EVIDENCE TO DECISION FRAMEWORK

Question: Should we screen for breast cancer in cisgendered women (and other adults assigned female at birth) aged 40 years and older and at average or moderately increased risk of breast cancer?

KNOWLEDGE QUESTIONS:	**KQ1**: (a) What are the benefits and harms of different mammography-based screening strategies compared to no screening in cisgendered women (and other adults assigned female at birth) aged 40 years and older at average* or moderately increased risk* of breast cancer? • (b) Do the benefits and harms differ by population characteristics (e.g., age, breast density, race and ethnicity, socioeconomic status, geographical area, family history)? **KQ2**: (a) What are the comparative benefits and harms of different mammography-based breast cancer screening strategies in cisgendered women, transgender men and nonbinary and others assigned female at birth aged 40 years and older and at average or moderately increased risk for breast cancer? (b) Do the comparative benefits and harms differ by population characteristics (e.g., age, breast density, race and ethnicity, socioeconomic status, geographical area, family history)? **KQ3**: What is the relative importance placed on the potential benefits and harms of mammography-based breast cancer screening? * For the purposes of this review, average risk refers to those without factors placing them at higher-than-average risk of cancer (i.e., about 12% lifetime risk) whereas those with moderately increased risk will include individuals with an elevated risk of breast cancer (e.g., dense breasts, one first degree relative with history of breast cancer). The review will not include studies focusing on those with high risk (e.g., at higher than 20% lifetime risk).	**BACKGROUND:** Breast cancer is the most common cancer and the second leading cause of cancer-related death among Canadian cisgendered women (and other adults assigned female at birth) (1). In 2024, it was estimated that 30,500 would be diagnosed with breast cancer, representing 25% of all new cancer cases in this group that year (2). It was also estimated that 5,500 would die from the disease, representing 13.5% of all cancer deaths among this group in 2024. The median age at which breast cancer is diagnosed in Canada is between 65 and 69 years, with approximately 88% of new cases being diagnosed in those over 50 years of age (3). Although less common, when they do occur, breast cancers at younger ages tend to be found at more advanced stages than older patients often resulting in an overall poorer prognosis (4). In 2017, the percentage of Canadian cis gendered women (and other adults assigned female at birth) diagnosed with stage III+ breast cancer ranged from 26.3% (30-39), 20.2% (40-49), 17.7% (50-59) and 13.9% (60-69) (4). There was a lack of race-specific data on screening outcomes in Canada. However, preliminary Canadian epidemiological data shows the median age at diagnosis is younger (52 to 60 years) than for white individuals (63 years) as well as the median age of death from breast cancer (55 to 71) vs 71 years (unpublished) (5). Black individuals (aged 40-49) and First Nations or Metis individuals (aged 60-69) have a decreased risk of breast cancer compared to white individuals; however, when cancer presents, they have a higher mortality rate (unpublished) (5). Black individuals also are more likely to be diagnosed with more aggressive (e.g., triple negative) breast cancer subtypes (6). Rates of mortality due to breast cancer in Canada have declined since the late 1980s, from 41.7 deaths per 100,000 people in 1989 to a projected rate of 21.8 deaths per 100,000 people in 2024 (2,3). Five-year net survival from breast cancer among Canadian cisgendered women (and other adults assigned female at birth) is estimated to be 89%. However, survival from breast cancer varies by stage at diagnosis, with five-year relative survival of 99.8% for stage 1, versus 23.2% for Stage IV (7). A decrease in mortality may be attributed to impact of screening and improvements in treatments for breast cancer (1). Time trend analysis of age-specific breast cancer incidence rates, based on the Canadian cancer registry data, showed statistically significant increasing trends for age 40-49 at 0.26% per year (between 1984-2019), 0.77% per year (between 2015-2019) and for age 50-54 at 0.38% per year (between 2005 – 2019) (8). Between 1984-2019 the incidence of breast cancer increased by 11.6 more/100,000 (40-49) and 32.2 more/100,000 (50-54) (8). Canada's first organized breast cancer screening program was introduced in British Columbia in 1988 and was quickly adopted by other provinces (9). All provinces and territories (excluding Nunavut) have implemented organized breast screening programs (9). As of 2024, Nunavut does not have an organized screening program for breast cancer but opportunistic screening is done in Iqaluit or during a visit to southern health centres (7,8,9). Mammography is the primary screening test for breast cancer in Canada, which involves administering a low-dose x-ray to identify abnormalities in breast tissue (9). All provinces and territories in Canada use digital radiography to conduct mammography; computed radiography is also used in Quebec (9). Other screening modalities may be considered depending on the patient's level of risk for developing breast cancer (i.e., tomosynthesis, MRI, and ultrasound) (9). In 2018, The Canadian Task Force on Preventive Health Care (CTFPHC) recommended screening with mammography every two to three years for average-risk individuals aged 50 to 74 years (12). Although routine screening with mammography is not recommended for those aged 40 to 49, the CTFPHC judged that some individuals in this demographic may wish to be screened after a shared decision-making process with their primary care provider (9). Consistent with the CTFPHC recommendations, all breast cancer screening programs in Canada allow individuals 50-74 years of age to book their screening appointment biennially (13–15). However, there are some variations in breast cancer screening practices between provinces and territories for the younger than 50 and older than 74 age groups. As of 2024, MB and QC require individuals in their 40s to have a referral (16,17) from a healthcare provider to book a screening appointment. In AB and NWT screening programs start at age 45 and require referrals for ages 40-44 (18,19). In BC, PEI, NS, and YT (20–23) individuals are encouraged to discuss the benefits and harms of screening with their healthcare provider, but do not need a referral and can book their appointment from age 40. ON, NB and SK (24–26) will also provide self-referral breast cancer screening for the 40-49 age group in late 2024 to early 2025. In May 2024, NL announced lowering the screening age from 50 to 40 with self-referral (effective date has not been announced) (27). Additionally, Nunavut requires referrals for all ages (including 50-74) as there is no organized program (7,8,9). After age 74, while all provinces and territories stop sending reminders for the upcoming appointment and many provinces require referrals to continue screening, BC, NL, MB, NS, NWT, and YT still allow for self-referral for breast cancer screening (14,16,20,22,23,28). Data suggests that there is confusion by primary care providers and some radiology departments regarding the 2018
POPULATION:	**KQ1**: Cisgendered women (and other adults assigned female at birth) aged ≥40 years of age and at average or moderately increased risk for breast cancer **KQ2**: Cisgendered women (and other adults assigned female at birth) aged ≥40 years of age and at average or moderately increased risk for breast cancer **KQ3**: Cisgendered women (and other adults assigned female at birth) ≥35 years of age (lower than 40 years, to allow for those considering screening in the near future) For studies of health state utilities related to a new cancer diagnosis or the impact of cancer treatments (exposures 5-7), participants will have or have experienced cancer or will be presented with hypothetical scenarios about cancer diagnosis and/or treatment.	
INTERVENTION/ EXPOSURE:	**KQ1**: Any mammography screening modality (i.e., film or digital mammography [2D mammography], digital breast tomosynthesis [3D mammography]) with or without clinical breast examination (CBE)/breast self-examination (BSE): (1) Alone (2) Digital mammography supplemented with tomosynthesis (3) Digital mammography (2 or 3D) supplemented with MRI (4) Digital mammography (2 or 3D) supplemented with ultrasound (5) Digital mammography (2 or 3D) supplemented with contrast enhanced mammography **KQ2**: Any mammography screening modality (i.e., film or digital mammography, digital breast tomosynthesis [3D mammography])	

Screening strategy (e.g., screening interval, age to start or stop screening, personalized screening based on risk and other characteristics)

Any mammography screening modality plus supplemental screening (e.g., ultrasound, MRI)

Any mammography screening modality plus supplemental screening for a defined population (e.g., negative mammography, dense breasts, age group)

KQ3: <u>For non-HSUV studies (focus on screening)</u>:

1. Screening for breast cancer using mammography, MRI, ultrasound;
2. Exposure to information on the expected magnitude of 1+ benefit and 1+ harm from screening (as per critical outcomes from KQ1);
3. Experience of additional testing (no cancer) and provided with information on benefits to make decisions for future screening; or iv) no exposure to screening or information but values (e.g. trade-offs) for 1+ benefit and 1+ harm are elicited by studies

<u>For HSUV studies</u>:

1. Prior to screening or, if necessary, negative screening result or no cancer sample within a study measuring another exposure of interest
2. Positive screening mammography (before results of diagnostic testing known)
3. Additional testing result, if possible, +/- biopsy (no cancer)
4. Invasive diagnostic testing (e.g., any form of biopsy or localization technique; cancer status not known)
5. True positive result (all treatment naïve) (may include new diagnosis if not clearly screen-detected)
6. Surgical treatment-related morbidity - variables of interest include†:
    - i) Complete mastectomy vs. partial mastectomy/lumpectomy
    - ii) Receipt of chemotherapy (yes/no)
        - (a) anthracycline vs. no anthracycline
    - iii) Receipt of radiotherapy (yes/no)
    - iv) Axillary lymph node dissection vs. sentinel lymph node biopsy

    † i) will have subgroup of chemotherapy vs not; ii) to iv) will have subgroups of type of surgery (breast conserving surgery, mastectomy, mixed/unspecified); both within- and between-study comparisons are eligible

7. Stage distribution (e.g., during treatment for Stage 0/1-2 vs. 3-4 or metastasized vs. not (each with chemotherapy Y/N, if reported, e.g., stage 1 vs 2); only using within-study comparisons

COMPARISON:

KQ1: No screening

KQ2: Standard population-based screening with film or digital mammography

KQ3: None; If studies compare two different versions of information/decision aids, each eligible arm will be considered separately.

MAIN OUTCOMES:

KQ1:

<u>Benefits</u>

<u>Critical</u>

1. Breast cancer related mortality
2. All-cause mortality
3. Treatment-related morbidity, measured by:
    - (a) Receipt of radiotherapy (yes/no)
    - (b) Receipt of chemotherapy (yes/no)
        - Subgroup by anthracycline vs no anthracycline
    - (c) Type of surgery: complete mastectomy vs partial mastectomy/lumpectomy
    - (d) Surgical management of axilla (axial lymph node dissection [ALND] vs sentinel lymph node biopsy)
4. Stage distribution of breast cancer
    - (a) Stage II and higher
    - (b) Stage III and higher
    - (c) Stage IV

<u>Important</u>

5. Breast cancer morbidity (e.g., adverse effects of treatment, physical/functional impairment). Measured using composite scores from different scales

<u>Harms</u>

recommendations; some interpret the guideline to suggest that women aged 40-49 should not have screening (rather than that a shared-discussion should take place and the woman's choice should be respected) and some radiology departments do not accept referrals for screening mammography in this age group (29–32).

Patients deemed to have a normal test result are notified and recalled back at regular intervals. In most provinces and territories, recall reminders for breast cancer screening are sent out at a 2-year interval; some patients may be recalled annually based on identified risk factors or age groups (e.g., 40-49 years, family history, and breast density) and/or radiologist recommendation (33). Patients with an abnormal or unclear test results are notified and contacted to arrange repeat imaging or diagnostic testing, which may involve further mammography, other breast imaging techniques (e.g., MRI, ultrasound), and biopsy. Locations for conducting diagnostic mammograms vary and can include screening centres, diagnostic imaging centers, and Breast Risk Assessment units.

In 2017, 78.5% of Canadian females aged 50 to 74 years self-reported receiving a mammogram (screening or diagnostic) in the past three years (34). Programmatic screening rates (ages 50-69) range 31.8% to 62.3% (2011-2012) (22). To address disparities in screening, several provinces and territories have employed targeted strategies to improve screening uptake, such as, screening awareness campaigns, mobile screening clinics, and resources showcasing inclusive language (9). Different strategies have specific intended audiences including Indigenous populations, rural or remote populations, underserved populations (e.g., racial or ethnic minorities, low income, immigrants, and refugees), and individuals who identify as LGBTQ2S+ (9).

Potential benefits of screening include reducing breast cancer mortality through the earlier detection and treatment of disease and decreasing morbidity by detecting cancer at an earlier stage (requiring less aggressive treatments). Potential harms of screening include additional testing and/or biopsies, anxiety and overdiagnosis (35–37). Overdiagnosis refers to screen-detected cancers that would not have become clinically apparent in the individual's lifetime absent of screening. Once a diagnosis is made this leads to standard treatment which can increase both physical side effects and increased psychological stress associated with receiving a diagnosis.

The 2018 CTFPHC recommendations on screening for breast cancer were informed by two evidence reviews (38–40). The first review was conducted by the Evidence Review and Synthesis Centre (ERSC) at the Ottawa Hospital Research Institute and focused on outcomes of breast cancer screening for individuals aged 40 to 74 years of age who are not at increased risk for breast cancer (39). The second review was on patient values and preferences (40).

The CTFPHC recommended the following in 2018:

Screening women aged 40 to 49 years: For women aged 40 to 49 years, we recommend not screening with mammography; the decision to undergo screening is conditional on the relative value a woman places on possible benefits and harms from screening (conditional recommendation; low-certainty evidence).

Screening women aged 50 to 69 years: For women aged 50 to 69 years, we recommend screening with mammography every 2 to 3 years; the decision to undergo screening is conditional on the relative value that a woman places on possible benefits and harms from screening (conditional recommendation; very low-certainty evidence).

Screening women aged 70 to 74 years: For women aged 70 to 74 years, we recommend screening with mammography every 2 to 3 years; the decision to undergo screening is conditional on the relative value that a woman places on possible benefits and harms from screening (conditional recommendation; very low-certainty evidence).

Some women aged 40 to 49 years may wish to be screened based on their values and preferences; in this circumstance, care providers should engage in shared decision-making with women who express an interest in being screened. Care providers should engage in shared decision-making with women aged 50 to 74 as those who place a higher value on avoiding harms as compared to a modest absolute reduction in breast cancer mortality may choose to not undergo screening.

Other screening modalities

We recommend not using magnetic resonance imaging, tomosynthesis or ultrasound to screen for breast cancer in women who are not at increased risk (strong recommendation; no evidence).

We recommend not performing clinical breast examinations to screen for breast cancer (conditional recommendation; no evidence).

We recommend not advising women to practice breast self-examination to screen for breast cancer (conditional recommendation; low-certainty evidence).

Critical

6. Overdiagnoses (We will calculate the number of excess diagnoses from prospective data with at least 10 years of follow up from the time of enrollment over 1,000 persons screened).

Important

7. Additional testing +/- biopsy (no cancer)
8. Additional testing with biopsy (no cancer)
9. Interval cancers (includes false negatives and clinically detected cancers before next screen or time equivalent)
    (a) Subgroup by Invasive vs DCIS

Benefits or harms

Critical

10. Health related quality of life (secondary outcome)

Important

11. Life years gained (or lost)

KQ2: Refer to KQ1 Outcomes

KQ3: Preference-based outcomes:

- HSUVs, *using hierarchy*:
    i) generic multi-attribute utility instruments (e.g., EuroQoL-5D, Health Utilities Index, or Short form-6D) by patients (or their proxies) (based on current status for exposure 6 but may be through recall for other exposures]);
    ii) if N<100 or all studies are high risk of bias for a given health state from i), use generic multi-attribute utility instruments in population sample (e.g. previous patients or eligible for screening) and TTO, SG (not VAS).
- Non HSUVs:
    - Estimated disutilities for each HSUV (vs. healthy population eligible for screening) using data from exposure 1 (if low or higher certainty), or from Canadian norms value set for females aged 40-70.
    - Preference weights from contingent valuation studies for benefit and harm outcomes
    - Relative ranking/rating or probability trade-offs between benefit and harm outcomes (e.g., ratings based on degree of importance to screening decision making)
    - Others will be considered

Indirect, non-preference based relative importance of outcomes based (inferred from) on:

- Willingness to be screened, acceptability or attitudes about screening, uptake of screening, intent to return for another screen

SETTING: Primary care settings in Canada; studies conducted in countries categorized as "Very High" on the Human Development Index (as defined by the United Nations Development Programme).

KQ1: Primary care or other settings generalizable to primary care, including referrals by primary care providers

KQ2: Settings and populations of women applicable to U.S. primary care settings

PERSPECTIVE: Population

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** ○ No ○ Probably no ○ Probably yes **X** Yes ○ Varies ○ Don't know	Screening for breast cancer was judged by the CTFPHC to be a priority problem. This is based on the incidence rate of breast cancer in Canada and the potential impact of early detection through screening (i.e., lower mortality and morbidity associated with less advanced stages at diagnosis). There are also variations in practice across Canada and uncertainty as to the relative importance individuals place on the potential harms and benefits of breast cancer screening. **Number of people affected (burden)** • In 2024, it was estimated that breast cancer was the most diagnosed cancer among Canadian cisgendered women (and other adults assigned female at birth), accounting for 25% of newly diagnosed cancer cases (2). It	Preliminary data from Statistics Canada (5) suggest that Black individuals (age 40-49) experience later stage at diagnosis and higher mortality (1 more/1000 over 10 years) than white individuals, despite similar

		was estimated that 30,500 cases would be diagnosed in 2024 (age-standardized incidence rate: 133.1 cases per 100,000) (2). • Approximately 88% of cases of breast cancer occur in individuals aged 50 years or older (3), however, this varies by race and ethnicity (see right column). • Breast cancer is the leading cause of cancer death for Canadian cisgendered women (and other adults assigned female at birth) aged 30-50 years. (41–43). • Although mortality is decreasing, it was estimated that 5,500 would die from breast cancer in 2024 with almost half of deaths occurring in the 50-74 age group (2). • Time trend analysis of age-specific breast cancer incidence rates, based on the Canadian cancer registry data, showed statistically significant increasing trends for age 40-49 at 0.26% per year (between 1984-2019), 0.77% per year (between 2015-2019) and for age 50-54 at 0.38% per year (between 2005 – 2019). Between 1984-2019 the incidence of breast cancer increased by 11.6 more/100,000 (40-49) and 32.2 more/100,000 (50-54) (8). **Stage at diagnosis:** • Data on stage at diagnosis is limited but shows that in 2017, approximately 18% of cases of breast cancer in Canada were diagnosed at later stages (i.e., Stage III and IV) (36). • Five-year net survival from breast cancer in Canada is about 89% and is impacted by stage at diagnosis, with survival significantly improved in early-stage disease (Stage I, 99.8% versus Stage IV, 23.2%) (7). **Variations in practice in different provinces** • Aligned with the CTFPHC recommendation, all provincial and territorial breast cancer screening programs provide self-referral screenings for individuals 50-74 years of age at average risk of breast cancer (13,14). As of 2024, Nunavut does not have an organized screening program for breast cancer but opportunistic screening is done in Iqaluit or during a visit to southern health centres (7,8,9). • Screening at age <50 years: ○ MB and QC require individuals 40-49 years of age to have a physician's referral to access screening (14,15). ○ BC, NS, PEI, and YT allow self-referral at age 40 (but do not actively recruit participants <50 years) (20–23). ○ Alberta and NWT lowered the recommended age for biennial breast cancer screening for average-risk individuals from 50 years to 45 years (18,19). ○ ON, NB, and SK announced that they will lower the screening age for average-risk individuals from 50 to 40 in late 2024 – early 2025 (24–26). ○ In May 2024, NL announced lowering the screening age from 50 to 40 (effective date has not been announced) (27). • Screening at age 75+ years: ○ BC, NL, MB, NS, NWT, and YT allow continued self-referral breast cancer screening (14,16,20,22,23,28). ○ ON, QC, AB, NB, PEI, and SK not only stop sending reminders to individuals for their next appointment but also require them to have a physician's referral to have a breast cancer screening (17,18,21,26,44,45).	or lower incidence rates. Black individuals also experience a higher proportion of more aggressive subtypes (e.g., triple negative). First Nations and Metis individuals experience higher mortality rates than white individuals (1 and 3 more /1000 respectively over 10 years) at age 60-69.

DESIRABLE EFFECTS

How substantial are the desirable anticipated effects?

KQ1: 40-74 (general population or moderately increased risk)

○ Little to none
○ Very small
X Small
○ Moderate
○ Large

○ Varies
○ Don't know

KQ1: 75+ (general population or moderately increased risk)

X Little to none
○ Very small
○ Small
○ Moderate
○ Large

○ Varies
○ Don't know

KQ2: screening interval
Annual vs Biennial or Triennial
40-75+ (general population or moderately increased risk)
X Little to none
○ Very small
○ Small
○ Moderate
○ Large

○ Varies
○ Don't know

KQ2: Screening modality
Tomosynthesis vs Digital mammography
40-75+, (general population or moderately increased risk (family history or dense breasts))

X Little to none
○ Very small
○ Small
○ Moderate
○ Large

○ Varies
○ Don't know

KQ1: For cisgendered women, transgender men and nonbinary and others assigned female at birth) ≥ 40 years of age and at average or moderately increased risk, what are the benefits of different mammography-based screening strategies as compared to no screening?

SUMMARY: JUDGEMENT OF BENEFITS

Age groups:

Breast cancer mortality: Using a threshold of *0.5/1000* the impact of screening age **40-49** on breast cancer mortality is very uncertain and ranges from little to no difference (0.27 fewer/1000) to a benefit (0.94 fewer/1000) (very low certainty). Using a threshold of *1.0/1000* this would be within the little to no difference (low to very low certainty) range. For ages **50-74**, using a threshold of *1.0/1000* it was very uncertain and ranged from little to no difference (0.5 (50-59), 0.65 (60-69) and 0.92 (70-74) fewer/1000) to a benefit (1.72 (50-59), 2.24 (60-69), 3.17 (70-74) fewer /1000) (very low certainty). Using a threshold of *0.5/1000* it would be within the benefit range (very low certainty). For ages **75+** using a threshold of *0.5 or 1.0 /1000* the impact of screening on breast cancer mortality was very uncertain and within the little to no difference (0 fewer/1000) range (very low certainty). The **lifetime mortality benefit** for screening ages 40-74 biennially was 6.97 fewer/1000 and 50-74 was 6.45 fewer/1000 (model, low certainty).

All-cause mortality: Using a threshold of *1/1000*, screening ages **40-59** may make little to no difference on all-cause mortality (low certainty). Results for age **60-69** were uncertain but also within the little to no difference range (very low certainty). We are very uncertain about the results for age **70-74** but results were in the range of a benefit (1.41 fewer/1000). There was no data for age 75+.

Treatment: Using a threshold of *3/1000*, data from the model showed that screening may result in a reduction in chemotherapy (3.63 fewer/1000) for age **40-49** (low certainty). Data was not available for ages **50-69** other than **over a lifetime (model)** which showed 0.75 more/1000 radiation, 12.4/1000 fewer chemo and 6.35 more breast surgeries (**50-74**) (low certainty). Data for age **70+** showed more radiation, less chemo less radical mastectomy with screening (low to very low certainty). Data on **all ages (≥40 years**) indicated that screening may make little to no difference on receipt of radiotherapy (threshold=*5/1000*) or chemotherapy (*threshold=3/1000*) (2.85 more/1000 and 0.14 fewer/1000 respectively) (low certainty). Data on **all ages (≥40 years**) was very uncertain for breast conserving surgery but in the range of little to no difference (0.4 fewer/1000) using a threshold of *2 fewer/1000*.

Stage: Using a threshold *of 3/1000* screening ages **40-49** may make little to no difference (1.68 fewer)/1000 on Stage II+ cancers with biennial screening (model, low certainty) but may reduce (3.05 fewer/1000) with annual screening. Using a threshold of *2/1000 and 1/1000* for Stage III+ and IV respectively, annual or biennial screening may make little to no difference for ages **40-49** (low certainty). Data was very uncertain for ages **50-59** but was within the little to no difference range for stage II+ (very low certainty). There was no data for ages 60-69 and very uncertain before and after studies for 70-74 showing mixed results. Data for **all ages (≥40 years)** was very uncertain but within the little to none and benefit range (threshold=3/1000) with 0.51-3 fewer/1000 stage II+ and little to none (1 fewer/1000) for stage III+ (threshold=2/1000).

Lifetime data from the model (screening age 50-74) showed 22.53 fewer stage II+, 11.39 fewer stage III+ and 3.39 fewer stage IV per 1000 (low certainty).

Life-years gained: There was no study reporting life years gained. The modelling data showed that biennial screening for 40-74 in comparison to 50-74 had 16.13 more life years gained per 1000 individuals over a lifetime (low certainty) and 11.22 more health-related quality of life per 1000 individuals over a lifetime (very low certainty).

Missing outcomes: There was no data available on axial lymph node dissection, sentinel lymph node biopsy or health-related quality of life.

Based on the range of benefits that crossed the threshold (see below), lifetime modeling data and Statistics Canada incidence and race-based data (see right column), the Task Force rated the magnitude as Small for ages 40-74 (general population). However, they noted that the benefit increases with age with all evidence (RCT, observational) reaching the 0.5/1000 threshold for breast cancer deaths prevented at ≥50 years.

40-49: 0.27-0.95 fewer/1000 breast cancer deaths, 2.23 fewer/1000 chemo

50-59: 0.50-1.72 fewer/1000 breast cancer deaths

60-69: 0.65-2.24 fewer/1000 breast cancer deaths

70-74: 0.93-3.17 fewer/1000 breast cancer deaths, 1.47/1000 fewer all-cause mortality deaths

Time trend analysis of age-specific breast cancer incidence rates, based on the Canadian cancer registry data, showed statistically significant increasing trends for almost all age groups from 1984 to 2019. The most recent years' data indicated that the rate of increase in age 40-49 was 0.77% (p=0.047, 2015-2019) and for age 50-54 it was 0.38% (P-value = 0.022, 2005 - 2019). Between 1984-2019 the incidence of breast cancer increased by 11.6 more/100,000 (40-49) and 32.2 more/100,000 (50-54). Breast cancer incidence increases were higher in the younger age groups as the annual percent change (APC) in the 20-29 and 30-39 age groups was 3.06% (P-value <0.001, 2001-2019) and 1.25% (P-value= 0.007, 2009-2019), respectively. The 45-49 age group was the only group with a non-significant increase in the breast cancer incidence rate with an APC of 0.24% (P-value= 0.058) since 2003 (8).

Unpublished data from Statistics Canada* (5) shows that the median age at diagnosis is younger (52 to 60 years) than for white individuals (63 years) as is the median age of death from breast cancer (55 to 71) vs 71 years. Canadian rates of cancer and death rates also vary. At age 40-49, there are more breast cancers diagnosed in Filipina (4 more/1000 over 10 years) and multi-ethnic (8 more/1000 over 10 years) women compared to White women. At age 50-59 there are more breast cancers diagnosed in Arab (7 more/1000 over 10 years) and Filipina (3 more/1000 over 10 years) women than among White women. At age 40-49 there are more deaths among Black women (1 more/1000 over 10 years) compared to White and more deaths in First Nations (1 more/1000 over 10 years) and Metis women (3 more/1000 over 10 years) at age 60-69. Additionally, in Black people, there is a higher proportion of aggressive subtypes of breast cancer (e.g., triple negative, Her2+ and Luminal B/B-like) are significantly more common in Black individuals.
**Estimate per 1,000 over 10 years rounded for clarity. Estimate over 10 years is based on mortality data up to 2019 and therefore assumes a constant mortality rate. Therefore, there is some uncertainty in this*

	KQ2: Screening modality **Supplementary Ultrasound or MRI vs Digital mammography alone** **40-75+, (moderately increased risk)** ○ Little to none ○ Small ○ Moderate ○ Large ○ Varies X Don't know	**All ages (40+):** 0.51-3.0 fewer/1000 stage II+ cancers **Based on a lack of or very uncertain evidence for ages 75+ (general population or moderately increased risk) the Task Force rated the magnitude as Little-to-none.** **Screening interval:** A previously conducted subgroup analysis by screening interval (2018 review) found that the validity of subgroup effects may lack credibility and any differences among subgroups are likely spurious. Newly added trial data did not report new findings or information was not reported and therefore subgroup analysis was not repeated. Annual vs biennial: We are very uncertain about the effects on advanced stage cancers from screening annually versus biennially (**all ages**) but the results showed no significant difference in stage IIB+ cancers. Using a threshold *of 3/1000* screening ages **40-49** may make little to no difference (1.68 fewer)/1000 on Stage II+ cancers with biennial screening (model, low certainty) but may reduce (3.05 fewer/1000) with annual screening. Annual vs triennial: We are very uncertain about the effects on annual versus triennial screening for breast-cancer mortality and all-cause mortality in 40 to 49-year-olds but results showed no significant difference for a reduction in mortality. Low certainty evidence indicates that annual versus triennial screening may make little-to-no difference for advanced stage cancers for 50 to 69-year-olds over 3 years. **Based on the majority of the evidence showing little to no impact of screening interval the Task Force rated the magnitude as Little to none for annual vs biennial or triennial.** **Screening modality:** Tomosynthesis vs digital mammography For 45-69, DBT versus digital mammography may make little-to-no difference for advanced stage cancers over two rounds. **Based on the majority of the evidence showing little to no impact of DBT vs digital mammography the Task Force rated the magnitude as Little-to-none.** Supplemental ultrasound No data Supplemental MRI No data **Based on a lack of evidence the WG rated the magnitude as Don't know.** **Moderately increased risk** Direct evidence on the effect of screening for people 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. **Moderate family history** Breast cancer mortality: Using a threshold of *0.5/1000* the impact of screening age **40-49** with moderate family history is very uncertain and ranges from little to no difference (0.44 fewer / 1000) to a benefit (1.51 fewer/1000) (very low certainty). Using a threshold of *1/1000* the range is the same but with low certainty for little to no difference (0.44 fewer/1000) and very low for a benefit (1.51 fewer/1000). For ages **50-59**, using a threshold of *1.0/1000* it was very uncertain and ranged from little to no difference (0.79 fewer/1000) to a benefit (2.76 fewer /1000) (very low certainty). Using a threshold of *0.5/1000* this would show a benefit (very low certainty). For 60-74, using a threshold of 0.5 or 1/1000 the results were very uncertain but within the benefit range (1.04-3.59 (60-69), 1.47-4.31 (70-74) fewer/1000) (very low certainty). There was no data for 75+ or for other outcomes. **Breast density**: Breast cancer mortality: Using a threshold of *0.5/1000* the impact of screening age **40-49** with dense breasts is very uncertain but within the benefit range (0.53-1.82 fewer/1000) (very low certainty). Using a threshold of *1/1000* there was low certainty for little to no difference (0.53 fewer/1000) and very low for a benefit (1.82 fewer/1000). For ages **50-59**, using a threshold of *1.0/1000* it was very uncertain and ranged from little to no difference (0.94 fewer/1000) to a benefit (3.28 fewer /1000) (very low certainty). Using a threshold of *0.5/1000* this would show a benefit	*estimate. Refer to Equity section for full tables.* **Breast cancer risk** may not be consistent across an ethnicity as it can vary among specific countries of the same ethnicity. It is unclear if the racial or ethnic disparities may be further affected by immigration status (i.e., Canadian born vs immigrants) and/or time lived in Canada. **Screening rates** may differ among immigrants (96). Generally, screening rates increased with increasing neighborhood income, the extent of the increase can vary among specific immigrant groups (e.g., between the highest and lowest income, Sub-Saharan African had the greatest difference (20%) and Caribbean and Latin American the lowest (3.6%)).(96) **Treatment – feedback from clinical experts** Evidence on treatment exposure cannot be viewed in isolation as an increase in radiation may indicate both a benefit (i.e., more cancers treated with lumpectomy + radiotherapy vs mastectomy) or a harm (overdiagnosis leading to overtreatment). Additionally, treatment (e.g., lumpectomy + radiotherapy vs mastectomy) is related to clinical factors that do not always correlate with stage of disease and also related to patient choice (values and preferences). Treatment such as chemotherapy also varies based on stage as well as cancer subtype. **Stage – feedback from clinical experts** Evidence on anatomic stage should also be interpreted with caution as prognosis varies by other factors (e.g., grade, receptor status). Prognostic/pathological stage incorporates these variables. **Her2, ER/PR** Data on Her2, ER/PR or other subtypes was not included as an outcome for the analysis as the subtype of breast cancer cannot be determined prior to or modified by screening. Unfortunately, data from the included studies in KQ1 did not subgroup outcomes by cancer subtype and therefore direct comparison was not available. The Task Force noted that Black individuals

(very low certainty). For 60-74, using a threshold of 0.5 or 1/1000 the results were very uncertain but within the benefit range (1.23-4.26 (60-69), 1.74-5.10 (70-74) fewer/1000) (very low certainty). There was no data for 75+ or for other outcomes.

As with the general population, the WG rated the magnitude as Small for ages 40-74 (Moderately increased risk population). Benefits may be increased for those at moderately increased risk due to an increase in baseline risk, although there was no direct evidence. As with the general population the benefits increased with age. All evidence (RCTs and observational) reaching the 0.5/1000 threshold for breast cancer deaths prevented at ≥50 years for family history and ≥40 years for breast density.

Race and ethnicity: No data in studies (see right column). The mean age at diagnosis and at death for non-white populations is younger than for white populations. Age-specific death rates for Black (at age 40-49) and First Nations or Metis (at age 60-69) populations compared to white populations. Black women are more likely to be diagnosed with aggressive subtypes.

The WG stressed the importance of considering the above data when making recommendations

All ages

All ages **Outcome** **Threshold (Regardless of certainty)**	**RCTs[1]** **Absolute effect (/1000 screens over 10 years)**	**Observational** **Absolute effect (/1000 screens over 10 years)** **(unless otherwise indicated (e.g., crude rates, relative risks))**	**Model** **lifetime effects (/1000 persons)** **Threshold not applicable**
Breast cancer mortality **1.0 and 0.5/ 1000**	Not applicable (Data grouped by age only)	**Studies of *before and after* screening programs were implemented** (time trends; crude rates; 2 studies) **ages 40-69** (a) Before screening: 0.62 breast cancer deaths/1000 vs After screening: 0.25/1000 person-years (RR=0.40 (0.34-0.48) (b) Before screening: 0.55/1000 vs After screening: 0.25/1000 person years (RR=0.46 (0.39-0.53) *(very low certainty)* **Threshold not applicable**	***Baseline: Breast cancer deaths with no screening**= 27.94 breast cancer deaths/1000)* **Compared to no screening:** Biennial screening for 50-74= 6.45 **fewer** breast cancer deaths/1000 **Compared to biennial 50-74** (i.e., given 6.45 fewer/1000 how much more would extending the age groups achieve?) Biennial 50-**79**: 0.16 **fewer**/1000 Biennial **45**-74: 0.27 **fewer**/1000 Biennial **40**-74: 0.52 **fewer**/1000 **Hybrid 40**-74: 0.82 **fewer**/1000 (i.e., screening annually 40-49 then biennial 50-74) Biennial: **40-79**: 0.68 **fewer**/1000 *(low certainty for 1/1000 threshold)* *(very low certainty for 0.5/1000 threshold)*
Breast cancer mortality by screening interval	Between study data: No significant difference between 12 annual, biennial or 18 months	No data	**Compared to biennial 40-74** **Hybrid 40**-74: 0.30 **fewer**/1000 (i.e., screening annually 40-49 then biennial 50-74) *(low certainty)*
Radiotherapy **5.0 / 1000**	2.85 more undergo radiotherapy/1000 (1.42-4.45 more) *(low certainty)*	No Data	***With no screening (baseline):*** *88.06/1000* **Compared to no screening:** Biennial screening for 50-74= 0.75 **more** undergo radiation/1000 **Compared to biennial 50-74:** Biennial 50-**79**: 0.12 **more**/1000 Biennial **45**-74: 0.41 **fewer**/1000 Biennial **40**-74: 0.89 **fewer**/1000 **Hybrid 40**-74: 1.32 **fewer**/1000 Biennial **40-79:** 0.78 **fewer**/1000 *(low certainty)*
Chemotherapy **2.0 / 1000**	0.14 fewer undergo chemo /1000 (0.79 fewer to 0.68 more) *(low certainty)*	No data	**With *no* screening (baseline):** 109.76/1000 **Compared to no screening:** Biennial 50-74: 12.4 **fewer** undergo chemo/1000 **Compared to biennial 50-74:** Biennial 50-**79**: 0.19 **fewer**/1000 Biennial **45**-74: 0.90 **fewer**/1000

have a higher risk of aggressive subtypes (e.g., triple negative) (unpublished Statistics Canada data) (5).

High risk of bias RCTs (e.g., CNBSS)
High risk of bias studies (e.g., CNBSS (97)) were removed during a sensitivity analysis showing similar results for 40-49 (RR of 0.86 (low risk) and 0.89 (high risk) and a slight change for 50-69 (RR of 0.83 (low risk) and 0.76 (high risk)) for breast cancer mortality (98). A 2009 sensitivity analysis done for the USPSTF found similar results (99).

Portal results

A number of Canadian studies were suggested by stakeholders which did not meet the inclusion criteria for this guideline.

Two Canadian studies about **breast density and high risk groups** were excluded:

1) Seely et al., 2022(100) (excluded at KQ1 due to ineligible comparator and at KQ2 due to the study design) compared the interval cancer rate in those breast screening programs with a policy of annual vs. those with biennial screening for individuals with dense breasts and found that annual programs resulted in 0.56 fewer interval cancers per 1000 individuals (0.89 versus 1.45 per 1000). (100)

2) Wu et al., 2021(101) (excluded at KQ1 and KQ2 due to having no comparator group) evaluated the added value of the supplemental breast ultrasound screening for individuals with dense breasts by performing a retrospective review of handheld sonographer-performed screening ultrasound exams at an academic breast imaging center, from January 1st to December 31st, 2019 (n=695). The first-year prevalence screen data of the breast screening ultrasound program had a cancer detection rate of 7 per 1000, and 12 biopsies were

[1] Intention to screen (short and long case accrual)

			Biennial **40**-74: 2.23 **fewer**/1000 **Hybrid 40**-74: 3.63 **fewer**/1000 Biennial **40-79:** 2.44 **fewer**/1000 *(low certainty)*	
Breast conserving surgery/ Mastectomy / Breast surgery **2.0 / 1000**	Mastectomy: 1.84 more undergo a mastectomy* /1000 (1.01-2.76 more) *(very low certainty)* *No data on breast conserving surgery	**Cohort - Adherence to screen** Breast conserving surgery: 0.9 more undergo breast conserving surgery vs a mastectomy/1000 Mastectomy: 0.4 fewer undergo a full mastectomy vs breast conserving surgery/1000 *(very low certainty)*	**With *no* screening (baseline):** 97.97/1000 **Compared to no screening:** Biennial 50-74: 6.35 **more** will undergo any breast surgery (e.g., mastectomy or breast conserving surgery)/1000 **Compared to biennial 50-74:** Biennial 50-**79:** 0.28 **more**/1000 Biennial **45**-74: 0.16 **fewer**/1000 Biennial **40**-74: 0.04 **more**/1000 **Hybrid 40**-74: 0.20 **more**/1000 Biennial **40-79:** 0.32 **more**/1000 *(low certainty)*	
Stage at diagnosis (Stage II+) **3.0 / 1000**	3 fewer stage II+/1000 (5 fewer to 1 more) *(low certainty)*	**Cohort - Adherence to screen** Cancer Diagnosed at Stage II or higher 0.51 fewer stage II+ /1000 (0.43- 0.58 fewer) *(very low certainty)* **Before vs After screening implementation: ages 40+** (crude rates) Late stage (Regional) Before screening: 0.87 late stage (regional spread) cancers/ 1000 PYs vs After screening: 0.77 / 1000 PYs *(very low certainty)* **Threshold not applicable**	**With *no* screening (baseline):** 125.79/1000 **Compared to no screening:** Biennial 50-74: 22.53 **fewer stage II+**/1000 **Compared to biennial 50-74:** Biennial 50-**79**: 0.74 **fewer**/1000 Biennial **45**-74: 0.63 **fewer**/1000 Biennial **40**-74: 1.68 **fewer**/1000 **Hybrid 40**-74: 3.05 **fewer**/1000 Biennial **40-79:** 2.48 **fewer**/1000 *(low certainty)*	
Stage at diagnosis (Stage III+) **2.0 / 1000**	1 fewer stage III+/1000 (1-0 fewer) *(very low certainty)*	**Cohort - Adherence to screen** Distant spread RR=0.44 (0.37-0.52) *(very low certainty)* **Threshold not applicable** **Before vs After screening implementation: 40+** (crude rates) Late stage (Regional) Before screening: 0.87 late stage (regional spread) cancers/ 1000 person-years (PY) vs After screening: 0.77 / 1000 PY *(very low certainty)* **Threshold not applicable**	**With *no* screening (baseline):** 44.17/1000 **Compared to no screening:** Biennial 50-74: 11.39 **fewer stage III+**/1000 **Compared to biennial 50-74:** Biennial 50-**79**: 0.38 **fewer**/1000 Biennial **45**-74: 0.28 **fewer**/1000 Biennial **40**-74: 0.83 **fewer**/1000 **Hybrid 40**-74: 1.40 **fewer**/1000 Biennial **40-79:** 1.22 **fewer**/1000 *(low certainty)*	
Stage at diagnosis (Stage IV) **1.0 / 1000**	No data	**Cohort - Adherence to screen** Distant spread RR=0.44 (0.37-0.52) *(very low certainty)* **Threshold not applicable** **Before vs After screening implementation: 40+** (crude rates) Late stage (Distant) Before screening: 0.17 late stage (distant spread) cancers/1000 PYs vs After screening: 0.18 / 1000 PYs *(very low certainty)* **Threshold not applicable**	**With *no* screening (baseline):** 12.41/1000 **Compared to no screening:** Biennial 50-74: 3.39 **fewer stage IV**/1000 **Compared to biennial 50-74:** Biennial 50-**79**: 0.09 **fewer**/1000 Biennial **45**-74: 0.09 **fewer**/1000 Biennial **40**-74: 0.25 **fewer**/1000 **Hybrid 40**-74: 0.41 **fewer**/1000 Biennial **40-79:** 0.34 **fewer**/1000 *(low certainty)*	
Stage by screening interval	No data	**40-79:** No difference in risk of stage IIB+ with annual vs biennial screening (range of adjusted relative risk ranged from 0.98 to 1.17) *(very low certainty)* **Threshold based on USPSTF (absolute numbers not available)**	**Hybrid (annual 40-49 + biennial 50-74) compared to biennial 50-74:** Stage II+ Hybrid 40-74= 3.05 **fewer**/1000 Stage III+ Hybrid 40-74: 1.40 **fewer**/1000 Stage IV Hybrid 40-74: 0.41 **fewer**/1000 *(low certainty)*	
Life-years gained **No threshold**	No data	No data	**With *no* screening (baseline):** 33,021.42 life years/1000 **Compared to no screening:** Biennial 50-74: 90.35 **more** life years/1000 **Compared to biennial 50-74:** Biennial 50-**79**: 1.21 **more**/1000 Biennial **45**-74: 9.56 **more**/1000 Biennial **40**-74: 16.13 **more**/1000 **Hybrid 40**-74: 23.99 **more**/1000 Biennial **40-79:** 17.37 **more**/1000	

performed in 9 patients (1.3%), of which 5 were malignant. (101).

