-49 showed little to no difference for breast cancer mortality among women with moderately increased risk (family history, ARD: 0.44 fewer per 1,000, 95% CI: 0.20 fewer to 0.64 fewer) or dense breasts (ARD: 0.53 fewer per 1,000, 95% CI:0.25 fewer to 0.77 fewer) (low certainty evidence)[47]. Using a MID threshold of 0.5 per 1,000, the above evidence was very uncertain and ranged from little to no benefit for family history to a benefit for those with dense breast (very low certainty evidence).

50-59: Using a MID threshold of 1.0 per 1,000, RCT evidence for ages 50-59 showed little to no difference for breast cancer mortality among women with moderately increased risk (family history, ARD: 0.79 fewer per 1,000, 95% CI: 0.37 fewer to 1.16 fewer) or dense breasts (ARD: 0.95 fewer per 1,000, 95% CI: 0.44 fewer to 1.39 fewer) (low certainty)[47]. Using a MID threshold of 0.5 per 1,000, the above evidence was very uncertain but showed a benefit for family history to a benefit for those with dense breast (very low certainty).

60-69: Using a MID threshold of 1.0 per 1,000, RCT evidence for ages 60-69 showed a benefit for breast cancer mortality among women with moderately increased risk (family history, ARD: 1.04 fewer per 1,000, 95% CI: 0.48 fewer to 1.52 fewer) or dense breasts (ARD: 1.23 fewer per 1,000, 95% CI:0.57 fewer to 1.80 fewer) (low certainty evidence)[47]. Using a MID threshold of 0.5 per 1,000, the above data was very uncertain but also showed a benefit (very low certainty).

70-74: Using a MID threshold of 1.0 or 0.5 per 1,000, RCT evidence for ages 70-74 was very uncertain and showed a benefit for breast cancer mortality among women with

moderately increased risk (family history, ARD: 1.47 fewer per 1,000, 95% CI: 0.69 fewer to 2.16 fewer) or dense breasts (ARD: 1.74 fewer per 1,000, 95% CI:0.81 fewer to 2.55 fewer) (very low certainty evidence)[47].

Observational studies:
40-49: Using a MID threshold of 1.0 or 0.5 per 1,000, observational data for ages 40-49 was very uncertain but indicated a benefit for breast cancer mortality. For women with family history, case-control studies showed: ARD=1.28 fewer per 1,000, (95% CI: 1.04 fewer to 1.48 fewer and cohort studies showed ARD=1.51 fewer per 1,000 (95% CI: 1.25 fewer to 1.71 fewer) (very low certainty evidence). For women at a moderately increased risk of breast cancer due to dense breasts, case-control studies showed: ARD=1.54 fewer per 1,000, (95% CI: 1.26 fewer to 1.79 fewer) and cohort studies showed ARD=1.82 fewer per 1,000 (95% CI: 1.51 fewer to 2.07 fewer) (very low certainty evidence).
50-59: Using a MID threshold of 1.0 or 0.5 per 1,000, observational data for ages 50-59 was very uncertain but indicated a benefit for breast cancer mortality. For women with family history case-control studies showed: ARD=2.33 fewer per 1,000, (95% CI: 1.91 fewer to 2.70 fewer and cohort studies showed ARD=2.76 fewer per 1,000 (95% CI: 2.28 fewer to 3.13 fewer) (very low certainty evidence). For women at a moderately increased risk of breast cancer due to dense breasts, case-control studies showed: ARD=2.77 fewer per 1,000, (95% CI: 2.27 fewer to 3.21 fewer) and cohort studies showed ARD=3.28 fewer per 1,000 (95% CI: 2.71 fewer to 3.72 fewer) (very low certainty evidence).
60-69: Using a MID threshold of 1.0 or 0.5 per 1,000, observational data for ages 60-69 was very uncertain but indicated a benefit for breast cancer mortality. For women with family history case-control studies showed: ARD=3.04 fewer per 1,000, (95% CI: 2.48 fewer to 3.52 fewer and cohort studies showed ARD=3.59 fewer per 1,000 (95% CI: 2.97 fewer to 4.07 fewer) (very low certainty evidence). For women at a moderately increased risk of breast cancer due to dense breasts, case-control studies showed ARD=3.61 fewer per 1,000, (95% CI: 2.95 fewer to 4.18 fewer) and cohort studies showed ARD=4.26 fewer per 1,000 (95% CI: 3.53 fewer to 4.84 fewer) and (very low certainty evidence).
70-74: Using a MID threshold of 1.0 or 0.5 per 1000, observational data for ages 70-74 was very uncertain but indicated a benefit for breast cancer mortality. For women with family history case-control studies showed: ARD=4.31 fewer per 1,000, (95% CI: 3.53 fewer to 5.00 fewer and cohort studies showed ARD=5.10 fewer per 1,000 (95% CI: 4.21 fewer to 5.78 fewer) (very low certainty evidence). For women at a moderately increased risk of breast cancer due to dense breasts, case-control studies showed ARD=5.10 fewer per 1,000, (95% CI: 4.18 fewer to 5.92 fewer) and cohort studies showed ARD=6.03 fewer per 1,000 (95% CI: 4.99 fewer to 6.84 fewer) (very low certainty evidence).

Mathematical model: No data

3. Other benefit outcomes

RCTs, observational studies, mathematical model: No data (for breast cancer morbidity (as measured by a tool), stage at diagnosis, treatment outcomes (including surgical management of the axilla), life-years gained or health-related quality of life)

Harms of screening

Women aged 40-49 years at average risk for breast cancer

1. Overdiagnosis

Summary: Using a MID threshold of 5.0 per 1,000, evidence from three RCTs[48–50] and one observational study[51] suggest that screening (versus no screening) may result in little to no difference to increased overdiagnosis of breast cancers among average risk women aged 40 to 49 years, but the evidence was very uncertain.

> RCTs: Using a MID threshold of 5.0 per 1,000, evidence from three RCTs[48–50] and one observational study[51] suggest that screening (versus no screening) may result in little to no difference in the overdiagnosis of breast cancers among average risk women aged 40 to 49 years, but the evidence was very uncertain (ARD: 1.95 more per 1,000, 95% CI: 0.89 more to 3.01 more). Updated evidence from one RCT suggest that overdiagnosis from screening in the 40s would occur in the 50s if women choose to be screened at that age[52].
>
> Observational studies: Using a MID threshold of 5.0 per 1,000, evidence from one observational study[51] suggests that screening (versus no screening) may result in an increase in overdiagnosis of breast cancers among average risk women aged 40 to 49 years, but the evidence was very uncertain (ARD: 14.2 more per 10,000 person-years (based on 8 year follow-up)) (very low certainty evidence).

2. CNBSS

Including or excluding the Canadian National Breast Screening Study (CNBSS) did not meaningfully change the findings for overdiagnosis (All RCTs including CNBSS: 1.95 per 1,000; Excluding CNBSS: 1.57 per 1,000).

3. Additional testing (no cancer)

Canadian screening program data: Using MID thresholds of 150 per 1,000 for additional imaging with or without biopsy (no cancer) and 15 per 1,000 for additional imaging with biopsy (no cancer), estimates for both outcomes exceeded the thresholds for important harm[47]. Among 1,000 women 40 to 49 years of age screened biennially over a 10 year period, 367.5 probably require additional imaging with or without biopsy but do not have cancer (moderate certainty evidence)[47]. Estimates for additional imaging with biopsy (no cancer) were 54.7 per 1,000 (moderate certainty evidence)[47].

4. Interval cancers

RCTs: Using a MID threshold of 6 per 1000 there were little to no interval cancers among women screening every 18 months (3 per 1000 over 10 years (low certainty)). Among these were 2.8 per 1000 invasive cancers (low certainty) and 0.2 per 1000 in situ cancers (very low certainty).

Women aged 50-59 years at average risk for breast cancer

1. Overdiagnosis

Summary: Using a MID threshold of 5.0 per 1,000, evidence from both RCTs and observational studies suggest that screening (versus no screening) may result in little to no difference in the overdiagnosis of breast cancer among average risk women aged 50 to 59 years.

> RCTs: Using a MID threshold of 5.0 per 1,000, evidence from 2 RCTs[48,49] suggest that screening (versus no screening) may result in little to no difference in the overdiagnosis of breast cancers among average risk women aged 50 to 59 (ARD: 1.93 more per 1,000, 95% CI: 0.24 more to 3.86 more, low certainty evidence).
>
> Observational studies: Using a MID threshold of 5.0 per 1,000, evidence from 2 observational studies[43,51] suggest that screening (versus no screening) may result in little to no difference in the overdiagnosis of breast cancers among average risk women aged 50 to 59, but the evidence is very uncertain (ARD estimates of 4.2 fewer per 10,000 person-years and 0.34 more per 1,000 individuals 50-69, very low certainty evidence).

2. CNBSS

Including or excluding the Canadian National Breast Screening Study (CNBSS) did not meaningfully change the findings for overdiagnosis (all RCTs including CNBSS: 1.93 per 1,000; Excluding CNBSS: 3.95 per 1,000). Excluding CNBSS almost doubled overdiagnosis, but it remained below the MID of 5 per 1,000.

3. Additional testing (no cancer)

Canadian screening program data: Using MID thresholds of 150 per 1,000 for additional imaging with or without biopsy (no cancer) and 15 per 1,000 for additional imaging with biopsy (no cancer), there was moderate certainty evidence that estimates for both outcomes exceeded the threshold for an important harm for this age group[47]. If starting screening at age 50 (i.e., initial and subsequent screens), additional imaging with or without biopsy (no cancer) and with biopsy (no cancer) were 365.5 per 1,000 and 46.2 per 1,000, respectively (moderate certainty evidence)[47]. If starting screening prior to age 50, additional imaging with or without biopsy (no cancer) and with biopsy (no cancer) between ages 50-59 (i.e., subsequent screens) also crossed the MID threshold at 286.4 per 1,000 and 34 per 1,000, respectively (moderate certainty evidence)[47].

4. Interval cancers

RCTs: Using a MID threshold of 6 per 1000 there were little to no interval cancers among women screening every 18 months (1.9 per 1000 over 10 years (low certainty)).

Women aged 60-69 years at average risk for breast cancer

1. Overdiagnosis

RCTs: No data.

Observational studies: Using a MID threshold of 5.0 per 1,000, findings from two observational studies[43,51] suggest little to no difference between screening and no screening on overdiagnosis of breast cancer (ARD estimates of 1.5 more per 10,000 person-years and 0.34 more per 1,000 individuals 50-69), but the evidence was very uncertain (very low certainty evidence).

2. Additional testing (no cancer)

Canadian screening program data: Using MID thresholds of 150 per 1,000 for additional imaging with or without biopsy (no cancer) and 15 per 1,000 for additional imaging with biopsy (no cancer), there was moderate certainty evidence that estimates for both outcomes exceeded the threshold for an important harm[47]. Additional imaging without biopsy (no cancer) and with biopsy (no cancer) were 257.2 per 1,000 and 32.8 per 1,000, respectively (moderate certainty evidence)[47].

3. Interval cancers

RCTs and observational studies: No data.

Women aged 70 years and older at average risk for breast cancer

1. Overdiagnosis

RCTs: No data.

Observational studies: There is low certainty evidence from one observational study[53] that screening women 70 years of age and older may result in more overdiagnosis of breast cancer (70-74 years: 20 more per 1,000; 75-84 years: 23 more per 1,000; 85+ years: 15 more per 1,000).

2. Additional testing (no cancer)

Canadian screening program data:

Using MID thresholds of 150 per 1,000 for additional imaging with or without biopsy (no cancer) and 15 per 1,000 for additional imaging with biopsy (no cancer), there was moderate certainty evidence that estimates for both outcomes exceeded the threshold for an important harm for women 70 years of age and older[47]. Additional imaging without biopsy (no cancer) and with biopsy (no cancer) were 220.4 per 1,000 and 30.4 per 1,000, respectively (moderate certainty evidence)[47].