KQ2 (102): Ontario Health Technology Advisory Committee (OHTAC), recommends publicly funding supplemental screening as an adjunct to mammography for people with extremely dense breasts.
Rationale: Evidence showed that supplemental screening for people with dense breasts detects more cases of breast cancer and leads to fewer interval cancers (breast cancer detected after negative screening mammography and before the next scheduled screening appointment). However, there was no evidence describing the impact of supplemental screening on mortality. The OHTAC considered the clinical, economic, patient preferences and values, and ethical evidence for people with dense breasts.

WG Feedback
-There is a lack of data informing if different interventions, age to start screening or screening interval would improve outcomes for different racial or ethnic groups (including those with more aggressive subtypes).
- Benefit of screening increases for those with a higher risk of breast cancer (e.g., family history or higher breast density).
- The impact of risk factors such as family history and dense breasts decreases as patients gets older.
- Detecting more invasive cancers using tomosynthesis is not necessarily a benefit as we did not see differences in outcomes such as stage of diagnosis or mortality and the detection rates amongst high breast density patients were not significantly different.
- There is no benefit data for using supplemental ultrasound. For specific cases, adding another modality for dense breasts may increase detection but it is unclear if this would lead to a benefit related to breast cancer mortality or treatment morbidity.

			(low certainty)
Health-adjusted life-years (HALYs) **No threshold**	No data	No data	**With *no* screening (baseline):** 25,354.12 HALYs/1000 **Compared to no screening:** Biennial 50-74: 42.21 **more** HALYs/1000 **Compared to biennial 50-74:** Biennial 50-**79**: 0.29 **more**/1000 Biennial **45**-74: 6.92 **more**/1000 Biennial **40**-74: 11.22 **more**/1000 **Hybrid 40**-74: 16.27 **more**/1000 Biennial **40-79:** 11.52 **more**/1000 *(very low certainty)*

40-49 (over 10 years):

40-49 Outcome Threshold (Regardless of certainty)	**RCTs[2] Absolute effect (/1000 screens over 10 years)**	**Observational Absolute effect (/1000 screens over 10 years) (unless otherwise indicated (e.g., crude rates, relative risks))**	**Model (/1000 persons)**
Breast cancer mortality **Using the 0.5 / 1000 threshold** (Note: there were two thresholds for breast cancer mortality)	**General Population:** 0.27-0.32 fewer (CI 0.11 to 0.52 fewer) *(low certainty)* **Moderately increased risk due to family history:** 0.44-0.52 fewer (0.17-84 fewer) *(very low certainty)* **Moderately increased risk due to high breast density:** 0.53-0.63 fewer (0.21-1.02 fewer) *(very low certainty)* NOTE: Subgroup analysis excluding high risk of bias RCTs (e.g., Canadian (CNBSS) study) also showed similar results (i.e., 0.23 fewer / 1000 (0.44 fewer to 0.02 more))	**Cohort (Adherence to screen) and Case control** **General Population:** 0.79-0.94 fewer (0.65-1.06 fewer) *(very low certainty)* **Moderately increased risk due to family history:** 1.28-1.51 fewer (1.04-1.71 fewer) *(very low certainty)* **Moderately increased risk due to high breast density:** 1.42-1.82 fewer (1.16-2.07 fewer) *(very low certainty)* **Before and After screening implementation** **2 studies** (crude rates) (a) Before: 0.20/ 1000 PYs vs After: 0.17 / 1000 PYs (very low certainty) (b) Before: 0.15/ 1000 PYs vs After: 0.12 / 1000 PYs (very low certainty) **Threshold not applicable** **Quasi-experimental** Comparing provinces with 40-49 self-referral and those without Breast cancer mortality Rate ratio: 0.92 (0.85-0.99) (with self-referral vs without) 10-year net survival rate: With 40-49 self referral: 84.8% vs Without: 82.9% (P=0.001) *(very low certainty)* **Threshold not applicable**	**Compared to biennial 50-74** Biennial **40**-74: 0.52 **fewer**/1000 **Hybrid 40**-74: 0.82 **fewer**/1000 1000 (screening annually 40-49 then biennial 50-74) *(very low certainty for 0.5/1000 threshold)*
Breast cancer mortality **Using the 1.0 / 1000 threshold** (Note: Same data as above but using a higher threshold)	**General Population:** 0.27-0.32 fewer (0.11 to 0.52 fewer) *(low certainty)* **Moderately increased risk due to family history:** 0.44-0.52 fewer (0.17-84 fewer) *(low certainty)* **Moderately increased risk due to high breast density:** 0.53-0.63 fewer (0.21-1.02) *(low certainty)* Subgroup analysis excluding high risk of bias RCTs (e.g., Canadian (CNBSS) study) also showed similar results (i.e.,	**Cohort (Adherence to screen) and case control** **General Population:** 0.79-0.94 fewer (0.65-1.06 fewer) *(very low certainty)* **Moderately increased risk due to family history:** 1.10-1.51 fewer (0.90-1.71 fewer) *(very low certainty)* **Moderately increased risk due to high breast density:** 1.54-1.82 fewer (1.16-2.07 fewer) *(very low certainty)* **Before and After screening implementation** (2 studies; crude rates) (a) Before: 0.20/ 1000 PYs vs After: 0.17 / 1000 PYs *(very low certainty)*	**Compared to biennial 50-74** Biennial **40**-74: 0.52 **fewer**/1000 **Hybrid 40**-74: 0.82 **fewer**/1000 *(low certainty for 1.0/1000 threshold)*

[2] Intention to screen (short and long case accrual)

	0.23 fewer / 1000 (0.44 fewer to 0.02 more))	(b) Before: 0.15/ 1000 PYs vs After: 0.12 / 1000 PYs *(very low certainty)* **Threshold not applicable** **Quasi-experimental**: Comparing provinces with 40-49 self-referral and those without Breast cancer mortality Rate ratio: 0.92 (0.85-0.99) (less with self-referral vs without) 10-year net survival rate: With 40-49 self referral: 84.8% vs Without: 82.9% (P=0.001) (*very low certainty)* **Threshold not applicable**	
Breast cancer mortality by screening interval **Using the 0.5 or 1.0 / 1000 threshold**	**Annual vs triennial:** RR=1.14 (0.59-1.27) Little to no difference in breast cancer mortality with annual vs triennial **Threshold not applicable**		**Compared to biennial 40-74** (lifetime effect): **Hybrid** 40-74: 0.30 **fewer**/1000 *(low certainty for 1/1000 threshold)* *(very low certainty for 0.5/1000 threshold)*
All-cause mortality **1 / 1000**	0.13 fewer (0-0.25 fewer) *(low certainty)*	No data (all ages only)	N/A
All-cause mortality by screening interval	**Annual vs triennial:** RR=1.20 (0.99-1.46) Little to no difference in breast cancer mortality with annual vs triennial *(very low certainty)* **Threshold not applicable**		N/A
Radiotherapy **5 / 1000**	No data (all ages only)	No data	**Compared to biennial 50-74** Biennial **40**-74: 0.89 **fewer** undergo radiotherapy/1000 **Hybrid 40**-74: 1.32 **fewer**/1000 *(low certainty)*
Chemotherapy **2 / 1000**	No data	No data	**Compared to biennial 50-74** Biennial **40**-74: 2.23 **fewer** undergo chemo/1000 **Hybrid 40**-74: 3.63 **fewer**/1000 *(low certainty)*
Mastectomy/ Breast conserving surgery **2 / 1000**	No data (all ages only)	No data	N/A
Breast surgery-all (Mastectomy or breast conserving surgery) **2 / 1000**	No data	No data	**Compared to biennial 50-74** Biennial **40**-74: 0.04 **more** will undergo any breast surgery (e.g., mastectomy or breast conserving surgery)/1000 **Hybrid 40**-74: 0.20 **more**/1000 *(low certainty)* **Threshold not applicable**
Stage at diagnosis (Stage II+) **3 / 1000**	1 more (1 to 3 more) *(very low certainty)*	**Quasi-experimental studies** Provinces with self-referral at 40-49 vs without (annual screening) Proportion at Stage II* 40-49 self-referral: 40.7% (407 per 1000) vs Without: 43.7% (437 per 1000) (p<0.001) *(very low certainty)* **Stage II not stage II+ therefore surrogate outcome* **Threshold not applicable**	**Compared to biennial 50-74** Biennial **40**-74: 1.68 **fewer** stage II+/1000 **Hybrid 40**-74: 3.05 **fewer**/1000 *(low certainty)*
Stage at diagnosis (Stage III+) **2 / 1000**	No data	**Quasi-experimental studies** Provinces screening 40-49 vs without (annual screening) Provinces with self-referral at 40-49 vs without (annual screening) Proportion at Stage III* 15.6% (156 per 1000) vs 18.3% (183 per 1000) (p<0.001) *(very low certainty)* **Stage III not stage III+* therefore surrogate outcome **Threshold not applicable**	**Compared to biennial 50-74** Biennial **40**-74: 0.83 **fewer** stage III+/1000 **Hybrid 40**-74: 1.40 **fewer**/1000 *(low certainty)*
Stage at diagnosis (Stage IV) **1 / 1000**	No data	**Quasi-experimental studies** Provinces screening 40-49 vs without (annual screening) Provinces with self-referral at 40-49 vs without (annual screening)	**Compared to biennial 50-74** (lifetime effect): Biennial **40**-74: 0.25 **fewer**/1000 **Hybrid 40**-74: 0.41 **fewer**/1000

		Proportion at Stage IV 3.9% (39 per 1000) vs 4.6% (46 per 1000) (p<0.001) *therefore surrogate outcome* *(very low certainty)* **Threshold not applicable**	*(low certainty)*
Life-years gained **No threshold**	No data	No data	**Compared to biennial 50-74** (lifetime effect): Biennial **40**-74: 16.13 **more** life years/1000 **Hybrid 40**-74: 23.99 **more**/1000 *(low certainty)*
HALYs **No threshold**	No data	No data	**Compared to biennial 50-74** (lifetime effect): Biennial **40**-74: 11.22 **more health-adjusted life years**/1000 **Hybrid 40**-74: 16.27 **more**/1000 *(very low certainty)*

50-59 (over 10 years):

50-59 **Outcome** **Threshold** **(Regardless of certainty)**	**RCTs**[3] **Absolute effect (/1000 screens over 10 years)**	**Observational** **Absolute effect (/1000 screens over 10 years)** **(unless otherwise indicated (e.g., crude rates, relative risks, per person years))**	**Model** **(/1000 persons)** **Thresholds not applicable**
Breast cancer mortality **Using the 0.5 / 1000 threshold** (Note: there were two thresholds for breast cancer mortality)	**General population** 0.50-0.59 fewer /1000 (0.20-0.92 fewer) *(very low certainty)* **Moderately increased risk (family history)** 0.79-0.95 fewer /1000 (0.32-1.54 fewer) *(very low certainty)* **Moderately increased risk (breast density)** 0.95-1.13 fewer /1000 (0.38-1.82 fewer) *(very low certainty)*	***Cohort (Adherence to screen) and Case control*** **General population** 1.45-1.72 fewer /1000 (1.19-1.95 fewer) *(very low certainty)* **Moderately increased risk (family history)** 2.33-2.76 fewer /1000 (1.91-3.13 fewer) *(very low certainty)* **Moderately increased risk (breast density)** 2.77-3.28 fewer /1000 (2.27-3.72 fewer) *(very low certainty)* ***Studies of Before and After screening programs were implemented*** *(time trends)* (crude rates: 2 studies) (a) Before screening: 0.49 /1000 PY vs After screening: 0.36 / 1000 PY (b) Before screening: 0.32 / 1000 PY vs After screening: 0.34 / 1000 PY (very *low certainty)* **Threshold not applicable** ***Quasi-experimental*** Provinces with self-referral screening at 40-49 vs Provinces screening 50+ Absolute difference in 10-year net survival rate: With 40-49 screening: 83.2% survival vs Without 40-49 screening: 83.5% survival (P=0.602) *(very low certainty)* **Threshold not applicable**	***Baseline: Breast cancer deaths with no screening (lifetime effect) = 3.45 breast cancer deaths/1000*** **Compared to no screening*** age band only: average events 50-59) 50-74 Annual: 0.44 **fewer** /1000 50-74 Biennial: 0.32 **fewer** /1000 40-74 Biennial: 0.81 **fewer** /1000 *note that some mortality benefits realized later are not captured in these numbers (see all ages) *(very low certainty)*
Breast cancer mortality **Using the 1.0 / 1000 threshold** (Note: Same data as above but using a higher threshold)	**General population** 0.50-0.59 fewer /1000 (0.20-0.92 fewer) *(very low certainty)* **Moderately increased risk (family history)** 0.79-0.95 fewer /1000 (0.32-1.54 fewer) *(very low certainty)* **Moderately increased risk (breast density)** 0.94-1.13 fewer /1000 (0.38-1.82 fewer) *(very low certainty)*	***Cohort (Adherence to screen) and Case control*** **General population** 1.45-1.72 fewer /1000 (1.19-1.95 fewer) *(very low certainty)* **Moderately increased risk (family history)** 2.33-2.76 fewer /1000 (1.91-3.13 fewer) *(very low certainty)* **Moderately increased risk (breast density)** 2.77-3.28 fewer /1000 (2.27-3.72 fewer) *(very low certainty)*	***Baseline: Breast cancer deaths with no screening (lifetime effect) = 3.45 breast cancer deaths/1000*** **Compared to no screening*** age band only: average events 50-59) 50-74 Annual: 0.44 **fewer** /1000 50-74 Biennial: 0.32 **fewer** /1000 40-74 Biennial: 0.81 **fewer** /1000 *note that some mortality benefits realized later are not

[3] Intention to screen (short and long case accrual)

			Studies of Before and After screening programs were implemented *(time trends)* (crude rates: 2 studies) (a) Before screening: 0.49 /1000 PY vs After screening: 0.36 / 1000 PY (b) Before screening: 0.32 / 1000 PY vs After screening: 0.34 / 1000 PY (very *low certainty)* **Threshold not applicable** ***Quasi-experimental*** Provinces with self-referral screening at 40-49 vs Provinces screening 50+ <u>Absolute difference in 10-year net survival rate:</u> With 40-49 screening: 83.2% survival Without 40-49 screening: 83.5% survival (P=0.602) *(very low certainty)* **Threshold not applicable**	captured in these numbers (see all ages) *(low certainty)*
All-cause mortality **1.0 / 1000**	0.31 fewer deaths /1000 (0-0.61 fewer) *(low certainty)*	No data	N/A
Radiotherapy **5.0 / 1000**	No data	No data	***<u>Baseline: Radiotherapy rate with no screening (lifetime effect)</u>*** 109.76/1000 **<u>Compared to no screening (lifetime effect):</u>** 50-74 Biennial: 0.75 **more** undergo radiation/1000 over lifetime *(low certainty)*
Chemotherapy **2.0 / 1000**	No data	No data	***<u>Baseline: Chemo rate with no screening (lifetime effect)</u>*** 109.76/1000 **<u>Compared to no screening (lifetime effect):</u>** 50-74 Biennial: 12.4 **fewer** undergo chemo/1000 *(low certainty)*
Breast surgery (Mastectomy or breast conserving surgery) **2.0 / 1000**	No data	No data	***<u>Baseline: Any breast surgery (mastectomy or breast conserving) with no screening (lifetime effect)</u>*** 97.97/1000 **<u>Compared to no screening (lifetime effect):</u>** 50-74 Biennial: 6.35 **more** will undergo any breast surgery (e.g., mastectomy or breast conserving surgery)/1000 *(low certainty)*
Stage at diagnosis (Stage II+) **3.0 / 1000**	0 fewer (no difference) in stage II+ cancers / 1000 (1 fewer to 2 more) *(very low certainty)*	**Quasi-experimental studies** Provinces with self-referral for screening at 40-49 (annual recall) vs provinces screening 50+ <u>Proportion at Stage II*</u> *(*Stage II not stage II+)* With 40-49 screening: 36.0% (360 per 1000) stage II cancers vs Without: 37.2% (372 per 1000) stage II cancers (p<0.001) *(very low certainty)* **Threshold not applicable**	**<u>Age band only: average events (crude rate) at age 50-59</u>** 50-74 annual screening: 9.54 stage II+/1000 40-74 biennial screening: 10.07 stage II+/1000 50-74 biennial screening: 11.01 stage II+/1000 *(low certainty)*
Stage at diagnosis (Stage III+) **2.0 / 1000**	No data	**Quasi-experimental studies** Provinces with self-referral for screening at 40-49 (annual recall) vs provinces with 50+ screening <u>Proportion at Stage III*</u> (**Stage III not stage III+)* With 40-49 screening: 12.3% (123 per 1000) stage III vs Without: 13.6% (136 per 1000) stage III cancers (p<0.001) *(very low certainty)* **Threshold not applicable**	**<u>Age band only: average events (crude rate) at age 50-59</u>** 50-74 annual screening: 2.50 stage III+/1000 40-74 biennial screening: 2.86 stage III+/1000 50-74 biennial screening: 3.22 stage III+/1000 *(low certainty)*
Stage at diagnosis (Stage IV) **1.0 / 1000**	No data	No data	**<u>Age band only: average events (crude rate) at age 50-59</u>** 50-74 annual screening: 0.87 stage IV/1000 40-74 biennial screening:

			0.81 stage IV/1000 50-74 biennial screening: 0.99 stage IV/1000 *(low certainty)*
Stage by <u>screening interval</u>	**<u>Annual vs triennial:</u>** **No statistical difference in Stage II+ or III+ by screening interval *(low certainty)* (1 RCT) Threshold based on USPSTF (absolute numbers not available)**		**<u>Annual vs biennial</u> <u>Age band only: average events 50-59</u>** Stage II+: 1.47 **fewer** Stage III+: 0.72 **fewer** Stage IV: 0.12 **fewer** **<u>Annual vs triennial:</u>** N/A *(low certainty)*
Life-years gained **No threshold**	No data	No data	**<u>With *no* screening (baseline) (lifetime effect):</u>** 33,021.42 life years/1000 **<u>Compared to no screening (lifetime effect):</u>** Biennial 50-74: 90.35 **more** life years/1000 *(low certainty)*
Health-adjusted life-years (HALYs) **No threshold**	No data	No data	**<u>With *no* screening (baseline) (lifetime effect):</u>** 25,354.12 HALYs/1000 **<u>Compared to no screening:</u>** Biennial 50-74: 42.21 **more** HALYs/1000 *(very low certainty)*

60-69 (over 10 years):

60-69 Outcome Threshold (Regardless of certainty)	**RCTs[4] Absolute effect (/1000 <u>screens</u> over 10 years)**	**Observational Absolute effect (/1000 <u>screens</u> over 10 years) (unless otherwise indicated (e.g., crude rates, relative risks, per person years))**	**Model (/1000 <u>persons</u>) Thresholds not applicable**
Breast cancer mortality **Using the 0.5 / 1000 threshold** (Note: there were two thresholds for breast cancer mortality)	**<u>General population</u>** 0.65-0.77 fewer /1000 (0.26 to 1.25 fewer) *(very low certainty)* **<u>Moderately increased risk (family history)</u>** 1.04-1.24 fewer /1000 (0.41 to 2 fewer) *(very low certainty)* **<u>Moderately increased risk (breast density)</u>** 1.23-1.48 fewer /1000 (0.49 to 2.38 fewer) *(low to very low certainty)*	***Cohort (Adherence to screen) and Case control*** **<u>General population</u>** 1.89-2.24 fewer /1000 (1.55 to 2.54 fewer) (very low certainty) **<u>Moderately increased risk (family history)</u>** 3.04-3.59 fewer /1000 (2.48 to 4.07 fewer) (very low certainty) **<u>Moderately increased risk (breast density)</u>** 3.61-4.26 fewer /1000 (2.95-4.84 fewer) (very low certainty) ***Studies of Before and After screening programs were implemented*** *(time trends)* (crude rates) (a) <u>60-69:</u> **Before** screening: 0.80 /1000 PYs vs **After** screening: 0.63 /1000 PYs (b) <u>60-74:</u> **Before** screening: 0.38 /1000 PYs vs **After** screening: 0.59 /1000 PYs *(very low certainty)* **Threshold not applicable**	***<u>Baseline: Breast cancer deaths with no screening (lifetime effect):</u>** 5.17/1000* **<u>Comparted to no screening*</u> (age band only: average events 60-69)** 50-74 Annual: 1.84 fewer /1000 50-74 Biennial: 1.34 fewer /1000 40-74 Biennial: 1.53 fewer /1000 *note that some mortality benefit realized later are not captured in these numbers (see all ages) *(very low certainty)*
Breast cancer mortality **Using the 1.0 / 1000 threshold** (Note: Same data as above but using a	**<u>General population</u>** 0.65-0.77 fewer /1000 (0.26-1.25 fewer) *(very low certainty)* **<u>Moderately increased risk (family history)</u>** 1.04-1.24 fewer /1000 (0.41 to 2 fewer) *(very low certainty)*	***Cohort (Adherence to screen) and Case control*** **<u>General population</u>** 1.89-2.24 fewer /1000 (1.55 to 2.54 fewer) *(very low certainty)* **<u>Moderately increased risk (family history)</u>** 3.04-3.59 fewer /1000 (2.48 to 4.07 fewer)	***<u>Baseline: Breast cancer deaths with no screening (lifetime effect):</u>** 5.17/1000* **<u>Comparted to no screening*</u> (age band only: average events 60-69)** 50-74 Annual: 1.84 fewer /1000 50-74 Biennial: 1.34 fewer /1000 40-74 Biennial: 1.53 fewer /1000

[4] Intention to screen (short and long case accrual)

higher threshold)	**Moderately increased risk (breast density)** 1.23-1.48 fewer /1000 (0.49-2.38 fewer) *(very low certainty)*	*(very low certainty)* **Moderately increased risk (breast density)** 3.61-4.26 fewer /1000 (2.95-4.84 fewer) *(very low certainty)* ***Studies of Before and After screening programs were implemented*** *(time trends)* (crude rates) (a) 60-69: **Before** screening: 0.80 /1000 PYs vs **After** screening: 0.63 /1000 PYs (b) 60-74: **Before** screening: 0.38 /1000 PYs vs **After** screening: 0.59 /1000 PYs *(very low certainty)* **Threshold not applicable**	*note that some mortality benefit realized later are not captured in these numbers (see all ages) *(low certainty)*
All-cause mortality **1 / 1000**	0.71 fewer/ 1000 (0-1.43 fewer) *(very low certainty)*	No data	N/A
Radiotherapy **5 / 1000**	No data	No data	***Baseline: Radiotherapy rate with no screening (lifetime effect):*** 109.76/1000 **Compared to no screening (lifetime effect):** Biennial 50-74: 0.75 **more** undergo radiotherapy /1000 over lifetime *(low certainty)*
Chemotherapy **2 / 1000**	No data	No data	***Baseline: Chemo rate with no screening (lifetime effect):*** 109.76/1000 **Compared to no screening (lifetime effect):** Biennial 50-74: 12.4 **fewer** undergo chemo/1000 *(low certainty)*
Breast surgery-all (Mastectomy or breast conserving surgery) **2 / 1000**	No data	No data	***Baseline: Any breast surgery (mastectomy or breast conserving) with no screening (lifetime effect):*** 97.97/1000 **Compared to no screening (lifetime effect):** Biennial 50-74: 6.35 **more** will undergo any breast surgery (e.g., mastectomy or breast conserving surgery)/1000 *(low certainty)*
Stage at diagnosis (Stage II+) **3 / 1000**	No data	No data	**Age band only: average events (crude rate) at age 60-69** 50-74 annual: 10.74/1000 40-74 biennial: 13.90/1000 50-74 biennial: 13.90/1000 *(low certainty)*
Stage at diagnosis (Stage III+) **2 / 1000**	No data	No data	**Age band only: average events (crude rate) at age 60-69** 50-74 annual: 2.57/1000 40-74 biennial: 3.83/1000 50-74 biennial: 3.84/1000 *(low certainty)*
Stage at diagnosis (Stage IV) **1 / 1000**	No data	No data	**Age band only: average events (crude rate) at age 60-69** 50-74 annual: 0.82/1000 40-74 biennial: 1.08/1000 50-74 biennial: 1.08/1000 *(low certainty)*
Life-years gained **No threshold**	No data	No data	**With *no* screening (baseline) (lifetime effect):** 33,021.42 life years/1000 **Compared to no screening (lifetime effect):** 50-74 Biennial: 90.35 **more** life years/1000

			(low certainty)
Health-adjusted life years (HALYs) **No threshold**	No data	No data	**With *no* screening (baseline) (lifetime effect):** 25,354.12 HALYs/1000 **Compared to no screening:** 50-74 Biennial: 42.21 **more** HALYs/1000 *(very low certainty)*

70-74 (over 10 years):

70-74 Outcome Threshold (Regardless of certainty)	**RCTs**[5] **Absolute effect (/1000 screens over 10 years)**	**Observational** **Absolute effect (/1000 screens over 10 years)** **(unless otherwise indicated (e.g., crude rates, relative risks, per person years))**	**Model** **(/1000 persons)** **Thresholds not applicable**
Breast cancer mortality **Using the 0.5 / 1000 threshold** (Note: there were two thresholds for breast cancer mortality)	**General population** 0.92-1.10 fewer /1000 (0.37-1.77 fewer) *(very low certainty)* **Moderately increased risk (family history)** 1.47-1.76 fewer /1000 (0.59-2.84 fewer) *(very low certainty)* **Moderately increased risk (breast density)** 1.74-2.09 fewer /1000 (0.70-3.36 fewer) *(very low certainty)*	***Cohort and Case control*** **General population** 0.81--3.17 fewer /1000 (0.19-3.60 fewer) *(very low certainty)* **Moderately increased risk (family history)** 4.31-5.10 fewer /1000 (3.53-5.78 fewer) *(very low certainty)* **Moderately increased risk (breast density)** 5.10-6.03 fewer /1000 (4.18-6.84 fewer) *(very low certainty)* ***Studies of Before and After screening programs were implemented*** *(time trends) (crude rates)* (a) Ages 60-74: Before screening: 0.38/1000 PYs vs After screening: 0.59 / 1000 PYs (N=40.7 million PYs) (b) Ages 70-79: Before screening: 1.12/1000 PYs vs After screening: 1.14/1000 PYs (N=323719) *(very low certainty)* **Threshold not applicable**	***Baseline: Breast cancer deaths with no screening (lifetime effect) =*** 8.99/1000 **Compared to no screening*** age band only: average events 70-79) 50-74 Annual: 3.94 **fewer** /1000 50-74 Biennial: 3.41 **fewer** /1000 40-74 Biennial: 2.95 **fewer** /1000 *note that some mortality benefits realized later are not captured in these numbers *(very low certainty)*
Breast cancer mortality **Using the 1.0 / 1000 threshold** (Note: Same data as above but using a higher threshold)	**General population** 0.92-1.10 fewer /1000 (0.37-1.77 fewer) *(very low certainty)* **Moderately increased risk (family history)** 1.47-1.76 fewer /1000 (0.59-2.84 fewer) *(very low certainty)* **Moderately increased risk (breast density)** 1.74-2.09 fewer /1000 (0.70-3.36 fewer) *(very low certainty)*	***Cohort and Case control*** **General population** 0.81--3.17 fewer /1000 (0.19-3.60 fewer) *(very low certainty)* **Moderately increased risk (family history)** 4.31-5.10 fewer /1000 (3.53-5.78 fewer) *(very low certainty)* **Moderately increased risk (breast density)** 5.10-6.03 fewer /1000 (4.18-6.84 fewer) *(very low certainty)* ***Studies of Before and After screening programs were implemented*** *(time trends) (crude rates)* (a) Ages 60-74: Before screening: 0.38/1000 PYs vs After screening: 0.59 / 1000 PYs (N=40.7 million PYs) (b) Ages 70-79: Before screening: 1.12/1000 PYs vs After screening: 1.14/1000 PYs (N=323719) *(very low certainty)* **Threshold not applicable**	***Baseline: Breast cancer deaths with no screening (lifetime effect) =*** 8.99/1000 **Compared to no screening*** age band only: average events 70-79) 50-74 Annual: 3.94 **fewer**/1000 50-74 Biennial: 3.41 **fewer** /1000 40-74 Biennial: 2.95 **fewer** /1000 *note that some mortality benefits realized later are not captured in these numbers *(low certainty)*

[5] Intention to screen (short and long case accrual)

All-cause mortality **1.0 / 1000**	1.41 fewer /1000 (0-2.81 fewer) *(very low certainty)*	No data	No data
Radiotherapy **5.0 / 1000**	No data	*Proportion of breast cancers treated with radiation* **Continue screening at 70-74:** 51% (50.3–51.8) vs **Stop screening at 69:** 39.9% (38.6–41.3) Absolute difference= 111 more per 1000 cancers *(low certainty)* **Threshold not applicable** *(Thresholds do not apply as denominator is per 1000 cancers (not women))*	***Baseline: Radiotherapy rate with no screening (lifetime effect):*** 88.06/1000 **Compared to no screening (lifetime effect):** Biennial 50-74: 0.75 **more** undergo radiation/1000 **over a lifetime** *(low certainty)*
Chemotherapy **2.0 / 1000**	No data	*Proportion of breast cancers treated with chemotherapy* **Continue screening at 70-74:** 15.2% (14.7–15.8) vs **Stop screening at 69:** 21.1% (20.0–22.1) *Absolute difference= 59 fewer per 1000 cancers* *(low certainty)* **Threshold not applicable** *(Thresholds do not apply as denominator is per 1000 cancers (not women))*	***Baseline: Chemo rate with no screening (lifetime effect):*** 109.76/1000 **Compared to no screening (lifetime effect):** Biennial 50-74: 12.4 **fewer** undergo chemo/1000 **over a lifetime** *(low certainty)*
Breast surgery (Mastectomy or breast conserving surgery) **2.0 / 1000**	No data	*Proportion of breast cancers treated with simple mastectomy* **Continue screening at 70-74:** 11.3% (10.8–11.8) vs **Stop screening at 69:** 10.4% (9.5–11.3) Absolute difference= 9 more per 1000 cancers *(low certainty)* **Threshold not applicable** *Proportion of breast cancers treated with radical mastectomy* **Continue screening at 70-74:** 13.9% (13.4–14.5) vs **Stop screening at 69:** 18.2% (17.0–19.4) *Absolute difference= 43 fewer per 1000 cancers* *(low certainty)* **Threshold not applicable** *(Thresholds do not apply as denominator is per 1000 cancers (not women))*	***Baseline: Any breast surgery (mastectomy or breast conserving) with no screening (lifetime effect):*** 97.97/1000 **Compared to no screening (lifetime effect):** Biennial 50-74: 6.35 **more** will undergo any breast surgery (e.g., mastectomy or breast conserving surgery)/1000 **over a lifetime** *(low certainty)*
Stage at diagnosis (Stage II+) **3.0 / 1000**	No data	No data	**Age band only: average events (crude rate) at age 70-79 (no data for 70-74 alone)** 50-74 Annual: 16.49 stage II+/1000 40-74 Biennial: 19.48 stage II+/1000 50-74 Biennial: 19.49 stage II+/1000 *(low certainty)*
Stage at diagnosis (Stage III+) **2.0 / 1000**	No data	***Studies of Before and After screening programs were implemented*** *(crude rates)* **Ages 70-75** (a) Screening uptake period 1998-2002 Before: 0.59 stage III+ / 1000 PYs vs After: 0.46 stage III+ / 1000 PYs (N=38442) *(very low certainty)* (b) Screening uptake period 2003-2011 Before: 0.59 stage III+/ 1000 PYs vs After: 0.52 stage III+/ 1000 PYs (N=38442) *(very low certainty)* **Threshold not applicable**	**Age band only: average events (crude rate) at age 70-79 (no data for 70-74 alone)** 50-74 Annual: 4.85 stage III+/1000 40-74 Biennial: 5.95 stage III+/1000 50-74 Biennial: 5.91 stage III+/1000 *(low certainty)*
Stage at diagnosis (Stage IV) **1.0 / 1000**	No data	No data	**Age band only: average events (crude rate) at age 70-79 (no data for 70-74 alone)** 50-74 Annual: 1.22 stage IV/1000 40-74 Biennial: 1.52 stage IV/1000 50-74 Biennial: 1.51 stage IV/1000 *(low certainty)*
Life-years gained **No threshold**	No data	No data	**With *no* screening (baseline) (lifetime effect):** 33,021.42 life years/1000

			<u>Compared to no screening (lifetime effect):</u> Biennial 50-74: 90.35 **more** life years/1000 *(low certainty)*
Health-adjusted life-years (HALYs) **No threshold**	No data	No data	**<u>With *no* screening (baseline) (lifetime effect):</u>** 25,354.12 HALYs/1000 **<u>Compared to no screening: (lifetime effect)</u>** Biennial 50-74: 42.21 **more** HALYs/1000 *(very low certainty)*

75+:

75+ Outcome **Threshold (Regardless of certainty)**	**RCTs[6] Absolute effect (/1000 <u>screens</u> over 10 years)**	**Observational** **Absolute effect (/1000 <u>screens</u> over 10 years)** **(unless otherwise indicated (e.g., crude rates, relative risks, per person years))**	**Model** **(/1000 <u>persons</u>)** **Thresholds not applicable**
Breast cancer mortality **Using the 0.5 and 1.0 / 1000 threshold** (Note: there were two thresholds for breast cancer mortality)	No data	**Among those who continue screening at 75+ (vs those who stop at age 74)** **<u>75 vs stopping at age 74:</u>** 0 to 0.1 fewer /1000 (0.63 fewer- 0.70 more) *(very low certainty)* ***Studies of Before and After screening programs were implemented*** *(time trends) (crude rates)* Ages 75-84: Before screening: 0.72 /1000 PYs vs After screening: 0.84 /1000 PYs (N=40.7 million PYs) **Threshold not applicable**	**<u>Compared to screening 50-74 (biennial)</u>** <u>Lifetime effect</u> Biennial 50-79: 0.16 **fewer** /1000 over a lifetime *(very low certainty)*
All-cause mortality **1 / 1000**	No data	No data	No data
Radiotherapy **5 / 1000**	No data	*Proportion of breast cancers treated with radiation* **Continue screening 75-84:** 41.2% (40.4–41.9) vs **Stop screening at 74:** 31.9% (30.7–33.1) Absolute difference= 93 more per 1000 cancers *(low certainty)* **Threshold not applicable** *(Thresholds do not apply as denominator is per 1000 cancers (not women))*	**<u>Compared to screening 50-74 (biennial):</u>** <u>Lifetime effect</u> Biennial 50-79: 0.12 **more** undergo radiotherapy /1000 over a lifetime *(low certainty)*
Chemotherapy **2 / 1000**	No data	*Proportion of breast cancers treated with chemo* **Continue screening 75-84:** 8.6% (8.3–9.1) vs **Stop screening at 74:** 11.5% (10.6–12.3) Absolute difference= 29 fewer per 1000 cancers *(low certainty)* **Threshold not applicable** *(Thresholds do not apply as denominator is per 1000 cancers (not women))*	**<u>Compared to screening 50-74 (biennial):</u>** <u>Lifetime effect</u> Biennial 50-79: 0.19 **fewer** undergo chemo/1000 over a lifetime *(low certainty)*
Breast surgery-all (Mastectomy or breast conserving surgery) **2 / 1000**	No data	*Proportion of breast cancers treated with simple mastectomy* **Continue screening 75-84:** 10.8% (10.3–11.2) vs **Stop screening at 74:** 10.1% (9.4–10.9) Absolute difference= 7 more per 1000 cancers *(low certainty)* **Threshold not applicable** *Proportion of breast cancers treated with radical mastectomy* **Continue screening 75-84:** 14.2% (13.7–14.6) vs **Stop screening at 74:** 17.0% (16.0–17.9) *Absolute difference= 28 fewer per 1000 cancers (low certainty)* **Threshold not applicable** *(Thresholds do not apply as denominator is per 1000 cancers (not women))*	**<u>Compared to screening 50-74 (biennial):</u>** <u>Lifetime effect</u> Biennial 50-79: 0.28 **more** undergo breast surgery (mastectomy or breast conserving)/1000 over a lifetime *(low certainty)*
Stage at diagnosis (Stage II+) **3 / 1000**	No data	No data	**<u>Age band only: average events (crude rate) at age 70-79</u> (no data for 75-79 alone)** 50-79 Annual: 15.83 stage II+/1000

[6] Intention to screen (short and long case accrual)

			40-79 Biennial: 19.31 stage II+/1000 50-79 Biennial: 19.34 stage II+/1000 *(low certainty)*
Stage at diagnosis (Stage III+) **2 / 1000**	No data	***Studies of Before and After screening programs were implemented*** *(time trends) (crude rates)* **Ages 76-80** a) Screening uptake period 1998-2002 Before screening: 0.66 stage III+ /1000 PYs vs After screening: 0.69 stage III+ /1000 PYs (N=38442) *(very low certainty)* b) Screening uptake period 2003-2011 Before screening: 0.66 stage III+/1000 PYs vs After screening: 0.67 stage III+ /1000 PYs (N=38442) *(very low certainty)* **Threshold not applicable**	**Age band only: average events (crude rate) at age 70-79 (no data for 75+ alone)** 50-79 Annual: 4.47 stage III+/1000 40-79 Biennial: 5.84 stage III+/1000 50-79 Biennial: 5.80 stage III+/1000 *(low certainty)*
Stage at diagnosis (Stage IV) **1 / 1000**	No data	No data	**Age band only: average events (crude rate) at age 70-79 (no data for 75+)** 50-79 Annual: 1.18 stage IV/1000 40-79 Biennial: 1.51 stage IV/1000 50-79 Biennial: 1.51 stage IV/1000 *(low certainty)*
Life-years gained	No data	No data	**Versus biennial 50-74:** Biennial 50-79: **1.21 more** life years /1000 over lifetime *(low certainty)*
Health-adjusted life years (HALYs)	No data	No data	**Versus biennial 50-74:** Biennial 50-79: **0.29 more** life years/1000 over lifetime *(very low certainty)*

KQ1i: Do the benefits differ by population characteristics (e.g., age, breast density, race and ethnicity, socioeconomic status, geographical area, family history)?

See above and right column for age groups and breast cancer mortality by moderately increased risk due to family history or breast density. No data for race, ethnicity, socioeconomic status or geography from the SR.

KQ2: What is the comparative effectiveness of different mammography-based breast cancer screening strategies on benefits?

(a) Does comparative effectiveness differ by population characteristics and risk markers (e.g., age, breast density, race and ethnicity, socioeconomic status, geographical area, family history)?