3. Interval cancers

RCTs and observational studies: No data.

Women aged ≥40 years (all ages) at average risk for breast cancer

1. Interval cancer

RCTs: RCT evidence[15,18–20,54] for interval cancer was suggestive of little to no difference irrespective of screening interval and diagnosis (i.e., invasive only, DCIS only, or invasive and DCIS) (ranging from 0.2 to 3.9 per 1,000 across screening intervals and diagnoses) (very low to low certainty evidence).

Observational studies: There was no evidence from observational studies regarding the effect of screening (versus no screening) on interval cancers for women aged ≥40 years at average risk for breast cancer.

Mathematical model: There is moderate certainty that compared to no screening, over a lifetime, interval cancers were: 21.45 per 1,000 for annual screening in ages 50-74, 33.72 per 1,000 for biennial screening in ages 50-74, and 36.91 per 1,000 for biennial screening in ages 40-74.

There is moderate certainty that compared to biennial screening in ages 50-74, over lifetime, interval cancers were: 12.27 fewer per 1,000 for annual screening in ages 50-74, 1.40 more per 1,000 for hybrid screening in ages 40-74, and 3.19 more per 1,000 for biennial screening in ages 40-74.

Annual versus biennial or triennial screening with mammography

Subgroup analysis by screening interval (previous 2018 review[5]) found that the validity of subgroup effects may lack credibility and observational studies did not report screening interval. Data other than mathematical modelling for this comparison were obtained from the USPSTF systematic review[3,55] with additional interpretation and GRADE analysis[55].

Biennial screening

Benefits

1. Mortality from any cause

RCTs, observational studies and mathematical model: No data.

2. Mortality from breast cancer

Mathematical model: MID thresholds do not apply to the lifetime estimates from the model. Model-based estimates suggest that among women screening from age 50 to 74 years, annual screening may result in 2.00 fewer breast cancer deaths per 1,000 women screened over a lifetime for all eligible women (i.e., 100% full participation and adherence) when compared to biennial screening (low certainty evidence). The effect of annual screening for women 40 to 49 years of age (switching to biennial from 50-74) versus biennial screening 40-74 was also estimated from the model. In this age group, annual screening resulted in a difference of 0.3 fewer breast cancer deaths per 1,000 women screened over a lifetime for all eligible women compared to biennial screening, but the evidence is very uncertain (very low certainty evidence).

3. Stage at diagnosis

Observational studies: Observational data for ages 40-79 suggests that there may be no difference between annual and biennial screening with respect to risk of Stage IIB or higher stage cancers (aRRs ranging from 0.98 to 1.17) or cancers with a less favourable prognosis (RRs ranging from 1.03 to 10.7), but the evidence was very uncertain (very low certainty evidence).

Mathematical model: MID thresholds do not apply to the lifetime estimates from the model. With respect to stage at diagnosis, annual screening in women 50 to 74 years of age may result in 10.43 fewer, 4.11 fewer, and 0.97 fewer Stage II or higher, Stage III or higher, and Stage IV breast cancers per 1,000 women screened over a lifetime for all eligible women, respectively (low certainty evidence) when compared to biennial screening. Annual screening in women 40 to 49 years of age may make little to no difference in breast cancers diagnosed at Stage II or higher (1.37 fewer per 1,000), Stage III or higher (0.57 fewer per 1,000) or at Stage IV (0.17 fewer per 1,000) where results are based on 1,000 women screened over a lifetime for all eligible women compared to biennial screening (low certainty evidence for all outcomes).

4. Treatment outcomes

Mathematical model: MID thresholds do not apply to the lifetime estimates from the model. Annual screening in women 50 to 74 years of age was estimated to result in 0.38 fewer breast cancers requiring radiotherapy, 6.56 fewer requiring chemotherapy, and 1.81 more requiring breast surgery per 1,000 women screened over a lifetime for all eligible women when compared to biennial screening (low certainty evidence). Regarding treatment outcomes in women 40 to 49 years of age, annual screening may make little to no difference in the number of breast cancers requiring chemotherapy (1.41 fewer per 1,000), those requiring radiotherapy (0.42 fewer per 1,000) and any breast surgery (0.15 more per 1,000) (low certainty for all outcomes) where results are based on 1,000 women screened over a lifetime for all eligible women compared to biennial screening (low certainty evidence for all outcomes).

5. Life-years gained

Mathematical model: For women 50 to 74 years of age, the model also estimated 30.05 more life-years gained (low certainty evidence) and 15.86 more health-adjusted life-years gained (very low certainty evidence) with annual screening per 1,000 women screened over a lifetime for all eligible women compared to biennial screening. For women 40 to 49 years of age, the model estimated 7.86 more life-years gained (low certainty evidence) and 5.05 more health-adjusted life-years gained (very low certainty evidence) with annual screening per 1,000 women screened over a lifetime for all eligible women.

Harms

1. Overdiagnosis

RCTs and observational studies: No data.

2. Additional testing (no cancer)

RCTs: No data.

Observational studies: Compared to biennial screening, there was moderate certainty evidence that annual screening with mammography or tomosynthesis probably results in more additional imaging with or without biopsy (no cancer) across all age groups by about 1.5 fold (in age 40-79, 140-189 more per 1,000) (moderate certainty evidence).

Mathematical model: MID thresholds do not apply to the lifetime estimates from the model. The model estimates for outcomes of additional testing (no cancer) with annual screening in ages 50-74 are (moderate certainty evidence): 569.60 more additional imaging with or without biopsy (no cancer) and 50.7 additional imaging and biopsy (no cancer) more per 1,000 women screened over a lifetime compared to biennial screening.

MID thresholds can be applied to estimates from the model that are for specific age group. Annual screening in ages 40-49 versus biennial screening from 40-74 probably leads to more additional imaging with or without biopsy (no cancer) (167.53 more per 1,000, versus MID threshold of 150) (moderate certainty evidence. However, it may make little to no difference on additional testing with imaging and biopsy (no cancer),but was close to the threshold (14.91 more per 1,000, versus MID threshold of 15) (moderate certainty evidence).

3. Interval cancers

RCTs: Findings from KQ1 (5 RCTs[47]) suggest little to no effect of annual compared to >24 month screening interval (age ≥40 years) on interval cancers (low certainty evidence[15,19,20,54,56]).

Observational studies: For interval cancers, the USPSTF review[3] included evidence from one observational study which found 22% of women with interval cancer after annual screening and 27.2% after biennial screening, but the evidence is very uncertain (very low certainty evidence).

Mathematical model: MID thresholds do not apply to the lifetime estimates from the model. Annual screening in women 50 to 74 years of age may result in 12.28 fewer interval cancers per

1,000 women screened over a lifetime for all eligible women compared to biennial screening (moderate certainty evidence). With higher certainty, the model indicated probably little to no difference between annual and biennial screening on interval cancers in women 40 to 49 years of age (1.78 fewer per 1,000) (moderate certainty evidence).

Triennial screening

There was very limited evidence on the effect of annual screening compared to triennial screening. Compared to triennial screening, annual screening may make little to no difference in breast cancer mortality and all-cause mortality among women 40 to 49 years of age based on one RCT and one observational study, but the evidence was very uncertain (very low certainty evidence). In women 50 to 69 years of age, annual screening may reduce the number of invasive interval cancers based on one RCT (low certainty evidence). Evidence on overdiagnosis for this comparison was very uncertain. No other outcomes were reported.

Digital breast tomosynthesis versus digital mammography

Evidence for this comparison was obtained from the USPSTF systematic review[3] with additional interpretation and GRADE analysis[55].

Benefits

1. Mortality from any cause

RCTs, observational studies, and mathematical model: No data.

2. Mortality from breast cancer

RCTs, observational studies, and mathematical model: No data.

3. Stage at diagnosis

RCTs and observational studies: Findings suggest that compared to digital mammography, tomosynthesis may make little to no difference on Stage II+, Stage III+, or other tumour prognostic characteristics among women 45 to 69 years of age at average risk for breast cancer over two rounds of screening 1-2 years apart (low certainty evidence). Evidence also suggested little to no difference between modalities for women with high breast density (i.e., BIRADS C/D or density grade 4) (low certainty evidence). This is based on two RCTs comparing tomosynthesis plus digital mammography to digital mammography alone, and one RCT and one observational study comparing tomosynthesis with synthetic mammography to digital mammography.

Mathematical model: No data.

4. Treatment outcomes

RCTs, observational studies, and mathematical model: No data.

5. Life-years gained

RCTs, observational studies, and mathematical model: No data.

Harms

1. Overdiagnosis

RCTs and observational studies: No data.

Mathematical model: No data.

2. Additional testing (no cancer)

RCTs and observational studies: Compared to digital mammography, tomosynthesis may make little to no difference on additional imaging with or without biopsy (no cancer) among average risk women aged 40 to 79 (low certainty evidence). This is based on two RCTs comparing tomosynthesis plus digital mammography to digital mammography alone, one RCT and one observational study comparing tomosynthesis with synthetic mammography to digital mammography, and one observational study comparing tomosynthesis to digital mammography.

Similar findings were reported when stratified by age (i.e., 40 to 49 and 50 to 69 years) and for women with high breast density (i.e., levels 3-4 Volpara Density Grade, extremely dense breasts using BIRADS). However, for women with lower breast density (i.e., levels 1-2), findings suggest that tomosynthesis may reduce additional testing with or without biopsy (no cancer) after one round of screening but may not after two rounds.

Mathematical model: No data.

3. Interval cancers

RCTs and observational studies: For interval cancers, there was probably little to no difference between modalities (moderate certainty evidence). This is based on two RCTs and 4 observational studies comparing tomosynthesis plus digital mammography to digital mammography alone, one RCT comparing tomosynthesis with synthetic mammography to digital mammography, and one observational study comparing tomosynthesis to digital mammography. Findings for interval cancers were consistent irrespective of age and breast density.

Mathematical model: No data.

Digital mammography with supplementary ultrasound versus digital mammography alone

Evidence for this comparison was obtained from the USPSTF systematic review[3] with additional interpretation and GRADE analysis[55].

Benefits

There was no evidence on the effect of supplementing mammography with ultrasound on most outcomes of interest.

Harms

4. Overdiagnosis

RCTs, observational studies and mathematical model: No data.

5. Additional testing (no cancer)

RCTs and observational studies: Among women of all ages (30 to 80+ years) with a moderately elevated risk for breast cancer (BIRADs 3/4 or at intermediate risk), mammography with supplementary ultrasound may increase additional testing with biopsy (no cancer) in the first round of screening by possibly two-fold (low certainty evidence). This is based on one observational study. It may have little to no effect on interval cancers for women of all ages at moderately elevated risk (BIRADs A/BV or C/D) in the first round of screening (low certainty evidence). This is based on 1 RCT and 1 observational study.

Mathematical model: No data.

6. Interval cancers

RCTs, observational studies and mathematical model: No data.

Digital mammography with supplementary breast MRI versus digital mammography alone

Evidence for this comparison was obtained from the USPSTF draft systematic review[3] with additional interpretation and GRADE analysis[55].

Benefits

There was no evidence on the effect of supplementing mammography with MRI on most outcomes of interest.

Harms

1. Overdiagnosis

RCTs, observational studies and mathematical model: No data.

2. Additional testing (no cancer)

RCTs, observational studies and mathematical model: No data.

3. Interval cancers

RCTs: Among women age 50 to 75 with extremely dense breasts, there is evidence to suggest that supplementing mammography with MRI may make little to no difference on interval cancers (2.5 less per 1,000) in the first round of screening (low certainty evidence). This is based on one available RCT comparing an invitation to MRI versus no invitation after a negative screening mammogram result among those with extremely dense breasts.

Observational studies and mathematical model: No data.

Patient Values and Preferences

Our review of 82 studies found that all of the examined outcomes for this guideline may be important for most patients of any age.