Screening interval:

Outcome **Threshold (Regardless of certainty)**	**Model: Screening 40-49 annual vs 40-49 biennial (per 1000 individuals)**	**Model: Lifetime annual vs biennial (per 1000 individuals) Thresholds not applicable**	
		40-74	**50-74**
Breast cancer mortality **0.5 and 1.0/ 1000**	**Annual: 0.3 fewer** (very low certainty)	**Annual: 2.28 fewer** (low certainty)	**Annual: 2.00 fewer** (low certainty)
All-cause mortality	N/A	N/A	
Radiotherapy **5/ 1000**	**Annual: 0.42 fewer** (low certainty)	**Annual: 0.78 fewer** (low certainty)	**Annual: 0.35 fewer** (low certainty)
Chemotherapy **2/ 1000**	**Annual: 1.41 fewer** (low certainty)	**Annual: 7.91 fewer** (low certainty)	**Annual: 6.53 fewer** (low certainty)
Breast surgery **No threshold**	**Annual: 0.15 more** (low certainty)	**Annual: 1.92 more** (low certainty)	**Annual: 1.81 more** (low certainty)
Life years gained **No threshold**	**Annual: 7.86 more** (low certainty)	**Annual: 37.72 more** (low certainty)	**Annual: 30.05 more** (low certainty)
HALYs **No threshold**	**Annual: 5.05 more** (very low certainty)	**Annual: 21.01 more** (very low certainty)	**Annual: 15.86 more** (very low certainty)

Screening modality:

Tomosynthesis

Tomosynthesis vs Digital mammography among average risk (unless otherwise specified) individuals: Multiple age groups

Outcome Thresholds based on USPSTF (absolute numbers not available)	Age groups	Study types	Results
Stage at diagnosis (reduction in Stage II+)	45-69	3 RCTs and 1 observational	45-69: Tomosynthesis may make little-to-no difference (compared to digital mammography) on Stage II+, III+ or other tumour prognostic characteristics for average risk individuals. *(Low certainty)*
Screen-detected invasive breast cancer (surrogate outcome)	45-69 (45-49 subgroup)	3 RCTs and 1 observational	45-69: Tomosynthesis may detect more invasive cancers over two rounds of screening (0.6 to 2.4 more per 1000) compared to digital mammography in average risk individuals. (Low certainty) Subgroups: • **Age: 45-49**: No statistical difference in the detection of invasive cancers between tomosynthesis and digital mammography. (1 RCT) *(Low certainty)* • May make no difference in cancer detection for **high breast density**: **BIRADS C/D or density grade 4** (2 RCTs) *(Low certainty)*

Supplementary ultrasound

Digital mammography + Supplemental ultrasound vs Digital mammography alone among average or moderately increased risk (e.g., high breast density): Multiple age groups

Outcome	Threshold	Age groups	Study types	Results
No data on benefits				

Supplementary MRI

Digital mammography + Supplemental MRI vs Digital mammography alone among moderately elevated risk individuals (e.g., high breast density): Multiple age groups

Outcome	Threshold	Age groups	Study types	Results
No data on benefits				

No other data available from studies (see additional considerations column)

FULL EVIDENCE TABLES

KQ1: Screening vs no screening

GRADE Summary of Findings Table – **Breast Cancer Mortality** (**RCTs, Short-Case Accrual**, Stratified by Age) over 10 years

Outcome Threshold (Regardless of certainty)	Model: 40-49 annual vs 40-49 biennial (per 1000 individuals)	Model: Lifetime annual vs biennial (per 1000 individuals) Threshold not applicable		RCT or Observational data: Annual vs Triennial 50-62 Threshold based on USPSTF (absolute numbers not available)	RCT or Observational data: Annual vs Biennial All ages Threshold based on USPSTF (absolute numbers not available)
		40-74	50-74		
Stage: II+ **3/ 1000**	**Annual: 1.37 fewer** (Low certainty)	**Annual: 11.71 fewer** (Low certainty)	**Annual: 10.43 fewer** (Low certainty)	50-62: Similar rates and no statistical differences in tumor size, nodal status, grade, or prognostic index for all invasive cancers diagnosed over 3 years. (Low certainty)	40-79: No statistically significant difference in stage IIB+ or "less favourable prognosis" (very low certainty)
Stage III+ **2/ 1000**	**Annual: 0.57 fewer** (low certainty)	**Annual: 4.66 fewer** (low certainty)	**Annual: 4.11 fewer** (low certainty)		No data
Stage IV **1/ 1000**	**Annual: 0.17 fewer** (low certainty)	**Annual: 1.11 fewer** (low certainty)	**Annual: 0.97 fewer** (low certainty)		No data

Mammography +/- CBE compared to Usual Care

Outcomes	Absolute effects		Relative effect (95% CI) §	№ of participants (studies) *	Quality of the evidence (GRADE) Clinical threshold of 0.5	Quality of the evidence (GRADE) Clinical threshold of 1.0	What happens
	Risk with Usual Care (Assumed Risk) ‡	**Absolute effect (95% CI)**					
Sub-Group: Breast-Cancer Mortality **40-49 years** Range of follow-up (yrs): 17.7 to 25.7	**General Population**		**RR 0.85** (0.78 to 0.93)	Unavailable (8 RCTs) [a] (46–51)	⊕⊕◯◯ LOW [b,c,d,e,f]	⊕⊕◯◯ LOW [b,c,d,e,f]	Using a threshold of 0.5 or 1 fewer deaths per 1,000, screening may make little to no difference in reducing breast cancer mortality over 10 years for individuals aged 40 to 49 years in a general population
	1.8 per 1,000	**0.27 fewer per 1,000** (from 0.13 fewer to 0.40 fewer)					
	Moderately increased risk due to family history				⊕◯◯◯ VERY LOW [b,c,d,f,g]	⊕⊕◯◯ LOW [b,c,d,e,f]	Using a threshold of 0.5 fewer deaths per 1,000, we are very uncertain whether screening decreases breast cancer mortality over 10 years for individuals aged 40 to 49 at moderately increased risk for breast cancer.
	2.9 per 1,000	**0.44 fewer per 1,000** (0.20 fewer to 0.64 fewer)					Using a threshold of 1 fewer death per 1,000, screening may make little to no difference in reducing breast cancer mortality over 10 years for individuals aged 40 to 49 years at moderately increased risk for breast cancer.
	Moderately increased risk due to dense breast				⊕◯◯◯ VERY LOW [b,c,d,f,g]	⊕⊕◯◯ LOW [b,c,d,e,f]	Using a threshold of 0.5 fewer deaths per 1,000, we are very uncertain whether screening decreases breast cancer mortality over 10 years for individuals aged 40 to 49 at moderately increased risk for breast cancer.
	3.5 per 1,000	**0.53 fewer per 1,000** (0.25 fewer to 0.77 fewer)					Using a threshold of 1 fewer death per 1,000, screening may make little to no difference in reducing breast cancer mortality over 10 years for individuals aged 40 to 49 years at moderately increased risk for breast cancer.
Sub-Group: Breast-Cancer Mortality **50-59 years** Range of follow-up (yrs): 18.0 to 30.0	**General Population**		**RR 0.85** (0.78 to 0.93)	Unavailable (6 RCTs) [a] (46,48,50,51)	⊕◯◯◯ VERY LOW [b,c,d,f,g]	⊕⊕◯◯ LOW [b,c,d,e,f]	Using a threshold of 0.5 fewer deaths per 1,000, we are very uncertain whether screening decreases breast cancer mortality over 10 years for individuals aged 50 to 59 a general population risk for breast cancer.
	3.3 per 1,000	**0.50 fewer per 1,000** (0.23 fewer to 0.73 fewer)					Using a threshold of 1 fewer death per 1,000, screening may make little to no difference in reducing breast cancer mortality over 10 years for individuals aged 50 to 59 years in a general population.
	Moderately increased risk due to family history				⊕◯◯◯ VERY LOW [b,d,f,g,h]	⊕◯◯◯ VERY LOW [b,c,d,f,g]	Using a threshold of 0.5 or 1 fewer deaths per 1,000, we are very uncertain whether screening decreases breast cancer mortality over 10 years for individuals aged 50 to 59 years at moderately increased risk for breast cancer.
	5.3 per 1,000	**0.79 fewer per 1,000** (0.37 fewer to 1.16 fewer)					
	Moderately increased risk due to dense breast				⊕◯◯◯ VERY LOW [b,d,f,g,h]	⊕◯◯◯ VERY LOW [b,c,d,f,g]	Using a threshold of 0.5 or 1 fewer deaths per 1,000, we are very uncertain whether screening decreases breast cancer mortality over 10 years for individuals aged 50 to 59 years at moderately increased risk for breast cancer.
	6.3 per 1,000	**0.95 fewer per 1,000** (0.44 fewer to 1.39 fewer)					
Sub-Group: Breast-Cancer Mortality **60-69 years** Range of follow-up (yrs): 13.1 to 30.0	**General Population**		**RR 0.85** (0.78 to 0.93)	Unavailable (4 RCTs) [h] (46,48,49,51)	⊕◯◯◯ VERY LOW [b,c,d,f,g]	⊕⊕◯◯ LOW [b,c,d,e,f]	Using a threshold of 0.5 fewer deaths per 1,000, we are very uncertain whether screening decreases breast cancer mortality over 10 years for individuals aged 60 to 69 in a general population.
	4.3 per 1,000	**0.65 fewer per 1,000** (0.30 fewer to 0.95 fewer)					Using a threshold of 1 fewer death per 1,000, screening may make little to no difference in reducing breast cancer mortality over 10 years for individuals aged 60 to 69 years in a general population.
	Moderately increased risk due to family history						Using a threshold of 0.5 or 1 fewer deaths per 1,000, we

	6.9 per 1,000	**1.04 fewer per 1,000** (0.48 fewer to 1.52 fewer)			⊕◯◯◯ VERY LOW b,d,e,f,h	⊕◯◯◯ VERY LOW b,c,d,f,g	are very uncertain whether screening decreases breast cancer mortality over 10 years for individuals aged 60 to 69 in at moderately increased risk.
	Moderately increased risk due to dense breast						
	8.2 per 1,000	**1.23 fewer per 1,000** (0.57 fewer to 1.80 fewer)					
Sub-Group: Breast-Cancer Mortality **70-74 years** Range of follow-up (yrs): 13.2 to 13.6	**General Population**		**RR 0.85** (0.78 to 0.93)	Unavailable (2 RCTs) (48,49)	⊕◯◯◯ VERY LOW b,d,f,g,h	⊕◯◯◯ VERY LOW b,c,d,f,g	Using a threshold of 0.5 or 1 fewer deaths per 1,000, we are very uncertain whether screening decreases breast cancer mortality over 10 years for individuals aged 70 to 74 years in a general population.
	6.1 per 1,000	**0.92 fewer per 1,000** (0.43 fewer to 1.34 fewer)					
	Moderately increased risk due to family history				⊕◯◯◯ VERY LOW b,d,e,f,h	⊕◯◯◯ VERY LOW b,c,d,f,g	
	9.8 per 1,000	**1.47 fewer per 1,000** (0.69 fewer to 2.16 fewer)					
	Moderately increased risk due to dense breast						
	11.6 per 1,000	**1.74 fewer per 1,000** (0.81 fewer to 2.55 fewer)			⊕◯◯◯ VERY LOW b,d,e,f,h	⊕◯◯◯ VERY LOW b,d,f,g,h	

‡The baseline risk represents the breast cancer mortality rate over 10 years in an unscreened group based on observational data reported by Coldman et al. (52). To calculate a moderately increased risk group, we used an estimate from Engmann et al. (53) 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 risk of 1.9 (54).
§ The relative effect is based on our previous systematic review and guideline (12) where a subgroup analysis of relative risk by age was assessed and no difference in RR among subgroups was detected and true differences resulting from age were deemed unlikely. Therefore, we used the RR for all ages rather than focusing on each decade of age as we had previously done in our 2018 guideline.
*The number of participants and studies reflect the previous analysis for each age decade, rather than the number of studies that are included in the relative effect estimate for all ages.
CI: Confidence interval; **RR:** Risk ratio

a. Two studies considered quasi-randomised (Stockholm (46) & Gothenburg (46)).
b. Randomisation and allocation concealment were either not reported or there were serious deficiencies in these areas, therefore we rated down once for risk of bias. A sensitivity analysis by risk of bias is presented in Supplemental Material, Appendix 1 and no differences in relative risk were detected between high risk and moderate risk of bias papers. True differences resulting from risk of bias were deemed unlikely, however we still rated down once due to concerns with risk of bias impacting the overall estimate.
c. All point estimates in our pooled analysis lie to one side of our threshold. We did not rate down for inconsistency.
d. Breast density was not addressed. Studies reported in Nystrom 2002 (49) and Nystrom 2016 (46) included one round of screening in the control group as part of the short-case accrual calculation. Therefore, the study estimates may be underestimated (a larger benefit from the intervention may be possible). Data are from trials initiated in the 1960s-1990s and the intervention groups were primarily screened with film mammography. Due to advances in mammography technology and treatment practices, we expect that the magnitude of screening effect may differ if applied to today's Canadian screening context. There are no high-quality clinical trials examining the impact of screening on breast cancer screening deaths using contemporary screening methods. We downrated once for indirectness.
e. Given the large sample size; an optimal sample size calculation was not warranted. The 95% CI does not cross the clinical decision threshold; therefore, we did not rate down for imprecision.
f. According to Egger et al. (55), 10 trials are needed to assess publication bias. We cannot assess publication bias due to insufficient number of trials, therefore, we did not rate down for publication bias.
g. Given the large sample sizes; an optimal sample size calculation was not warranted. The 95% CI crosses the clinical decision threshold; therefore, we rated down once for imprecision.
h. Approximately half of the point estimates in our pooled analysis lie on either side of our threshold. We rated down once for inconsistency.

GRADE Summary of Findings Table – **Breast Cancer Mortality (RCTs, Long-Case Accrual**, Stratified by Age) over 10 years

Mammography +/- CBE compared to Usual Care

Outcomes	Absolute effects		Relative effect (95% CI) §	№ of participants (studies)*	Quality of the evidence (GRADE) Clinical threshold of 0.5	Quality of the evidence (GRADE) Clinical threshold of 1.0	Comments
	Risk with Usual Care (Assumed Risk) ‡	**Absolute effect (95% CI)**					
Sub-Group: Breast-Cancer Mortality **40-49 years** Range of follow-up (yrs): 17.7 to 25.7	**General Population**		**RR 0.82** (0.71 to 0.94)	Unavailable (6 RCTs)[a] (47,50,56–58)	⊕⊕◯◯ LOW b,c,d,e,f	⊕⊕◯◯ LOW b,c,d,e,f	Using a threshold of 0.5 or 1 fewer deaths per 1,000, screening may make little to no difference in reducing breast cancer mortality over 10 years for individuals aged 40 to 49 years in a general population.
	1.8 per 1,000	**0.32 fewer per 1,000** (from 0.11 fewer to 0.52 fewer)					
	Moderately increased risk due to family history				⊕◯◯◯ VERY LOW b,c,d,f,g	⊕⊕◯◯ LOW b,c,d,e,f	Using a threshold of 0.5 fewer deaths per 1,000, we are very uncertain whether screening decreases breast cancer mortality over 10 years for individuals aged 40 to 49 at moderately increased risk for breast cancer. Using a threshold of 1 fewer death per 1,000, screening may make little to no difference in reducing breast cancer mortality over 10 years for individuals aged 40 to 49 years at moderately increased risk for breast cancer.
	2.9 per 1,000	**0.52 fewer per 1,000** (0.17 fewer to 0.84 fewer)					
	Moderately increased risk due to Dense breasts						
	3.5 per 1,000	**0.63 fewer per 1,000** (0.21 fewer to 1.02 fewer)					
Sub-Group: Breast-Cancer Mortality (50-59 years) Range of follow-up (yrs): 18 to 30	**General Population**		**RR 0.82** (0.71 to 0.94)	Unavailable (5 RCTs)[a] (50,56–58)	⊕◯◯◯ VERY LOW b,d,f,g,h	⊕⊕◯◯ LOW b,d,e,f,h	Using a threshold of 0.5 fewer deaths per 1,000, we are very uncertain whether screening decreases breast cancer mortality over 10 years for individuals aged 50 to 59 a general population risk for breast cancer. Using a threshold of 1 fewer death per 1,000, screening may make little to no difference in reducing breast cancer mortality over 10 years for individuals aged 50 to 59 years in a general population.
	3.3 per 1,000	**0.59 fewer per 1,000** (0.20 fewer to 0.96 fewer)					
	Moderately increased risk due to family history				⊕◯◯◯ VERY LOW b,d,f,g,h	⊕◯◯◯ VERY LOW b,d,f,g,h	Using a threshold of 0.5 or 1 fewer deaths per 1,000, we are very uncertain whether screening decreases breast cancer mortality over 10 years for individuals aged
	5.3 per 1,000	**0.95 fewer per 1,000** (0.32 fewer to 1.54 fewer)					

	Moderately increased risk due to Dense breasts						
	6.3 per 1,000	**1.13 fewer per 1,000** (0.38 fewer to 1.83 fewer)					50 to 59 years at moderately increased risk for breast cancer.
Sub-Group: Breast-Cancer Mortality (60-69 years) Range of follow-up (yrs): 13.1 to 30.0	**General Population**		**RR 0.82** (0.71 to 0.94)	Unavailable (3 RCTs) (57,58)	⨁◯◯◯ VERY LOW b,d,f,g,h	⨁◯◯◯ VERY LOW b,d,f,g,h	Using a threshold of 0.5 or 1 fewer deaths per 1,000, we are very uncertain whether screening decreases breast cancer mortality over 10 years for individuals aged 60 to 69 years in a general population.
	4.3 per 1,000	**0.77 fewer per 1,000** (0.26 fewer to 1.25 fewer)					
	Moderately increased risk due to family history				⨁⨁◯◯ LOW b,d,e,f,h	⨁◯◯◯ VERY LOW b,d,f,g,h	Using a threshold of 0.5 fewer deaths per 1,000, screening may reduce breast cancer mortality over 10 years for individuals aged 60 to 69 years at moderately increased risk. Using a threshold of 1 fewer death per 1,000, we are very uncertain whether screening decreases breast cancer mortality over 10 years for individuals aged 60 to 69 years at moderately increased risk for breast cancer.
	6.9 per 1,000	**1.24 fewer per 1,000** (0.41 fewer to 2 fewer)					
	Moderately increased risk due to Dense breasts						
	8.2 per 1,000	**1.48 fewer per 1,000** (0.49 fewer to 2.38 fewer)					
Sub-Group: Breast-Cancer Mortality (70-74 years) # Randomised: 18,233 # Analyzed: unclear Range of follow-up (yrs): 13.2-13.6	**General Population**		**RR 0.82** (0.71 to 0.94)	Unavailable (2 RCTs) (57)	⨁◯◯◯ VERY LOW b,d,f,g,h	⨁◯◯◯ VERY LOW b,d,f,g,h	Using a threshold of 0.5 or 1 fewer deaths per 1,000, we are very uncertain whether screening decreases breast cancer mortality over 10 years for individuals aged 70 to 74 years in a general population.
	6.1 per 1,000	**1.10 fewer per 1,000** (0.37 fewer to 1.77 fewer)					
	Moderately increased risk due to family history				⨁⨁◯◯ LOW b,d,e,f,h	⨁◯◯◯ VERY LOW b,d,f,g,h	Using a threshold of 0.5 fewer deaths per 1,000, screening may reduce breast cancer mortality over 10 years for individuals aged 70 to 74 at moderately increased risk for breast cancer. Using a threshold of 1 fewer death per 1,000, we are very uncertain whether screening decreases breast cancer mortality over 10 years for individuals aged 70 to 74 years at moderately increased risk for breast cancer.
	9.8 per 1,000	**1.76 fewer per 1,000** (0.59 fewer to 2.84 fewer)					
	Moderately increased risk due to Dense breasts						
	11.6 per 1,000	**2.09 fewer per 1,000** (0.70 fewer to 3.36 fewer)					

‡The baseline risk represents the breast cancer mortality rate over 10 years in an unscreened group based on Canadian observational data reported by Coldman et al. (59). To calculate moderately increased risk group, we used an estimate from Engmann et al. (53) 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 risk of 1.9 (54).
§ The relative effect is based on our previous systematic review and guideline where a subgroup analysis of relative risk by age was assessed and no difference in RR among subgroups was detected and true differences resulting from age were deemed unlikely. Therefore, we used the RR for all ages rather than focusing on each decade of age as we had previously done in our 2018 guideline.
*The number of participants and studies reflect the previous analysis for each age decade, rather than the number of studies that are included in the relative effect estimate for all ages.

a. One study considered quasi-randomised (Gothenburg) (56).
b. Randomisation and allocation concealment were either not reported or there were serious deficiencies in these areas, therefore we rated down once for risk of bias.
c. All point estimates in our pooled analysis lie to one side of our threshold. We did not rate down for inconsistency .
d. Breast density was not addressed. For some studies, the control group received screening after the screening period. Studies reported in Nystrom 2002 (49) and Nystrom 2016 (46) included one round of screening in the control group as part of the short-case accrual calculation. Therefore, the study estimates may be underestimated (a larger benefit from the intervention may be possible). Downrated once for indirectness. Data are from trials initiated in the 1960s-1990s and the intervention groups were primarily screened with film mammography. Due to advances in mammography technology and treatment practices, we expect that the magnitude of screening effect may differ if applied to today's Canadian screening context. There are no high-quality clinical trials examining the impact of screening on breast cancer screening deaths using contemporary screening methods.
e. Given the large sample sizes; an optimal sample size calculation was not warranted. The 95% CI does not cross the clinical decision threshold; therefore, we did not rate down for imprecision.
f. According to Egger et al. (55),10 trials are needed to assess publication bias. We cannot assess publication bias due to insufficient number of trials, therefore, we did not rate down for publication bias.
g. Given the large sample sizes; an optimal sample size calculation was not warranted. The 95% CI crosses the clinical decision threshold; therefore, we rated down once for imprecision.
h. Approximately half of the point estimates in our pooled analysis lie on either side of our threshold. We rated down once for inconsistency.

GRADE Summary of Findings Table – **Breast cancer mortality (Adherence to screen (cohort) studies, by age) over 10 years**

Screening with mammography* compared to no screening

Outcomes	Absolute effects		Range of relative effects (95% CI)**	№ of participants (studies)	Quality of the evidence (GRADE) Clinical threshold of 0.5 or 1.0	What happens
	Risk with Usual Care (Assumed Risk) ‡	**Absolute effect (95% CI)**				
Sub-Group: Breast-Cancer Mortality (40-49 years) Range of follow-up (yrs): 10.0 to 22.0	**General population**		**RR 0.48** (0.41 to 0.57)	Unavailable (4 studies) (59–62)	⨁◯◯◯ VERY LOW a,b,c,d,f,g	Using a threshold of 0.5 or 1 fewer deaths per 1,000, we are very uncertain whether screening decreases breast cancer mortality over 10 years for individuals aged 40 to 49 years in a general population.
	1.8 per 1,000	**0.94 fewer per 1,000** (0.77 to 1.06 fewer)				
	Moderately increased risk due to family history					
	2.9 per 1,000	**1.51 fewer per 1,000** (1.25 to 1.71 fewer)				
	Moderately increased risk due to breast density					
	3.5 per 1,000	**1.82 fewer per 1,000** (1.51 fewer to 2.07 fewer)				
Sub-Group: Breast-Cancer Mortality (50-59 years)	**General Population**		**RR 0.48** (0.41 to 0.57)	Unavailable (4 studies) (59–62)	⨁◯◯◯ VERY LOW a,b,c,d,f,g	Using a threshold of 0.5 or 1 fewer deaths per 1,000, we are very uncertain whether screening decreases breast cancer mortality over 10 years for individuals aged 40 to 49 years in a general population.
	3.3 per 1,000	**1.72 fewer per 1,000** (from 1.42 to 1.95 fewer)				
	Moderately increased risk due to family history					
	5.3 per 1,000	**2.76 fewer per 1,000** (from 2.28 to 3.13 fewer)				

Range of follow-up (yrs): 10.0 to 22.0	**Moderately increased risk due to breast density**					
	6.3 per 1,000	**3.28 fewer per 1,000** (2.71 fewer to 3.72 fewer)				
Sub-Group: Breast-Cancer Mortality (60-69 years) Range of follow-up (yrs): 10.0 to 22.0	**General population**		**RR 0.48** (0.41 to 0.57) 64)	Unavailable (4 studies) (59–62)	⊕◯◯◯ VERY LOW [a,b,c,d,f,g]	Using a threshold of 0.5 or 1 fewer deaths per 1,000, we are very uncertain whether screening decreases breast cancer mortality over 10 years for individuals aged 40 to 49 years in a general population.
	4.3 per 1,000	**2.24 fewer per 1,000** (from 1.85 to 2.54 fewer)				
	Moderately increased risk due to family history					
	6.9 per 1,000	**3.59 fewer per 1,000** (2.97 to 4.07 fewer)				
	Moderately increased risk due to breast density					
	8.2 per 1,000	**4.26 fewer per 1,000** (3.53 fewer to 4.84 fewer)				
Sub-Group: Breast-Cancer Mortality (70-74 years) Range of follow-up (yrs): 10.0 to 22.0	**General Population**		**RR 0.48** (0.41 to 0.57)	Unavailable (4 studies) (59–62)	⊕◯◯◯ VERY LOW [a,b,c,d,f,g]	Using a threshold of 0.5 or 1 fewer deaths per 1,000, we are very uncertain whether screening decreases breast cancer mortality over 10 years for individuals aged 40 to 49 years in a general population.
	6.1 per 1,000	**3.17 fewer per 1,000** (2.62 to 3.60 fewer)				
	Moderately increased risk due to family history					
	9.8 per 1,000	**5.10 fewer per 1,000** (from 4.21 to 5.78 fewer)				
	Moderately increased risk due to breast density					
	11.6 per 1,000	**6.03 fewer per 1,000** (4.99 fewer to 6.84 fewer)				

‡The baseline risk (in the control group) was not representative of all included studies. Numerators and/or denominators were either unclear or not reported for some studies. For the age subgroup calculations, the baseline risk for each age group was taken from the Coldman cohort study (59). To calculate moderately increased risk group, we used an estimate from Engmann et al. (52) 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 risk of 1.9 (54).
§ The relative effect is based on our previous systematic review and guideline where a subgroup analysis of relative risk by age was assessed and no difference in RR among subgroups was detected and true differences resulting from age were deemed unlikely. Therefore, we used the RR for all ages rather than focusing on each decade of age as we had previously done in our 2018 guideline.
*Studies varied between film and digital mammography.
** Pooling was performed for a screening adherence analysis. To note that Coldman reported a standardized mortality ratio (SMR) however, it has been noted in the literature that an SMR can approximate a RR when the mortality rate in the control group is less than 10 per 1000 for a one-year period in a 10-year age band (Symons and Taulbee, 1981 (63)). The statistical heterogeneity of this estimate is high (I^2=94%). Other sensitivity analyses for combining these four studies are provided in Supplemental KQ1 GRADE Material, Appendix 3.

a. We rated down once for the lack of adjustment for important confounding factors across studies, including use of hormone replacement therapy, socioeconomic status, or other adjustment for self-selection bias. Lack of reporting or measurement of population at increased risk of breast cancer (Duffy (61), Morrell (62)). Studies did not report average follow-up length and reasons for loss to follow-up are not reported (Duffy (61), Morrell (62)).
b. Heterogeneity is very high across studies (I2=94%); (p-value<0.0001). Estimates from studies included rate ratios, risk ratios and standardized mortality ratios, with varying degrees of adjustment for confounding factors. We are unable to explain the high statistical heterogeneity through sensitivity analyses (Supplemental KQ1 GRADE Material, Appendix 3), however, all individual estimates point to a reduction in BC mortality. Similarly, all point estimates in our pooled analysis lie to one side of our threshold, therefore we did not rate down for inconsistency.
c. We did not rate for indirectness as both the studies (Duffy (61) and Coldman (59)) are population-based studies representing general population..
d. The 95% CI does not cross the clinical decision threshold; therefore, we did not rate down for imprecision.
e. The 95% CI crosses the clinical decision threshold; therefore, we rated down once for imprecision.
f. We did not rate up for the magnitude of effect because not all plausible confounders (e.g., age, hormone replacement therapy, breast density, elevated risk), were adjusted for, decreasing our confidence in the estimated effect. Following GRADE guidance, the RR is on the threshold of being considered a large effect (i.e., RR either >2.0 or <0.5 based on consistent evidence from at least 2 studies, with no plausible confounders).
g. According to Egger et al. (55), 10 studies are needed to assess publication bias. We cannot assess publication bias due to insufficient number of trials, therefore, we did not rate down for publication bias.

GRADE Summary of Findings Table – **Breast cancer mortality (observational stop-start analysis, by age)**

"Continue Screening" After Baseline Examination compared to "Stop Screening" After Baseline Examination

Outcomes	Absolute effects		Hazard ratio (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE) Clinical threshold of 0.5	Quality of the evidence (GRADE) Clinical threshold of 1.0	What happens
	Baseline risk with stopping screening	**Absolute effect (95% CI)**					
Sub-Group: Breast-Cancer Mortality (70-74 years) Range of follow-up (yrs): 8	**General population**		**HR 0.78** (0.63 to 0.95)	1235459 (1 study) (64)	⊕◯◯◯ VERY LOW [a,b,c,d,e]	⊕◯◯◯ VERY LOW [a,b,c,d,e,g]	Using a threshold of 0.5 or 1 fewer deaths per 1,000, we are very uncertain whether continuing screening decreases breast cancer mortality over 10 years for individuals aged 70 to 74 years in a general population.
	3.7 per 1,000	**0.81 fewer per 1,000** (from 0.19 to 1.37 fewer)					
Sub-Group: Breast-Cancer Mortality (75-84) Range of follow-up (yrs): 8	**General Population**		**HR 1.00** (0.83 to 1.19)	1403735 (1 study) (64)	⊕◯◯◯ VERY LOW [a,b,c,d,e]	⊕⊕◯◯ LOW [a,b,c,d,e,g]	Using a threshold of 0.5 fewer deaths per 1,000, we are very uncertain whether continuing screening decreases breast cancer mortality over 10 years for individuals aged 75 to 84 years in a general population. Using a threshold of 1 fewer death per 1,000, continuing screening may make little to no difference in reducing breast cancer mortality over 10 years for individuals aged 75 to 84 years in a general population.
	3.7 per 1,000	**0.0 fewer per 1,000** (from 0.63 fewer to 0.70 more)					

a. We did not downrate for risk of bias. Study was judged to be of moderate quality using the JBI critical appraisal tool for cohort studies.
b. We did not downrate for inconsistency (only one study included).
c. We did not downrate for indirectness. The study answers the question of stopping versus continuing screening and all patients have received at least one baseline mammography.
d. The 95% CI crosses the clinical decision threshold; therefore, we rated down once for imprecision.
e. We did not rate up for the magnitude of effect because the effect size did not meet the threshold for uprating. Following GRADE guidance, the RR is on the threshold of being considered a large effect (i.e., RR either >2.0 or <0.5 based on consistent evidence from at least 2 studies, with no plausible confounders).
f. The 95% CI does not cross the clinical decision threshold and we did not rate down for imprecision.
g. According to Egger et al. (55), 10 studies are needed to assess publication bias. We cannot assess publication bias due to insufficient number of trials, therefore, we did not rate down for publication bias

GRADE Summary of Findings Table – **Breast cancer mortality (Quasi-experimental, sub-groups)**

Before-and-after BC screening program / Jurisdictions with or without BC screening program in 40-49 years

Outcomes	Before BC screening implementation (N)	After BC screening implementation (N)	Relative effect (95% CI)	№ of participants (studies)	Certainty of evidence (GRADE)
Breast Cancer Mortality Sub-group: 40-49 (Age) Follow-up (yrs.): Unavailable**Error! Bookmark not defined.**	0.20/1,000 person-years	0.17/1,000 person-years	Unavailable	N=323719 (1 Study) (65)	⊕◯◯◯ VERY LOW[1,5,6,7]
Breast Cancer Mortality Sub-group: 40-49 (Age) Follow-up (yrs.): 11 years	0.15/1,000 person-years	0.12/1,000 person-years	Unavailable	N= 40.7 million person-years (1 Study) (66)	⊕◯◯◯ VERY LOW[2,5,6,7]
Breast Cancer Mortality Sub-group: 50-59 (Age) Follow-up (yrs.): Unavailable**Error! Bookmark not defined.**	0.49/1,000 person-years	0.36/1,000 person-years	Unavailable	N=323719 (1 Study) (65)	⊕◯◯◯ VERY LOW[1,5,6,7]
Breast Cancer Mortality Sub-group: 50-59 (Age) Follow-up (yrs.): 11 years	0.32/1,000 person-years	0.34/1,000 person-years	Unavailable	N= 40.7 million person-years (1 Study) (66)	⊕◯◯◯ VERY LOW[2,5,6,7]
Breast Cancer Mortality Sub-group: 60-69 (Age) Follow-up (yrs.): Unavailable**Error! Bookmark not defined.**	0.80/1,000 person-years	0.63/1,000 person-years	Unavailable	N=323719 (1 Study) (65)	⊕◯◯◯ VERY LOW[1,5,6,7]
Breast Cancer Mortality Sub-group: 70-79 (Age) Follow-up (yrs.): Unavailable**Error! Bookmark not defined.**	1.12/1,000 person-years	1.14/1,000 person-years	Unavailable	N=323719 (1 Study) (65)	⊕◯◯◯ VERY LOW[1,5,6,7]
Breast Cancer Mortality Sub-group: 60-74 (Age) Follow-up (yrs.): 11 years	0.38/1,000 person-years	0.59/1,000 person-years	Unavailable	N= 40.7 million person-years (1 Study) (66)	⊕◯◯◯ VERY LOW[2,5,6,7]
Breast Cancer Mortality Sub-group: 75-84 (Age) Follow-up (yrs.): 11 years	0.72/1,000 person-years	0.84/1,000 person-years	Unavailable	N= 40.7 million person-years (1 Study) (66)	⊕◯◯◯ VERY LOW[2,5,6,7]
Incidence of fatal breast cancer within 10 years of diagnosis Sub-group: Screening participation (No; during the active screening period) Follow-up (yrs.): 10 years	0.62/1,000 person-years	0.25/1,000 person-years	Relative Risk: **0.40** (0.34 to 0.48)	N=52,438 (Mean no. of women aged 40 to 69 years); (1 study) (67)	⊕◯◯◯ VERY LOW[3,5,6,7]
Incidence of fatal breast cancer within 10 years of diagnosis Sub-group: Screening participation (Pre-screening period) Follow-up (yrs.): 10 years	0.55/1,000 person-years	0.25/1,000 person-years	Relative Risk: **0.46** (0.39 to 0.53)	N=52,438 (Mean no. of women aged 40 to 69 years); (1 study) (67)	⊕◯◯◯ VERY LOW[3,5,6,7]
Incidence-based BC mortality rate ratio Subgroup: 40-49 years Follow-up (yrs.): 10 years	Provincial/territorial mammography screening programs not including women aged 40-49 years: NR	Provincial/territorial mammography screening programs including women aged 40-49 years: NR	Rate Ratio: 0.92; 95% CI, 0.85 to 0.99	N=21,103 (68)	⊕◯◯◯ VERY LOW[4,5,6,8]
10-year net survival **(surrogate outcome)** Subgroup: 40-49 years Follow-up (yrs.): 10 years	Provincial/territorial mammography screening programs not including women aged 40-49 years: 10-year net survival (95% CI): 82.9 (82.3 to 83.5)	Provincial/territorial mammography screening programs including women aged 40-49 years: 10-year net survival (95% CI): 84.8 (83.8 to 85.8)	Absolute difference in NS rates: 1.9 percentage points (P=0.001)	N=21,103 (68)	⊕◯◯◯ VERY LOW[4,5,6,8]
10-year net survival **(surrogate outcome)** Subgroup: 50-59 years Follow-up (yrs.): 10 years	Provincial/territorial mammography screening programs not including women aged 40-49 years: 10-year net survival (95% CI): 83.4 (82.9 to 83.8)	Provincial/territorial mammography screening programs including women aged 40-49 years: 10-year net survival (95% CI): 83.2 (82.2 to 84.1)	Absolute difference in NS rates: -0.3 percentage points (P=0.602)	N=29,814 (68)	⊕◯◯◯ VERY LOW[4,5,6,8]

1. We did not downrate for RoB. Study assessed at low risk of bias (RoB score for JBI Quasi-experimental tool=7/9). Study reported no data on reliability of outcomes and average follow-up period.
2. We downrated once for RoB. Study at moderate risk of bias (RoB score for JBI Quasi-experimental tool=5/9). Different number of participants across comparative groups. No information on lost to follow-up participants. No data on reliability of outcome measures.
3. We downrated once for RoB. Study at moderate risk of bias (RoB score for JBI Quasi-experimental tool=6/9). No information on control group, loss-to follow-up patients and reliability of outcome measures
4. We did not downrate for RoB. Study at low risk of bias (RoB score for JBI Quasi-experimental tool=7/9). Noted that there may be differences in the participants and access to care/treatment across screening and non-screening jurisdictions beyond screening that could impact survival differences.
5. Unable to evaluate imprecision using thresholds, as the baseline rates were not available to allow the calculation of absolute effects. Therefore, a minimally contextualized approach was used. The total population is large (>2000) and there is a large event rate (>300). We did not downrate for imprecision.
6. Not downrated for inconsistency. Single study evaluated outcome (unable to evaluate heterogeneity).
7. Downrated once for indirectness. Pre-screening periods ranged across studies between 1958 and 2004. There are population-level differences that may affect mortality beyond the introduction of mammography screening between the pre-screening period and the post-screening period.
8. Downrated once for indirectness. Study assessed the effect of screening programs on outcomes of interest, rather than the effect of individual-level mammography screening. Not all women in screening jurisdictions participated in screening and it is unknown if BCs were diagnosed by screening or through other means (e.g., interval cancers, symptoms).

GRADE Summary of Findings Table – **Breast cancer mortality (<u>case-control studies,</u> <u>by age</u>) <u>over 10 years</u>**
Screening with mammography* compared to no screening

Outcomes	Absolute effects		Range of relative effects (95% CI)**	№ of participants (studies)	Quality of the evidence (GRADE) Clinical threshold of 0.5 or 1.0	What happens
	Risk with Usual Care (Assumed Risk) ‡	Absolute effect (95% CI)				
Sub-Group: Breast-Cancer Mortality **40-49 years** Range of follow-up (yrs): 11.0 to 38.0	**General Population**		**OR 0.56** (0.49 to 0.64)	Unavailable (7 studies) (69–75)	⊕◯◯◯ VERY LOW [a,b,c,d,e,f]	Using a threshold of 0.5 or 1 fewer deaths per 1,000, we are very uncertain whether screening decreases breast cancer mortality over 10 years for individuals aged 40 to 49 years at a moderately increased risk for breast cancer.
	1.8 per 1,000	**0.79 fewer per 1,000** (0.65 fewer to 0.92 fewer)				
	Moderately increased risk due to family history					
	2.9 per 1,000	**1.28 fewer per 1,000** (1.04 fewer to 1.48 fewer)				
	Moderately increased risk due to breast density					
	3.5 per 1,000	**1.54 fewer per 1,000** (1.26 fewer to 1.79 fewer)				
Sub-Group: Breast-Cancer Mortality **50-59 years** Range of follow-up (yrs): 11.0 to 38.0	**General Population**		**OR 0.56** (0.49 to 0.64)	Unavailable (7 studies) (69–75)	⊕◯◯◯ VERY LOW [a,b,c,d,e,f]	Using a threshold of 0.5 or 1 fewer deaths per 1,000, we are very uncertain whether screening decreases breast cancer mortality over 10 years for individuals aged 50 to 59 years at a moderately increased risk for breast cancer.
	3.3 per 1,000	**1.45 fewer per 1,000** (1.19 fewer to 1.68 fewer)				
	Moderately increased risk due to family history					
	5.3 per 1,000	**2.33 fewer per 1,000** (1.91 fewer to 2.70 fewer)				
	Moderately increased risk due to breast density					
	6.3 per 1,000	**2.77 fewer per 1,000** (2.27 fewer to 3.21 fewer)				
Sub-Group: Breast-Cancer Mortality **60-69 years** Range of follow-up (yrs): 11.0 to 38.0	**General Population**		**OR 0.56** (0.49 to 0.64)	Unavailable (7 studies) (69–75)	⊕◯◯◯ VERY LOW [a,b,c,d,e,f]	Using a threshold of 0.5 or 1 fewer deaths per 1,000, we are very uncertain whether screening decreases breast cancer mortality over 10 years for individuals aged 60 to 69 years at a moderately increased risk for breast cancer.
	4.3 per 1,000	**1.89 fewer per 1,000** (1.55 fewer to 2.19 fewer)				
	Moderately increased risk due to family history					
	6.9 per 1,000	**3.04 fewer per 1,000** (2.48 fewer to 3.52 fewer)				
	Moderately increased risk due to breast density					
	8.2 per 1,000	**3.61 fewer per 1,000** (2.95 fewer to 4.18 fewer)				
Sub-Group: Breast-Cancer Mortality **70-74 years** Range of follow-up (yrs): 11.0 to 38.0	**General Population**		**OR 0.56** (0.49 to 0.64)	Unavailable (7 studies) (69–75)	⊕◯◯◯ VERY LOW [a,b,c,d,e,f]	Using a threshold of 0.5 or 1 fewer deaths per 1,000, we are very uncertain whether screening decreases breast cancer mortality over 10 years for individuals aged 70 to 74 years at a moderately increased risk for breast cancer.
	6.1 per 1,000	**2.68 fewer per 1,000** (2.20 fewer to 3.11 fewer)				
	Moderately increased risk due to family history					
	9.8 per 1,000	**4.31 fewer per 1,000** (3.53 fewer to 5.0 fewer)				
	Moderately increased risk due to breast density					
	11.6 per 1,000	**5.10 fewer per 1,000** (4.18 fewer to 5.92 fewer)				

‡The baseline risk (in the control group) was not representative of all included studies. Numerators and/or denominators were either unclear or not reported for some studies. For the age subgroup calculations, the baseline risk for each age group was taken from the Coldman cohort study (59). For the age subgroup calculations, the baseline risk for each age group was taken from the Coldman cohort study (59). To calculate moderately increased risk group, we used an estimate from Engmann et al. (52) 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 risk of 1.9 (54).
§ The relative effect is based on our previous systematic review and guideline where a subgroup analysis of relative risk by age was assessed and no difference in RR among subgroups was detected and true differences resulting from age were deemed unlikely. Therefore, we used the RR for all ages rather than focusing on each decade of age as we had previously done in our 2018 guideline.

*Studies varied between film and digital mammography.
** Absolute risks were calculated using odds ratios (all adherence to screen exposure).

a. We rated down once for risk of bias. Cases and controls were not age matched (De Troeyer (75) and van der Waal (73)) or failed to adjust for important confounding factors related to self-selection bias (De Troeyer (75), Maroni (74), Van der Waal (73), Massat (71), Pocobelli (70), Paap (69) and Ripping (72)). Several studies did not provide screening details or confirm all women were invited to screening (Massat (71), Pocobelli (70), Paap (69), Ripping (72)). Average follow-up length not clearly reported across studies.
b. All individual estimates point to a reduction in BC mortality, so we did not downrate for inconsistency.
c. We did not downrate for indirectness since the studies used population-based approach and are reflective of general population.
d. Given the large sample sizes; an optimal sample size calculation was not warranted. The 95% CI does not cross the clinical decision threshold; therefore, we did not rate down for imprecision.
e. We did not rate up for the magnitude of effect because not all plausible confounders (e.g., age, hormone replacement therapy, breast density), were adjusted for, decreasing our confidence in the estimated effect. Following GRADE guidance, the RR is not considered a large effect (i.e., RR either >2.0 or <0.5 based on consistent evidence from at least 2 studies, with no plausible confounders).
f. According to Egger et al. (55), 10 studies are needed to assess publication bias. We cannot assess publication bias due to insufficient number of trials, therefore, we did not rate down for publication bias.

GRADE Summary of Findings Table – **All-cause mortality (RCTs,** stratified by age) over 10 years
Mammography +/- CBE compared to Usual Care

Outcomes	Absolute effects		Relative effect § (95% CI)	№ of participants* (studies)	Quality of the evidence (GRADE)	What happens?
	Risk with Usual Care (Assumed Risk) ‡	Absolute effect (95% CI)				
Sub-Group: All-Cause Mortality (40-49 years) # Randomised: 311,066 # Analyzed: Unclear Range of follow-up (yrs): 7.9 to 17.7	12.7 per 1,000	**0.13 fewer per 1,000** (0 fewer to 0.25 fewer)	**RR 0.99** (0.98 to 1.00)	Unavailable (7 RCTs) [a] (49,76–81)	⊕⊕◯◯ LOW [b,c,d,e,f]	Using a threshold of 1 fewer death per 1,000, screening may make little to no difference in reducing mortality from any cause over 10 years for individuals aged 40 to 49 years.

Sub-Group: All-Cause Mortality (50-59 years) # Randomised: 79,749 # Analyzed: 79,695 Range of follow-up (yrs): 7.9 to 13.0	30.6 per 1,000	**0.31 fewer per 1,000** (0 fewer to 0.61 fewer)	**RR 0.99** (0.98 to 1.00)	79,695 (3 RCTs) (77,80)	⊕⊕◯◯ LOW [b,c,d,e,f]	Using a threshold of 1 fewer death per 1,000, screening may make little to no difference in reducing mortality from any cause over 10 years for individuals aged 50 to 59 years.
Sub-Group: All-Cause Mortality (60-69 years) # Randomised: 39,681 # Analyzed: 39,681 Range of follow-up (yrs): 7.9	71.3 per 1,000	**0.71 fewer per 1,000** (0 fewer to 1.43 fewer)	**RR 0.99** (0.98 to 1.00)	39,681 (2 RCTs) (77)	⊕⊕◯◯ VERY LOW [b,c,d,f,g]	Using a threshold of 1 fewer death per 1,000, we are very uncertain whether screening decreases mortality from any cause over 10 years for individuals aged 60 to 69 years.
Sub-Group: All-Cause Mortality (70-74 years) # Randomised: 17,646 # Analyzed: 17,646 Range of follow-up (yrs): 7.9	140.6 per 1,000	**1.41 fewer per 1,000** (0 fewer to 2.81 fewer)	**RR 0.99** (0.98 to 1.00)	17,646 (2 RCTs) (77)	⊕◯◯◯ VERY LOW [b,c,d,f,g]	Using a threshold of 1 fewer death per 1,000, we are very uncertain whether screening decreases mortality from any cause over 10 years for individuals aged 70 to 74 years.

‡The baseline risk has been calculated using deaths and age-specific mortality rates data from Statistics Canada and estimated over a 10-year period (82).
§ Following the same logic as breast cancer mortality, the relative effect is based on our previous systematic review and guideline (12) where a subgroup analysis of relative risk by age was assessed and no difference in RR among subgroups was detected and true differences resulting from age were deemed unlikely. Therefore, we used the RR for all ages rather than focusing on each decade of age as we had previously done in our 2018 guideline.
*The number of participants and studies reflect the previous analysis for each age decade, rather than the number of studies that are included in the relative effect estimate for all ages.

a. Two studies considered quasi-randomised (Stockholm (78) & Gothenburg (81))
b. Randomisation and allocation concealment were either not reported or there were serious deficiencies in these areas, we downrated once for risk of bias.
c. All point estimates in our pooled analysis lie to one side of our threshold. We did not rate down for inconsistency.
d. Breast density was not addressed. For some studies, the control group received screening after the screening period. Studies reported in Nystrom 2002 (49) and Nystrom 2016 (46) included one round of screening in the control group as part of the short-case accrual calculation. Therefore, the study estimates may be underestimated (a larger benefit from the intervention may be possible). Downrated once for indirectness. Data are from trials initiated in the 1960s-1990s and the intervention groups were primarily screened with film mammography. Due to advances in mammography technology and treatment practices, we expect that the magnitude of screening effect may differ if applied to today's Canadian screening context. There are no high-quality clinical trials examining the impact of screening on breast cancer screening deaths using contemporary screening methods.
e. Not downrated for imprecision i) The number of events and total population are large (>300 threshold for events); and (ii) the 95%CIs include the null, but do not cross clinical decision threshold (1 fewer or 1 more). Given the large sample sizes, an optimal sample size calculation was not warranted.
f. According to Egger et al. (55), 10 trials are needed to assess publication bias. We cannot assess publication bias due to insufficient number of trials, therefore, we did not rate down for publication bias.
g. Downrated once for imprecision. i) The number of events and total population are large (>300 threshold for events); and (ii) the 95%CIs include the null and cross the clinical decision threshold (1 fewer or 1 more). Given the large sample sizes, an optimal sample size calculation was not warranted.

GRADE Summary of Findings Table – **Stage at Diagnosis (RCTs)**
Screening with film mammography (with or without CBE) compared to usual care

Outcomes	Absolute Effects		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with Usual Care (Assumed Risk)	**Absolute effect (95% CI)**				
Invasive Breast Cancer Diagnosed at Stage II or higher (all ages)* 9.1 per 1000		**3 fewer per 1,000** (from 5 fewer to 1 more)	**RR 0.72** (0.49 to 1.06)	5 RCTs (83)	⊕◯◯◯ VERY LOW [a,b,c,d,e,l]	Using a threshold of 3 fewer breast cancers diagnosed at stage II or higher per 1,000, we are very uncertain whether screening decreases the number of individuals with stage II+ at diagnosis in those at general population risk for breast cancer (all ages).
Invasive Breast Cancer Diagnosed at Stage II or higher (Ages 40-49 years)* 2.6 per 1000		**1 more per 1,000** (from 1 more to 3 more)	**RR 1.55** (1.23 to 2.11)	1 RCT (83)	⊕◯◯◯ VERY LOW [f,g,d,h,l]	Using a threshold of 3 fewer breast cancers diagnosed at stage II or higher per 1,000, we are very uncertain whether screening makes little to no difference on the number of individuals with stage II+ at diagnosis in those at general population risk for breast cancer (40-49 years).
Invasive Breast Cancer Diagnosed at Stage II or higher (Ages 50-59 years)* 4.6 per 1000		**0 fewer per 1,000** (from 1 fewer to 2 more)	**RR 1.09** (0.82 to 1.45)	1 RCT (83)	⊕◯◯◯ VERY LOW [f,g,d,h,l]	Using a threshold of 3 fewer breast cancers diagnosed at stage II or higher per 1,000, we are very uncertain whether screening makes little to no difference on the number of individuals with stage II+ at diagnosis in those at general population risk for breast cancer (50-59 years).
Invasive Breast Cancer Diagnosed at Stage III or higher (60-69)* 2.2 per 1000		**1 fewer per 1,000** (from 1 fewer to 0 fewer)	**RR 0.64** (0.47 to 0.88)	3 RCTs (83)	⊕◯◯◯ VERY LOW [i,j,d,k,l]	Using a threshold of 2 fewer breast cancers being diagnosed at stage III or higher per 1,000, we are very uncertain whether screening makes little to no difference on the number of individuals with stage III+ at diagnosis in those at general population risk for breast cancer (all ages).

**Rates calculated using number of participants with stage II+ or stage III+ reported in Tarone 1995 (83) for included trials and the number of participants randomized reported as per USPSTF 2016.
CI: Confidence interval; **RR:** Risk ratio

a. One study considered quasi-randomised (Stockholm (83))
b. Downrated once for risk of bias. Randomisation and allocation concealment were either not reported sufficiently (Malmo I, HIP (83)) or there were serious deficiencies in these areas (CNBSS-I, Stockholm (83)).
c. Approximately half of the point estimates in our pooled analysis lie on either side of our threshold. We rated down once for inconsistency.
d. Data are from trials initiated in the 1960s-1990s and the intervention groups were primarily screened with film mammography. Due to advances in mammography technology and treatment practices, we expect that the magnitude of screening effect may differ if applied to today's Canadian screening context. There are no high-quality clinical trials examining the impact of screening on breast cancer screening deaths using contemporary screening methods.
e. Downrated once for imprecision. CI crosses threshold for benefit of breast cancer screening for proportion of patients diagnosed at stage II or higher.
f. Downrated once for risk of bias. High risk of bias due to concerns with randomisation method and allocation concealment (CNBSS I (83)).
g. Not downrated for inconsistency. Single study evaluated outcome.
h. Downrated once for imprecision. Low number of events (fewer than 300) and confidence interval crosses threshold for harm.

i. Downrated once for risk of bias. High risk of bias due to risk of bias in randomization and allocation concealment (Stockholm (83)) and use of local endpoint committee for blinding of outcomes (HIP (83)).
j. All point estimates in our pooled analysis lie to one side of our threshold. We did not rate down for inconsistency.
k. Did not downrate for imprecision. Large population and CI does not cross below the threshold for benefit of breast cancer screening for proportion of population diagnosed at stage III.
l. According to Egger et al. (55), 10 trials are needed to assess publication bias. We cannot assess publication bias due to insufficient number of trials, therefore, we did not rate down for publication bias.

GRADE Summary of Findings Table – **Stage at Diagnosis (Observational studies, all ages) Screening with mammography* compared to no screening**

Outcomes	Absolute effects		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with Usual Care (Assumed Risk)	**Absolute effect (95% CI)**				
Distant degree of spread at diagnosis	NR	**Not estimable****	**RR 0.44 (0.37 to 0.52)**	1 study (62) (869,857)	⨁◯◯◯ VERY LOW a,b,c,d,e	We are very uncertain about if screening with mammography compared to no screening reduces the proportion of individuals with distant degree of breast cancer spread at diagnosis
Stage II+ at diagnosis	1.81 per 1000	0.51 fewer per 1000 (0.43 fewer to 0.58 fewer)	**Incidence Rate Ratio 0.72 (0.68 to 0.76)**	1 study (84) (413,447)	⨁◯◯◯ VERY LOW b,c,e f,g,	Using a threshold of 3 fewer breast cancers being diagnosed at stage II or higher per 1,000, we are very uncertain whether screening makes little to no difference in the number of individuals with stage II+ at diagnosis in those at general population risk for breast cancer.

***The corresponding risk** (and its 95% confidence interval) is based on **the assumed risk** in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**Study did not provide baseline risk values for usual care or breast cancer screening groups to calculate absolute risk.
CI: Confidence interval; **RR:** Risk ratio

a. Downrated twice for risk of bias. Study at high risk of bias (RoB score for JBI cohort tool=4/11). Non-screening population inferred from census-derived population data rather than individual data and lack of reporting on outcome measurement. Lack of adjustment for important confounding factors (use of HRT, breast density). Unclear report of average follow-up time for population and no description of number of women lost to follow-up.
b. Not downrated for inconsistency. Single study evaluated outcome (unable to evaluate heterogeneity).
c. Not downrated for indirectness. Studies used population-based approach which was reflective of general population
d. Not downrated for imprecision. Unable to calculate absolute effects to determine if benefit for threshold is crossed, so a minimally contextualized approach was used. The total population is large (>2000) and there is a large event rate (>300). Given the large sample sizes and that the confidence interval does not include the null value, an optimal sample size calculation is not warranted.
e. According to Egger et al. (55), 10 studies are needed to assess publication bias. We cannot assess publication bias due to insufficient number of trials, therefore, we did not rate down for publication bias.
f. Downrated once for risk of bias. Study at moderate risk of bias (RoB score for JBI cohort tool=7/11). Lack of adjustment for important confounding factors (use of HRT, breast density). No description of number of women lost to follow-up.
g. Not downrated for imprecision. Large population and CI does not cross threshold for breast cancer screening benefit for stage III at diagnosis.

GRADE Summary of Findings Table – **Stage at Diagnosis** (**Quasi-experimental, Sub-groups)**
Before-and-after BC screening program implementation/ Jurisdictions with or without BC screening program in 40-49 years

Outcomes	Rates		Relative effect (95% CI)	№ of participants (studies)	Risk of bias (Score)
	Before BC screening implementation (N)	**After BC screening implementation (N)**			
Advanced stage defined as stages III and IV as per the TNM classification Sub-group: 70-75 years (Screening uptake period; 1998-2002)[2] Follow-up (yrs.): Unavailable	0.59 per 1000 person-year	0.46 per 1000 person-year	Incidence Rate Ratio: **0.79**[1] (0.71 to 0.87)	N= 38442 (1 study) (85)	⨁◯◯◯ VERY LOW [3,6,7,8]
Advanced stage defined as stages III and IV as per the TNM classification Sub-group: 76-80 years (Screening uptake period; 1998-2002)[2] Follow-up (yrs.): Unavailable	0.66 per 1000 person-year	0.69 per 1000 person-year	Incidence Rate Ratio: **1.04**[1] (0.94 to 1.17)	N= 38442 (1 study) (85)	⨁◯◯◯ VERY LOW [3,6,7,8]
Advanced stage defined as stages III and IV as per the TNM classification Sub-group: 70-75 years (Screening uptake period; 2003-2011)[2] Follow-up (yrs.): Unavailable	0.59 per 1000 person-year	0.52 per 1000 person-year	Incidence Rate Ratio: **0.88**[1] (0.81 to 0.97)[1]	N= 38442 (1 study) (85)	⨁◯◯◯ VERY LOW [3,6,7,8]
Advanced stage defined as stages III and IV as per the TNM classification Sub-group: 76-80 years (Screening uptake period; 2003-2011)[2] Follow-up (yrs.): Unavailable	0.66 per 1000 person-year	0.67 per 1000 person-year	Incidence Rate Ratio: **1.02**[1] (0.92 to 1.13)	N= 38442 (1 study) (85)	⨁◯◯◯ VERY LOW [3,6,7,8]
Sub-group: Late stage (Regional) Follow-up (yrs.): Unavailable	0.87 per 1000 person-year	0.77 per 1000 person-year	Unavailable	Unavailable**Error! Bookmark not defined.** (1 Study) (86)	⨁◯◯◯ VERY LOW [4,6,7,8]
Sub-group: Late stage (Distant) Follow-up (yrs.): Unavailable	0.17 per 1000 person-year	0.18 per 1000 person-year	Unavailable	Unavailable**Error! Bookmark not defined.** (1 Study) (86)	⨁◯◯◯ VERY LOW [4,6,7,8]

Proportion of BC diagnosed at Stage II (surrogate outcome) Subgroup: 40-49 years	Jurisdictions without organised screening programs for women 40–49 with annual recall: 437 per 1,000	Jurisdictions with organised screening programs for women 40–49 with annual recall: 407 per 1,000	Unavailable p < 0.001	Unavailable (1 Study) (87)	⊕◯◯◯ VERY LOW [5,6,7,9]	
Proportion of BC diagnosed at Stage III (surrogate outcome) Subgroup: 40-49 years	Jurisdictions without organised screening programs for women 40–49 with annual recall: 183 per 1,000	Jurisdictions with organised screening programs for women 40–49 with annual recall: 156 per 1,000	Unavailable p < 0.001	Unavailable (1 Study) (87)	⊕◯◯◯ VERY LOW [5,6,7,9]	
Proportion of BC diagnosed at Stage IV (surrogate outcome) Subgroup: 40-49 years	Jurisdictions without organised screening programs for women 40–49 with annual recall: 46 per 1,000	Jurisdictions with organised screening programs for women 40–49 with annual recall: 39 per 1,000	Unavailable p = 0.001	Unavailable (1 Study) (87)	⊕◯◯◯ VERY LOW [5,6,7,9]	
Proportion of BC diagnosed at Stage II (surrogate outcome) Subgroup: 50-59 years	Jurisdictions without organised screening programs for women 40–49 with annual recall: 37 per 1,000	Jurisdictions with organised screening programs for women 40–49 with annual recall: 360 per 1,000	Unavailable p = 0.003	Unavailable (1 Study) (87)	⊕◯◯◯ VERY LOW [5,6,7,9]	
Proportion of BC diagnosed at Stage III (surrogate outcome) Subgroup: 50-59 years	Jurisdictions without organised screening programs for women 40–49 with annual recall: 136 per 1,000	Jurisdictions with organised screening programs for women 40–49 with annual recall: 123 per 1,000	Unavailable p < 0.001	Unavailable (1 Study) (87)	⊕◯◯◯ VERY LOW [5,6,7,9]	
Proportion of BC diagnosed at Stage IV (surrogate outcome) Subgroup: 50-59 years	Jurisdictions without organised screening programs for women 40–49 with annual recall: NR	Jurisdictions with organised screening programs for women 40–49 with annual recall: NR	Unavailable	Unavailable (1 Study) (87)	⊕◯◯◯ VERY LOW [5,6,7,9]	

1. Unadjusted incidence rate ratio (IRR)
2. Comparison of screening period to pre-screening period of 1995-1997.
3. Study at Low risk of bias (RoB score for JBI Quasi-experimental tool=7/9). No information on loss-to follow-up patients and reliability of outcome measures.
4. Study at moderate risk of bias (RoB score for JBI Quasi-experimental tool=6/9). No information on control group, loss-to follow-up patients and reliability of outcome measures
5. Study at low risk of bias (RoB score for JBI Quasi-experimental tool=8/9). Noted that there may be differences in access to care across screening and non-screening jurisdictions beyond screening that could impact the stage of BC diagnosis.
6. Unable to evaluate imprecision using thresholds, as the baseline rates were not available to allow the calculation of absolute effects. Therefore, a minimally contextualized approach was used. The total population is large (>2000) and there is a large event rate (>300). We did not downrate for imprecision.
7. Not downrated for inconsistency. Single study evaluated outcome (unable to evaluate heterogeneity).
8. Downrated once for indirectness. Pre-screening periods ranged across studies between 1958 and 2004. There are population-level differences that may affect mortality beyond the introduction of mammography screening between the pre-screening period and the post-screening period.
9. Downrated once for indirectness. Study assessed the effect of screening programs on outcomes of interest, rather than the effect of individual-level mammography screening. Not all women in screening jurisdictions participated in screening and it is unknown if BCs were diagnosed by screening or through other means (e.g., interval cancers, symptoms).

GRADE Summary of Findings Table – **Treatment (RCTs, all ages)**

Screening with mammography (with or without CBE) compared to usual care

Outcomes	Absolute effects		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	What happens
	Risk with Usual Care (Assumed Risk)**	Absolute effect (95% CI)				
Number of mastectomies Mean follow up: 7-9 years	9.2 per 1000	**1.84 more per 1000** (from 1.01 more to 2.76 more)	**RR 1.20 (1.11 to 1.30)**	250479 (5 RCTs) (88)	⨁◯◯◯ VERY LOW a,b,c,d,i	Using a threshold of 2 fewer breast cancers requiring a full mastectomy per 1,000, we are very uncertain whether screening makes little to no difference in the number of mastectomies over 7-9 years in those in a general population.
Number treated with radiotherapy Mean follow up: 7-9 years	8.9 per 1000	**2.85 more per 1000** (from 1.42 more to 4.45 more)	**RR 1.32 (1.16 to 1.50)**	100383 (2 RCTs) (88)	⨁⨁◯◯ LOW b,e,f,g,i	Using a threshold of 5 fewer breast cancers requiring radiotherapy per 1,000, screening may make little to no difference in the number treated with radiotherapy over 7-9 years in those in a general population.
Number treated with chemotherapy Mean follow up: 7-9 years	3.6 per 1000	**0.14 fewer per 1000** (from 0.79 fewer to 0.68 more)	**RR 0.96 (0.78 to 1.19)**	100383 (2 RCTs) (88)	⨁⨁◯◯ LOW b,e,f,h,i	Using a threshold of 2 fewer breast cancers requiring chemotherapy per 1,000, screening may make little to no difference in the number treated with chemotherapy over 7-9 years in those at a general population risk of breast cancer.

Outcomes	Absolute effects		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	What happens
	Risk with Usual Care (Assumed Risk)	Absolute effect (95% CI)				
Breast cancers with conservative surgery as treatment	1.83 per 1000	**0.9 more per 1000**	**Rate ratio 1.5** (1.4 to 1.6)	413,447 (1 study) (84)	⨁◯◯◯ VERY LOW a,b,c,d,e	We are very uncertain about the effects of screening with mammography compared to no screening on the proportion of individuals with Breast cancers with conservative surgery as treatment
Breast cancers requiring a mastectomy	1.24 per 1000	**0.4 fewer per 1000**	**Rate ratio 0.68** (0.63 to 0.72)	413,447 (1 study) (84)	⨁◯◯◯ VERY LOW a,b,c,d,e	We are very uncertain about the effects of screening with mammography compared to no screening on the proportion of individuals with Breast cancers requiring a mastectomy

*__The corresponding risk__ (and its 95% confidence interval) is based on __the assumed risk__ in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

a. Study at moderate risk of bias (RoB score for JBI cohort tool=7/11). Lack of adjustment for important confounding factors (use of HRT). No description of number of women lost to follow-up.
b. Not downrated for inconsistency. Single study evaluated outcome (unable to evaluate heterogeneity).
c. Downrated once for indirectness. Study measures screening adherence instead of the intention to screen (screening invitation) and most screening took place before 2000. No information was provided on the proportion of the population at high-risk of breast cancer.
d. Not downrated for imprecision. Large population and CI does not cross threshold for breast cancer screening benefit for breast cancers requiring a full mastectomy.
e. Cannot assess publication bias (insufficient number of trials)

GRADE Summary of Findings Table – **Treatment (Observational Studies, by age subgroup, stop screening analysis)**
"Continue Screening" After Baseline Examination compared to "Stop Screening" After Baseline Examination

a. Downrated once for risk of bias. Randomisation and allocation concealment were either not reported (Malmo I, Swedish two county [Kopparberg] (88)) or there were serious deficiencies in these areas (CNBSS 1&2, Stockholm (88)).
b. All point estimates in our pooled analysis lie to one side of our threshold. We did not rate down for inconsistency.
c. Downrated once for indirectness. Data are from trials initiated in the 1960s-1990s and the intervention groups were primarily screened with film mammography. Due to advances in mammography technology and treatment practices, we expect that the magnitude of screening effect may differ if applied to today's Canadian screening context. There are no high-quality clinical trials examining the impact of screening on breast cancer treatment-related morbidity using contemporary screening methods. For some studies, the control group received screening after the screening period (Stockholm and Swedish Two County [Kopparberg] (88)).
d. Downrated once for imprecision. CI crosses threshold for breast cancer screening harm for breast cancers requiring a full mastectomy (versus lumpectomy).
e. Downrated once for risk of bias. Randomisation and allocation concealment were not reported (Malmo I, Swedish two county [Kopparberg] (88)).
f. Downrated once for indirectness. Trial data is from trials mainly initiated in the 1970s-1980s and the intervention groups were primarily screened with film mammography. Due to advances in mammography technology and treatment practices, we expect that the magnitude of screening effect would differ if applied to today's Canadian screening context. In one of the studies, the control group received screening after the screening period (Swedish Two County [Kopparberg (88)]).
g. Not downrated for imprecision. The CI does not cross the threshold for breast cancer screening harm for breast cancers requiring radiotherapy.
h. Not downrated for imprecision. The CI does not cross the threshold for breast cancer screening benefit or harm for breast cancers requiring chemotherapy.
i. According to Egger et al. (55), 10 trials are needed to assess publication bias. We cannot assess publication bias due to insufficient number of trials, therefore, we did not rate down for publication bias.

GRADE Summary of Findings Table – **Treatment (Observational Studies, all ages, adherence to screen analysis)** Screening with mammography* compared to no screening

KQ2: Comparison of screening interval

FULL EVIDENCE TABLES

GRADE Summary of Findings Table –**Annual vs biennial screening (RCTs or Observational (NRSI=non-randomized study of intervention)**

Outcomes	70-74 Age Subgroup	75-84 Age Subgroup	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
Simple mastectomy # of follow-up (yrs): 8.0	The proportion of women (aged 70-74) diagnosed with breast cancer who received simple mastectomy in the continue screening strategy was 11.3 (10.8–11.8) and 10.4 (9.5–11.3) in the stop screening strategy group (absolute difference 9 more per 1,000). (Outcome not applicable to thresholds as denominator is total breast cancers)	The proportion of women (aged 75-84) diagnosed with breast cancer who received simple mastectomy in the continue screening strategy was 10.8 (10.3–11.2) and 10.1 (9.4–10.9) in the stop screening strategy group (absolute difference 7 more per 1,000) (Outcome not applicable to thresholds as denominator is total breast cancers)	2,639,194 (1 study) (64)	⨁⨁◯◯ LOW a,b,c,d,e	We found low certainty evidence comparing the proportions of women requiring simple mastectomy among those who continued mammography screening and those who stopped screening in their 70s (70-74 and 75-84 age groups).
Radical mastectomy # of follow-up (yrs): 8.0	The proportion of women (aged 70-74) diagnosed with breast cancer who received radical mastectomy in the continue screening strategy was 13.9 (13.4–14.5) and 18.2 (17.0–19.4) in the stop screening strategy group (absolute difference 43 fewer per 1,000). (Outcome not applicable to thresholds as denominator is total breast cancers)	The proportion of women (aged 75-84) diagnosed with breast cancer who received radical mastectomy in the continue screening strategy was 14.2 (13.7–14.6) and 17.0 (16.0–17.9) in the stop screening strategy group (absolute difference 28 fewer per 1,000).. (Outcome not applicable to thresholds as denominator is total breast cancers)	2,639,194 (1 study) (64)	⨁⨁◯◯ LOW a,b,c,d,e	We found low certainty evidence comparing the proportions of women requiring radical mastectomy among those who continued mammography screening and those who stopped screening in their 70s (70-74 and 75-84 age groups).
Radiotherapy # of follow-up (yrs): 8.0	The proportion of women (aged 70-74) diagnosed with breast cancer who received radiotherapy in the continue screening strategy was 51.0 (50.3–51.8) and 39.9 (38.6–41.3) in the stop screening strategy group (absolute difference 111 more per 1,000). (Outcome not applicable to thresholds as denominator is total breast cancers)	The proportion of women (aged 75-84) diagnosed with breast cancer who received radiotherapy in the continue screening strategy was 41.2 (40.4–41.9) and 31.9 (30.7–33.1) in the stop screening strategy group (absolute difference 93 more per 1,000). (Outcome not applicable to thresholds as denominator is total breast cancers)	2,639,194 (1 study) (64)	⨁⨁◯◯ LOW a,b,c,d,e	We found low certainty evidence comparing the proportions of women requiring radiotherapy among those who continued mammography screening and those who stopped screening in their 70s (70-74 and 75-84 age groups).
Chemotherapy # of follow-up (yrs): 8.0	The proportion of women (aged 70-74) diagnosed with breast cancer who received chemotherapy in the continue screening strategy was 15.2 (14.7–15.8) and 21.1 (20.0–22.1) in the stop screening strategy group (absolute difference 59 fewer per 1,000). (Outcome not applicable to thresholds as denominator is total breast cancers)	The proportion of women (aged 75-84) diagnosed with breast cancer who received chemotherapy in the continue screening strategy was 8.6 (8.3–9.1) and 11.5 (10.6–12.3) in the stop screening strategy group (absolute difference 29 fewer per 1,000).. (Outcome not applicable to thresholds as denominator is total breast cancers)	2,639,194 (1 study) (64)	⨁⨁◯◯ LOW a,b,c,d,e	We found low certainty evidence comparing the proportions of women requiring chemotherapy among those who continued mammography screening and those who stopped screening in their 70s (70-74 and 75-84 age groups).

a. We did not downrate for risk of bias. Study was judged to be of moderate quality using the JBI critical appraisal tool for cohort studies.
b. We did not downrate for inconsistency (only one study included).
c. We did not downrate for indirectness. The study answers the question of stopping versus continuing screening and all patients have received at least one baseline mammography.
d. Unable to evaluate imprecision using thresholds, as the baseline rate of treatment is not provided in the "stop screening" group to allow the calculation of absolute effects. Therefore, a minimally contextualized approach was used. The total population is large (>2000) and there is a large event rate (>300). We did not downrate for imprecision.
e. According to Egger et al. (55), 10 studies are needed to assess publication bias. We cannot assess publication bias due to insufficient number of trials, therefore, we did not rate down for publication bias

Outcome	No. and design USPSTF study quality	Findings	GRADE	What happens?
Stage distribution of any invasive breast cancer	1 NRSI (89) (BCSC data US: 1996 to 2012; n = 15,440) Fair quality	40-79 years (data stratified by decade and menopausal status; case-only analysis): No difference in risk of stage IIB+ (range of aRRs 0.98 to 1.17) or less favourable prognosis (range of RRs 1.03 to 10.7) cancers diagnosed after a biennial compared with annual interval (≥2 rounds in group) for any age group.	**Very low** ⨁⊖⊖⊖ due to ROB, **indirectness**, and imprecision Indirectness: comparison (case-only analysis)	We are very uncertain about the effects on advanced stage cancers from screening annually versus biennially.

No data: Breast-cancer mortality, All-cause mortality, Treatment-related morbidity, Breast cancer morbidity, Health-related quality of life, Screen-detection of invasive breast cancer, Detection of invasive breast cancer over follow-up, Stage distribution of screen-detected breast cancer

NRSI=non-randomized study of intervention

GRADE Summary of Findings Table –**Annual versus Triennial screening (RCTs or Observational (NRSI=non-randomized study of intervention)**

Outcome	No. and design USPSTF study quality	Findings	GRADE	What happens? (Based on USPSTF thresholds)
Breast-cancer mortality	1 NRSI (90) (Finland; 1985-1995; n=14,765) Fair quality 1 RCT (91) (UK 1989-1996) N=76,022 Fair quality	40-49 years: No difference in breast cancer mortality from annual versus triennial film mammography (20.3 versus 17.9 per 100,000 PY; RR 1.14, 95% CI 0.59 to 1.27) at 13 years. Intention-to-screen analysis. RCT never reported mortality outcome as planned.	**Very low** ⨁⊖⊖⊖ due to ROB, indirectness, and imprecision Indirectness: pre- 2014 for treatment outcome	We are very uncertain about the effects of annual versus triennial screening for breast-cancer mortality in 40 to 49-year-olds. No data was examined for older ages.
All-cause mortality	1 NRSI (90) (Finland; 1985-1995; n=14,765) Fair quality 1 RCT (91) (UK 1989-1996) N=76,022 Fair quality	40-49 years: No difference in all-cause mortality from annual versus triennial film mammography (230.9 versus 192.6 per 100,000 PY; RR 1.20, 95% CI 0.99 to 1.46) at 13 years. Intention-to-screen analysis. RCT never reported mortality outcome as planned.	**Very low** ⨁⊖⊖⊖ due to ROB, indirectness, and imprecision Indirectness: pre- 2014 for treatment outcome	We are very uncertain about the effects of annual versus triennial screening for all-cause mortality in 40 to 49-year-olds. No data was examined for older ages.
Screen-detection of invasive breast cancer (indirect outcome)	1 RCT (91) (UK 1989-1996) N=76,022 Fair quality	50-62 years: More invasive cancers screen-detected over 3 years with annual screening screen (4.42 per 1000 versus 2.70 per 1000; RR: 1.64 [95% CI, 1.28 to 2.09])	**Low** ⨁⨁⊖⊖ due to ROB (and single study) Indirect outcome but did not rate down	(Indirect outcome) Annual versus triennial screening may lead to more screen-detected invasive cancers for 50 to 69-year-olds over 3 years.
Detection of all invasive breast cancers over follow-up	1 RCT (91) (UK 1989-1996) N=76,022 Fair quality	50-62 years: Total number of invasive cancers similar between groups over 3 years (6.26 per 1000 versus 5.4 per 1000; RR: 1.16, 95% CI 0.96 to 1.40)	**Low** ⨁⨁⊖⊖ due to ROB and imprecision Indirect outcome but did not rate down	(Indirect outcome) Annual versus triennial screening may not lead to detection of more invasive cancers for 50 to 69-year-olds over 3 years.
Stage distribution of any invasive breast cancer	1 RCT (91) (UK 1989-1996; n=76,022 Fair quality	50-62 years: similar rates and no statistical differences by screening interval in tumor size, nodal status, grade, or prognostic index for all invasive cancers diagnosed over 3 years. Stage II+ or III+ NR.	**Low** ⨁⨁⊖⊖ due to ROB and imprecision Some but not serious indirectness; no data specific to stage II+ or III+ reported; only 3 years of screening and limited ages but added applicability into conclusions	Annual versus triennial screening may make little-to-no difference for advanced stage cancers for 50 to 69-year-olds over 3 years. No data was examined for other ages.
No data: Treatment-related morbidity, Breast cancer morbidity, Health-related quality of life, Stage distribution of screen-detected breast cancer				

NRSI=non-randomized study of intervention

KQ2: Comparison of screening modalities

FULL EVIDENCE TABLES

GRADE Summary of Findings Table –**Digital breast tomosynthesis versus digital mammography (RCTs or Observational (NRSI=non-randomized study of intervention)**

Outcome	No. and design USPSTF study quality	Findings	GRADE	What happens?
Screen-detection of invasive cancer	**3 RCTs with 2 rounds** N=129,492 2 Good quality (i) RETomo (92) Italy [2014-2017]; n=26,877; 45-69 years [9% BI-RADs 4]; DBT/DM versus DM but DM at 2nd round both groups 1 [45-49 years; 38%] or 2 [50-69] years later) (ii) To-BE (93) Norway [2016-2020]; n=28,749; 50-69 years [7% BI-RADs 4]; DBT/sDM versus DM but DBT/sDM at 2nd round for both groups 2 years later or next screening round) 1 Fair quality (Proteus Donna (94); Italy [2004-2017];	Round 1: DBT higher invasive cancer detection (3 RCTs pooled RR 1.41, 95% CI 1.20 to 1.64, I^2 8%, n = 129,492) with absolute differences ranging from 0.6 to 2.4 more per 1000 screened. Similar results were seen in the NRSI (2.3 more per 1000 screened; RR 1.43, 95% CI 1.22 to 1.67; unadjusted). Round 2: No significant difference was found (3 RCTs pooled RR 0.87, 95% CI 0.73 to 1.05, I^2 0%, n = 105,064). The NRSI found lower detection at round 2 for the study group screened with DBT/sDM at round one (1.3 fewer per 1000 screened; RR 0.71, 95% CI 0.55, 0.92); unadjusted). Subgroups **RETomo RCT**: DBT resulted in a higher invasive cancer detection at the first round of screening for women ages 50 to 69 (RR: 1.60, 95% CI 1.10 to 2.30) and for women with nondense breasts [BI-RADS A/B] (RR: 1.80, 95% CI 1.10 to 3.00), but at the next round of screening when all were screened with DM, there was not a statistically significant	Low ⨁⨁⊖⊖ due to inconsistency and indirectness Indirectness: serious concerns about use of same device at round 2 Indirect outcome but did not rate down for this	Indirect outcome DBT versus DM may detect more invasive cancers over two rounds of screening among 45-69 year-olds.

			n=73,866; 46-68 years [density NR]; DBT/DM versus DM <u>but DM in 2nd round both groups</u> [1 year 46-49 or 2 years 50-68]) **1 NRSI with 2 rounds** Norway (95) [2014-2017]; n=98,927; 50-69 years [density NR]; DBT/sDM versus DM but 2nd round with DM 2 years later Fair quality	difference in invasive cancer detection. (RRs 1.0 and 0.97). For women aged 45-49 and women with dense breasts (BI-RADS C/D) there was no statistical difference in the detection of invasive cancers at either round of screening (round 1: RR=1.9 (95% CI, 0.89 to 4.1) and RR=1.5 (95% CI, 0.94 to 2.5) (but still same direction as overall findings) and round 2: RR=0.50 (95% CI, 0.20 to 1.2) and RR=0.64 (95% CI, 0.34 to 1.2). **To-BE** (using Volpara Density Grade): Round 1: density grades 1-3 RRs 1.07 to 1.16 versus density grade 4 RR=1.97 (95% CI, 0.47 to 8.21) Round 2: density grades 1-3 (0.82 to 1.04) versus grade 4 RR=0.66 (95% CI, 0.26 to 1.70)		
		Stage distribution of screen-detected breast cancer	Same as above	<u>Stage II+</u>: No significant differences within any of the 3 RCTs in the detection of Stage II+ at either round. Rates at round 1 were 1.2 per 1000 (Proteus Donna) or 1.3-1.6 per 1000 (RETomo & To-Be) in both groups. Results were inconsistent at round two with one trial nearing statistical significance for more stage II+ cancers from DBT/sDM (RETomo 1.2 versus 0.5 per 1000; RR 2.53 [95% CI 0.98 to 6.53]) and the other two trials in the direction of reduced stage II+ cancer in the DBT arm (Proteus Donna 0.7 versus 1.1 per 1000 and To-Be 1.4 versus 2.2 per 1000). <u>Stage III+</u>: RETomo (round 1: 0.2 versus 0.1 per 1000; round 2: 0.2 versus 0.3 per 1000). No clear evidence of stage shift. Stage not reported by NRSI. The three trials and NRSI reported tumor characteristics that inform staging such as tumor diameter, histologic grade, and node status. No statistically significant differences in these or other individual tumor prognostic characteristics were reported at the first or second round of screening for any of the included studies, but statistical power was limited for comparisons of less common tumor types.	**Low** ⨁⨁⊖⊖ due to indirectness and imprecision Indirectness: serious concerns about use of same device at round 2	DBT versus digital mammography may make little-to-no difference for advanced stage cancers over two rounds.
		No data: Breast-cancer mortality, All-cause mortality, Treatment-related morbidity, Breast cancer morbidity, Health-related quality of life, Detection of all invasive breast cancers over follow-up, Stage distribution of any invasive cancer				

NRSI=non-randomized study of intervention

UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

KQ1: 40-75+ (general population or moderately increased risk)

○ Little to none
○ Very small
X Small
○ Moderate
○ Large

○ Varies
○ Don't know

KQ2: screening interval
Annual vs Biennial or Triennial
40-75+ (general population or moderately increased risk)
○ Little to none
X Very small
(slightly more harms than biennial)
○ Small
○ Moderate
○ Large

○ Varies
○ Don't know

KQ2: Screening modality
Tomosynthesis vs Digital mammography
40-75+, (general population or moderately increased risk)

X Little to none
(same rating of harms as for DM alone)
○ Very small
○ Small
○ Moderate
○ Large

○ Varies
○ Don't know

KQ2: Screening modality
Supplementary Ultrasound vs Digital mammography alone
40-75+, (general population or moderately increased risk)
○ Little to none

KQ1: For cisgendered women, transgender men and nonbinary and others assigned female at birth ≥ 40 years of age and at average or moderately increased risk, what are the harms of different mammography-based screening strategies as compared to no screening?

SUMMARY: JUDGEMENT OF HARMS

Age groups:

Overdiagnosis: Using a threshold of 5*/1000,* screening ages **40-59** may cause little to no overdiagnosis (1.95/1000 (40-49) and 1.93/1000 (50-59) (low certainty). Data for **60-69** was very uncertain but within the little to no difference (1.5/1000) range (3.4/1000 for 50-59) (very low certainty). For ages **70+** data was very uncertain but within the harm range (20/1000 (**70-74**) and 15-23/1000 (**75+**)). Modeling data was very uncertain but within the little to no difference range (1.63/1000 over a lifetime (**50-74**)).