Studies[57] examining the impact ("disutility") on one's quality of life for patients who have experienced one of the outcomes included participants of all ages. They found all of the possible outcomes from screening had an important impact on a patient's quality of life (disutility ≥0.04 on scale 0-1). Diagnosis and treatment of cancer (of any stage and including overdiagnosed cancers) may be much more important than having additional testing (low certainty evidence), especially when considering the shorter timeframe the additional testing would likely impact one's life. However, the additional testing still resulted in important disutility. Findings suggested that the impacts from treatment of an advanced vs early stage cancer (e.g., whether chemotherapy was needed) may be similar.

Studies[57] asking women to make trade-offs between specific outcomes found that for patients 40 years and older, at least a majority (>50%) and possibly a large majority (>75%) probably accept up to six cases of overdiagnoses to prevent one death from breast cancer (moderate certainty evidence). Other evidence with low certainty evidence found that:

- for patients 50-69 years (studies did not include women in their forties), a large majority may think that reducing breast cancer mortality is beneficial even if there is no impact on all-cause mortality.

- for patients 40 years and older, there may be considerable variation in preferences though a majority may accept that a few hundred per 1000 women screened experience additional testing (no cancer) with 10-15 requiring biopsy (no cancer) to prevent one breast cancer death over 10 years.
- for patients 40 years and older, a large majority may accept that at least 25 women experience a recall for more testing to prevent one advanced stage breast cancer.

Studies[57] providing participants with varying estimates of the benefits and harms from screening found acceptability of screening went down as the overall benefits decreased in magnitude across all age groups but was most evident for women in their forties. The uncertainty for the variability in ages 50-74 also varied depending on whether the individual had previously been screened.

Evidence based on different benefit-to-harm ratios found that for low net benefit scenario (i.e., per 1000 screened over 10 year, 0.5 breast-cancer deaths prevented, 239-330 additional tests without cancer, and 2 to 10 overdiagnoses; 2 of 3 studies also had 0.5 all-cause mortality prevented in 1000 screened):

- a majority of those aged 40-49 may not weigh the benefits as greater than the harms (low certainty evidence).
- a large majority of those aged 50-59 may weigh the benefits as greater than the harms (low certainty evidence).

For moderate and high net benefit scenarios:

- a majority but possibly not a large majority of patients aged 40 to 49 may weigh the benefits as greater than the harms from screening (low certainty evidence).
- a majority and possibly a large majority may weigh the benefits as greater than the harms for ages 50 to 69 (low to moderate certainty evidence).

For moderate-to-low net benefit scenario of those who have recently screened:

- a large majority of those aged 70 to 71 probably think the benefits outweigh the harms for continuing to screen (moderate certainty evidence).
- a majority in their mid-70s to early 80s may also prefer to continue screening (low certainty evidence). The impact of one's life expectancy on this preference was unclear.

Based on the results of the systematic review above, there was limited variability. However, the working group also considered the feedback from patient partners and clinical experts which includes how individuals' perception of a small number (i.e., not important vs extremely important) can be highly variable and the differences in how women value the benefits compared to the harms is not always influenced by statistical data. When providing benefits and harms, some may not proceed with screening when informed about the potential harms of screening, and particularly about overdiagnosis. Another important element to take into account is women's' personal experience (e.g., having a family member with breast cancer). The decision whether to screen or not can be an emotional one. The systematic review may accurately capture the full range of preferences or importance that women put on the various outcomes of screening. It is also important to note the lack of studies with diverse populations, race and ethnicity-specific populations, or studies based in Canada for all age groups.

Therefore, the Task Force considered there may be possibly important variability in values and preference and how that informs a subsequent informed decision to be screened. Generally, women likely want screening strategies to prevent breast cancer mortality especially for those at increased risk, but there is variability in the decision to be screened when fully informed (using a small net benefit scenario).

Canadian Epidemiological Data on Breast Cancer

Trends in incidence: Age-standardized incidence of breast cancer in Canada has remained relatively stable over time[58] However, recent Statistics Canada data provides insights into age-specific trends for women of younger ages.

Between 1984-1988 and 2015-2019, incidence rates have risen across age groups between 40-54. Specifically, per 100,000 women, there has been an increase of 11.6 more for ages 40-49, 5.6 more for ages 40-44, 11.6 more for ages 45-49, and 32.2 more for ages 50-54[9]. This translates to statistically significant increases in estimated average annualized breast cancer incidence rates of 0.26% for ages 40-49, 0.19% for ages 40-44, 0.31% for ages 45-49, and 0.59% for ages 50-54[9]. Data are not available by screening status (i.e., screened versus unscreened women).

Trends in mortality: Over a similar period, the Canadian age-standardized mortality rate for breast cancer has decreased from 41.7 deaths per 100,000 in 1989 to an estimated rate of 21.8 deaths per 100,000 in 2024 [2], with an average annual percent change of –1.7% from 1984-2020[2]. Canadian data on mortality trends by age group over time is lacking.

Comparison to the US (2015-2019): Recent changes to US guidelines were partly based on an increase in breast cancer incidence among women 40-49, with an average annual increase of 2% from 2015-2019 (from 162 per 100,000 in 2015 to 172 per 100,000 in 2019)[3,59]. Canada has lower incidence rates and has seen smaller increases in breast cancer incidence compared to the US. From 2015-2019, Canada saw an average annual percent change of 0.77% for women age 40-49 (overall change from 136.45 per 100,000 in 2015 to 140.76 in 2019). But similarly to Canada, breast cancer mortality in the US has continued to decline at an average annual rate of about -1.3% from 2011 to 2020[60].

Race and Ethnicity[61]: Statistics Canada provided data on breast cancer incidence, stage, subtype, and mortality by ethnicity. Breast cancer incidence and stage at diagnosis included data up to 2015 and mortality findings included data up to 2019. The following race/ethnicity categories were included: First Nations, Métis, Inuit, South Asian, Chinese, Black, Filipino, Latin American, Arab, Southeast Asian, West Asian, Korean, Japanese, Multiple Ethnicities, White and Other. Preliminary unpublished data from Statistics Canada suggest disparities in breast cancer outcomes among different racial and ethnic groups in Canada in comparison to the White population (which is the largest demographic group).