Additional imaging +/- biopsy (no cancer): Using a threshold of *150/1000*, screening ages **40-79** probably leads to a harm with 367.5 (**40-49**), 286.4-365.5 (**50-59**), 257.2 (**60-69**) and 220.4 (**70-79**) per 1000 screens.

Additional imaging with biopsy (no cancer): Using a threshold of *15/1000*, screening ages **40-79** probably leads to a harm with 54.7 (**40-49**), 34.0-46.2 (**50-59**), 32.8 (**60-69**) and 30.4 (**70-79**) per 1000 screens.

Based on the range of harms that crossed the threshold (see below), lifetime modeling data and WG feedback (see right column), the Task Force rated the magnitude as Small for ages ≥40 years. It was noted that the magnitude of additional testing (no cancer) decreased as age increased but remained above the threshold for all age groups. Overdiagnosis did not reach the threshold for 40-59 and limited for other age groups, but could be important (particularly for ages 70+).

40-49: 367.5/1000 additional imaging +/- biopsy (no cancer), 54.7/1000 additional imaging with biopsy (no cancer)

50-59: 286.4-365.5/1000 additional imaging +/- biopsy (no cancer), 54.7/1000 additional imaging with biopsy (no cancer)

60-69: 257.2/1000 additional imaging +/- biopsy (no cancer), 32.8/1000 additional imaging with biopsy (no cancer)

70-79: 220.4/1000 additional imaging +/- biopsy (no cancer), 30.4/1000 additional imaging with biopsy (no cancer).

70-74: 20/1000 overdiagnosis

75+: 15-23/1000 overdiagnosis

Screening interval:

Annual vs biennial (40-79):Using a threshold of *150/1000* and 15/1000 respectively, annual probably leads to more (140-180 more/1000) (imaging +/- biopsy) and 50 more/1000 (imaging + biopsy) additional testing (no cancer). Other evidence was very uncertain but showed less interval cancers with annual screening.

Annual vs triennial: Using a threshold of 6/1000, annual screening may make little to no difference (1 fewer / 1000) on interval cancers over 3 years for ages 40-62. Other evidence was very uncertain but in the direction of no difference for overdiagnosis.

Interval cancers: Data for interval cancers was very uncertain. Using a threshold of 6*/1000,* screening all ages **40+** within <12 months, 13-24 months or >24 months was within the little to no difference range for interval cancers (3.9/1000 (<12 months), 3.1/1000 (13-24 months), 3.9/1000 (>24 months) (very low certainty).

The WG rated the harms from screening annually ≥40 years as slightly higher than screening biennially (i.e., increased testing (no cancer)). Therefore there the difference between annual vs biennial or triennial was 'Very small'.

Screening modality:

A separate analysis excluding CNBSS from the overdiagnosis results showed less overdiagnosis for 40-49 (1.57 vs 1.97 / 1000) but more overdiagnosis for 50-59 (3.94 vs 1.93 / 1000).

WG Feedback
- While the callback for additional testing and biopsy affects many individuals (healthcare resources) we recognize it may not be important for all individuals.
- There is not a lot of data for 60+, undesirable effects could be less (e.g., clinical detection ability also improves due to fattier breast tissue), but it is difficult to know.
- The impact of additional surgeries and the impact of a surgery on a 75+ year old person is important to consider (e.g., surgical risks increase in this age group).

- There is no clear increased harm by tomosynthesis.
- While uncertain, there appears to be some possible harms due to supplementary ultrasound.
- There is a lack of data on supplemental MRI (e.g., increase biopsies), so the impact on health with its finding of possibly reducing interval cancers is not clear.

X Very small
X Small
(slightly higher rating of harms than for DM alone (=Small to Moderate harms)
○ Moderate
○ Large

○ Varies
○ Don't know

KQ2: Screening modality
Supplementary MRI vs Digital mammography alone
40-75+, (general population or moderately increased risk)
○ Little to none
○ Very small
○ Small
○ Moderate
○ Large

○ Varies
X Don't know

DBT vs DM may make little to no difference on additional imaging +/- biopsy (no cancer), additional imaging + biopsy (no cancer) and interval cancers.

Moderately increased risk due to breast density:

Supplemental ultrasound: May increase additional testing +/- biopsy (no cancer) for BIRADs level 3/4 and may not reduce interval cancers for C/D vs A/B density subgroups.

Supplemental MRI: Using a threshold *of 6/1000* it may make little to no difference (2.5 fewer / 1000) on interval cancers for extremely dense breasts

Annual vs biennial probably leads to more additional testing +/- biopsy (no cancer) when subgrouped by density (less so with BIRADs A).

DBT vs DM may make little to no difference on additional testing +/- biopsy (no cancer) and interval cancers when subgrouped by density levels 1/2 vs 3/4 or 'extremely dense breasts.

Moderately increased risk: Family history:

Supplemental ultrasound may increase additional testing +/- biopsy (no cancer) 'intermediate risk' individuals

The WG rated the harms from screening with DBT as the same as screening with DM. Therefore there was Little to no difference between DBT vs DM for harms. For supplementary ultrasound, based on the increased additional testing and lack of impact for interval cancers in dense breasts the WG rated the harms as higher (Small to moderate). Therefore, the difference between supplementary ultrasound vs DM alone was a Very small to small increase in harms. Due to the lack of data on harms for supplementary ultrasound the WG rated the harms as Don't know.

All ages:

All ages Outcome **Threshold (Regardless of certainty)**	**RCTs[7] and Observational studies[8] – Absolute effect (/1000 screens)**	**Other (e.g., CPAC registry data, online portal article submission)**	**Model – lifetime effects (/1000 persons)** **Thresholds not applicable**
Over-diagnosis **5 / 1000** (crude numbers and by screening interval)	No data	No data	**Invasive + DCIS** **Total cancers overdiagnosed** (crude numbers) Annual 50-74: 2.04/1000 Biennial 50-74: 1.63/1000 Biennial 40-74: 1.72/1000 **Compared to biennial 50-74:** **Annual** 50-74: 0.40 **more**/1000 **Hybrid 40**-74: 0.15 **more**/1000 Biennial **40**-74: 0.09 **more**/1000 Biennial 50-**79**: 0.06 **more**/1000 Biennial **40**-**79**: 0.15 **more**/1000 *(very low certainty)*
Additional imaging with or without biopsy (no cancer) **150 / 1000** (crude numbers and by screening interval)	**RCT:** No data **Cohort: Screening Interval data only** **Annual vs biennial** 40-79: 140-180 more with annual screening/ 1000 screens **Annual** screening was associated with higher cumulative rates across all density groups. *(Moderate certainty)* **Threshold not applicable**	**Over 10 years: 50-74** (crude numbers): **(2019 CPAC data from BC, AB, ON, NB, PE, NL)** 385.5 /1000 individuals	**Crude numbers** Annual 50-74: 1,236/1000 Biennial 50-74: 666/1000 Biennial 40-74: 840/1000 **Compared to biennial 50-74:** **Annual** 50-74: 570 **more**/1000 **Hybrid 40**-74: 341 **more**/1000 Biennial **40**-74: 173 **more**/1000 Biennial 50-**79**: 17 **more**/1000 Biennial **40**-**79**: 191 **more**/1000 *(moderate certainty)*
Additional imaging no biopsy (no cancer) No threshold	No data	No data	**Crude numbers** Annual 50-74: 1,126/1000 Biennial 50-74: 607/1000 Biennial 40-74: 765/1000 **Compared to biennial 50-74:** **Annual** 50-74: 519 **more**/1000 **Hybrid 40**-74: 311 **more**/1000 Biennial **40**-74: 158 **more**/1000

[7] Intention to screen
[8] Adherence to screen

			Biennial 50-**79**: 15 **more**/1000 Biennial **40**-**79**: 174 **more**/1000 *(moderate certainty)*
Additional imaging and biopsy (no cancer) **15 / 1000** (crude numbers and by screening interval)	**RCT:** No data **Cohort: Screening Interval data only** **Annual vs biennial** (Annual vs biennial) 40-79: 50 more with annual screening/ 1000 screens *(moderate certainty)*	No data	**Crude numbers** Annual 50-74: 110/1000 Biennial 50-74: 59/1000 Biennial 40-74: 75/1000 **Compared to biennial 50-74:** **Annual** 50-74: 51 **more**/1000 **Hybrid 40**-74: 30 **more**/1000 Biennial **40**-74: 15 **more**/1000 Biennial 50-**79**: 1 **more**/1000 Biennial **40**-**79**: 17 **more**/1000 *(moderate certainty)*
Interval cancer (Cancer detected after a normal screening mammo-gram but before the next scheduled mammo-gram) **6 / 1000** (crude numbers and by screening interval)	**RCT** (per 1000 screens Over 5 years) **Crude numbers by screening interval** Invasive + DCIS *Screening interval <=12 months* 3.9/1000 *(low certainty)* *Screening interval 13-24 months* 3.1/1000 *(very low certainty)* *Screening interval >24 months* 3.9/1000 *(low certainty)* Invasive only *Screening interval =18 months* 2.8/1000 *(very low certainty)* **Threshold not applicable** *DCIS only* *Screening interval =18 months* 0.2/1000 *(very low certainty)* **Threshold not applicable** **Cohort: Crude percentages by screening interval** Invasive + DCIS (40-79): **Annual**: 22% cancers were interval vs **Biennial** 27.2% cancers **Threshold not applicable**	Seely et al., 2022 (excluded due to study design) breast screening programs (age 40+) with a policy of **annual vs. those with biennial screening** for women with **dense breasts** **0.56 fewer** interval cancers per 1000 individuals (0.89 vs 1.45 per 1000). **Threshold not applicable**	**Invasive + DCIS** **Crude numbers** Annual 50-74: 21.45/1000 Biennial 50-74: 33.72/1000 Biennial 40-74: 36.91/1000 **Compared to biennial 50-74:** **Annual** 50-74: 12.27 **fewer**/1000 **Hybrid 40**-74: 1.41 **more**/1000 Biennial **40**-74: 3.19 **more**/1000 Biennial 50-**79**: 1.17 **fewer**/1000 Biennial **40**-**79**: 2.00 **more**/1000 *(moderate certainty)*

40-49 (over 10 years):

40-49 Outcome Threshold	**RCTs[9] – Absolute effect (/1000 screens)**	**Observational[10]**	**Other (i.e., CPAC or provincial registry data)**	**Model (/1000 persons)**
Overdiagnosis **5 / 1000**	**Invasive + DCIS** 1.95 /1000 (0.89-3.01 more) *(very low certainty)* **Invasive only** 1 /1000 (0-1 more) **Threshold not applicable** *(low certainty)*	**Invasive + DCIS** Age 49-52: Crude rates of breast cancer in screened vs unscreened Screened: 3.87/ 1000 PY vs Unscreened: 2.45/ 1000 PY 1.42 more /1000 PYs = 14.2 / 1000 over 10 years RR=1.49 (1.18-1.88) *(very low certainty)* **Threshold not applicable**	N/A	**Invasive + DCIS** **Compared to biennial 50-74** Biennial **40**-74: 0.09 **more**/1000 **Hybrid 40**-74: 0.15 **more**/1000 *(very low certainty)*
Overdiagnosis by screening interval **5 / 1000**	No data	Ages 40-49 Annual vs triennial RR=0.98 (0.75-1.29) *(very low certainty)* **Threshold not applicable**	N/A	**Invasive + DCIS** **Compared to biennial 40-74** **40**-74 **Hybrid**: 0.06 **more**/1000 *(very low certainty)*

[9] Intention to screen (short and long case accrual)
[10] Adherence to screen

Additional imaging with or without biopsy needed (no cancer) **150 / 1000**	No data	No data	4 biennial rounds **2011-2012 CPAC data** 367.5 / 1000 screens *(moderate certainty)* **2019 BC Data** 477.6 / 1000 screens *(moderate certainty)*	**Crude numbers 40-49 age band (average events 40-49):** Annual: 672 /1000 Biennial: 392 /1000 *(moderate certainty)*
Additional imaging no biopsy (no cancer) No threshold	No data	No data	4 biennial rounds **2011-2012 CPAC data** 312.8 / 1000 screens *(moderate certainty)*	**Crude numbers 40-49 age band (average events 40-49):** Annual: 612 /1000 Biennial: 357 /1000 *(moderate certainty)*
Additional imaging and biopsy needed (no cancer) **15 / 1000**	No data	No data	4 biennial rounds **2011-2012 CPAC data** 54.7 / 1000 screens *(moderate certainty)*	**Crude numbers 40-49 age band (average events 40-49):** Annual 40-74: 60/1000 Biennial 40-74: 35/1000 *(moderate certainty)*
Interval cancer **6 / 1000**	Age 39-49 Screening interval: 18 months **Invasive + DCIS** 3/1000 (2.1-4.2) *(low certainty)* **Invasive only** 2.8/1000 (1.9-3.9) *(low certainty)* **Threshold not applicable** **DCIS only** 0.2/1000 (0.02-0.6) *(low certainty)* **Threshold not applicable**	No data	N/A	**Invasive + DCIS** **Crude numbers 40-49 age band (average events 40-49):** Annual: 3.94/1000 Biennial: 6.43/1000 *(moderate certainty)*
Interval cancer by screening interval **6 / 1000**		**Invasive + DCIS** Annual vs triennial: No difference in interval cancers (Low certainty) **Threshold based on USPSTF (absolute numbers not available)**	N/A	**Invasive + DCIS** **Compared to biennial 40-74** (lifetime effect) **Hybrid 40**-74: 1.78 **fewer**/1000 *(moderate certainty)*

50-59 (over 10 years):

50-59 Outcome	RCTs[11] – Absolute effect (/1000 screens)	Observational studies[12]	Other (e.g., CPAC registry data, online portal article submission)	Model (/1000 persons)
Overdiagnosis **5 / 1000**	**Invasive + DCIS** 1.93 more / 1000 (0.24 to 3.86 more) *(very low certainty)* **Invasive only** 1.18 more / 1000 (0.71 fewer to 3.06 more) *(low certainty)* **Threshold not applicable**	**Invasive + DCIS** Screened vs unscreened (crude incidence rates of cancer) Age 49-52 **Screened**: 3.87 / 1000 PYs vs **Unscreened**: 2.45 / 1000 PYs RR=1.49 (1.18-1.88) 1.42 more /1000 PYs = 14.2 / 1000 over 10 years Age 53-59 **Screened**: 2.77 / 1000 PYs vs **Unscreened**: 3.19 / 1000 PYs 0.42 less /1000 PYs = 4.2 fewer/ 1000 over 10 years	N/A	**Invasive + DCIS** **Total cancers overdiagnosed** (lifetime effect) 50-74 Annual: 2.04 cancers overdiagnosed /1000 50-74 Biennial: 1.63 cancers overdiagnosed/1000 **Thresholds not applicable** *(very low certainty)*

[11] Intention to screen
[12] Adherence to screen

		Age 50-69 **Screened:** 3.74 / 1000 women vs **Unscreened:** 3.40 / 1000 women 0.34 more /1000 PYs = 3.4/ 1000 over 10 years *(very low certainty)*		
Additional imaging with or without biopsy (no cancer) **150 / 1000**	No data	No data	Over 4 biennial rounds **2011-2012 CPAC data** if starting screening at 50: 365.5/1000 screens if started at <50 years): 286.4/1000 screens *(moderate certainty)* **2019 British Columbia data** if starting screening at 50: 410.5/1000 screens if started at <50 years: 252.4/1000 screens *(moderate certainty)*	**Age band only: average events at age 50-59** 40-74 Annual: 507/1000 50-74 Annual: 557/1000 40-74 Biennial: 257/1000 50-74 Biennial: 308/1000 *(moderate certainty)*
Additional imaging no biopsy (no cancer) No threshold	No data	No data	Over 4 biennial rounds **2011-2012 CPAC data** if start screening at 50: 319.3/1000 screens if started at <50 years: 252.4/1000 screens *(moderate certainty)* *British Columbia data not available*	**Age band only: average events at age 50-59** 40-74 Annual: 462/1000 50-74 Annual: 507/1000 40-74 Biennial: 234/1000 50-74 Biennial: 280/1000 *(moderate certainty)*
Additional imaging and biopsy (no cancer) **15 / 1000**	No data	No data	Over 4 biennial rounds **2011-2012 CPAC data** if starting screening at 50: 46.2/1000 screens if started at <50 years: 34.0/1000 screens *(moderate certainty)* *British Columbia data not available*	**Age band only: average events at age 50-59** 40-74 Annual: 45 /1000 50-74 Annual: 50 /1000 40-74 Biennial: 23 /1000 50-74 Biennial: 27 /1000 *(moderate certainty)*
Interval cancer (Cancer detected after a normal screening mammogram but before the next scheduled mammogram) **6 / 1000** (crude rates and by screening interval)	**Invasive and DCIS (crude rate)** 18 month interval: 1.9 /1000 (1.2-3.0) experienced an interval cancer (Invasive; no DCIS detected) *(low certainty)*	Annual vs triennial (50-62) 1 fewer interval cancers / 1000 screens over 3 years *(low certainty)*	N/A	**Age band only: average events (crude rates) at age 50-59** 40-74 Annual: 4.33/1000 50-74 Annual: 4.61/1000 40-74 Biennial: 7.74/1000 50-74 Biennial: 7.89/1000 *(moderate certainty)*

60-69 (over 10 years)

60-69 Outcome Threshold	RCTs[13] Absolute effect (/1000 screens)	Observational[14]	Other (i.e., CPAC or provincial registry data)	Model Lifetime effects (/1000 persons)
Overdiagnosis **5 / 1000**	No data	**Invasive + DCIS** Screened vs control (crude incidence rates of cancer) Age 50-69 **Screened**: 3.74 / 1000 women vs **Unscreened**: 3.40 / 1000 women 0.34 more /1000 PYs = 3.4/ 1000 over 10 years Age 60-69 **Screened**:3.59/1000 person years vs **Unscreened**: 3.44/1000 person years 0.15 more /1000 PYs = 1.5/ 1000 over 10 years *(very low certainty)*	N/A	**Invasive + DCIS** **Total cancers overdiagnosed** (crude rate) (lifetime effect) 50-74 Annual: 2.04/1000 50-74 Biennial: 1.63/1000 **Threshold not applicable** *(very low certainty)*
Additional imaging with or without biopsy needed (no cancer) **150 / 1000**	No data	No data	Over 4 biennial rounds **2011-2012 CPAC data** 257.2 / 1000 screens *(moderate certainty)* **2019 BC data** 238.4/1000 screens *(moderate certainty)*	**Age band only: average events 60-69** 40-74 Annual: 418/1000 50-74 Annual: 418/1000 40-74 Biennial: 213/1000 50-74 Biennial: 213/1000 *(moderate certainty)*
Additional imaging no biopsy (no cancer)	No data	No data	Over 4 biennial rounds **2011-2012 CPAC data** 224.4 / 1000 screens *(moderate certainty)* *British Columbia data not available*	**Age band only: average events 60-69** 40-74 Annual: 381/1000 50-74 Annual: 381/1000 40-74 Biennial: 194/1000 50-74 Biennial: 194/1000 No threshold *(moderate certainty)*
Additional imaging and biopsy needed (no cancer) **15 / 1000**	No data	No data	4 biennial rounds **2011-2012 CPAC data** 32.8 / 1000 screens *(moderate certainty)* *British Columbia data not available*	**Age band only: average events 60-69** 40-74 Annual: 37/1000 50-74 Annual: 37/1000 40-74 Biennial: 19/1000 50-74 Biennial: 19/1000 *(moderate certainty)*
Interval cancer **6 / 1000**	No data	No data	No data	**Age band only: average events 60-69** 40-74 Annual: 4.69/1000 50-74 Annual: 4.70/1000 40-74 Biennial: 9.14/1000 50-7 4Biennial: 9.15/1000 *(moderate certainty)*

70-74

[13] Intention to screen (short and long case accrual)
[14] Adherence to screen

70-74 Outcome	RCTs	Observational studies[15]	Other (e.g., CPAC registry data, online portal article submission)	Model (/1000 persons) Thresholds not applicable
Overdiagnosis Screen-detected cancers that otherwise would not have caused symptoms or death (Can be calculated as the excess number of cancers in the screened vs unscreened groups over a long enough time period) **5 / 1000**	No data	**Comparison of cancer rates (Invasive + DCIS) in screened vs unscreened individuals over 10 years** **Screened:** 61/1000 vs **Unscreened:** 41/1000 20/1000 (HR 1.47; 95% CI 1.19-1.81) *(low certainty)* Comparison of adjusted 8-year cumulative risk of breast cancer diagnosis in screened vs unscreened: **Screened** 5.3% vs **Unscreened** 3.9% *(very low certainty)*	N/A	**Total cancers overdiagnosed** (lifetime effect) 50-74 Annual: 2.04 cancers overdiagnosed /1000 **over a lifetime** 50-74 Biennial: 1.63 cancers overdiagnosed/1000 **over a lifetime** *(very low certainty)*
Additional imaging with or without biopsy (no cancer) **150 / 1000**	No data	No data	Over 4 biennial rounds **2011-2012 CPAC data (70+)** 220.4/1000 screens *(moderate certainty)* **2019 British Columbia data (70+)** 269.6/1000 screens *(moderate certainty)*	**Age band only: average events at age 70-79 (no data for 70-74 alone)** 40-74 Annual: 179.61/1000 50-74 Annual: 179.79/1000 40-74 Biennial: 97.80/1000 50-74 Biennial: 102.74/1000 *(moderate certainty)*
Additional imaging no biopsy (no cancer)	No data	No data	Over 4 biennial rounds **2011-2012 CPAC data (70+)** 190/1000 screens *(moderate certainty)* *British Columbia data not available*	**Age band only: average events at age 70-79 (no data for 70-74 alone)** 40-74 Annual: 163.62/1000 50-74 Annual: 163.79/1000 40-74 Biennial: 89.10/1000 50-74 Biennial: 93.59/1000 *(moderate certainty)*
Additional imaging and biopsy (no cancer) **15 / 1000**	No data	No data	Over 4 biennial rounds **2011-2012 CPAC data (70+)** 30.4/1000 screens *(moderate certainty)* *British Columbia data not available*	**Age band only: average events at age 70-79 (no data for 70-74 alone)** 40-74 Annual: 15.99/1000 50-74 Annual: 16/1000 40-74 Biennial: 8.70/1000 50-74 Biennial: 9.14/1000 *(moderate certainty)*
Interval cancer (Cancer detected after a normal screening mammogram but before the next scheduled mammogram) **6 / 1000**	No data	No data	N/A	**Age band only: average events (crude rates) at age 70-79 (no data for 70-74 alone)** 40-74 Annual: 5.97/1000 50-74 Annual: 5.95/1000 40-74 Biennial: 8.62/1000 50-74 Biennial: 8.69/1000 *(moderate certainty)*

75+

75+ Outcome Threshold	RCTs	Observational[16]	Other (i.e., CPAC or provincial registry data)	Mode – lifetime effects (/1000 persons) Thresholds not applicable
Overdiagnosis Screen-detected cancers that otherwise would not have caused symptoms or death (Can be calculated as the excess number of cancers in the screened vs unscreened groups over a long	No data	**Comparison of cancer rates (Invasive + DCIS) in screened vs unscreened individuals over 10 years** Ages 75-84 **Screened**: 49 / 1000 vs **Unscreened**: 26 / 1000 (HR 1.92; 95% CI 1.60-2.30) *(low certainty)* 23/1000 Age 85+ **Screened**: 28/1000 vs **Unscreened**: 13/1000	N/A	**Total cancers overdiagnosed (Invasive + DCIS)** **Versus biennial 50-74:** Biennial 50-79: 0.06 more /1000 *(very low certainty)*

[15] Adherence to screen
[16] Adherence to screen

enough time period) **5 / 1000**		15/1000 (HR 2.20; 95% CI 1.43-3.40) *(low certainty)* **Comparison of adjusted 8-year cumulative risk of breast cancer diagnosis in screened vs unscreened:** **Screened** (ages 75-85): 5.8% vs **Unscreened** (stopped at 74): 3.9% *(very low certainty)* Threshold not applicable		
Additional imaging with or without biopsy needed (no cancer) **150 / 1000**	No data	No data	Over 4 biennial rounds **2011-2012 CPAC data (70+)** 220.4 / 1000 screens *(moderate certainty)* **2019 BC Data** 269.6/1000 screens *(moderate certainty)*	**Age band only: average events 70-79** **(no data for 75-79 alone)** 40-74 Annual: 179.61/1000 50-74 Annual: 179.79/1000 40-74 Biennial: 97.80/1000 50-74 Biennial: 102.74/1000 *(moderate certainty)*
Additional imaging no biopsy (no cancer) No threshold	No data	No data	Over 4 biennial rounds **2011-2012 CPAC data (70+)** 190 / 1000 screens *(moderate certainty)* *British Columbia data not available*	**Age band only: average events 70-79** **(no data for 75-79 alone)** 40-74 Annual: 163.62/1000 50-74 Annual: 163.79/1000 40-74 Biennial: 89.10/1000 50-74 Biennial: 93.59/1000 *(moderate certainty)*
Additional imaging and biopsy needed (no cancer) **15 / 1000**	No data	No data	4 biennial rounds **2011-2012 CPAC data (70+)** 30.4 / 1000 screens *(moderate certainty)* *British Columbia data not available*	**Age band only: average events 70-79** **(no data for 75-79 alone)** 40-74 Annual: 15.99/1000 50-74 Annual: 16/1000 40-74 Biennial: 8.70/1000 50-74 Biennial: 9.14/1000 *(moderate certainty)*
Interval cancer (Cancer detected after a normal screening mammogram but before the next scheduled mammogram) **6 / 1000**	No data	No data	No data	**Age band only: average events 70-79** **(no data for 75-79 alone)** 40-79 Annual: 3.94/1000 50-79 Annual: 3.94/1000 40-79 Biennial: 7.79/1000 50-79 Biennial: 7.88/1000 *(moderate certainty)*

KQ1i: Do the harms differ by population characteristics (e.g., age, breast density, race and ethnicity, socioeconomic status, geographical area, family history)?

No data available

KQ2: What is the comparative effectiveness of different mammography-based breast cancer screening strategies on harms?

Screening interval:

Screening modality:

Tomosynthesis (DBT) vs digital mammography (DM):

Tomosynthesis vs Digital mammography among average risk individuals (unless otherwise specified): Multiple age groups

Outcome	Model: 40-49 annual vs 40-49 biennial (per 1000 women)	Model: Lifetime annual vs biennial (per 1000 women) Thresholds not applicable		RCT or Observational data: Annual vs Triennial: 50-62	RCT or Observational data: Annual vs Biennial All ages
		40-74	50-74		
Additional testing no cancer 150/1000	Annual: 167.53 more (moderate certainty)	Annual: 737.02 more (moderate certainty)	Annual: 569.60 more (moderate certainty)	No data	Annual: 140-180 more (moderate certainty)
Additional imaging + biopsy (no cancer) 15/1000	Annual: 14.91 more (moderate certainty)	Annual: 65.59 more (moderate certainty)	Annual: 50.7 more (moderate certainty)		Annual: 50 more (moderate certainty)
Overdiagnosis 5/1000	Annual: 0.06 more (very low certainty)	Annual: 0.46 more (very low certainty)	Annual: 0.41 more (very low certainty)		No data
Interval cancers 6/1000	Annual: 1.78 fewer (moderate certainty)	Annual: 13.81 fewer (moderate certainty)	Annual: 12.28 fewer (moderate certainty)	50-62: 1 fewer / 1000 interval cancers over 3 years. (Low certainty)	(a) Annual: 22.2% cancers were interval Biennial: 27.2% cancers were interval (very low certainty) Threshold not applicable (b) Annual vs biennial: 0-0.8 fewer / 1000 (low certainty)

Outcome	Age group	Study types	Results Thresholds based on USPSTF (i.e., absolute numbers not available) unless otherwise indicated
Additional testing +/- biopsy (no cancer) 150/1000	40-79	3 RCTs and 2 observational	Tomosynthesis may make little-to-no difference (compared to digital mammography) on additional testing +/- biopsy (no cancer) for average risk individuals. Approximately 2-3% (20-30 per 1000 screened) over 10 years/3+ rounds when screening biennially (Low certainty) **Based on TF threshold** Subgroups: • Age: stratification by ages 45-49 and 50-69 showed no significant differences at either round for either group (1 RCT) • Screening interval: Slightly lower additional testing +/- biopsy (no cancer) with tomosynthesis with annual screening (50% versus 56%) and similar rates with biennial screening (36% versus 38%). (1 observational) • May result in no significant difference among high breast density (levels 3-4) may reduce additional testing +/- biopsy (no cancer) for lower breast density (levels 1-2) (1 RCT). • No difference for those with extremely dense breasts (1 observational).

Additional testing with biopsy (no cancer) 15/1000	40-79	1 RCTs and 1 observational	Tomosynthesis may make little-to-no difference (compared to digital mammography) on additional testing +/- biopsy (no cancer) for average risk individuals (1 RCT, 1 observational). (Low certainty) Subgroups: • Screening interval: May make no difference in cumulative additional testing +/- biopsy (no cancer) with biopsy regardless of screening interval (1 observational) • At round 1 – significantly fewer additional testing with biopsy (no cancer) among low breast density individuals and more additional testing with biopsy (no cancer) among those with high breast density (3-4). No difference over 2 rounds (1 RCT). • No difference in cumulative additional testing +/- biopsy (no cancer) with biopsy for those with extremely dense breasts (1 observational).
Interval cancer 6/1000	54-79	3 RCTs and 5 observational	Tomosynthesis (vs digital mammography) probably little-to-no difference for interval cancers. (3 RCTs, 5 NRSIs). (**Moderate certainty)** Subgroups: • No significant findings related to **age** and interval cancers (Moderate evidence) (1 RCT and 2 observational) • No significant findings related to **breast density** and interval cancers (Moderate evidence) (2 RCTs 1 observational)

Supplementary ultrasound

Digital mammography + Supplemental ultrasound vs Digital mammography alone among moderately elevated risk individuals (e.g., high breast density): Multiple age groups

Outcome	Age group	Study types	Results Thresholds based on USPSTF (absolute numbers not available)
Additional testing with biopsy (no cancer) 15/1000	30-80+	1 observational	Supplementing digital mammography with ultrasound may increase additional testing with biopsies (no cancer) by possibly 2-fold among a population with elevated risk (BIRADs 3/4 or those at 'intermediate risk') (Low certainty)
Interval cancer 6/1000	30-80+	1 RCT and 1 observational	Supplementing digital mammography with ultrasound may not reduce interval cancers at the first round for BIRADs A/B or C/D (Low certainty)

Supplementary MRI

Digital mammography + Supplemental MRI vs Digital mammography alone among moderately elevated risk individuals (e.g., high breast density): Multiple age groups

Outcome	Age group	Study types	Results
Interval cancer 6/1000	50-75	1 RCT	Supplementing digital mammography with MRI may not reduce interval cancers (2.5 fewer/1000) at the first round for individuals with **extremely dense breasts** *(Low certainty)* Based on Task Force threshold

KQ2i: Does comparative effectiveness differ by population characteristics and risk markers (e.g., age, breast density, race and ethnicity, socioeconomic status, geographical area, family history)?

Screening interval:
No data
Screening modality:
See above

FULL EVIDENCE TABLES

KQ1: Screening vs no screening

GRADE Summary of Findings Table - **Overdiagnosis (RCTs)**

Outcomes	Absolute effects		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	What happens
	Risk with Usual Care (Assumed Risk)	Absolute effect (95% CI)				
Main analysis: Overdiagnosis invasive + in situ cancers (40-49 years) Range of follow-up (yrs): 9 to 15 years	17.7 per 1,000	**1.95 more per 1,000** (from 0.89 more to 3.01 more)	**RR 1.11** (1.05 to 1.17)	293,152 (3 RCTs) [a] (103–105)	⊕◯◯◯ VERY LOW [a,b,c,d,e]	Using a threshold of 5, we are very uncertain whether screening leads to at least 5 overdiagnosed cancers in individuals aged 40 to 49 years.

Other analysis: Overdiagnosis invasive cancers only (40-49 years) Range of follow-up (yrs): 9 to 15 years	16.7 per 1,000	**1 more per 1,000** (from 0 to 2 more)	**RR 1.06** (1.00 to 1.12)	293,152 (3 RCTs) [a] (103–105)	⊕⊕◯◯ LOW [a,c,d,e,f]	Using a threshold of 5, screening may lead to little to no difference in overdiagnosed invasive cancers in individuals aged 40 to 49 years
Main analysis: Overdiagnosis invasive + in situ cancers (50-59 years) Range of follow-up (yrs): 10 to 15 years	24.1 per 1,000	**1.93 more per 1,000** (from 0.24 more to 3.86 more)	**RR 1.08** (1.01 to 1.16)	132,231 (2 RCTs) [a] (103,104)	⊕⊕◯◯ LOW [a,c,d,e,f]	Using a threshold of 5, screening may lead to little to no difference in overdiagnosed cancers in individuals aged 50 to 59 years.
Other analysis: Overdiagnosis invasive cancers only (50-59 years) Range of follow-up (yrs): 10 to 15 years	23.5 per 1,000	**1.18 more per 1,000** (from 0.71 fewer to 3.06 more)	**RR 1.05** (0.97 to 1.13)	132,231 (2 RCTs) [a] (103,104)	⊕⊕◯◯ LOW [a,c,d,e,f]	Using a threshold of 5, screening may lead to little to no difference in overdiagnosed invasive cancers in individuals aged 50 to 59 years.

a. We downrated once for risk of bias. Randomisation and allocation concealment were either not reported or there were serious deficiencies in these areas.
b. Approximately half point estimates in our pooled estimate cross our threshold, we downrated once for inconsistency.
c. Downrated once for indirectness. Data are from trials initiated in the 1960s-1990s and some trial estimates included participants outside the previously defined age decades (e.g., in the 40-49 age decade, one study included some individuals in their 50s).
d. Not rated down for imprecision. Clinical decision threshold set at 5.
e. Not downrated for publication bias. Cannot assess publication bias (insufficient number of trials).
f. Not downrated for inconsistency; all point estimates in our pooled analysis lie to one side of our threshold.

GRADE Summary of Findings Table- **Overdiagnosis (Observational, by age)**

Mammography +/- CBE compared to Usual Care

Outcomes	**Summary‡**	№ of participants (studies)	Quality of the evidence (GRADE)	What happens
Overdiagnosis invasive + in situ cancers (40-49 years) Range of follow-up (yrs): 8 years Screening interval: biennial	One study reported the number of invasive and in situ breast cancers among women 49 to 52 years and found a rate of 3.87 per 1,000 person years in the screened group and 2.45 per 1,000 person years in the unscreened group [RR 1.49 (95% CI 1.18 to 1.88)].	Unclear (1 study) (106)	⊕◯◯◯ VERY LOW [a-e]	We are very uncertain whether screening leads to at least 5 overdiagnosed cancers in individuals aged 40 to 49 years.
Overdiagnosis invasive + in situ cancers (50-59 years) Range of follow-up (yrs): 8 to 13 years Screening interval: biennial	Two studies reported the number of invasive and in situ breast cancers. One study reported among 53- to 59-year-olds and found a rate of 2.77 per 1,000 person years in the screened group and 3.19 per 1,000 person years in the unscreened group. The second study found a rate of 3.74 per 1,000 individuals in the screening group and 3.40 per 1,000 individuals in the control group among 50- to 69-year-olds.	Unclear (2 studies) (84,106)	⊕◯◯◯ VERY LOW [a,d-g]	We are very uncertain whether screening leads to at least 5 overdiagnosed cancers in individuals aged 50 to 59 years.
Overdiagnosis invasive + in situ cancers (60-69 years) Range of follow-up (yrs): 8 to 13 years Screening interval: biennial	Two studies reported the number of invasive and in situ breast cancers. One study reported among 60- to 69-year-olds and found a rate of 3.59 per 1,000 person years in the screened group and 3.44 per 1,000 person years in the unscreened group. The second study found a rate of 3.74 per 1,000 individuals in the screening group and 3.40 per 1,000 individuals in the control group among 50- to 69-year-olds.	Unclear (2 studies) (84,106)	⊕◯◯◯ VERY LOW [a,d-g]	We are very uncertain whether screening leads to at least 5 overdiagnosed cancers in individuals aged 60 to 69 years.
Overdiagnosis invasive + in situ cancers (70-74 years) Range of follow-up (yrs): 15 years Screening interval: 3 years	One study reported the number of invasive and in situ breast cancers among women 70 to 74 years and found a rate of 61 per 1,000 individuals in the screened group and 41 per 1,000 individuals in the unscreened group [HR 1.47 (95% CI 1.19 to 1.81)].	19,925 (1 study) (107)	⊕⊕◯◯ LOW [b,d,e,h,i]	Screening may lead to at least 5 overdiagnosed cancers in 1,000 individuals aged 70 to 74 years.
Overdiagnosis invasive + in situ cancers (75 years and older) Range of follow-up (yrs): 15 years Screening interval: 3 years	One study reported the number of invasive and in situ breast cancers among women 75 to 84 years and found a rate of 49 per 1,000 individuals in the screened group and 26 per 1,000 individuals in the unscreened group (HR 1.92 (95% CI 1.60 to 2.30)]. The same study reported for those aged 85 years or older and found a rate of 28 per 1,000 individuals in the screened group and 13 per 1,000 individuals in the unscreened group [HR 2.20 (95% CI 1.43 to 3.40)].	34,710 (1 study) (107)	⊕⊕◯◯ LOW [b,d,e,h,i]	Screening may lead to at least 5 overdiagnosed cancers in 1,000 individuals aged 75 years or older.

‡ We did not pool due to variations in reporting (e.g., different denominators such as person years). Results are narratively summarized.

a. A number of studies did not adjust for age and hormone therapy use (significant confounders) and also did not adjust or address for lead time bias.
b. Reporting of estimates varied between studies. One cannot be confident that the same methodological approach was used.
c. Some studies had either included high risk subjects in their cohort, or did not mention whether they were excluded.
d. Narrative analysis. Effect sizes were not provided consistently across studies.
e. Cannot assess publication bias (insufficient number of studies)
f. Overdiagnosis characteristics were extracted as reported in the overviews.

GRADE Summary of Findings Table - **Interval Cancers – (RCTs)**

Outcomes	Impact	№ of participants (studies)	Quality of the evidence (GRADE)	What happens
Invasive and DCIS (All ages) – screening interval **<=12 months** # R: 44,925 # A: Unclear Range of follow-up (yrs): 5.0	3.9 (95% CI 3.4 to 4.5) interval cancers (Invasive and DCIS) were detected in the mammography arm per 1000 women (176/44,925 randomized) over the follow-up period of five years (screening interval 12 months).	Unclear (1 RCT) (50)	⊕⊕◯◯ LOW [a,b,c,d,j]	Using a threshold of 6 interval cancers over 10 years, screening may lead to little to no difference in interval cancers (invasive and DCIS). We cannot comment on the comparative effectiveness of breast cancer screening for interval cancers, as interval cancers detected by screening cannot be measured in a non-screening comparator group. Interpretation of this estimate should be informed by additional data that is reflective of the current Canadian context.

Invasive and DCIS (All ages) – screening interval **13-24 months** # R: 62,222 # A: Unclear Range of follow-up (yrs): 4.8-7.0	3.1 (95% CI 2.6 to 3.7) interval cancers (Invasive and DCIS) were detected in the mammography arm per 1000 women over the follow-up period of 4.8-7 years (screening interval 18 months).	Unclear (2 RCTs) (46,78)	⊕◯◯◯ VERY LOW e,f,c,d,j	Using a threshold of 6 interval cancers over 10 years, we are very uncertain if screening leads to little to no difference in interval cancers (invasive and DCIS). We cannot comment on the comparative effectiveness of breast cancer screening for interval cancers, as interval cancers detected by screening cannot be measured in a non-screening comparator group. Interpretation of this estimate should be informed by additional data that is reflective of the current Canadian context.
Invasive and DCIS (All ages) – screening interval **>24 months** # R: 77,080 # A: Unclear Range of follow-up (yrs): 7.0	3.9 (95% CI 3.4 to 4.3) interval cancers (Invasive and DCIS) were detected in the mammography arm per 1000 women (298/77,080 randomised) over the follow-up period of 7 years (screening interval 23-33 months).	Unclear (1 RCT) (48)	⊕⊕◯◯ LOW a,b,c,d,j	Using a threshold of 6 interval cancers over 10 years, screening may lead to little to no difference in interval cancers (invasive and DCIS). We cannot comment on the comparative effectiveness of breast cancer screening for interval cancers, as interval cancers detected by screening cannot be measured in a non-screening comparator group. Interpretation of this estimate should be informed by additional data that is reflective of the current Canadian context.
Invasive Only (All ages) – 18-month screening interval # R: 61,968 # A: Unclear Mean follow-up (yrs): 4.8-7.0	2.8 (95% CI 2.4 to 3.3) interval cancers (Invasive cancers) were detected in the mammography arm per 1000 women over the follow-up period of 4.8-7 years (screening interval 18 months).	Unclear (2 RCTs) (56,78)	⊕◯◯◯ VERY LOW e,g,c,d,j	Using a threshold of 6 interval cancers over 10 years, we are very uncertain if screening leads to little to no difference in interval cancers (invasive only). We cannot comment on the comparative effectiveness of breast cancer screening for interval cancers, as interval cancers detected by screening cannot be measured in a non-screening comparator group. Interpretation of this estimate should be informed by additional data that is reflective of the current Canadian context.
DCIS Only (All ages) – 18-month screening interval # R: 61,968 # A: Unclear Mean follow-up (yrs): 4.8-7.0	0.2 (95% CI 0.1 to 0.5) interval cancers (DCIS cancers) were detected in the mammography arm per 1000 women over the follow-up period of 4.8-7 years (screening interval 18 months).	Unclear (2 RCTs) (56,78)	⊕◯◯◯ VERY LOW e,h,c,d,j	Using a threshold of 6 interval cancers over 10 years, we are very uncertain if screening leads to little to no difference in interval cancers (DCIS). We cannot comment on the comparative effectiveness of breast cancer screening for interval cancers, as interval cancers detected by screening cannot be measured in a non-screening comparator group. Interpretation of this estimate should be informed by additional data that is reflective of the current Canadian context.
Age group 39-49 years (Invasive and DCIS) – 18-month screening interval # R: 11,724 # A: Unclear Mean follow-up (yrs): 4.8-7.0	3.0 (95% CI 2.1 to 4.2) interval cancers (Invasive and DCIS) were detected in the mammography arm per 1000 women (35/11,724 randomised) over the follow-up period of 4.8-7 years (screening interval 18 months).	Unclear (1 RCT) (56)	⊕⊕◯◯ LOW i,b,c,d,j	Using a threshold of 6 interval cancers over 10 years, screening may lead to little to no difference in interval cancers (invasive and DCIS). We cannot comment on the comparative effectiveness of breast cancer screening for interval cancers, as interval cancers detected by screening cannot be measured in a non-screening comparator group. Interpretation of this estimate should be informed by additional data that is reflective of the current Canadian context.
Age group 39-49 years (Invasive Only) – 18-month screening interval # R: 11,724 # A: Unclear Mean follow-up (yrs): 4.8-7.0	2.8 (95% CI 1.9 to 3.9) interval cancers (Invasive) were detected in the mammography arm per 1000 women (33/11,724 randomised) over the follow-up period of 4.8-7 years (screening interval 18 months).	Unclear (1 RCT) (56)	⊕⊕◯◯ LOW i,b,c,d,j	Using a threshold of 6 interval cancers over 10 years, screening may lead to little to no difference in interval cancers (invasive). We cannot comment on the comparative effectiveness of breast cancer screening for interval cancers, as interval cancers detected by screening cannot be measured in a non-screening comparator group. Interpretation of this estimate should be informed by additional data that is reflective of the current Canadian context.
Age group 39-49 years (DCIS Only) – 18-month screening interval # R: 11,724 # A: Unclear Mean follow-up (yrs): 4.8-7.0	0.2 (95% CI 0.02 to 0.6) interval cancers (DCIS) were detected in the mammography arm per 1000 women (2/11,724 randomised) over the follow-up period of 4.8-7 years (screening interval 18 months).	Unclear (1 RCT) (56)	⊕⊕◯◯ LOW i,b,c,d,j	Using a threshold of 6 interval cancers over 10 years, screening may lead to little to no difference in interval cancers (DCIS). We cannot comment on the comparative effectiveness of breast cancer screening for interval cancers, as interval cancers detected by screening cannot be measured in a non-screening comparator group. Interpretation of this estimate should be informed by additional data that is reflective of the current Canadian context.
Age group 50-59 years (Invasive and DCIS) – 18-month screening interval # R: 9,926 # A: Unclear Mean follow-up (yrs): 4.8-7.0	1.9 (95% CI 1.2 to 3.0) interval cancers (Invasive; no DCIS detected) were detected in the mammography arm per 1000 women (19/9,926 randomised) over the follow-up period of 4.8-7 years (screening interval 18 months).	Unclear (1 RCT) (56)	⊕⊕◯◯ LOW i,b,c,d,j	Using a threshold of 6 interval cancers over 10 years, screening may lead to little to no difference in interval cancers (invasive and DCIS). We cannot comment on the comparative effectiveness of breast cancer screening for interval cancers, as interval cancers detected by screening cannot be measured in a non-screening comparator group. Interpretation of this estimate should be informed by additional data that is reflective of the current Canadian context.

a. Downrated once for risk of bias due to a lack of reporting for how interval cancers were detected and unclear reporting on who was used in the analysis.
b. Not downrated for inconsistency. Single study evaluated for outcome.
c. Downrated once for indirectness. Data are from trials initiated in the 1960s-1990s and the intervention groups were primarily screened with film mammography. Due to advances in mammography technology and treatment practices, we expect that the magnitude of screening effect may differ if applied to today's Canadian screening context. There are no high-quality clinical trials examining the impact of screening on interval cancers using contemporary screening methods.
d. The 95% CI does not cross the clinical decision threshold; therefore, we did not rate down for imprecision.
e. Downrated once for risk of bias. Studies ranged from moderate to high risk of bias. Lack of reporting for how interval cancers were detected and unclear reporting on who was used in the analysis.
f. Inconsistency is moderately high (I^2 = 61%). Rated down once.
g. Inconsistency is moderately high (I^2 = 52%). Rated down once.
h. Inconsistency is moderately high (I^2 = 57%). Rated down once.
i. Downrated once for risk of bias. Lack of reporting for how interval cancers were detected and missing important demographic details in intervention group.
j. According to Egger et al. (55), 10 trials are needed to assess publication bias. We cannot assess publication bias due to insufficient number of trials, therefore, we did not rate down for publication bias.

GRADE Summary of Findings Table – **Additional imaging with or without biopsy (no cancer)**

Outcomes	**Calculated Estimate (2011-2012 CPAC Data)**** (33)	**Calculated Estimate (2019 British Columbia Data)**** (108)	Quality of the evidence*	What happens
Additional imaging with or without biopsy (no cancer) over 10 years (40-49 years)†	**367.5 per 1000**	**477.6 per 1000**	⊕⊕⊕◯ MODERATE a,b,c,d,e	Screening probably leads to at least 150 women requiring additional imaging with or without biopsy (no cancer) in 1000 women screened every 2-3 years over a 10-year period (40-49 years).

Additional imaging with or without biopsy (no cancer) over 10 years (50-59 years)†	**365.5 per 1000**	**410.5 per 1000**	⊕⊕⊕◯ MODERATE [a,b,c,d,e]	Screening probably leads to at least 150 women requiring additional imaging with or without biopsy (no cancer) in 1000 women screened every 2-3 years over a 10-year period (50-59 years, started screening at age 50)
Additional imaging with or without biopsy (no cancer) over 10 years (50-59 years)‡	**286.4 per 1000**	**252.4 per 1000**	⊕⊕⊕◯ MODERATE [a,b,c,d,e]	Screening probably leads to at least 150 women requiring additional imaging with or without biopsy (no cancer) in 1000 women screened every 2-3 years over a 10-year period (50-59 years, started screening prior to age 50)
Additional imaging with or without biopsy (no cancer) over 10 years (60-69 years)‡	**257.2 per 1000**	**238.4 per 1000**	⊕⊕⊕◯ MODERATE [a,b,c,d,e]	Screening probably leads to at least 150 women requiring additional imaging with or without biopsy (no cancer) in 1000 women screened every 2-3 years over a 10-year period (60-69 years)
Additional imaging with or without biopsy (no cancer) over 10 years (70+ years)‡	**220.4 per 1000**	**269.6 per 1000**	⊕⊕⊕◯ MODERATE [a,b,c,d,e]	Screening probably leads to at least 150 women requiring additional imaging with or without biopsy (no cancer) in 1000 women screened every 2-3 years over a 10-year period (70+ years)

*GRADE ratings are not typically applied to the context of primary evidence sets generated by analyses of quality indicator surveillance data. However, our judgements of the overall certainty of evidence have been informed by similar considerations used in the GRADE process for effectiveness data.
†Scenario 1: Assuming started biennial screening in current age decade (calculated using one initial screen and three subsequent screens over a 10-year period).
‡Scenario 2: Assuming started biennial screening in prior age decade (calculated using four subsequent screens over a 10-year period).
**Data Sources: Using data from the 2011- 2012 CPAC report (33), we estimated the approximate rate of additional imaging with or without biopsy (no cancer) for women in each age decade over a 10 year-period (Table 7A). The BC estimates were estimated using breast screening program outcome indicators by 10-year age groups for 2019 for the "overall" risk groups (Table 9). See supplemental KQ1 GRADE Material, Appendix 6, part E for an example calculation.
Additional imaging estimates per screening cycle were calculated by subtracting cancer detection rates (invasive + DCIS) from abnormal call rates, stratified by age decade and if data were related to an "initial" or "subsequent" screen. We assumed women received four screens over a 10-year period, if the majority of women would receive a screen every 2-3 years (approximating biennial screening for the majority, noting that NS, PEI, NWT and AB recommend annual screening in 40-49). Scenario 1 assumes women start screening in that age decade and receive four screens over 10 years (one initial and three subsequent) (age groups: 40-49 and 50-59†). Scenario 2 assumed women started screening in prior age decades and therefore received four subsequent screens over a 10-year period (age groups: 50-59‡, 60-69, 70+).

a. The CPAC quality indicator data was used from the Canadian Breast Cancer Screening Database (CBCSD), which contained relatively complete data from participating provinces and territories for the quality indicators of interest in 2011-2012. The BC estimates were estimated using breast screening program outcome indicators by 10-year age groups for 2019, which should contain complete data. We did not downrate for risk of bias.
b. Estimates were calculated using quality indicators from screen-level data. Thus, we have no measure of imprecision in the data. All point estimates cross the minimum threshold for important effect (150 women with no cancer who require either imaging alone or imaging plus biopsy per 1000 screens).
c. We did not downrate for inconsistency. All age estimates for both the CPAC and the BC data fall above our threshold of 150 patients requiring additional imaging with or without biopsy (no cancer) per 1000 screens.
d. There appears to be an increase in recall rates over time (see Supplemental KQ1 GRADE Material, Appendix 6) depending on the data source. However, our conclusions about the rates of additional imaging with or without biopsy (no cancer) are unlikely to change, as the rates remain relatively consistent using more recent CPAC data and provincial data and above our clinical decision threshold. We did not downrate for indirectness.
e. We uprated our overall conclusion to moderate certainty of evidence as imaging recall estimates are similar across different data sources and consistently cross our threshold for clinical decision making.

GRADE Summary of Findings Table – **Additional imaging no biopsy (no cancer)**

Outcomes	**Calculated Estimate (2011-2012 CPAC Data)**** (33)	Quality of the evidence*	What happenes
Additional imaging no biopsy (no cancer) over 10 years (40-49 years)†	**312.8 per 1000**	⊕⊕⊕◯ MODERATE [a,b,c,d]	Screening probably leads to at least 150 women requiring additional imaging no biopsy (no cancer) in 1000 women screened every 2-3 years over a 10-year period (40-49 years)
Additional imaging no biopsy (no cancer) over 10 years (50-59 years)†	**319.3 per 1000**	⊕⊕⊕◯ MODERATE [a,b,c,d]	Screening probably leads to at least 150 women requiring additional imaging no biopsy (no cancer) in 1000 women screened every 2-3 years over a 10-year period (50-59 years, started screening at age 50)
Additional imaging no biopsy (no cancer) over 10 years (50-59 years)‡	**252.4 per 1000**	⊕⊕⊕◯ MODERATE [a,b,c,d]	Screening probably leads to at least 150 women requiring additional imaging no biopsy (no cancer) in 1000 women screened every 2-3 years over a 10-year period (50-59 years, started screening prior to age 50)
Additional imaging no biopsy (no cancer) over 10 years (60-69 years)‡	**224.4 per 1000**	⊕⊕⊕◯ MODERATE [a,b,c,d]	Screening probably leads to at least 150 women requiring additional imaging no biopsy (no cancer) in 1000 women screened every 2-3 years over a 10-year period (60-69 years)
Additional imaging no biopsy (no cancer) over 10 years (70+ years)‡	**190 per 1000**	⊕⊕⊕◯ MODERATE [a,b,c,d]	Screening probably leads to at least 150 women requiring additional imaging no biopsy (no cancer) in 1000 women screened every 2-3 years over a 10-year period (70+ years)

*GRADE ratings are not typically applied to the context of primary evidence sets generated by analyses of quality indicator surveillance data. However, our judgements of the overall certainty of evidence have been informed by similar considerations used in the GRADE process for effectiveness data.
†Scenario 1: Assuming started biennial screening in current age decade (calculated using one initial screen and three subsequent screens over a 10-year period).
‡Scenario 2: Assuming started biennial screening in prior age decade (calculated using four subsequent screens over a 10-year period).
**Data Sources: Using data from the 2011- 2012 CPAC report (33), we estimated the approximate rate of additional imaging with or without biopsy (no cancer) for women in each age decade over a 10 year-period (Table 7A).
Additional imaging estimates per screening cycle were calculated by subtracting cancer detection rates (invasive + DCIS) and the additional imaging and biopsy (no cancer) from the abnormal call rates, stratified by age decade and if data were related to an "initial" or "subsequent" screen. See supplemental KQ1 GRADE Material, Appendix 6, part E for an example calculation.
We assumed women received four screens over a 10-year period, if the majority of women would receive a screen every 2-3 years (approximating biennial screening for the majority, noting that NS, PEI, NWT and AB recommend annual screening in 40-49). Scenario 1 assumes women start screening in that age decade and receive four screens over 10 years (one initial and three subsequent) (age groups: 40-49 and 50-59†). Scenario 2 assumed women started screening in prior age decades and therefore received four subsequent screens over a 10-year period (age groups: 50-59‡, 60-69, 70+).

a. The CPAC quality indicator data was used from the Canadian Breast Cancer Screening Database (CBCSD), which contained relatively complete data from participating provinces and territories for the quality indicators of interest in 2011-2012.
b. Estimates were calculated using quality indicators from screen-level data. Thus, we have no measure of imprecision in the data. All point estimates cross the minimum threshold for important effect (threshold used was 150 women who do not have cancer and require additional imaging and no biopsy per 1000 screens).
c. There appears to be an increase in recall rates over time (see Supplemental KQ1 GRADE Material, Appendix 6) depending on the data source. However, our conclusions about the rates of additional imaging no biopsy (no cancer) are unlikely to change, as the rates remain relatively consistent using more recent CPAC data and provincial data and above our clinical decision threshold. We did not downrate for indirectness.
d. We uprated our overall conclusion to moderate certainty of evidence as imaging recall estimates are similar across different data sources and consistently cross our threshold for clinical decision making.

GRADE Summary of Findings Table – **Additional imaging with biopsy (no cancer)**

Outcomes	**Calculated Estimate (2011-2012 CPAC Data)** (33)	Quality of the evidence*	What happens
Additional imaging and biopsy (no cancer) over 10 years (40-49 years)†	**54.7 per 1000**	⊕⊕⊕◯ MODERATE [a,b,c,d]	Screening probably leads to at least 15 women requiring additional imaging and biopsy (no cancer) in 1000 women screened every 2-3 years over a 10-year period (40-49 years) (Moderate certainty) [a,b,c,d]
Additional imaging and biopsy (no cancer) over 10 years (50-59 years)†	**46.2 per 1000**	⊕⊕⊕◯ MODERATE [a,b,c,d]	Screening probably leads to at least 15 women requiring additional imaging and biopsy (no cancer) in 1000 women screened every 2-3 years over a 10-year period (50-59 years, started screening at age 50) (Moderate certainty) [a,b,c,d]
Additional imaging and biopsy (no cancer) over 10 years (50-59 years)‡	**34.0 per 1000**	⊕⊕⊕◯ MODERATE [a,b,c,d]	Screening probably leads to at least 15 women requiring additional imaging and biopsy (no cancer) in 1000 women screened every 2-3 years over a 10-year period (50-59 years, started screening prior to age 50) (Moderate certainty) [a,b,c,d]
Additional imaging and biopsy (no cancer) over 10 years (60-69 years)‡	**32.8 per 1000**	⊕⊕⊕◯ MODERATE [a,b,c,d]	Screening probably leads to at least 15 women requiring additional imaging and biopsy (no cancer) in 1000 women screened every 2-3 years over a 10-year period (60-69 years) (Moderate certainty) [a,b,c,d]

Additional imaging and biopsy (no cancer) over 10 years (70+ years)‡	**30.4 per 1000**	⊕⊕⊕◯ MODERATE [a,b,c,d]	Screening probably leads to at least 15 women requiring additional imaging and biopsy (no cancer) in 1000 women screened every 2-3 years over a 10-year period (70+ years) [a,b,c,d]

*GRADE ratings are not typically applied to the context of primary evidence sets generated by analyses of quality indicator surveillance data. However, our judgements of the overall certainty of evidence have been informed by similar considerations used in the GRADE process for effectiveness data.
†Scenario 1: Assuming started biennial screening in current age decade (calculated using one initial screen and three subsequent screens over a 10-year period).
‡Scenario 2: Assuming started biennial screening in prior age decade (calculated using four subsequent screens over a 10-year period).
**Data Sources: Using data from the 2011- 2012 CPAC report (33), we estimated the approximate rate of additional imaging with or without biopsy (no cancer) for women in each age decade over a 10 year-period (Table 7A).
Additional imaging estimates per screening cycle were calculated based on reported non-malignant biopsy rates, stratified by age decade and if data were related to an "initial" or "subsequent" screen. See supplemental KQ1 GRADE Material, Appendix 6, part E for an example calculation.
We assumed women received four screens over a 10-year period, if the majority of women would receive a screen every 2-3 years (approximating biennial screening for the majority, noting that NS, PEI, NWT and AB recommend annual screening in 40-49). Scenario 1 assumes women start screening in that age decade and receive four screens over 10 years (one initial and three subsequent) (age groups: 40-49 and 50-59†). Scenario 2 assumed women started screening in prior age decades and therefore received four subsequent screens over a 10-year period (age groups: 50-59‡, 60-69, 70+).

a. The CPAC quality indicator data was used from the Canadian Breast Cancer Screening Database (CBCSD), which contained relatively complete data from participating provinces and territories for the quality indicators of interest in 2011-2012. The BC estimates were estimated using breast screening program outcome indicators by 10-year age groups for 2019, which should contain complete data. We did not downrate for risk of bias.
b. Estimates were calculated using quality indicators from screen-level data. Thus, we have no measure of imprecision in the data. All point estimates cross the minimum threshold for important effect (15 women requiring additional imaging and biopsy per 1000 screens).
c. The rates of additional imaging and biopsies (no cancer) appear to have remained consistent over time based on provincial data sources (Appendix 6, part B). We did not downrate for indirectness.
d. We uprated our overall conclusion to moderate certainty of evidence as imaging recall estimates are similar across different data sources and consistently cross our threshold for clinical decision making.

KQ2: Age to Stop Screening
FULL EVIDENCE TABLE

GRADE Summary of Finding Table - **Age to stop screening**

Outcome	No. and design (study period and size) of included studies Study quality	Findings	GRADE certainty	What happens?
Overdiagnosis	1 NRSI (64) (US Medicare; 1999-2008; n = 1,058,013), Fair quality	More cancers diagnosed in continue screening strategy: adjusted 8-year cumulative risk of breast cancer diagnosis 70-74: 5.3% versus 3.9% (95% CI NR) 75-85: 5.8% versus 3.9% (95% CI NR)	**Very low** ⊕⊖⊖⊖ due to ROB and imprecision Some but not serious indirectness: high probability of living ≥10 more years; only 8-years follow-up	We are very uncertain about the effects on overdiagnosis from continuing screening beyond 70 years.
No data: False-positive rate requiring imaging only or imaging plus biopsy (cumulative over multiple rounds), False-positive rate requiring imaging plus biopsy (cumulative over multiple rounds), Interval cancers				

KQ2 – Comparison of Screening interval

FULL EVIDENCE TABLES

GRADE Summary of Findings Table - **Annual vs biennial screening**

Outcome	No. and design USPSTF study quality	Findings	GRADE	What happens? Based on USPSTF thresholds
Additional testing +/- biopsy (no cancer) (cumulative over multiple rounds)	2 NRSI N=905,514 (US BCSC (109); n = 903,495; 2005-2018 and US academic centre (110) n = 2,019; 2014-2015) Fair quality	BCSC: calculated estimated cumulative 10-years for DBT/sDM or DM screening approximately 50% of those undergoing annual screening had at least one additional testing +/- biopsy (no cancer), compared with approximately 35% of those undergoing biennial screening (*not including prevalence screens; similar rates for DBT and DM)*. ~140-180 more per 1000 Subgroups: Age: Annual screening was associated with higher cumulative additional testing +/- biopsy (no cancer) for all age groups (i.e., DM: 40-49 19.4%, 50-59 20.0%, 60-69 18.6%, 70-79 17.3% more; DBT: 40-49 14.6%, 50-59 16.3%, 60-69 14.7%, 70-79 11.2% more) Density: Annual screening was associated with higher cumulative additional testing +/- biopsy (no cancer) recalls across density groups (less so with BI-RADS A) One NRSI from a US academic centre reported higher odds (OR 2.2, 95% CI 1.7 to 2.8) of an additional testing +/- biopsy (no cancer) result over a median of 8.9 years.	**Moderate** ⊕⊕⊕⊖ Some but not serious indirectness: US data but relative effects should be similar in Canada; no prevalent screen data included (so would underestimate this); data for DM still applies	**Annual versus biennial screening with DM or DBT probably leads to more (possibly 1.5-fold) additional testing +/- biopsy (no cancer) across all age groups.**
Additional testing (no cancer) findings at biopsy	1 NRSI (109) (BCSC US; 2005-2018; n=903,495) Fair quality	BCSC data calculated estimated cumulative 10-years for DBT/sDM or DM screening annual screening resulted in ~50 additional testing with biopsy (no cancer) per 1,000 screened over 10 years (annual ~115 per 1,000 versus biennial ~66 per 1,000). (*not including prevalence screens; similar rates for DBT and DM*)	**Moderate** ⊕⊕⊕⊖ Some indirectness: US data but relative effects should be similar in Canada; no prevalent screen data	**Annual versus biennial screening with DM or DBT probably leads to more (possibly 1.5 to 2.0-fold) additional testing with biopsy**

		Subgroups: Age: Annual screening was associated with higher cumulative additional testing with biopsy (no cancer)for all age groups (i.e., DM 40-49 5.2%, 50-59 5.6%, 60-69 5.2%, 70-79 4.1% more; DBT: 40-49 4.8%, 50-59 5.0%, 60-69 4.7%, 70-79 4.0% more) Density: Annual screening was associated with higher cumulative additional testing with biopsy (no cancer) across density groups (less so with BI-RADS A)	included (so would underestimate this); data for DM still applies	**(no cancer) across all age groups.**
Interval cancers	1 NRSI (89) (BCSC US; 1996-2012; n=15,440) Fair quality	Unadjusted percent with interval cancer for people screened negative after an annual (22.2%; followed for 12 mos) or biennial screening (27.2%; followed for 24 mos) interval.	**Very low** ⨁⊖⊖⊖ due to ROB, indirectness, imprecision Indirectness: comparison (case-only analysis)	We are very uncertain about the effects on interval cancers from annual versus biennial screening.
No data: Overdiagnosis				

NRSI=non-randomized study of intervention

Annual versus Triennial screening

Outcome	No. and design USPSTF study quality	Findings	GRADE	What happens?
Interval cancers	1 RCT (91) (UK: 1989-1996; n=76,022) Fair quality 1 NRSI (90) (Finland; 1985-1995; n=14,765) Fair quality	RCT (50-62 years) estimated 1 fewer invasive interval cancers in the annual screening arm (1.8 versus 2.7 per 1,000 screened; RR: 0.68 [95% CI 0.50 to 0.92]). NRSI (40-49 years) found no difference in interval cancer incidence (p = 0.22).	**Low** ⨁⨁⊖⊖ due to ROB and inconsistency Some but not serious indirectness; 3 years in RCT; added applicability into conclusions	**Annual versus triennial screening may slightly reduce the number of invasive interval cancers for 50 to 69-year-olds over 3 years.**
Overdiagnosis (data not used in review)	1 NRSI (90) (Finland; 1985-1995; n=14,765) Fair quality	NRSI (40-49 years): breast cancer incidence over mean 9.8 years was similar for those invited to annual screening (141.1 per 100,000 person-years) and those invited to triennial screening (144.0 per 100,000 person-years) (RR: 0.98 [95% CI 0.75 to 1.29)	**Very low** ⨁⊖⊖⊖ due to ROB (and single study) No serious indirectness when applying to 40-49 years	We are very uncertain about the effects of annual versus triennial screening for overdiagnosis in 40 to 49-year-olds.
No data Additional testing +/- biopsy (no cancer) rate (cumulative over multiple rounds), Additional testing rate +/- biopsy (cumulative over multiple rounds)				

NRSI=non-randomized study of intervention

Digital breast tomosynthesis versus digital mammography

Outcome	No. and design USPSTF study quality	Findings	GRADE	What happens? Based on USPSTF thresholds
Additional testing +/- biopsy (no cancer) findings at screening	3 RCTs with 2 rounds N=129,492 2 Good quality (i) RETomo (92) Italy [2014-2017]; n=26,877; 45-69 years [9% BI-RADs 4]; DBT/DM versus DM but DM at 2nd round both groups 1 [45-49 years; 38%] or 2 [50-69] years later) (ii) To-BE (93) Norway [2016-2020]; n=28,749; 50-69 years [7% BI-RADs 4]; DBT/sDM versus DM but DBT/sDM at 2nd round for both groups 2 years later or next screening round) 1 Fair quality (Proteus Donna (94); Italy [2004-2017]; n=73,866; 46-68 years [density NR]; DBT/DM versus DM but DM in 2nd round both groups [1 year 46-49 or 2 years 50-68]) 2 NRSIs	Three RCTs and one NRSI reported additional testing +/- biopsy (no cancer) rates at two rounds of screening, and results were mixed. In round 1 the RCTs had mixed findings (rates approx. 3-5%; Proteus Donna RR 1.22 versus To-Be RR 0.72) and in round 2 were consistent for no difference (but using same device). One NRSI calculated (using probabilities from mean 3.3 rounds) the estimated (via discrete-time survival modeling to account for censoring) cumulative probability of at least one additional testing +/- biopsy (no cancer) recall over 10 years of screening and suggested slightly lower additional testing +/- biopsy (no cancer) recall with DBT with annual interval (50% versus 56%) and similar rates with biennial screening (36% versus 38%). Subgroups: Age: RETomo, stratified by ages 45-49 and 50-69 with no significant differences at either round for either group Density: To-Be stratified by density suggested lower additional testing +/- biopsy (no cancer) at round 1 for 1/2 (RR: 0.58 [0.43 to 0.80] and 0.66 [0.54 to 0.81]) but not for 3/4; at round 2 no significant difference for any group BCSC data, in stratified analyses there was not a statistical difference in cumulative additional testing +/- biopsy (no cancer) among those with extremely dense breasts in any age group	**Low** ⨁⨁⊖⊖ due to ROB and inconsistency Not serious indirectness: only 2 rounds in RCTs, round 2 in RCTs used similar device between groups (used for ROB); US data for multiple rounds but relative effects should be similar in Canada	**DBT versus digital mammography may reduce additional testing +/- biopsy (no cancer).** **Note: This did not reach the Task Force threshold of 150/1000)**

	Norway (95); n=98,927; see above) BCSC US (109) [2005-2018]; n=903,495 Fair quality			
additional testing (no cancer) findings at biopsy	1 RCT (see above) To-Be (93) Good quality 1 NRSI BCSC US (109) (903,495) 40-79 Fair quality	One trial reported no significant difference in additional testing with biopsy (no cancer) (round 1: RR: 0.85 (95% CI, 0.69 to 1.05); round 2: RR: 0.99 (95% CI: 0.80 to 1.24). One NRSI calculated (using probabilities from mean 3.3 rounds) the estimated cumulative probability of at least one additional testing (no cancer) at biopsy over 10 years of screening and suggested no difference in cumulative additional testing with biopsy (no cancer) for DBT versus DM regardless of screening interval (11-12% annual, 7% biennial). Subgroups: Density: To-Be stratified analysis by density, at round 1 significantly fewer biopsies with DBT in groups 1 (RR 0.57 [0.33 to 1.00] and 2 (RR 0.64 [0.46 to 0.89]), with higher from DBT for groups 3 RR 1.79 [1.23 to 2.61] and 4 RR 1.12 (p<<0.05). No significant differences at round 2 (using DM) BCSC data, in stratified analyses there was not a statistical difference in cumulative additional testing with biopsy (no cancer)among those with extremely dense breasts in any age group	**Low** ⨁⨁⊖⊖ due to ROB and imprecision Not serious indirectness: only 2 rounds in RCTs, round 2 in RCTs used similar device between groups (used for ROB); US data for multiple rounds but relative effects should be similar in Canada	**DBT versus digital mammography may make little-to-no difference for additional testing with biopsy (no cancer) over multiple rounds.**
Interval cancers	3 RCTs Good quality: RETomo (92), To-Be (93) Fair quality: Proteus Donna (94) (12-month follow-up for those ages 45 to 49 years and 24-month follow-up for those ages 50 to 69 years) 5 NRSIs Fair quality 1 DBT versus DM (BCSC US (111) [2011-2018]; n=504,427; 40-79 years) 4 DBT/DM versus DM (2 US (112,113) [2015-2017 & 2011-2015], Norway (95) [2014-2017], Sweden (114) [2010-2015]) N=4,816,610	Three RCTs did not find difference in interval (invasive) cancer rates (pooled RR = 0.87, 95% CI 0.64 to 1.17, k = 3 RCT, n = 130,196, I^2 = 0%). (**Figure 10**) Five NRSI had inconsistent results - three did not find differences, one commercial claims registry study (US; n=4,580,698) reported more interval (invasive) cancers with DBT (adj difference: 0.07 per 1000 screens, 99% CI 0.01 to 0.12), and one (Sweden; n=40,107) comparing trial participants to an age-matched population reported fewer interval (invasive) cancers with DBT (1.4 versus 2.7 per 1,000, RR 0.53, 95% CI 0.32 to 0.87). (all differences small). There were no significant differences when studies (3 RCTs and 2 NRSIs) examined only DCIS (RCT RRs ~1.0). Subgroups: Age: RETomo and two NRSI reported no significant findings related to the relationship between age and interval cancer outcomes. Density: RETomo and To-Be, and one analysis of BCSC data, found no statistically significant differences in the incidence of interval cancer for the breast density stratified comparisons.	**Moderate** ⨁⨁⨁⊖ due to imprecision Some but not serious indirectness: studies differed in the timeline of follow up and method of identifying interval cancers; in RCTs data from round 1 only but NRSI had multiple rounds	**DBT versus digital mammography probably makes little-to-no difference for interval cancers over multiple rounds.**
No data: Overdiagnosis (only reported on DCIS at round 1 in 3 RCTs (did not find differences in DCIS, screen-detected lesions that could contribute to over- detection, at round 1 (pooled RR 1.33, 95% CI 0.92 to 1.93, k = 3 RCT, n = 130,196, I2 = 0%) or round 2 (pooled RR 0.75, 95% CI 0.49 to 1.14, k = 3 RCT, n = 130,196, I2 =0%).				

NRSI=non-randomized study of intervention

Supplementation with ultrasound

Outcome	No. and design USPSTF study quality	Findings	GRADE	What happens?
Additional testing with biopsy (no cancer) findings at biopsy	1 NRSI (BSSC US (115) [2000-2013]; n=18,562; 30-80+ years; 65% BI-RADS 3/4 NR; 35% "intermediate risk") Fair quality	NRSI: RR=2.23 (95% CI, 1.93 to 2.58)	**Low** ⨁⨁⊖⊖ for ROB Indirectness: One round only and elevated risk population but noted in conclusions	**Supplementing digital mammography with ultrasound may increase additional testing with biopsy (no cancer) (possibly 2-fold) at the first round among a population with elevated risk**
Interval cancers	1 RCT (J-START (116) Japan [2007-2011]; n=72,717; **40-49 years**; 58% dense breasts; DM/US versus DM for 2 rounds [only 1 round reported]) Fair quality and 1 NRSI (115)	RCT (invasive): 0.4 (DM/US) versus 0.8 (DM) per 1,000 screened; RR 0.58, 95% CI 0.31 to 1.08 NRSI (invasive and DCIS): 1.5 (DM/US) versus 1.9 (DM) per 1,000 screened; aRR 0.67, 95% CI 0.33 to 1.37 Subgroups: Density: J-START stratified analysis, similar RRs and no statistically significant difference for either group (A/B versus C/D)	**Low** ⨁⨁⊖⊖ due to ROB and imprecision Indirectness: One round only and elevated risk population but noted in conclusions	Supplementing digital mammography with ultrasound may not reduce interval cancers at the first round among a population with elevated risk

CERTAINTY OF EVIDENCE

Supplementation with MRI

Outcome	No. and design USPSTF study quality	Findings	GRADE	What happens?
Interval cancers	1 RCT (117) (DENSE The Netherlands [2011-2016]; n=40,373; 50-75; 100% extremely dense breasts (Volpara category D); invitation versus not to MRI after a negative screening mammogram result among biennial screening program) (2 of 3 rounds reported but only 1st reports comparative data) Good quality	Reduced invasive interval cancer (follow-up 2 years) with invitation to screening for those with extremely dense breasts and negative mammogram (2.2 versus 4.7 per 1,000 invited to screening, RR 0.47, 95% CI 0.29 to 0.77). Any interval cancer 2.5 versus 5.0 per 1000; RD -2.5 (95% CI, 1.0 to 3.7) Among the 20 interval cancers in MRI group, 4 were among those who had received MRI (59%). Ages 50-75 No subgroup analyses.	Low ⨁⨁⊖⊖ (single study and limitations from poor adherence 59%) Indirectness: specific population and 1 round only but added to conclusions	**Supplementing digital mammography with MRI may reduce interval cancers at the first round for individuals with extremely dense breasts** **Note: This did not reach the Task Force threshold of 6/1000)**
No data: Overdiagnosis, Additional testing (no cancer) only reported for MRI group (no comparator)				

What is the overall certainty of the evidence of effects?

X Very low
○ Low
○ Moderate
○ High

○ No included studies

KQ1: For cisgendered women, transgender men and nonbinary and others assigned female at birth ≥ 40 years of age and at average or above average risk, what are the benefits and harms of different mammography-based screening strategies as compared to no screening?

Very low certainty

KQ1i: Do the benefits and harms differ by population characteristics (e.g., age, breast density, race and ethnicity, socioeconomic status, geographical area, family history)?

Very low certainty

KQ2: What is the comparative effectiveness of different mammography-based breast cancer screening strategies on benefits and harms?

Age to stop: Very low certainty evidence
Screening interval:
- Annual vs biennial: Very low certainty (all ages)
- Triennial vs annual: Very low certainty (all ages)

Screening modality:
- DBT vs DM: Very low certainty (all ages) – missing critical outcomes

KQ2i: Does comparative effectiveness differ by population characteristics and risk markers (e.g., age, breast density, race and ethnicity, socioeconomic status, geographical area, family history)?

Breast density:
- Annual vs biennial: Very low certainty (missing critical outcomes)
- DBT vs DM: Very low certainty (missing critical outcomes)
- Supplementation with Ultrasound: Very low certainty (missing critical outcomes)
- Supplementation with MRI: Very low certainty (missing critical outcomes)

Race and ethnicity: No SR data
Moderately increased risk: Very low certainty (missing critical outcomes)

SUMMARY JUDGEMENT – CERTAINTY
Overall the certainty of the evidence was very low for all outcomes due to down-rating of evidence or missing critical outcomes

VALUES

Is there important uncertainty about or variability in how much people value the main outcomes?

Variability: 40-75+ (general population or moderately increased risk)

○ Important variability
X Possibly important variability
○ Probably no important variability
○ No important variability

○ Varies
○ Don't know

Uncertainty of variability: 40-75+ (general population or moderately increased risk)

○ Important uncertainty
X Possibly important uncertainty
○ Probably no important uncertainty
○ No important uncertainty

○ Varies
○ Don't know

KQ3: What is the relative importance placed on the potential benefits and harms of mammography-based breast cancer screening?

SUMMARY JUDGEMENT – VALUES AND PREFERENCES

- HSUV data showed significant disutility from a positive screening mammography, additional testing +/- biopsy (no cancer), cancer diagnosis (across all stages) and interval cancer
- We are very uncertain about the disutility from mastectomy without adjuvant treatment vs. BCS/partial mastectomy with radiation (low to moderate certainty)
- Limited disutility from mastectomy vs partial mastectomy (all receiving adjuvant treatments), chemotherapy vs no chemotherapy (among a mixed surgical population) and Stage III vs stage I-II (low certainty)
- No significant disutility from radiation vs no radiation and Stage II-III vs Stage I (low certainty)
- High net benefit scenario: Majority weigh the benefits as greater than the harms (low to moderate certainty)
- Moderate net benefit scenario: Majority and possibly a large majority may weigh the benefits as greater than the harms for 50-59 and 70-71 year olds whereas a majority but possibly not a large majority for 75+ (low to moderate certainty)
- Low net benefit scenario: Majority may not weigh the benefits as greater than the harms (40-49), but a large majority of 50 to 59 year-olds may weigh the benefits as greater than the harms (low certainty)
- Trade-off studies: For those ≥ 40 years, at least a majority (>50%) and possibly a large majority (>75%) probably accept up to 6 cases of overdiagnoses to prevent 1 death from breast cancer (moderate certainty). Among 50 to 69 year-olds, a large majority may think that reducing breast-cancer mortality is beneficial even if there is no impact on all-cause mortality (low certainty). For patients ≥ 40 years, a majority may accept a few hundred among 1000 people experience additional testing to prevent one death from breast cancer over 10 years (low certainty). For patients ≥ 40 years, a large majority may accept that at least 25 people experience an additional testing to prevent one advanced stage breast cancer (low certainty).

- The 'low-moderate net benefit' scenario was deemed most reflective of what was found in the systematic review (e.g., 0.5-2 deaths prevented, 160-300 additional tests (no cancer), 2-20 overdiagnoses)
- Based on the results of the systematic review (see above), there was limited variability in patient values and preferences. However, the WG also considered the HSUV and feedback from the patient partners and clinical experts (see right column). Therefore, the overall for ≥40 there was possibly important variability in patient values and preferences
- The uncertainty about the above variability was possibly important for due to the lack of studies in diverse populations or within Canada
- The uncertainty for the variability in ages ≥40 also varied depending on whether the individual had previously screened. There were also similar concerns about the lack of studies in diverse populations within Canada.

All ages

Health-state (Ages 40-79)	Disutility*	Certainty
Positive screening mammography	0.07	Moderate
Cancer diagnosis (across all stages)	0.08	Moderate
Additional imaging+/-biopsy (no cancer)	0.03-0.04	Low
Radiation vs no radiation	0.01-0.02	Low
Mastectomy vs partial mastectomy (all Receiving adjuvant treatments)	0.02-0.03	Low
Chemotherapy vs no chemotherapy (among a mixed surgical population)	0.02-0.04	Low
Stage III vs stage I-II	0.03	Low
Stage II-III vs stage I	0.02	Low
Interval cancer (50-79)	0.08	Low

Health state utility values: Calculates the 'Disutility' caused by different health states. For example if 'perfect health' is 1 and having a biopsy is 0.85 then the disutility caused by the biopsy is 0.15 (1 - 0.85). A disutility ≥ 0.037 is considered important.
*Disutility was measured using a generic health-related quality of life scale; it may not account for all aspects of disutility caused by cancer specific health states.

	CTFPHC threshold	Threshold / life saved	To prevent 1 advanced stage breast cancer
Overdiagnosis	5/ 1000	**Age 40+:** Large majority accept up to 6 cases of overdiagnosis per life saved *(moderate certainty)* **Age 50+:** Large majority may accept at least 3 cases of overdiagnosis per life saved *(low certainty)*	

Feedback from patient partners and clinical experts

- Lack of diversity in patient values and preferences study populations
- Lack of studies in Canadian populations
- Personal and professional experience of a larger variation in patient values and preferences.
- Importance of being informed of benefits and harms
- Patients: Importance of finding cancer early (vs lower importance of additional testing or overdiagnosis)
- Importance of considering the individuals choice and own values and preferences
- False positives = changed to additional testing (no cancer)
-Variation in patient values and preferences due to multiple factors (race, ethnicity, family history, breast density), not a 'one-size fits all' situation
- Importance of life years gained or life expectancy (e.g., extending to 40-49 vs 75+).
-Importance of considering the impact of a cancer diagnosis on younger individuals (e.g., young families, loss of income, etc.)
- Considerations of other comorbidities among those 75+ (varies by individual)
- Lack of clarity for physicians on current guideline (i.e., individuals 40-49 being refused mammography); also some radiology departments decline referrals for screening in this age group.

Screening participation rates (ages 50-69) may show variability in preferences to screen (i.e., 54% participation rate (range 31.8% to 62.3%) in 2011-2012), however, access to screening (rural/remote, equity) also affects uptake (33).