The median age at diagnosis for non-White women is younger (52 to 60 years) than for White women (63 years), as is the median age of death from breast cancer (55 to 71) vs 71 years.

Incidence rates also vary by race/ethnicity. The lifetime risk of breast cancer in Black, Chinese, First Nation, and South Asian populations is lower than the risk in White populations. At age 40-49, there are more breast cancers diagnosed among Filipina (37.2 more/100,000 person years (PYs); 3.7 more /1,000 over 10 years*) and multi-ethnic women (77.4 more/100,000 PYs; 7.7 more/1,000 over 10 years*) compared to White women. At age 50-59, there are more breast cancers diagnosed among Arab (65.7 more/100,000 PYs; 6.6 more/1,000 over 10 years*) and Filipina (34.7 more/100,000 PYs; 3.5 more/1,000 over 10 years*) women compared to White women. Other non-White populations had lower or similar rates of breast cancer incidence than White women for all age groups (40-79 years).

Additionally, some non-White populations show a higher proportion of aggressive subtypes of breast cancer (e.g., triple negative), compared to White. While 62.3% of breast cancer cases among White women were classified as less aggressive luminal A, significantly lower proportion were observed among Black (37.9%), Filipina (51.7%), South Asian (52.0%), Chinese (53.2%), and First Nations (55.2%) women. Furthermore, proportions of triple negative cancers were significantly higher among Black women compared to White women (20.5% versus 9.5%), but lower among Filipina (5.4%).

When considering the stage at diagnosis, significantly lower proportions of cases were diagnosed at stage I among Filipina (38.6%), Black (39.2%), South Asian (40.6%), and First Nations (40.7%) women compared to White women (46.5%). Additionally, compared to White women (17.0%), a higher proportion of cancers were diagnosed at stage III or IV (26.3%) for Black women, while a lower proportion were diagnosed at stage III or IV (13.1%) for Chinese women.

For Black women 40-49 years, the mortality rate is higher (21.4 deaths/100,000 PYs, 95%CI: 15.6 to 27.2) compared to White women (15.3/100,000 PYs, 95%CI:14.4 to 16.3) or a difference of approximately 0.61 per 1,000 over 10 years* . Additionally, among women 60-69, both First Nations (64.7/ 100,000 PYs, 95%CI: 53.5 to 76.2) and Métis women (79.2/100,000 PYs, 95%CI: 59.2 to 99.2) experience a higher mortality rates by 1.13 and 2.58 per 1000 over 10 years*, respectively, compared to White women (53.4 /100,000 PYs, 95%CI: 51.7 to 55.2). For the remaining age groups, mortality rates were the same or lower than White women.

*Estimate of 1,000 over 10 years are based on rate differences between groups with 100,000PY denominators, then converted to per 10,000PY. The estimates are based on incidence data up to 2015 and mortality data up to 2019. Using this data to estimate case numbers over 10 years would assume a constant rate into the future. We are also not able to calculate a 95% confidence interval for the estimates at this time. Therefore there is some uncertainty in these estimates.

Rationale

Across all age groups, the Task Force considered that all evidence related to benefits of screening (RCTs, observational, modelling) was of low or very low certainty. Also, while relative effects across these study designs differed, absolute benefits did not vary substantially. Based on these factors, the Task Force considered the range of estimates of benefit and harms from these different data sources. In evaluating the range of effects from various studies, the Task Force considered that estimates from RCTs may underestimate the benefits for those who undergo screening due to the use of intention to screen approaches. Observational studies address this issue by focusing on those who do undergo screening but are likely to overestimate the benefits of screening due to selection or other biases [62]. Modelling estimated a 'perfect'

screening scenario with 100% of women screened and adhering to screening and had findings that typically fell within the range of estimates from RCTs and observational studies, recognising modelling comes with its own assumptions. Benefits may be increased for those at moderately increased risk due to family history or breast density, although there was no direct evidence.

Evidence for the harms of additional imaging and biopsies was of greater certainty as the data came directly from Canadian screening programs. Since the best available data was from 2011-12 screening years, additional imaging (no cancer) may be slightly underestimated as these rates have since increased[63]. For those at moderately increased risk due to family history or breast density, harms data were not available either directly or indirectly.

New data on breast cancer outcomes by ethnicity point to disparities in incidence, subtypes, stage at diagnosis, and mortality for certain age groups. However, it is currently not known how alternative screening strategies for differing race/ethnicities would impact health outcomes in Canada. A recent modelling exercise (2021) done in the US showed that if Black women started screening at 40 years old and White women at 50, the discrepancy in death rate from breast cancer between Black and White women would decrease from 3/1000 to 1/1000[64]. These data may not apply to the Canadian context given different epidemiological trends, health systems, and population demographics. Modelling for women of specific ethnicities was attempted for this Task Force guideline update by a specialized team (IHE) but it is currently impossible with available Canadian data.

Various factors, including genetic predispositions (e.g., higher likelihood of developing triple-negative cancer), environmental factors and/or social determinants (e.g., access to healthcare, structural racism), may contribute to the observed racial and ethnic disparities in breast cancer incidence and mortality. The extent to which each factor contributes to these disparities remains unknown [10]. The Task Force recognizes that these inequities are not simply the result of biological differences, but also include systemic racism and other health disparities.