In 2017, 78.5% of Canadian females aged 50 to 74 years self-reported receiving a mammogram (screening or diagnostic) in the past three years (34).

Further explanation of differing HSUVs

Mastectomy vs partial mastectomy

Some individuals may receive a potential "false sense of security" believing that having mastectomy (or bilateral mastectomy) will mean that "cancer can't come back."

Chemo vs no chemo

Chemo lasts a short time (but can still have late/long-term effects); endocrine therapy can last 5-10 years and can cause persistent side effects that can be quite problematic/ upsetting for individuals even if they do not receive chemotherapy. Sometimes

Additional imaging +/- biopsy (no cancer)	150/1000	**Age 40+:** Majority may accept "A few hundred" / 1000 additional tests (no cancer) per life saved *(low certainty)*	**Age 40+:** Large majority may accept at least 25 additional tests (no cancer) to prevent 1 advanced stage cancer *(low certainty)*
Additional imaging + biopsy (no cancer)	15/1000	**Age 40+:** A large majority may accept 10-15 additional imaging + biopsy tests per life saved *(low certainty)*	**Age 40+:** Large majority may accept at least 4 additional imaging + biopsy *tests to prevent 1 advanced stage cancer (low certainty)*
All-cause mortality	1/1000	**Age 50-69:** >75% of patients may think that reducing breast-cancer mortality by 2-5 fewer/1000 is beneficial even if there is no impact on all-cause mortality.	

40-49

Low net-benefit scenario	• Majority may not weigh the benefits as greater than the harms from screening (low certainty)
Moderate net-benefit scenario	• Information on overdiagnosis may be quite important for many individuals (low certainty)
High net-benefit scenario	• Majority may weigh the benefits as greater than the harms from screening (low certainty). • Accept 100-300 additional imaging+/- biopsy (no cancer) per life saved over 10 years (low certainty) (TF threshold of 150 / 1000 screens)

Individuals aged 40-49 were provided with difference 'scenarios'* (i.e., net benefits and harms) for breast cancer screening and asked how they would weigh the benefits and harms.
*Using the results from KQ1 (i.e., 0.27-0.94 fewer breast cancer deaths / 1000 and 367-477 additional tests) the most applicable 'scenario' would be the low to moderate net benefit scenario that was provided to individuals (i.e., 0.5-2/1000 fewer deaths and up to 300 additional tests)
Note: These studies were performed in Australia and New Zealand in mostly white populations

50-59

Low net-benefit scenario	• 50-59: Large majority of 50 to 59-year-old patients may weigh the benefits as greater than the harms (low certainty)
Moderate net-benefit scenario	• 50-59: Majority and possibly a large majority of patients probably weigh the benefits as greater than the harms (moderate certainty)
High net-benefit scenario	• 50-59 and 50-69: Large majority probably weigh the benefits as greater than the harms (moderate certainty) • 50-59: A rate of 80-120 /1000 additional tests (no cancer) were important to decision making *(low certainty)* • 50-69: >75% may think that reducing breast-cancer mortality is beneficial even if there is no impact on all-cause mortality reductions *(low certainty)*

60-69

High net-benefit scenario	• 50-69: Large majority probably weigh the benefits as greater than the harms (moderate certainty) • 50-69: >75% may think that reducing breast-cancer mortality is beneficial even if there is no impact on all-cause mortality reductions (low certainty)

70-74

Moderate to low net-benefit scenario	• 70-71: A large majority of patients who have recently screened probably think the benefits outweigh the harms (moderate certainty)

75+

Moderate to low net-benefit scenario	• 75+: a majority but possibly not a large majority may weigh the benefits as greater than the harms for continuing to screen (low certainty)

FULL EVIDENCE TABLES

Health-state utility values (HSUV):

Number of included studies; Sample size	Findings	GRADE[1]	What does the evidence say?
Disutility of positive screening mammography (before diagnostic testing)			
N=3 studies (36,118,119) N=565 participants	**Pooled utilities (95% CI):** 0.87 [0.86, 0.89] **Disutility from healthy comparator (95% CI):** 0.94 [0.93, 0.94] – 0.87 [0.86, 0.89] = 0.07 [0.05, 0.09]	⨁⨁⨁⨀ MODERATE [a,b] (some inconsistency and some risk of bias)	**The disutility value for a positive screening mammography is probably 0.07.**
Disutility after biopsy (diagnostic results not known)			
N=1 study (118) N=102 participants	**Pooled utilities (95% CI):** 0.79 [0.75, 0.83] **Disutility from healthy comparator (95% CI):** 0.94 [0.93, 0.94] – 0.79 [0.75, 0.83] = 0.15 [0.11, 0.19]	⨁⨀⨀⨀ VERY LOW [a,b,d] (single study-lack of consistency, risk of bias, and imprecision)	We are very uncertain about the disutility of receiving a biopsy, before the results are known
Disutility of knowledge of additional testing +/- biopsy (no cancer)			
N=2 studies (36,119) N=696 participants	**Pooled utilities (95% CI):** 0.90 [0.89, 0.91]	⨁⨁⨀⨀ LOW [a,c] (risk of bias, indirectness for concerns about applicability to	**The disutility value for additional testing +/- biopsy (no cancer) may be 0.03 to 0.04.**

individuals with higher risk disease where the decision to take chemo is more clear because the benefits are much larger experience less anxiety/disutility.

<u>WG feedback on variability in patient values and preferences</u>

- How individual perceive a small number (i.e., not important vs extremely important) is variable.
- When providing benefits and harms, important elements to take into account is each individuals' personal experience (e.g., have a friend or family member with breast cancer, social media). The decision whether to screen or not can be an emotional one. The differences in how people value the benefits vs harms is not always influenced by statistical data, but it's a good tool for discussion.
- For those over 70 years old, they are either motivated by a lifetime of screening to continue or not; they are very unlikely to start now. Those in relatively good health are likely to see more benefits than harms but that can change if the patient has underlying health issues and the harms can impact independence or mobility.
- Despite large ranges in preferences/values, there is prospective RCT level data that when women are informed about the potential harms of screening, and particularly about over-diagnosis, fewer women want to proceed with screening
- There is incomplete information about harms for 75+
- For those with moderately increased risk, the range of importance likely increases if the individual has had experience in the family. Those with dense breast are more likely to go for screening when they are aware of breast density as a risk factor.
- Studies on racial and ethnic differences are limited, many of which we don't have data on values and preferences. There are also differences across ages groups. It is unclear if these differences are generalizable to a heterogeneous population.
- A one size approach counters the observed variability in values in preferences.

<u>WG feedback on uncertainty</u>

- Studies are challenging to interpret a lack of diverse populations or Canadian data.
- Clinicians are aware of the very large range of preferences as seen in the clinics, you can never assume how an individual person will judge the importance of something.
- Given the responses received (i.e., public, patient partners, clinical experts), it is not uncertain that there is variability in values and preference and a subsequent

	Disutility from healthy comparator (95% CI): 0.94 [0.93, 0.94] - 0.90 [0.89, 0.91] = 0.04 [0.03, 0.05]	duration follow-up, disutility might be slightly overestimated)	
Disutility of additional testing with biopsy (no cancer)			
N=1 study (118) N=78 participants	**Pooled utilities (95% CI):** 0.77 [0.72, 0.82] **Disutility from healthy comparator (95% CI):** 0.94 [0.93, 0.94] – 0.77 [0.72, 0.82] = 0.17 [0.12, 0.22]	⊕⊖⊖⊖ VERY LOW [a,b,d] (risk of bias, lack of consistency, imprecision)	We are very uncertain about the disutility of additional testing with biopsy (no cancer) result after invasive testing, with results unknown
True positive result, before treatment			
N=9 studies (120–128) N=6,657 participants	**Pooled utilities (95% CI):** 0.86 [0.85, 0.86] **Disutility from healthy comparator (95% CI):** 0.94 [0.93, 0.94] – 0.86 [0.85, 0.86] = 0.08 [0.07, 0.09]	⊕⊕⊕⊖ MODERATE [b,c] (some concerns about inconsistency across studies and some indirectness based on within study age group data indicating differences across age, and no studies specific to screen-detected cancers [but few stage IV])	**The disutility of a screen-detected cancer is probably 0.08,** but may be higher for older ages and advanced stage operable cancer
Interval cancer			
N=1 study (using VAS) (129) N=131 participants	Screen-detected 45.7 (20.5) vs. Interval 48.5 (20.7).	⊕⊕⊖⊖ LOW [a,b,d] (some concerns about risk of bias, some concerns about inconsistency, and indirectness)	The disutility for interval cancer may be similar to a screen-detected cancer

*Reasons for rating down certainty: a=risk of bias, b=inconsistency/lack of consistency, c=indirectness, d=imprecision

HSUVs, treatment health states: T1<12 months from surgery

Number of included studies; Sample size	Findings	GRADE†	GRADE overall	What does the evidence say?
Disutility of mastectomy vs. BCS/partial mastectomy				
Within study: N=3 studies (125,130,131) N=1,546 participants	**Disutility, within study (95% CI):** 0.03 [0.02, 0.05]	⊕⊕⊖⊖ Low [a,b] (risk of bias, inconsistency)	⊕⊕⊖⊖ Low [a,b] (ROB and inconsistency between types of adjuvant therapy received as well as indication from direct measurements that disutility may be higher)	**The disutility of a mastectomy versus a BCS/partial mastectomy (all patients receiving adjuvant treatments) may be at least 0.02 to 0.03.**
Between study: BCS, N=5 studies (125,130–133) N=1,682 participants Mastectomy, N=7 studies (125,127,130,131,134–136) N=1,942	**Pooled BCS utilities (95% CI):** 0.82 [0.81, 0.83] **Pooled mastectomy utilities (95% CI):** 0.80 [0.79, 0.80] **Disutility, between study (95% CI):** 0.02 [0.01, 0.03]	⊕⊕⊖⊖ Low [a,b] (inconsistency and risk of bias)		We are very uncertain about the disutility from mastectomy without adjuvant treatment vs. BCS/partial mastectomy with radiation.
Disutility of adjuvant chemotherapy vs. none				
Within study: N=2 studies (126,137) N=1,011 participants	**No meta-analysis** **Ring 2021, n=780 (95% CI):** -0.01 [-0.04, 0.02] **Hall 2015, n=231 (95% CI):** 0.76 [0.73, 0.79] - 0.75 [0.71, 0.79] = 0.01	⊕⊕⊖⊖ Low [a,d] (risk of bias and imprecision) For little-to no difference in utility	⊕⊕⊖⊖ Low [b,c] (inconsistency, indirectness)	**The disutility of adjuvant chemotherapy may be 0.02-0.04 among a mixed surgical population.** **For disutility of 0.02 from chemotherapy in a mixed surgical population. Subgroup findings indicated slightly more disutility with advanced stages**
Between study: Adjuvant chemo: N=7 studies (126,127,131,137–140) N=1,234 participants (1 study N=NR by arm, N=231 overall) No Adjuvant chemotherapy N=5 studies (124–126,137,141) N=2,447 participants (1 study N=NR by arm, N=231 overall)	**Pooled adjuvant chemotherapy utilities** (95% CI): 0.85 [0.84, 0.85] **Pooled no adjuvant chemotherapy utilities (95% CI):** 0.84 [0.83, 0.84] without high ROB studies: 0.87 [0.86, 0.88] **Disutility, removing serious ROB studies (95% CI):** 0.02 [0.01, 0.03]	⊕⊕⊖⊖ Low [b,c] (inconsistency [unexplained by subgroups], indirectness [comparisons]) For disutility of 0.02 from chemotherapy in a mixed surgical population. Subgroup findings indicated slightly more disutility when removing effects from radiation.		
Disutility of adjuvant radiation vs. none				
Within study: N=4 studies (130,133,136,137) N=1,587 participants	**Disutility, within study (95% CI):** 0.01 [-0.01, 0.02] removing high ROB -0.01 [-0.02, 0.01]	⊕⊕⊕⊖ Moderate [b] (inconsistency) For little-to no difference in utility	⊕⊕⊕⊖ Moderate [b] (inconsistency)	**There is probably little to no disutility from adjuvant radiation among those receiving BCS/partial mastectomy or mastectomy, where many are receiving chemotherapy**
Between study: Adjuvant radiation: N=8 studies (125,127,130–133,136,137)	**Pooled adjuvant radiation utilities (95% CI):** 0.83 [0.82, 0.83]. Removing serious ROB studies: 0.83 [0.82, 0.83]	⊕⊕⊖⊖ Low [b] (very serious inconsistency unexplained by type of surgery		

informed decision to be screened.
- For those over 70+, it would be very hard to motivate them to start screening based on the evidence, but it would be difficult to discourage individuals who have been screening for the past essentially 20 years.
- There is incomplete information about harms for those over 75 years old and they have a very diverse population at that age in terms of health and values.
- It is not uncertain that people want screening strategies to prevent breast cancer mortality especially for those at increased risk; it is also not uncertain that there is variability in the decision to be screened when fully informed (using a small net benefit scenario).
- The systematic review cannot accurately capture the range of feelings of importance (i.e., we are not able to know for those who feel that this is extremely important, how well informed they are).
- There was also no Canadian or ethnicity-specific data, so the results may not be representative to the general Canadian population.

N= 2,174 participants (1 study N=NR by arm, N=231 overall) No adjuvant radiation: N=8 studies (125,130,133,134,136–138,140) N=1,547 participants Direct methods: N=3 studies; N=449	**Pooled no adjuvant radiation utilities (95% CI):** 0.81 [0.80, 0.82] removing serious ROB studies: 0.81 [0.80, 0.82] **Disutility, between study (95% CI):** -0.02 [-0.03, -0.01]	and chemotherapy)		
Disutility of ALND vs. SLND				
Within study: No evidence Between study: N=1 study (131) N=364 participants	**Pooled ALND utilities (95% CI):** 0.85 [0.84, 0.86] **Pooled SLNB utilities (95% CI):** no evidence **Disutility, between study (95% CI):** no evidence	No evidence		No evidence
Disutility of advanced stage vs. not advanced stage (Stage II-III vs. I)				
Within study: N=2 studies (142,143) N=1,412 participants	**Disutility, within study (95% CI):** 0.02 [0.01, 0.03]	⊕⊕⊖⊖ Low [b,d] (lack of consistency due to 88% weight of one study, imprecision)		There may be a disutility of 0.02, from having stage II-III vs. I among a mixed surgical and adjuvant treatment population.
Disutility of advanced stage vs. not advanced stage (Stage III vs. I-II)				
Within study: N=2 studies (142,143) N=1,412	**Disutility, within study (95% CI):** 0.03 [0.02, 0.05]	⊕⊕⊖⊖ Low [b,d] (lack of consistency due to 71% weight of one study, imprecision)		There may be a disutility of 0.03, from having stage III vs. I-II among a mixed surgical and adjuvant treatment population.

*Reasons for rating down certainty: a=risk of bias, b=inconsistency/lack of consistency, c=indirectness, d=imprecision

HSUVs, treatment health states: T2>24 months from surgery

Number of included studies; Sample size	Findings	GRADE	GRADE overall	What does the evidence say?
Disutility of Mastectomy vs. BCS/partial mastectomy				
Within study: N=5 studies (125,144–147) N=3,820 participants	**Disutility, within study (95% CI):** 0.00 [-0.01, 0.02] Removing high ROB studies: 0.00 [-0.01, 0.02]	⊕⊕⊕⊖ Moderate [c] (indirectness of mastectomy therapies) Little-to-no disutility from mastectomy	⊕⊕⊕⊖ Moderate [c] (indirectness of mastectomy therapies)	There is probably little-to-no disutility from mastectomy vs. BCS/partial mastectomy with radiation >2 years from surgery.
Between study: BCS, N=6 studies (125,127,144–148) N=2,017 participants Mastectomy, N=6 studies (125,136,144–147) N=2,702 participants	**Pooled BCS utilities (95% CI): 0.89 [0.88, 0.89]** Removing high ROB studies: 0.84 [0.83, 0.85] **Pooled mastectomy utilities (95% CI)**: 0.86 [0.85, 0.86] Removing serious ROB studies: 0.83 [0.82, 0.84] **Disutility, between study (95% CI):** 0.03 [0.02, 0.04] **Disutility, excluding serious ROB studies (95% CI):** 0.01 [-0.00, 0.02]	⊕⊕⊕⊖ Moderate [c] (indirectness across different adjuvant treatments)		
Disutility of adjuvant chemotherapy vs none.				
Within study: no evidence	No evidence	No evidence	No evidence	No evidence
Between study: Adjuvant chemo: N=2 studies (127,139) N=272 participants No Adjuvant chemo: N=1 study (147) N=278 participants	**Pooled adjuvant chemotherapy utilities (95% CI): 0.91 [0.91, 0.92]** **Pooled no adjuvant chemotherapy utilities (95% CI): 0.86 [0.84, 0.88]** **Disutility, between study (95% CI):** -0.05 [-0.07, -0.03]	⊕⊖⊖⊖ Very low [b,d] (very serious imprecision, lack of consistency)	⊕⊖⊖⊖ Very low [b,d] (very serious imprecision, lack of consistency)	We are very uncertain about the disutility of adjuvant chemotherapy vs none >2 years from surgery.
Disutility of adjuvant radiation vs. none				
Within study: N=2 studies (136,147) N=1,183	**Disutility, within study (95% CI):** -0.00 [-0.03, 0.03]	⊕⊕⊕⊖ Moderate [b] (imprecision) Little-to-no disutility from adjuvant radiation vs none.	⊕⊕⊕⊖ Moderate [b] (inconsistency) Little-to-no disutility from adjuvant radiation vs none.	There is probably little-to-no disutility from adjuvant radiation vs none >2 years from surgery.
Between study:	**Pooled adjuvant radiation utilities (95% CI): 0.83 [0.83, 0.83]**	⊕⊕⊕⊖		

Adjuvant radiation: N=9 studies (125,127,136,144–149) N=5,646 No Adjuvant radiation: N=4 studies (136,144,146,147) N=838	Removing serious ROB studies: **0.80 [0.80, 0.80]** **Pooled no adjuvant radiation utilities (95% CI):** 0.86 [0.86, 0.87] Removing serious ROB study: 0.81 [0.79, 0.83] **Disutility, between study (95%** CI): 0.03 [0.02, 0.04] Disutility, excluding serious ROB studies: 0.01 [-0.01, 0.03]	Moderate [b] (unexplained inconsistency) Little-to-no disutility from adjuvant radiation vs none.		
ALND vs. SLND				
Within study: no evidence	No evidence	No evidence	No evidence	No evidence
Between study: N=1 study (147) N=102	**Pooled ALND utilities (95% CI): 0.78 [0.73, 0.83]** **Pooled SLND utilities (95% CI):** no evidence **Disutility, between study (95% CI):** no evidence	No evidence		
Disutility of Advanced stage vs. not advanced stage				
	No evidence	No evidence	No evidence	No evidence

*Reasons for rating down certainty: a=risk of bias, b=inconsistency/lack of consistency, c=indirectness, d=imprecision

Non-HSUV Studies Providing Direct Preference Data, by outcome comparison

Included studies; Sample size	Findings	GRADE	What does the evidence say?
BC Mortality versus Overdiagnosis			
Across all ages			
2 studies (150,151) Davey 2005, Reder 2017 N=1019	An RCT of an online decision aid in those aged 50, at first invitation (n=913; 50 yrs, 33% previously screened) (1 fewer in 200 BC deaths over 20 years and no reduction in all-cause mortality vs. 50 FP and 1 overdiagnosed in 200 screened) (moderate ROB) and computer-assisted telephone interviews with convenience sample at primary care clinic (n=106; 45-70 yrs; 91% previous screening) with sequential presentation of four screening scenarios with first three indicating i) BC morality using relative terms (34% reduction), ii) BC mortality using absolute terms (4 vs 6 in 1000 over 10 years), and iii) all-cause mortality "screening will not increase your chance of living longer". (none of the first 3 scenarios mentioned harms) (low ROB)• In the RCT there were positive intentions to screen for 82% after reading about a reduction in BC but not all-cause mortality, and in the interviews, women were somewhat less willing to be screened after being presented with information on all-cause mortality (definitely: 53% and probably: 31%) after that on breast-cancer mortality (definitely: 78% and probably: 14%).• In the RCT 83% had a positive attitude about screening, and during the interviews only 16% of participants stated that the information on all-cause mortality should definitely be presented to women (40% stated probably), compared with 73% and20% when asked about the absolute effects of BC mortality.• At 3 months, 65% of the women in the RCT had attended screening.	⊕⊕⊖⊖ LOW Indirectness due to one population of screeners and need to rely on intentions data in the RCT that also provided other information to women. Imprecision around the "large majority"	**For patients 50 or older, at least a large majority (>75%) of patients may think that reducing breast-cancer mortality is beneficial even if there is no impact on all-cause mortality**
5 studies (152–156) Stiggelbout 2020, Hersch 2013, Sicsic 2018, Van den Bruel 2015, Wong 2015 N=2,652 (range 50-810)	Main analysis: Community samples using i) an online survey using choice sets varying by rates of overdiagnosis and its required treatments (Netherlands and Australia), ii) focus groups (Australia), and iii) an online discrete choice experiment (DCE; France). • 50-57% (varying across types of treatment) would always participate in screening, even with a 1:6 ratio of breast cancer deaths avoided to cancers overdiagnosed. No associations between acceptance and age, previous experience of an additional testing +/- biopsy (no cancer), or having a friend or relative with breast cancer. Previous screening associated with higher acceptance of overdiagnosis for all scenarios (P < 0.001). 33% correct on question asking for definition of the outcome. (low ROB) • 30% overdiagnosis (i.e., 11 among 38 cancers) was "acceptable and of limited impact" (on average 5:1); 50% overdiagnosis (i.e., 19 among 38 cancers; 10:1) thought to possibly deter some women, especially younger women, or necessitate careful consideration by others. (low ROB) • Mean 14.1 overdiagnosed cases acceptable for preventing 1 death from BC; a majority (>50%), large majority (≥75%) and almost all (≥90%) would accept <10:1, ≤6:1, and ≤4:1. Previous screening experience was not a significant predictor. (moderate ROB) • Two other studies at high risk of bias: an online survey eliciting simple trade-offs (UK) and study asking about the relative importance of these outcomes when making decisions based on a decision aid (Hong Kong). • A large majority would accept between 50 and 120 overdiagnoses per life saved (high risk of bias from up to 20% 18-35 yrs in sample). (high ROB) • 22% (BC mortality) and 5% (overdiagnosis) thought the data was important for decision making. (high ROB)	⊕⊕⊕⊖ MODERATE Indirectness (some limitation of understanding of this outcome)	**For patients 40 or older, at least a majority (>50%) and possibly a large majority (>75%) of patients probably accept up to 6 cases of overdiagnoses to save one death from breast cancer. Though an upper limit was not examined.**
50 to 69-year-olds			
2 studies (157,158) Hersch 2015, Waller 2014 N=1,833	RCT in Australia and UK using decision aids or surveys with and without data on rates of overdiagnosis • BC mortality (4 vs. 8 in 1000 over 20 years) and overdiagnosis (19 in 1000) were very important for 67% and 45% in intervention vs. 79% and 57% in control, i.e. 5:1 ratio did not appear to change the relative importance of the outcomes for decision making, but direct trade-off (low ROB) • Intentions to probably/definitely screen 92%, though there was a shift in intentions by one level (e.g. from definitely to	⊕⊕⊖⊖ LOW Lack of consistency from heavy reliance on 1 study	**For patients 50 and older, a large majority of women may accept at least 3 overdiagnoses to prevent one BC death though an upper limit was not examined.**

	probably) for 4.5% of women (9.1% for the simple 3:1 ratio group). 48% failed to understand that screening increases cancer diagnosis (low ROB)	Indirectness due to reliance on intentions and very limited understanding and lack of denominator in one study	
BC Mortality versus Additional testing +/- biopsy (no cancer)			
Across all ages			
3 studies (150,156,159) Schwartz 2000, Davey 2005, Wong 2015 N=675 (range 90-479)	• Population-based US survey (80%, 63%, and 37% would accept 100, 500, or 10,000 or more additional testing +/- biopsy (no cancer) per life saved over a 10-year (high ROB) • Neither willingness to screen or positive attitudes changed from before to after hearing about additional testing +/- biopsy (no cancer) (for willingness 78% vs. 79% and positive attitudes 85% vs. 79%). Both BC mortality and additional testing +/- biopsy (no cancer) were very important or important for most (95% and 87%) (low ROB) • In decision aid with data about BC mortality (20% reduction) and additional testing +/- biopsy (no cancer) (10%), the information was important for decision making in 22% and 5% of participants, respectively (high ROB)	⊕⊕⊖⊖ LOW ROB Imprecision about estimate of "majority"	**For patients 40 or older, there may be considerable variation in preferences though almost all patients may accept that 25-50 and a majority may accept that a few hundred among 1000 experience additional testing +/- biopsy (no cancer) to prevent one death from BC mortality over 10 years.**
40 to 49-year-olds			
2 studies (160,161) Lewis 2003, Nekhlyudov 2008 N=272	US clinic samples • For 1 fewer BC deaths to 300 additional testing +/- biopsy (no cancer) per 1000 screened, 83% stated BC mortality was more (for 75% much more) important than additional testing +/- biopsy (no cancer) (low ROB) • 1 fewer BC deaths per 1000 screened increased intentions almost twice (56% vs. 29%) as often as did an additional testing +/- biopsy (no cancer) rate of 100 per 1000; (moderate ROB)	⊕⊕⊖⊖ LOW Some (-0.5) inconsistency Indirectness from possible confounding Some (-0.5) imprecision	**For patients in their 40s, at least a majority of patients probably accept at least 100 and may accept at least 300 additional testing +/- biopsy (no cancer) per life saved over 10-years.**
50 to 59-year-olds			
3 studies (157,162,163) Hersch 2015, Gyrd-Hansen 2000, Yasunaga 2007 N=1483	• RCT in Australia using decision aids: BC mortality (4 vs. 8 dying in 1000 over 20 yrs) was very important for about 1.5 times (e.g. 79% vs. 52%) as many people as was the data on additional testing +/- biopsy (no cancer) (412 in 1000) (ratio 1:100), regardless of whether data on overdiagnosis data was presented (low ROB) • DCE in Denmark: BC mortality was many times more influential for acceptance than additional testing +/- biopsy (no cancer) (preference weights 0.061 vs. -0.0003); 30% to 100% reduction in mortality may have influenced findings (low ROB) • Willingness to pay (Japan), reduced mortality by 20% with and without additional testing +/- biopsy (no cancer) (80 per 1000): reduced by about 25% when presented with the harms data (high ROB)	⊕⊕⊖⊖ LOW ROB Inconsistency	**For patients 50-59 years of age, even in scenarios of relatively high reductions in BC mortality, additional testing +/- biopsy (no cancer) rates of 80-120 or higher per 1000 may be important information for a large minority of patients when making decisions about screening.**
BC Mortality versus Additional testing with biopsy (no cancer)			
Across ages			
1 study (154) Sicsic 2018 n=812	• DCE; France n=810): mean willingness-to-accept value was 47.8 additional testing with biopsy (no cancer) per prevented BC death when screening until age 74; 95% would accept between 6.7 and 127.3 additional testing with biopsy (no cancer); 92% would accept 10 additional testing with biopsy (no cancer), 63% would accept 20, and 48% would accept 30 additional testing with biopsy (no cancer) per life saved (moderate ROB)	⊕⊕⊖⊖ LOW Lack of consistency Imprecision around to 10-15	**For patients 40 or older, a large majority of patients may accept that between 10-15 people experience an additional testing with biopsy (no cancer) to prevent one BC death over many years. This trade-off may be an overestimate for what is acceptable over a 10-year timeframe.**
Stage Distribution (reduced advanced disease) versus Additional testing +/- biopsy (no cancer)			
Across ages			
3 studies (164–166) Bilger 2020, Ganott 2006, Jafri 2008 N=2,881	• DCE in Singapore including stage info on distribution (i.e., BC cancer survival rates of 25%, 50%, 65%, and 90%) and additional testing +/- biopsy (no cancer) (5%, 15%, and 30%); when survival changed from 25% to 90% (14.5% more (23% relative effects) participants would undergo screening; from 25% to 65% the change in acceptance increased by 9.9%. When the additional testing +/- biopsy (no cancer) rate was reduced from 30% to 5% (e.g. 25-unit change), uptake only increased 1.4% (2% in relative terms (low ROB) • Two US clinic samples using same questionnaire: Willingness to accept more additional testing +/- biopsy (no cancer) (15% vs. 10%) for early detection (described as 1 in 200 cancers found vs. 1 in 300) (i.e. 50 more additional testing +/- biopsy (no cancer) vs. 2 cancers detected earlier per 1000) (indirect outcome) ○ 97% White participants (n=1570; ≥40 years [41% 40-49 years]): 86% acceptable; small differences in subgroups of previously screened, previous additional testing +/- biopsy (no cancer) or invasive procedures, age (<60 vs ≥60 years) and family history of breast cancer (high ROB) ○ Underserved and predominantly minority population (n=911; ≥ 40 years [32% aged 40-49]): more White than Black and Hispanic women agreed (76% vs. 54% and 59%) and fewer being unsure (11% vs. 27% and 24%) about the trade-off (high ROB at screening visit)	⊕⊕⊖⊖ LOW ROB Indirectness for outcome	**For patients 40 or older, a large majority of patients may accept that at least 25 people experience an additional testing +/- biopsy (no cancer) to prevent one advanced stage cancer.**
Stage distribution (reduced advanced disease) versus Additional testing with biopsy (no cancer)			
Across ages			

2 studies (165,166) Ganott 2006, Jafri 2008 N=2,481	US clinic samples using questionnaires: Willingness to accept more additional testing with biopsy (no cancer) (1 in 60 to 1 in 40) in order for the chance that if cancer is diagnosed it may be detected earlier (described as 1 in 200 cancers found vs. 1 in 300) (i.e., 8 more additional testing with biopsy (no cancer) to detect 2 cancers earlier, per 1000) (indirect outcome) • 97% White participants (n=1570; ≥40 years [41% 40-49 years]): 82% agreed, with small differences in subgroups • Underserved and predominantly minority population (n=911; ≥ 40 years [32% aged 40-49]): more White than Black and Hispanic women agreed (75% vs. 53% and 65%) and fewer being unsure (11% vs. 27% and 24%) • Both high ROB	⊕⊕⊖⊖ LOW ROB Indirectness for outcome and whether findings apply to all ethnicities	**For patients 40 or older, a large majority of patients may accept that at least 4 people experience an additional testing with biopsy (no cancer)to prevent one advanced stage cancer.**
Treatment burden (reduced mastectomy) versus Additional testing with biopsy (no cancer)			
Across ages			
1 study (164) Bilger 2020 N=400	• DCE in community sample in Singapore: type of surgery (3 levels: no change, changes in feel/appearance of breast, or lose an entire breast) for comparisons with additional testing (no cancer) (5%, 15%, and 30%); compared with no change, not losing a breast increased acceptance by 4.8% (7.5% in relative terms) and not having a change in appearance increased acceptance by 2.1%, compared with the increased acceptance of 1.4% (2.1% in relative terms) with a large change in additional testing +/- biopsy (no cancer) from 30% to 5% (i.e. 25 units) (low ROB)	⊕⊕⊖⊖ LOW Lack of consistency imprecision about the estimate of majority	**For patients 40 or older, avoiding mastectomy may be much more important than experiencing an additional testing (no cancer) for a majority of patients.**

Non-HSUV Studies Providing Indirect Data from Making Inferences from Attitudes, Intentions, And Behaviors, by age and judgement of net benefit presented

Included studies; Sample size	Findings	GRADE	What does the evidence say?
40 to 49-year-olds			
Relatively high net benefit scenario			
6 studies (167–172) Laza-Vásquez 2022, Roberto 2020, Schonberg 2020a, Seitz 2016, Driedger 2017, Elkin 2017 N = 4,826	Benefits presented only using relative effects (e.g. 20% reduction) or a natural frequency that was judged high and/or not presenting any numerical information on overdiagnosis (n=3); 4 studies provided patients with their own predicted risk for BC; in 3 there was also the opportunity to discuss the information during a clinic visit (1 low ROB, 5 high ROB) • Attitudes: 3 studies: high (88% and 92%) in two studies (N=1,388; 1 with 40-59yrs), but also positive attitudes (62.7%) towards personalized screening (e.g., limiting screening to higher-risk women in their 40s); 1 (n=168) reported that 83% of participants strongly agreed/agreed that benefits outweigh the risks • Intentions: 5 studies: in 1 study (ages 40-59) 98-99% (across 2 interventions) had positive intentions; in 3 studies (40s) fewer patients had intentions (e.g., 77% over next 6 months, 19-31% would not screen/would wait until 50s, mean score of 68 ± 40 on 0-100 scale); high (92%) for personalized screening in 1 study; in Canadian study (n=46), 21% 35-49 yrs stated age 40 was when screening should start • Attendance: 2 studies: at 16 ± 5.4 months 42% in US study (36% non-Caucasian) and 84% at an unknown follow-up 1 study (40-59 yrs) • Subgroups: Data in 3 studies by risk groups were somewhat inconsistent but at most showing small differences (e.g. n=2,918, 19-24% low risk vs. 24-31% intending not to screen in 40s	⊕⊕⊖⊖ LOW Indirectness Inconsistency	**In a relatively high net benefit scenario, a majority but possibly not a large majority of patients in their 40s may weigh the benefits as greater than the harms from screening. Preferences may be similar for patients with different levels of breast cancer risk.**
Relatively moderate net benefit scenario			
1 study (173) Valentine 2022 N=2,120	Community sample 49.5 ± 7.8 yrs with complex intervention (net benefit: 2 fewer BC deaths, 160 additional testing +/- biopsy (no cancer) and 20 overdiagnoses in 1000 over 11 years) (low ROB) • Intentions: 88.5% of 40-49 yrs had intentions at baseline; preferences lowered after each subsequent stage of the intervention, reducing to 53% after the first stage (didactic information with benefit/harms) then to 28-30% after all four stages (including a detailed explanation of overdiagnosis and narrative of a biopsy experience).	⊕⊖⊖⊖ VERY LOW Lack of consistency Very serious indirectness (mean age 49.5) ⊕⊕⊖⊖ LOW Lack of consistency Indirectness	In a relatively moderate net benefit scenario, it is unclear how patients in their 40s weigh the benefits as greater than the harms from screening. Information on overdiagnosis may be quite important for many.
Relatively low net benefit scenario			
3 studies (174–176) Saver 2017, Mathieu 2010, Paul 2008 N=459	Community samples with information in deliberative jury, video intervention and decision aid. (all moderate ROB) • Attitudes: 2 studies: 10/11 voters changed their mind from *for* to *against* provision of screening for 40-49 yrs; video intervention reduced scores about the benefits being greater than the harms (-0.65 on 5-point scale; [p <0.001]) • Intentions: 2 studies: video lowered (pre: 85% intended/6% unsure vs. post: 49% intended/20% unsure and after decision aid 39% did not intend to start screening (18% unsure); 9% had adequate knowledge after decision aid	⊕⊕⊖⊖ LOW Indirectness Imprecision (sample size)	**In a relatively low net benefit scenario, a majority of patients in their 40s may not weigh the benefits as greater than the harms from screening.**
Focus on 50-year-olds			
Relatively high net benefit scenario			
5 studies (151,168,177–180)	European studies from organized screening program lists; most 1 in 200 lives saved with 1-2 overdiagnoses (1 high ROB study; low to moderate knowledge scores across studies)	⊕⊕⊕⊖ MODERATE Indirectness	**In a relatively high net benefit scenario, a large majority of 50-year-old patients**

Berens 2015, Gummersbach 2015, Perez-Lacasta 2019 (associated paper Lo´pez-Panisello 2023), Reder 2017, Roberto 2020 N=6,904	• Attitudes: 4 studies: positive attitudes in 74% to 94% • Intentions: 5 studies: intentions to screen 82% to 83% in 3 studies, and in 2 positive intentions (e.g. above mid-point in scale) in 82% and 99%. 1 study found that intentions reduced at a 3-month follow-up (from 82% to 65%) • Attendance: 2 studies: 63% at 3 months and 84% at unknown timing • Subgroups: in Germany: those with previous (2%) or a family history (17%) of BC were more willing to screen (97% vs. 73%; p=0.009) (n=353); immigrants had more positive attitudes (mean scores 4.6 to 5.1 vs. 4.2 on -8 to +8 scale) but lower intentions (75%-77% vs. 83% for non-immigrants) • Mediation: knowledge directly worsened attitude towards screening (p = 0.002), but not intentions (p = 0.334)		**probably weigh the benefits as greater than the harms from screening.**
Ongoing screening in 50-69 years			
Relatively high net benefit scenario			
6 studies (171,181–185) Waller 2013, Lawrence 2000, Toledo-Chavarri 2017, Driedger 2017, Bourmaud 2016, Haakenson 2006 N=16,864 (1 RCT 16,000)	Patients across a range of settings and ages with previous screening histories of around 75% (46% to 99%); 3 used focus groups, 2 RCTs comparing a decision aid vs informative brochure with standard invitation letters, and validated decision aid • Attitudes: 2 studies: "few" focus-group participants changed their attitudes based on information on overdiagnosis; in Canadian study 35% 50-59 yrs said screening should start at 40, 29% age 50, and 35% uncertain • Intentions: 3 studies: 93% in one US study and described in two European qualitative studies as "remaining high overall" and "a vast majority of those who had already considered screening (≥90%) would participate" • Attendance: 2 studies; 40.3% in large high ROB RCT from France (previous year 50%; no differences across ages); 98.3% attendance in US RCT (high ROB)	⊕⊕⊕⊖ MODERATE Indirectness Some inconsistency from RCT in France but in context of little screening so not serious	**In a relatively high net benefit scenario, a large majority of 50 to 69-year-old patients probably weigh the benefits as greater than the harms from screening.**
Focus on 50-year-olds			
Relatively moderate net benefit scenario			
1 study (157,186,187) Hersche 2015 (associated Hersche 2017 & 2021) N=879	RCT among 48-50 yrs from community compared decision aids with and without data on overdiagnosis • Attitudes: 69% and 81% positives attitude at 1 mo and 2 yrs • Intentions: 74% and 82% intentions to screen at 1 mo and 2 yrs • Attendance: 55% (self-reported) and 70% (via public records) at 2 yrs • Mediation: reduced positive intentions vs control group (87% at 1 mo) mediated by greater knowledge of overdiagnosis and the subsequent reduction in positive attitudes (adequate knowledge of overdiagnosis 55% at 1 mo)	⊕⊕⊕⊖ MODERATE Some concern about lack of consistency but large low ROB study so did not rate down Indirectness	**In a relatively moderate net benefit scenario, a majority and possibly a large majority of patients 50 years old probably weigh the benefits as greater than the harms from screening.**
Ongoing screening in 50 to 69-year-olds			
Relatively moderate net benefit scenario			
1 study (188) Baena-Canada 2018 N=20	Citizen's jury (n=20 enrolled with 15 attending some sessions and 13 voting) of eligible screening program participants in Spain (data: range 1 fewer BC deaths in 235 to 2 life saved in 1 or 2000; 4% fewer need for chemo, 5% fewer with advanced stage, 3-10% additional testing +/- biopsy (no cancer), 1 in 77 to 10 in 1000 overdiagnoses) (high ROB) Attitudes: 85% agreed that health authority should continue to offer screening to those 50-69 yrs (100% favourable at baseline)	⊕⊖⊖⊖ VERY LOW ROB Lack of consistency Indirectness	In a relatively moderate net benefit scenario, it is uncertain how 50 to 69-year-old patients weigh the benefits versus harms from screening.
Focus on 50 to 59-year-olds			
Relatively low net benefit scenario			
3 studies (173,188,189) Henriksen 2015, Valentine 2022, Baena-Canada 2015 N=2,481	Qualitative study in a primary care clinic in Denmark (n=6), an RCT in the US using a public survey platform and an RCT among screening program attendees in Spain at moderate, low and high (screening attenders; 18% well informed) ROB • Attitudes: 1 study: 99% positive attitude (n=355) based on leaflet based on the 2008 Cochrane review risk estimates (200 additional testing +/- biopsy (no cancer) and 10 overdiagnoses to prevent 1 BC death in 2000 over 10 years) • Intentions: 3 studies: 99% intended to screen (n=355); intentions reduced in 40-59 yrs from 84% to 53% after the first stage (didactic information with benefit/harms) then to 28-30% after all four stages of complex intervention with 4 stages of information; 1 of 6 reconsidered their decision to start screening when invited based on information on overdiagnosis	⊕⊕⊖⊖ LOW Inconsistency Indirectness	**In a relatively low net benefit scenario, a large majority of 50 to 59-year-old patients may weigh the benefits as greater than the harms from screening.**
70 years and older			
Relatively high net benefit scenario			
2 studies (190,191) Pappadis 2018, Braithwaite 2023 N=73	Evaluation of a tailored decision aid (n=14) and mixed-methods study (n=59) using qualitative narratives focused on overdiagnosis (10% to 30% of cancers diagnosed via figures and scenarios) (high ROB) • Intentions: 2 studies: 1 of 11 analyzed would stop screening; 44% supported mammograms and 49% intended to continue screening (20% and 37% for those indicting good understanding of overdiagnosis)	⊕⊖⊖⊖ VERY LOW ROB Indirectness Imprecision	Under relatively high net benefit scenarios, it is uncertain how patients 70 years old and over weigh the benefits and harms.
70 to 71-year-olds			
Relatively moderate-to-low net benefit scenario			
1 study (192) Mathieu 2007	RCT (n=734) in Australia compared a decision aid to a standard brochure among 70 to 71-year-old screeners (2 lives saved per 1000 over 10 years vs. 135 additional	⊕⊕⊕⊖ MODERATE Indirectness	**In a moderate-to-low net benefit scenario, a large majority of patients 70-71 years of**

N=734	testing +/- biopsy (no cancer), 15 overdiagnoses and 9 interval cancers) (low ROB) • Attitudes: 95% positive attitudes • Intentions: 86% intended (with 5% more unsure) to continue screening • Attendance: at 1 mo, 6% had participated and 76% indicated they were in the process of arranging to be screened	Some concern about lack of consistency but large low ROB trial so did not rate down	**age who have recently screened probably think the benefits outweigh the harms for continuing to screen.**
75 years and older			
Relatively moderate-to-low net benefit scenario			
3 studies (169,193,194) Schonberg 2020b, Schonberg 2014, Cadet 2021a N=634	One RCT (n=546; age 79.8 [3.7]) and 2 pre-post trials (N=88) among US primary care clinics measured screening intentions and, in 2, screening attendance after exposure to a decision aid for recent screeners aged 75 and older. Aids depicted a reduction of BC mortality by 1 per 1000 screened (e.g. 3 vs. 4 die in 1000) but in 2 the time horizon was 5 yrs whereas in 1 it was (n=43) it was 10 yrs. 2 mentioned 4 in 1000 would avoid a large cancer and ranges of 100-200 additional testing +/- biopsy (no cancer) and 11-13 overdiagnoses per 1000 (2 low and 1 moderate ROB) • Intentions: 3 studies: intentions reduced (by ≥1 level on 15-point scale) for 24.5% (n=546); 56% intentions to continue screening (vs. 82% at pre-test) (n=45); in 18 medical records at 6 mos, 67% noted continuing screening, 22% discontinuation and 22% indecision • Attendance: 2 studies: 51% at 18 mos vs. 100% 2 yrs prior (n=546); 63% at 15-mos vs. 85% 2-yrs prior (n=45) • Subgroups: no effects on attendance by patient age, educational level, life expectancy, or breast cancer risk (≥3 vs <3% 5-yr risk)(n=546); those having <9 yrs life expectancy had lower intentions (50% vs. 63%) and attendance (52% vs. 78%)(n=45)	⊕⊕⊖⊖ LOW Indirectness Imprecision (about not large majority)	**For patients aged 75 years to their early 80s who have recently screened, a majority but possibly not a large majority may weigh the benefits as greater than the harms for continuing to screen. It is unclear what impact life expectancy has on this preference.**

BALANCE OF EFFECTS

Does the balance between desirable and undesirable effects favour the intervention or the comparison?