Women aged 40-49 years

The Task Force considered there may be a small benefit of screening in this age group in terms of mortality reduction (range across all study types did not meet MID threshold of 1/1000 but crossed MID threshold of 0.5/1000). In modelling, screening at 40 versus 50 was also associated with a small reduction in the number requiring chemotherapy, and Stage III and higher cancers (which is reflected in the mortality benefit). Harms of screening (additional imaging or biopsies) in this age group were also judged to be small, but exceeded thresholds of minimally important difference (367.5 and 54.7 per 1000 over 10 years, respectively, versus MID thresholds of 150 and 15, respectively) and were more likely to occur than in other age groups. Compared to the evidence examined in 2018, overdiagnosis was slightly less (2/1000 versus 3/1000) and did not meet a MID threshold of 5/1000. Evidence from the AGE trial suggests that overdiagnosis that would occur in ages 40-49 would occur anyway in ages 50-59 if the individual screens at that age, however being overdiagnosed at an earlier age may be seen as additionally harmful to some [52]. Although more data was identified in this guideline update than in the 2018 guideline, overall magnitude of benefits and harms did not differ substantially from that found in 2018.

Recent data suggests increasing rates of breast cancer in this age group (0.7% annual increase from 2015-2019). More information is needed to understand potential etiologies, including the potential impact of overdiagnosis, societal reproductive changes, obesity, alcohol intake, sedentary lifestyles, and immigration patterns, to inform potential mitigation strategies. Increased incidence is not an immediate trigger for increased screening, as incidence does not necessarily correlate to worse health outcomes. While the age-standardized incidence of breast cancer has remained relatively stable over time[58] and age-specific incidence has increased for some groups [9], age-standardized mortality due to breast cancer has declined by approximately 47% since 1989, from41.7 deaths per 100,000 in 1989 to an estimated rate of 22.1 deaths per 100,000 in 2023 [65] (2024 projection: 21.8 death per 100,000) [2]. Canadian data on mortality by age group over time is lacking, but US data (where age-standardized mortality has decreased similarly to Canada) suggest similar trends in mortality reduction for those under 50 (1.4% average annual decrease, 2007-2022) and those 50-64 (1.9% average annual decrease, 2008-2022)[66].

Data on patient values suggested that the majority of women in this age group provided with a scenario of benefits and harms similar to what was identified in our review of evidence may not weigh the benefits as greater than the harms. It was also unclear if a majority of women in this age group would be accepting of the number of additional imaging and biopsies required per life saved (based on studies or modelling) or advanced stage cancer avoided (based on modelling). Health state utility data suggested that some experience significant disutility from additional testing without cancer. There was also limited disutility depending on stage at diagnosis (Stage III vs I-II). At the same time, studies suggested a tolerance for overdiagnosis greater than what was seen in studies (although this was for a group aged 40 and over, not exclusively those aged 40-49). The Task Force considered that with the findings above, some variability and uncertainty existed in patient values and preferences, and there were concerns about generalizability of these studies to the diversity of the Canadian population. This variability was also highlighted by patient partners and clinical experts supporting the guideline, who stated that some women may place a smaller value on harms of screening, as long as there is a mortality benefit.

While both the benefits and harms of screening were judged as small, given patient preference data and the likelihood of additional imaging, biopsies, and overdiagnosis compared to lives saved, the Task Force judged that overall the harms may outweigh the benefits for this age group, and conditionally suggests against screening (as per GRADE methodology). However, the Task Force considered that some women (e.g., those at moderately increased risk) may achieve greater benefit, and that information on values and preferences is not definitive, and variation exists. Additionally, some racial/ethnic groups (e.g., Inuit, Filipina, Arab) have a younger age at diagnosis and death, and Black women have higher mortality rates in this age group. Because of this uncertainty and variability in the preferences of women eligible for screening, the Task Force puts a strong emphasis on informed patient choice. A one size approach would counter the observed variability in values in preferences. Women in this age group who have been provided clear and transparent information about the benefits and harms of screening, and choose to be screened, should be referred to screening every 2-3 years.

Women aged 50-74 years

Across these age groups, slightly greater benefits were seen in terms of mortality (likely exceeding MID thresholds of 1 per 1,000), with a trend towards greater benefit seen with increasing age. Evidence was limited from RCTs and observational studies on other benefit outcomes. Harms in terms of additional imaging and biopsies without cancer were also smaller in this age group, and became smaller with increasing age, although still exceeding thresholds (ranging from 365.5 to 220.4 per 1,000 over 10 years for additional tests (no cancer) and 46.2 to 30.4 for biopsies (no cancer) versus MID thresholds of 150 and 15 respectively). For those age 50-59 we estimated 2 overdiagnosed cases per 1,000 (compared to 3/1000 in 2018). Overdiagnosis data was limited for other age groups. While overdiagnosis likely occurs across these age groups, due to a lack of data, it's uncertain whether rates exceed MID thresholds of 5/1000 women screened. Overall, findings from RCTs and observational studies on benefits and harms demonstrate a similar balance of benefits and harms as identified in the 2018 guideline.

Patient values and preferences data suggests that women in this age group generally weigh the benefits as greater than the harms under a variety of theoretical levels of benefit. Data also suggest that some (probably a minority) of women would consider the rates of additional imaging or biopsy as important relative to the mortality benefits. Some variability exists in the data, and there were some concerns about generalizability of these studies to the diversity of the Canadian population.

Based on the more favourable balance of benefits and harms in this age group, which improves with age, as well as patient values and preferences data weighing benefits over harms, the Task Force conditionally recommends in favour of screening every 2-3 years in this age group. Given that benefits and harms are still small, and that there is potential variability in patient values and preferences, informed patient decision making is still important for women 50-74 years.

Women aged 75+ years

There were no RCT data available for this age group, and very low certainty observational studies did not identify differences in mortality screening beyond age 74. At the same time, observational studies of overdiagnosis found high rates of overdiagnosis in those who screened when they were 75-84 years. Also, rates of additional imaging and biopsies surpassed MID thresholds, and could be important, particularly given the lack of evidence of benefit.

Modelling examined the potential impact of extending screening from 74 to 79 years. In most scenarios this led to very small differences in breast cancer mortality (0.16 fewer breast cancer deaths per 1,000 women screened over a lifetime for 50-79 vs 50-74) and stage at diagnosis (0.38 fewer Stage III and higher cancers per 1,000 women screened over a lifetime for 50-79 vs 50-74). Modelling estimated extending from 50-74 to 50-79 biennially would add 15 additional imaging without cancer and 1.5 additional biopsies without cancer per 1,000 women screened.

All evidence sources, although uncertain, suggest limited benefit, and some potential harms with screening beyond 74. Therefore, the Task Force conditionally recommends against screening in this age group.

Screening Interval

There was limited evidence from RCTs or observational studies examining the potential benefits of screening annually versus biennially or triennially on patient-important outcomes. It is very

uncertain whether annual screening improves mortality or stage distribution, based on the studies identified, although it may identify more cancers. At the same time, studies suggested annual screening leads to more unnecessary additional testing. Modelling carried out for this guideline assessed annual screening strategies, which suggested annual testing might have a small effect on reducing mortality, and late stage cancer diagnoses. However, it greatly increases the number of additional imaging tests and biopsies (from 606.90 to 1125.81 per 1,000 lifetime additional imaging without cancer to; and from 59.29 to 109.99 per 1,000 lifetime additional unnecessary biopsies for screening 50-74).

As in 2018, the Task Force continues to recommend screening every 2-3 years, since the best evidence of benefit comes from studies using this interval, and annual strategies likely increase harms with uncertain benefit for patient-important outcomes.

Screening Modality

Comparative effectiveness studies did not show clinically important differences between digital mammography and tomosynthesis (3D mammography).

Supplemental screening with ultrasound or MRI

Our evidence review did not identify any data on patient-important outcomes (mortality, life-years, stage/treatment) from supplemental screening with ultrasound or MRI for women with dense breasts or otherwise at moderately increased risk. Uncertain evidence found that it may not reduce interval cancers. Limited evidence suggested that supplemental screening with ultrasound may increase unnecessary biopsies. Given the lack of data on important benefit outcomes, and potential (although uncertain) harms, the Task Force conditionally recommends against supplemental screening as a general screening approach.

Considerations for Implementation

The Task Force considered what the recommendations mean from three perspectives: eligible women, primary care providers and breast screening program providers. High-risk patients should consult their local resources to determine the best course of action.

Primary care providers should implement this recommendation by providing women aged 40-74 with clear facts on the benefits and harms of breast screening in absolute numbers (e.g., using tools developed by the Task Force). Any women in this age range that are informed and indicate an interest in being screened should be referred for screening every 2-3 years. As the balance of benefits and harms improves with age, initiating these discussions with patients is of higher priority for those aged 50-74. Given the suggestion against screening in women aged 40-49, providers may prioritize other health care needs for this age group, although in some cases they may choose to provide information to women within this age group so individuals can start to think about whether they would choose to be screened, and at what age.

The Task Force is concerned about anecdotal reports that women aged 40-49 have been denied referrals to screening by primary care providers even when they expressed a desire, based on their interpretation of the Task Force's 2018 guideline. Patients who come to their primary care provider expressing an interest in being screened should be provided transparent

information on the benefits and harms, and if they choose to be screened, referred for screening. Clinicians are aware of the large range of preferences seen in their clinics as one can never assume how an individual will balance the relative importance of screening.

Breast cancer screening should only be considered for women with a reasonable life expectancy and in good enough health to undergo tests and treatments.

The Task Force recognizes that many Canadians do not have access to a primary care provider. Women aged 40-74 should be able to get information about the benefits and harms of screening (either by their own means, from a provider, or from a screening program) expressed in absolute numbers, and be able to consider how they personally value the balance between potential benefits and harms of screening. If they have access to a primary care provider, they may speak to their provider about being screening. If they do not have access to a primary care provider, they may be able to access screening through their provincial/territorial program (discussed further below).

While the Task Force does not explicitly develop recommendations for screening programs, these programs should ensure they are providing women with clear information on the benefits and harms of screening in absolute numbers. A number of provincial programs have extended self-referral or other mechanisms to those age 40-49, expanding access for those who choose to be screened. If clear information about the benefits and harms of screening is provided and allows these women to make an informed choice, this is consistent with the Task Force's recommendations which emphasize the importance of patient choice.

Gaps in knowledge

Across all age groups, evidence related to benefits of screening (RCTs, observational, modelling) was of low or very low certainty and lacked data comparing screening strategies. There was not enough published evidence for the Task Force to provide race- and ethnicity-specific screening recommendations. We do not have information on the balance between benefits and harms of screening in women of diverse races and ethnicities. More research is urgently needed on breast cancer etiology to further understand the observed differences in incidence and mortality by race/ethnicity and determine if modifiable factors exist. More detailed data on the impact of screening on patient-important health outcomes for women of different ethnicities is also needed, particularly for groups where we see higher rates of mortality (e.g., Black, Indigenous). We therefore join the United States Preventive Services Task Force (USPSTF) in calling for more research into how to change the incidence and resultant outcomes from breast cancer in these populations. We also need more collection of race and ethnicity-based data in Canadian programs and registries.

Additional newer studies (i.e., screening initiated after the year 2000) using modern screening technologies and treatments are needed to provide evidence on the comparative effects of different approaches to screening (e.g., based on age, modality) on mortality and other important outcomes such as stage at diagnosis. Across all age groups more information is needed about the extent of overdiagnosis.

Research is needed to determine the appropriate screening strategy for populations with dense breasts. Research reflecting different categories of breast density, additional rounds of supplemental screening, and reporting on outcomes such as breast cancer mortality and stage at diagnosis is needed.

Regarding patient values and preferences for breast cancer screening, future studies providing different descriptions of additional testing (no cancer) (referred to as 'false positives' in the studies) are needed to learn whether providing more accurate information during a recall for more testing would influence patient reactions to a subsequent positive or negative result. Few studies presented participants with information on the potential for avoiding some treatment such as chemotherapy and it is unknown to what impact this could have on preferences. Additional evidence considering the perspectives of ethnographically and socioeconomically diverse populations is needed, particularly in Canada. Studies measuring health state utility values from Canada were also lacking.

Next Steps

The Task Force wants your input on these draft recommendations. The public comment period for this guideline will last for 6 weeks, from May 30, 2024 to July 11, 2024 The final guideline will include a summary of the input received and how it was addressed.

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