40-49 and 75+ in average to moderately increased risk
○ Favours the comparison
X Probably favours the comparison
○ Does not favour either the intervention or the comparison
○ Probably favours the intervention
○ Favours the intervention

○Varies
○Don't know

50-74 in average to moderately increased risk
○ Favours the comparison
○ Probably favours the comparison
○Does not favour either the intervention or the comparison
X Probably favours the intervention
○ Favours the intervention

○Varies
○Don't know

Annual vs Biennial in average to moderately increased risk
○ Favours the comparison
X Probably favours the comparison
○ Does not favour either the intervention or the comparison
○ Probably favours the intervention
○ Favours the intervention

SUMMARY JUDGEMENT – BALANCE OF BENEFITS AND HARMS

40-49: The Task Force considered there may be a small benefit of screening in this age group (reduction in mortality, number requiring chemo, and stage 3+ cancers) and small harms (additional imaging +/- biopsies). Compared to the evidence examined in 2018, overdiagnosis was slightly less (2/1000 versus 3/1000). Overall the data on patient values and preferences (SR, feedback from patient partners and clinical experts) showed possibly important variability and uncertainty. 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. However, the Task Force considered that some women (e.g., those at moderately increased risk) may achieve greater benefit, and that variation in patient values and preferences exists. Therefore, individuals in this age group who have been provided clear and transparent information about the benefits and harms of screening, and wish to be screened, should be referred to screening every 2-3 years.

50-74: Across these age groups the Task Force considered there may be a small benefit which increases with age. Harms were also small and additional testing (no cancer) became smaller with increasing age. There was also possibly important variability and uncertainty in patient values and preferences, but leaning more towards weighing the benefits as greater than the harms under a variety of theoretical levels of benefit. Based on the more favourable balance of benefits and harms in this age grouping, which improves with age, as well as patient values and preferences data, 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 in this group.

75+ years
There were no differences in mortality screening beyond age 74 and an overall very small benefit due to lower rates of chemotherapy and radical mastectomy. Rates of overdiagnosis were high and additional imaging and biopsies remain important resulting in small harms). Modelling also showed very small differences in breast cancer mortality and stage at diagnosis and small harms (overdiagnosis and additional testing (no cancer)). Therefore, the Task Force conditionally recommends against screening in this age group.

Screening Interval
It is very uncertain whether annual screening improves mortality or stage distribution, resulting in a benefit of 'little to none'. Additionally, there were small harms due to the increase in additional testing (no cancer). The Task Force continues to recommend screening every 2-3 years, as 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 individuals 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.

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

	○Varies ○Don't know **Tomosynthesis in average to moderately increased risk** ○ Favours the comparison ○ Probably favours the comparison X Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○Varies ○Don't know **Supplementary ultrasound or MRI in moderately increased risk** ○ Favours the comparison X Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○Varies ○Don't know	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 (248). 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, recognizing 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 (249). 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 (222). 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(250). 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 (103). 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 (39), and age-specific incidence has increased for some groups, age-standardized mortality due to breast cancer has declined by approximately 47% since 1984 (41.7 deaths per 100,000 in 1989 to an estimated rate of 22.1 deaths per 100,000 in 2023)(2,6). 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) (251). 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 race and ethnicity (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.	
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** **If expanding screening <50 or >74 or increasing screening frequency (e.g., annual)** o Large costs X Moderate costs o Negligible costs and savings o Moderate savings oLarge savings oVaries oDon't know **If expanding screening modalities** o Large costs o Moderate costs o Negligible costs and savings o Moderate savings oLarge savings oVaries X Don't know (Unknown – no data)	**SUMMARY JUDGEMENT – RESOURCES REQUIRED** **Screening 50-74 = Status quo** **Age to start screening: Moderate if expanded** **Age to stop screening: Moderate if expanded** **Screening interval: Moderate if less than biannual** **Screening modality: Unknown** A systematic cost-effectiveness analysis was not conducted as part of the systematic review. We did not attempt to estimate exact costs associated with recommendations. Reduction in the age of initiation of screening, or shortening of the interval of screening will necessarily entail increased resources for the additional screening tests performed, follow-up of abnormal results, and treatment. Use of modalities other than digital mammography (e.g., DBT) may require additional resources in jurisdictions where they are not already in use. Model Results – Number of screens: Model results – accrued costs, 2024-2100	A Health Report from Statistics Canada indicates that while the main cost driver of a screening program is the frequency of screening, resource requirements also depend on the age of individuals being screened (Stats Can 2015). Costs were calculated for screening and subsequent treatment as well as the indirect costs of lost productivity. Clinical expert feedback: There are health workforce challenges related to breast cancer screening (e.g., availability of technologists, pathologists) being experienced in many provinces. Diagnostic wait times, and wait times to receive pathology report after a biopsy are already limited resources; these wait times will likely significantly lengthen with addition of routine screening in age 40-49 (more dense tissue, more call-backs, more biopsies, etc.)

Age group	Interval	Number of screens, per 1000 people	Number of screens, per 1000 people vs 50-74 biennial
40 - 74	Annual	29,557.92	16,872.29
40 - 79	Annual	31,069.87	18,384.24
45 - 74	Annual	27,307.04	14,621.40
45 - 79	Annual	28,819.25	16,133.62
50 - 74	Annual	24,235.26	11,549.62
50 - 79	Annual	25,748.68	13,063.04
40 - 74	Biennial	15,291.65	2,606.01
40 - 79	Biennial	15,686.51	3,000.88
45 - 74	Biennial	13,983.95	1,298.32
45 - 79	Biennial	14,413.04	1,727.40
50 - 74	Biennial	12,685.64	Reference
50 - 79	Biennial	13,067.19	381.55
40 - 74	Hybrid	18,019.85	5,334.21
40 - 79	Hybrid	18,401.80	5,716.16
45 - 74	Hybrid	15,764.89	3,079.25
45 - 79	Hybrid	16,146.69	3,461.05

Scenario Parameters					
Interval	*Start Age*	*End Age*	*All Ages*	*Vs biennial 50-74*	*Vs biennial 50-74 by year*
Annual	40	74	$ 45,642,763,901	$ 6,453,170,229	$ 84,910,135
		79	$ 46,133,798,777	$ 6,944,205,105	$ 91,371,120
	45	74	$ 44,631,223,675	$ 5,441,630,002	$ 71,600,395
		79	$ 45,122,670,814	$ 5,933,077,141	$ 78,066,804
	50	74	$ 43,364,235,416	$ 4,174,641,744	$ 54,929,497
		79	$ 43,856,342,231	$ 4,666,748,558	$ 61,404,586
Biennial	40	74	$ 40,266,899,688	$ 1,077,306,015	$ 14,175,079
		79	$ 40,406,920,638	$ 1,217,326,966	$ 16,017,460

	45	74	$ 39,781,084,114	$ 591,490,441	$ 7,782,769
		79	$ 39,928,740,945	$ 739,147,272	$ 9,725,622
	50	74	$ 39,189,593,673	Reference	Reference
		79	$ 39,324,734,545	$ 135,140,872	$ 1,778,169
Hybrid	40	74	$ 41,475,631,233	$ 2,286,037,560	$ 30,079,442
		79	$ 41,611,026,290	$ 2,421,432,617	$ 31,860,955
	45	74	$ 40,461,787,024	$ 1,272,193,352	$ 16,739,386
		79	$ 40,596,659,980	$ 1,407,066,307	$ 18,514,030
No Screening			$ 34,771,778,699	-$ 4,417,814,973	-$ 58,129,144

CERTAINTY OF EVIDENCE OF REQUIRED

What is the certainty of the evidence of resource requirements (costs)?

o Very low
o Low
o Moderate
o High

X No included studies

SUMMARY JUDGEMENT – CERTAINTY OF EVIDENCE OF RESOURCE REQUIREMENTS

As noted above, we did not attempt to estimate exact costs of potential recommendations. The model was not graded for cost

COST EFFECTIVENESS

Does the cost-effectiveness of the intervention favour the intervention or the comparison?

o Favours the comparison
o Probably favours the comparison
o Does not favour either the intervention or the comparison
X Probably favours the intervention (model)
o Favours the intervention

o Varies
o No included studies

SUMMARY JUDGEMENT – COST-EFFECTIVENESS

We did not evaluate any cost-effectiveness studies in our systematic review. Cost-effectiveness was evaluated in the modeling analysis and probably favours the intervention for all scenarios.
'Probably favours the intervention' was selected as there was no GRADE assessment of the model for cost-effectiveness

Model results – cost-effectiveness analysis

Scenario Parameters			Incremental Net Monetary Benefit (Higher = More Cost-Effective)	
Frequency	*Start Age*	*EndAge*	*All Ages*	*Vs biennial 50-74*
Annual	40	74	$94,355,757,103	$38,136,015,018
		79	$95,638,663,390	$39,418,921,305
	45	74	$87,485,058,104	$31,265,316,019
		79	$88,790,425,417	$32,570,683,332
	50	74	$74,465,601,898	$18,245,859,813
		79	$75,702,161,697	$19,482,419,612
Biennial	40	74	$70,328,053,386	$14,108,311,301
		79	$70,708,329,539	$14,488,587,454
	45	74	$64,992,773,194	$14,488,587,454
		79	$65,490,921,298	$9,271,179,213
	50	74	$56,219,742,085	Reference
		79	$56,584,334,209	$364,592,124
Hybrid	40	74	$75,967,280,899	$19,747,538,814
		79	$76,336,543,637	$20,116,801,552
	45	74	$69,118,366,845	$12,898,624,760
		79	$69,489,038,741	$13,269,296,656

This analysis was conducted using a willingness to pay threshold of $ 100,000 per QALY gained.

Note: QALYS in the model are of very low certainty.

All screening scenarios included in the modeling are cost-effective, as their incremental net monetary benefits are above 0.

EQUITY

What would be the impact on health equity?

Recommendation <u>for</u> screening 40-49 and 75+ (general population or moderately increased risk

○ Reduced
○ Probably reduced
○ Probably no impact
○ Probably increased
○ Increased
X Varies
○ Don't know

Recommendation <u>against</u> screening 40-49 and 75+ (general population or moderately increased risk)

○ Reduced
○ Probably reduced
○ Probably no impact
○ Probably increased
○ Increased
X Varies
○ Don't know

Recommendation <u>for</u> screening 50-74 (general population or moderately increased risk)

○ Reduced
○ Probably reduced
X Probably no impact
○ Probably increased
○ Increased
○ Varies
○ Don't know

Recommendation <u>against</u> screening 50-74, (general population or moderately increased risk)

○ Reduced
X Probably reduced
○ Probably no

EQUITY

SUMMARY JUDGEMENT – EQUITY

A recommendation for screening in ages 50 to 74 probably has no impact on health equity as it represents the status quo and aligns with screening policies and practice of most provinces and territories. A recommendation for screening in ages 40-49 and 75+ would result in a variation in health equity. There is some indirect evidence to suggest it may improve health equity for certain groups (see right column). Lowering the screening age to 40 could also improve equity for those aged 40-49, particularly if they are unable to self-refer. However, if the comparison is at a population level, it may worsen health equity. For example, people with symptoms or diagnostic reasons may experience delays due to an increase in mammography and additional testing from the screening population. For those 75+ the impact on equity also varies. For those with good health and >10 years life expectancy it would allow for equal access to screening. However, individuals at age 75+ are more likely to have other comorbidities and healthcare resources could be better placed for them to focus on their other health care needs. A recommendation against screening ages 50-74 would probably reduce health equity and would be against the status quo.

As for screening modalities, DBT may perform similarly to DM. A recommendation in favour of DBT as an additional screening modality could help increase access by giving patients more options for screening, although availability of technologists to carry out the screening may be a limiting factor. Additionally, DBT may only be available in specific areas such as urban centres. There is also a lack of research data for different ethnic groups and screening modalities. There was limited evidence regarding the impacts of supplemental screening with ultrasound or MRI for individuals with dense breasts, therefore the equity was unknown or possibly variable.

Equity consideration also includes access to information to understand the pros and cons, having a family doctor or healthcare professional, and using explicit language for recommendations and informed decisions at any age.

Preliminary unpublished data (5) 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). Breast cancer incidence and stage at diagnosis included data up to 2015 and mortality findings included data up to 2019.

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

Race or Ethnicity	Median age at breast cancer diagnosis	Median age at death from breast cancer
White	63	71
Japanese	60	71
Metis	58	64
First Nation	57	64
South Asian	57	62
Black	56	61
Chinese	56	62
Latin American	56	62
South-east Asian	56	63
Multi-ethnic	55	59
Filipina	54	58
Inuit	54	55
Arab	53	58
Korean	52	61
West Asian	52	63

- Breast cancer <u>incidence</u> rates also vary by race or 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. However, Filipina, Multi-ethnic and Arab individuals do not have correspondingly higher death rates in these age groups.
    - 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).

Although population-based screening programs for breast cancer have been implemented across Canada, Black, Indigenous and immigrant populations are disproportionately underrepresented in regular screening, and Black and Indigenous patients experience higher breast cancer mortality than white patients (unpublished Statistics Canada data). However, the impact of ethnicity on cancer incidence and mortality is infrequently studied in Canada because Canadian registries do not routinely collect race and ethnicity data. Important measures that the medical community can undertake to promote equitable access to screening and other healthcare services include:

- Improving the representation of minority groups (e.g., Black people) in the healthcare team,
- Employing cultural awareness training for healthcare providers,
- Using multilingual and lay health educators and
- Tailoring health information to a patient's health literacy and cultural understanding.

At the system level, Canadian race and ethnicity data are needed to fully understand where disparities remain and how thoughtfully designed interventions can improve access and outcomes in cancer care (225).

Individuals with mobility disabilities in Canada are also less likely to access cancer screening, even when they have a primary care provider. These individuals have difficulties in arranging and attending health-related appointments and experience normative assumptions about their bodies in the healthcare system. Training health providers and providing accessible equipment and screening technologies complemented by on-site attendant care can ease the equitable access of individuals with mobility disabilities to screening (226).

impact
o Probably increased
o Increased
o Varies
o Don't know

Recommendation <u>for or against</u> screening annually vs biennial or triennial (general population or moderately increased risk)

o Reduced
o Probably reduced
o Probably no impact
o Probably increased
o Increased
o Varies
X Don't know

Recommendation <u>for or against</u> screening with tomosynthesis or supplemental screening (ultrasound or MRI) (general population or moderately increased risk)

o Reduced
o Probably reduced
o Probably no impact
o Probably increased
o Increased
o Varies
X Don't know

*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.

Incidence rate by ethnicity and age

	40-49		50-59		60-69		70-79	
	Rate per 100,000 PY (95% CI)	**Ratio**	**Rate per 100,000 PY** (95% CI)	**Ratio**	**Rate per 100,000 PY** (95% CI)	**Ratio**	**Rate per 100,000 PY** (95% CI)	**Ratio**
Arab	168.7 (126-211.3)	1.23 (0.96-1.59)	286.5 (217.9-355.1)	1.3 (1.02-1.65)*	272.2 (177.9-366.5)	0.79 (0.56-1.12)	251.8 (128.4-375.2)	0.64 (0.39-1.04)
Filipina	174.1 (150.9-197.2)	1.27 (1.11-1.46)*	255.5 (223.5-287.5)	1.16 (1.02-1.31)*	326.5 (277.9-375.2)	0.95 (0.81-1.1)	344.2 (270.6-417.8)	0.87 (0.71-1.08)
Multi-ethnic	214.3 (153.7-275)	1.57 (1.18-2.08)*	215.8 (149.8-281.9)	0.98 (0.72-1.33)	360.9 (244.6-477.2)	1.05 (0.6-1.44)	341.6 (179.2-504)	0.87 (0.54-1.4)
Black	108 (90-126)	0.79 (0.67-0.93)^	174.8 (147-202.6)	0.79 (0.67-0.93)^	230.5 (191.9-269.1)	0.67 (0.56-0.79)^	284.4 (225-343.9)	0.72 (0.59-0.89)^
Chinese	151.1 (136.5-165.7)	1.1 (1-1.22)	197.3 (179.7-214.8)	0.89 (0.82-0.98)^	239.3 (213.7-264.9)	0.69 (0.62-0.77)^	225.8 (194-257.7)	0.57 (0.5-0.66)^
First Nation	107.4 (94.4-120.4)	0.78 (0.69-0.89)^	224.6 (203.1-246.2)	1.02 (0.92-1.12)	344.5 (308.5-380.4)	1.0 (0.9-1.11)	341.2 (289.6-392.8)	0.87 (0.74-1.01)
Inuit	92.3 (51.9-132.8)	0.67 (0.43-1.05)	128.9 (69.2-188.5)	0.58 (0.37-0.93)^	NR	NR	NR	NR
Korean	125 (86.3-163.8)	0.91 (0.67-1.25)	152.9 (104.9-200.8)	0.69 (0.51-0.95)^	207.7 (126.3-289.2)	0.6 (0.41-0.89)^	NR	NR
Latin American	86.9 (63-110.7)	0.63 (0.48-0.84)^	165.1 (127.0-203.3)	0.75 (0.59-0.94)^	260.1 (193.2-327.0)	(0.75 (0.58-0.98)^	NR	NR
South Asian	104.7 (92-117.5)	0.77 (0.68-0.87)^	201.4 (180.5-222.3)	0.91 (0.82-1.01)	259.1 (230.8-287.4)	0.75 (0.67-0.84)^	249.9 (212.3-287.4)	0.63 (0.55-0.74)^
South-East Asian	73 (48.1-97.9)	0.53 (0.38-0.75)^	102.8 (70.1-135.5)	0.47 (0.34-0.64)^	219.9 (147-292.7)	0.64 (0.46-0.89)^	177.1 (87.5-266.8)	0.45 (0.27-0.75)^
Japanese	172.8 (113.8-231.8)	1.26 (0.9-1.78)	272.2 (180.7-363.6)	1.23 (0.88-1.73)	371.6 (256.5-486.8)	1.08 (0.79-1.47)	326.8 (196-457.5)	0.83 (0.56-1.24)
Metis	96.1 (74.6-117.5)	0.7 (0.56-0.88)	205.3 (172.1-238.5)	0.93 (0.79-1.09)	296.8 (242.8-350.8)	0.86 (0.72-1.03)	398.6 (300.2-497.1)	1.01 (0.79-1.3)
Other	122.1 (69.9-174.4)	0.89 (0.58-1.37)	157.6 (91.7-223.4)	0.71 (0.47-1.08)	262.6 (157.6-367.7)	0.76 (0.51-1.14)	433.8 (238.7-628.9)	1.1 (0.7-1.73)
West Asian	163.1 (118.8-207.4)	1.19 (0.91-1.57)	231 (170.5-291.5)	1.05 (0.8-1.36)	263.5 (169.2-357.7)	0.76 (0.53-1.09)	NR	NR
White	136.9 (133.2-140.6)	1.00	220.8 (216.3-225.3)	1.00	344.9 (338,5-351.4)	1.00	393.6 (384.9-402.4)	1.00

*Statistically significantly higher than white
^Statistically significantly lower than white
NR – Not reported (missing data due to no sparse data that could not be reported)

- Breast cancer <u>mortality</u> rates also vary by race or ethnicity
    - 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* .
    - 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.

Estimated death rate by ethnicity and age

	40-49		50-59		60-69		70-79	
	Rate per 100,000 PY (95% CI)	**Ratio**	**Rate per 100,000 PY** (95% CI)	**Ratio**	**Rate per 100,000 PY** (95% CI)	**Ratio**	**Rate per 100,0 00 PY** (95% CI)	**Ratio**
Black	21.4 (15.6-27.2)	1.40 (1.06-1.85)*	37.1 (28.2-46.0)	1.14 (0.9-1.46)	56.2 (42.8-69.7)	1.05 (0.83-1.34)	68.4 (48.8-87.9)	0.77 (0.58-1.03)
Chinese	14.1 (10.6-17.7)	0.92 (0.71-1.2)	18 (14-22.1)	0.56 (0.44-0.70)^	30.7 (24-37.3)	0.57 (0.46-0.71)^	32.7 (23.4-41.9)	0.37 (0.28-0.49)^
First Nation	15.9 (12.0-19.9)	1.04 (0.81-1.34)	33.6 (27.3-40)	1.04 (0.85-1.26)	64.7 (53.3-76.2)	1.21 (1.01-1.45)*	96.9 (76.6-117.3)	1.09 (0.88-1.35)
Metis	10.3 (4.70-15.9)	0.67 (0.39-1.16)	26.8 (17.6-35.9)	0.83 (0.59-1.16)	79.2 (59.2-99.2)	1.48 (1.15-1.91)*	100.5 (65.7-135.3)	1.13 (0.80-1.60)
South Asian	8.30 (5.50-11.0)	0.54 (0.39-0.76)^	22.5 (17.3-27.8)	0.69 (0.55-0.88)^	35 (27.2-42.8)	0.66 (0.52-0.82)^	41.1 (30-52.3)	0.46 (0.35-0.61)^
South-East Asian	NR	NR	13.7 (5.2-22.1)	0.42 (0.23-0.78)^	NR	NR	NR	NR
Arab	16.1 (8-24.2)	1.00 (0.63-1.75)	35.1 (20.1-50.1)	1.08 (0.7-1.66)	49.7 (24.5-74.8)	0.93 (0.56-1.54)	NR	NR
Filipina	15.1 (9.8-20.4)	0.99 (0.69-1.41)	36.7 (27.7-45.7)	1.13 (0.88-1.45)	39.9 (27.5-52.3)	0.75 (0.55-1.02)	62.5 (40.1-84.9)	0.7 (0.49-1.01)
Latin American	NR	NR	27.8 (17.1-38.4)	49.7 (30.6-68.8)	NR	NR	NR	NR
Multi-ethnic	NR	NR	32.5 (13.3-51.8)	1.00 (0.55-1.81)	54.6 (22.3-86.9)	1.02 (0.57-1.85)	NR	NR
Japanese	NR	NR	NR	NR	NR	NR	77.9 (29.6-126.2)	0.88 (0.47-1.63)
White	15.3 (14.4-16.3)	1.00	32.5 (31.2-33.7)	1.00	53.4 (51.7-55,2)	1.00	88.7 (85.8-91.6)	1.00

Despite improvements in early detection and treatment of breast cancer, Black individuals continue to have the highest breast cancer mortality rate in the United States (227). Based on a modeling study conducted by Chapman et al., 2021 (224), Black individuals experience earlier onset, more severe disease, and higher mortality from breast cancer than White individuals. This modeling study concluded that initiation of biennial screening mammography ten years earlier in Black individuals could reduce mortality disparities by 57%, with acceptable trade-offs. However, this conclusion should be considered with caution as the authors did a benefit-to-harm analysis that mainly focused on early harms. There is also a risk of miscategorization, as they used crude racial categorizations for this analysis. Additionally this data was from the United States and may not be generalizable to Canada. Focus on race and ethnicity should not distract healthcare providers from consideration of other social determinants of health (e.g., income, rural/urban, environmental exposures, etc.) that influence not only access to and quality of health care but also the development of harder-to-detect/treat types of breast cancers such as HR-negative breast cancers (228).

Call-back, diagnostic wait times, and wait times to receive pathology report after a biopsy are already limited resources; these wait times will likely significantly lengthen with addition of routine screening in age 40-49 (more dense tissue, more call-backs, more biopsies, etc.)

- 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, the median age at diagnosis for non-White women is younger (52 to 60 years) than for White women (63 years). There were 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.

- The findings of increased mortality at younger ages among Black individuals aligns with evidence from the US (195). It is not known to what degree genetic factors (e.g., higher likelihood of developing triple negative cancer) versus environmental or social factors (e.g., access, structural racism, etc.) contribute to disparities in mortality.

Contextual question

A targeted library-assisted literature search found n=28 studies which provided conflicting results on race and ethnicity and breast cancer disparities. This could be due to the variation in comparisons found in these studies (e.g., immigrants vs Canadian born, immigrants vs long term residents, time lived in Canada vs long term time or Canadian born). Data was reported on the national or provincial level (i.e., Manitoba, British Columbia vs Ontario) and most studies used population level databases but the type and number of databases varied.

In general, breast cancer risk estimates vary between ethnicities, but may also vary within an ethnic group as it can vary among specific countries that might fall under the same ethnicity. For example, immigrants from Western Europe have a significantly higher risk; however, country-specific data show that only those from the UK are at significantly higher risk while the rest may be at higher or lower risk, but none reached statistical significance (196). Another example is while the risk is not significantly different for sub-Saharan African immigrants in Ontario or British Columbia compared to non-immigrants (196,197), it is significantly higher for those from Kenya in British Columbia (196). Preliminary data suggests cancer diagnosis may gradually converge to Canadian-born levels after years lived in Canada (198). Therefore, it is unclear if differences related to race and ethnicity may be influenced by immigration status (i.e., Canadian born vs. immigrants) and/or time lived in Canada.

There is a lack of studies reporting racial or ethnicity-specific breast cancer mortality and stage at diagnosis. A few studies have indicated that Indigenous population generally have poorer survival and is more likely to be diagnosed at later stage compared to non-Aboriginal. For example, Ontario non-First Nation individuals were 1.5 times more likely to have their breast cancer diagnosed by screening and First Nation individuals who were not screened were five times more likely to detect their breast cancer at a later stage (199).

Individuals of Ashkenazi Jewish are also at higher risk, although this is likely due to higher rates of BRCA1 and BRCA2 gene mutations (200). Individuals with dense breasts are likely also at higher risk for cancer and mortality from cancer (54).

We did not identify any studies in our systematic reviews or ancillary searches that provided data on disparities in health outcomes (e.g., morality, stage at diagnosis) for other population groups as per the PROGRESS+ factors (201).

Disparities in screening

In Canada, there are also disparities related to screening access and participation. Indigenous patients remain under-screened for breast cancer compared to non-Indigenous Canadians. (202–204) A key barrier to breast cancer screening among Indigenous populations is a strained relationship with the Canadian healthcare system due to past governmental policies regarding assimilation and a lack of cultural competency. (202,205) Moreover, Indigenous patients living in remote communities have the added challenges related to transportation to screening centres and sparse healthcare resources. (204,205) Low participation rates for breast cancer screening have been reported among immigrant and ethno-racial populations across Canada. (203,206–208) Barriers to breast cancer screening among these populations greatly vary and include limited access to a primary care provider, language barriers, limited health literacy, perceived conflicts with modesty, and limited trust in the health care system. (96,208,209) Physician characteristic can have an impact on screening rates for immigrants. Having a physician of the same region may significantly increase screening rates for some races/ethnicities (e.g., South Asian, Eastern Europe and Central Asian, Middle East and North Africa), but having a female physician (regardless of time lived in Canada) is associated with higher screening for all groups except immigrants from USA, Australia, and New Zealand (96).

Barriers for those living in rural and remote areas include proximity to screening centers and travel costs. Canadians of low socioeconomic status and living in low-income neighborhoods are less likely to undergo regular screening for breast cancer compared those of higher socioeconomic status. (9,210–213) The extent of the difference can vary among specific immigrant groups (e.g., between the highest and lowest income, in Ontario, Sub-Saharan African had the greatest difference (19%) and Caribbean and Latin American the lowest (3.6%)) (96). Key factors contributing to this disparity include lack of a healthcare provider, lack of transportation, conflicts with work, and low health literacy around the importance of screening.(214–216) Compounding the potential issue, several under-screened populations often intersect with one another (e.g., Indigenous patients living in remote communities, immigrants living in low-income areas) and share multiple barriers to breast cancer screening. Individuals who identify as LGBTQ2S+ are also less likely to undergo screening for breast cancer due to barriers such as discomfort around mammograms and potential for discrimination by healthcare providers. (217–219) Recently, inequities were further exacerbated by the COVID-19 pandemic through the delays in receiving mammograms, diagnosis, and treatment (220–222).

To address disparities in screening, several provinces and territories have employed targeted strategies to improve screening uptake among certain population groups (e.g., racial or ethnic minorities, individuals in rural or remote communities, Indigenous populations, individuals with low socioeconomic status, recent immigrants, and individuals who identify as LGBTQ2S+) (9), such as screening awareness campaigns, mobile screening clinics, and resources showcasing inclusive language (9).

Impact of screening age

		We do not have any direct evidence on the impact of lowering the age of screening on health inequities. Given that Black individuals experience higher rates of more aggressive cancer types at younger ages, there could potentially be a benefit of earlier screening in this group. However, the impact of screening on these subtypes is unknown . Other studies (mostly in the US) suggest lowering the age to initiate breast cancer screening according to ethnicity due to disparities in breast cancer outcomes among minority groups (87,223,224). A recent US modelling study showed that initiating breast cancer screening ten years earlier for Black patients (versus Caucasian) would reduce disparities in breast cancer mortality by 57% (224). However, it is unknown whether these results would apply to the Canadian context. Notably, there is limited information related to engagement in the screening, diagnostic, and treatment pathways by different population groups in Canada. While disparities are likely in part related to genetic factors, this is unlikely to be the only cause. Availability of timely diagnosis and effective treatments may also be important factors. As noted above, a number of barriers to accessing screening exist. Changing the screening age is unlikely to directly impact these factors, although it may help increase awareness of the importance of screening. A recommendation for screening in ages 50 to 74 probably has no impact on health equity, as it represents the status quo regarding the CTFPHC recommendations and aligns with screening policies and practice of most provinces and territories. *Impact of screening intervals* We have no direct evidence on the impact of varying screening intervals (e.g., annual versus biennial) on disparities in health outcomes. Evidence from our KQ2 suggests that annual screening may slightly reduce interval cancers among 50-62 but may make little-to-no difference for ages 40-49. However, it's unclear how these results might vary for more aggressive cancer subtypes. Evidence was limited related to the impact of different screening intervals for individuals with dense breasts. Barriers related to screening access might be of greater importance for shorter screening intervals (e.g., annual) given that it effectively doubles the amount of screening that patients need to access (compared to current recommendations). A recommendation for screening every 2 or 3 years probably has no impact on health equity, as it represents the status quo regarding the Task Force recommendations and aligns with screening policies and practice of most provinces and territories. *Impact of types of screening tests* If effective, screening modalities that improve breast cancer morbidity and mortality compared to digital mammography for higher risk populations (e.g., high breast density, family history, Black, First Nations or Metis individuals) could improve equity in screening. However, implementation of tomosynthesis, ultrasound or MRI only in certain jurisdictions (e.g., urban centres, higher socio-economic regions) would reduce overall equity. Evidence from KQ2 suggests that DBT may perform similarly to DM. A recommendation in favour of DBT as an additional screening modality could help increase access by giving patients more options for screening, although availability of technologists to carry out the screening may be a limiting factor. There was limited evidence regarding the impacts of supplemental screening with ultrasound or MRI for individuals with dense breasts.	

ACCEPTABILITY

Is the intervention acceptable to key stakeholders?

40-74

Eligible population, Healthcare providers and policy makers: (general population or moderately increased risk)

○ No
○ Probably no
X Probably yes
○ Yes
○ Varies
○ Don't know

75+

Eligible population: (general population or moderately increased risk)

○ No
○ Probably no
X Probably yes
○ Yes
○ Varies
○ Don't know

Healthcare providers and policy makers: (general population or moderately increased risk)

○ No
○ Probably no
○ Probably yes
○ Yes
○ Varies
x Don't know

Annual vs biennial or triennial:

Eligible population (General population risk)

○ No
○ Probably no
○ Probably yes
○ Yes
○ Varies
x Don't know

Eligible population

ACCEPTABILITY

SUMMARY JUDGEMENT – ACCEPTABILITY

A recommendation for breast cancer screening age 50-74 is probably acceptable to the eligible population (see participation rates in right column) and acceptable to governments and healthcare providers as it is the status quo.

40-49
Screening age 40-49 is probably acceptable but there may be some variability. KQ3 SR results show that in a relatively low net benefit scenario (e.g., 0.5 fewer per 1,000 screened) individuals 40-49 may not weigh the benefits as greater than the harms. But there were concerns as these studies did not involve diverse populations and were not conducted in Canada. Screening 40-49 is probably acceptable to healthcare providers but some may have concerns of overdiagnosis and additional testing +/- biopsy (no cancer). Additionally, the acceptability of shared decision-making (SDM) should also be considered. It is also unclear if SDM is acceptable to all healthcare providers due to the additional burden of time. A recommendation for lowering age of screening initiation to 40 years is probably acceptable to governments as the provinces who screen individuals in their 40s have managed to support such a program.

75+
Acceptability to primary care providers is unknown as they may need to focus more on other co-morbidities in their patients aged 75+. Nonetheless, it may be acceptable to patients 75+ that are healthy without co-morbidities. Acceptability to policy makers (governments) is unknown.

Screening intervals
It is uncertain how acceptable screening annually would be to eligible individuals (general population), but for those at moderately increased risk annual screening may be acceptable (Probably yes). Due to a lack of capacity to screen everyone annually and the increased burden of additional tests (no cancer) annual screening is probably not acceptable to healthcare providers and policy makers. However, this varies based on risk and it may be acceptable for those at moderately increased risk.

Screening modalities
DBT and supplemental ultrasound may be acceptable, if accessible, for eligible individuals, healthcare providers and policy makers but with some variation. Some primary care providers that have patients with increased breast density and would like clarity about next steps; at the same time, it may not be acceptable to many healthcare providers as it is a large burden on the healthcare system. Family physicians working in urban areas may likely accept as it may be of interest to their patients, however, those in more rural/remote areas would find it very challenging especially if there is no centres close by since their patients already face more barriers to attending regular screening (e.g., time off work). Some may be more comfortable with ultrasound than mammogram and patients may want tests despite lack of evidence for benefit. The cost of infrastructure and implementing of another modality (e.g., tomosynthesis) may be a barrier to acceptability for policy makers (governments).

The acceptability of supplemental MRI to the eligible population (moderately increased risk) varies based on accessibility and weighing of the benefits and harms. Supplemental MRI is probably not to not acceptable to healthcare providers due to the lack of data on benefits and increased burden on the healthcare system. It is unknown if supplemental MRI is acceptable to policy makers.

Acceptability to Patients
In 2017, 78.5% of Canadian females aged 50 to 74 years reported receiving a mammogram (screening or diagnostic) in the past three years (34). The only available data on Canadian organized screening programs was from 2011-2012 and showed a participation rate of 54% (age 50-69) with a range of 31.8% to 62.3% by province (9). This implies that screening is generally acceptable but with variation. Qualitative research (229–231) has shown that patients are generally accepting of screening for breast cancer due to the opportunity for early intervention and prevention of breast cancer related mortality. Data from KQ3 found that in a low net benefit scenario (1-2/1000 deaths prevented, 100-200/1000 additional tests (no cancer), 10-15/1000 overdiagnosed), individuals aged >50 years weighed the benefits as greater than the harms. However, KQ3 found that a majority of individuals aged 40-49 may not weigh the benefits as greater than the harms from screening under a low net benefit scenario (i.e., 0.5 fewer deaths and up to 300 additional tests (no cancer)). Further studies in a diverse Canadian population are needed to better understand patient values and preferences. A recent poll among 1510 Canadians reported that 89% believed routine screening should begin before age 50, although the results are not published which limits the ability to assess the results (e.g., demographics of participants, how questions were framed, etc.) (232).

Commonly perceived harms of breast cancer screening among patients include exposure to radiation, false negative results, pain and discomfort, psychological stress, unnecessary testing from additional testing +/- biopsy (no cancer) results, and overdiagnosis (229). In light of the various benefits and harms of screening for breast cancer, patients agree that it is important for them to have access to the information (i.e., benefits and risks of screening) that will enable them to make an informed decision regarding breast cancer screening. (229,230,233) Patients also value importance of screening being framed as a choice (230,233). Framing screening for breast cancer as a choice is especially important given variations in screening beliefs, access to screening, and personal values among patients (230,233).

Participation rate (ages 50-69, 2011-2012) in organized screening programs may show variability in preferences to screen (i.e., 54% participation rate (range 31.8% to 62.3%)). Screening participation also varies by age, with the highest participation rate in the 60-69 age group (59.8%) followed by the 50-59 (49.8%), 70+ (21.5%), and 40-49 age groups (9.2%). However, access to screening (rural/remote, equity, referral requirement for certain age groups) also affects uptake (9).

In 2017, 78.5% of Canadian females aged 50 to 74 years self-reported receiving a mammogram (screening or diagnostic) in the past three years (34).

Provincial screening policies:
<u>40-49</u>
NS (22) and PEI (21) recommend annual screening
<u>Moderate family history</u>
BC, AB, SK, ON, NS, PEI, NL and YK refer all patients with moderate family history for annual screening.
MB and NWT refer based on radiologist recommendation (e.g., 1-2 years) (9,242).
<u>Dense breasts</u>
AB and ON, refer all patients with extremely dense breasts (BIRADS D) for annual screening. YT, NT, NU, SK, PE, and NL recommend *more frequent screening* but does not indicate the interval and NB, NS base this on radiologist recommendations (9,242)

Ontario Health recommends that supplemental ultrasound, MRI or DBT for extremely dense breasts (BIRADS D) be publicly funded (243).

	(moderately increased risk) ○ No ○ Probably no X Probably yes ○ Yes ○ Varies ○ Don't know **Healthcare providers and policy makers (general population)** ○ No X Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know **Healthcare providers and policy makers (moderately increased risk)** ○ No ○ Probably no ○ Probably yes ○ Yes X Varies ○ Don't know **Tomosynthesis** **Eligible population, Healthcare providers and Policy makers (General population risk and moderately increased risk)** ○ No ○ Probably no **X** Probably yes ○ Yes ○ Varies ○ Don't know **Supplementary ultrasound** **Eligible population, Healthcare providers and Policy makers (Moderately increased risk)** ○ No ○ Probably no **X** Probably yes ○ Yes ○ Varies ○ Don't know	Organized breast cancer screening programs throughout Canada are mainly covered by provincial and territorial governments and therefore screening tends to be of low cost to patients. (234,235) However, some patients (e.g., those living in rural and remote areas) may face additional costs regarding transportation and accommodation to visit screening centers and to access follow-up care. Moreover, patients of low socioeconomic status may face costs associated with lost wages due to missed work or for childcare. In response to such barriers, provincial and territorial governments have implemented mitigation strategies to promote screening uptake and acceptability among patients (9). It is uncertain how acceptable screening annually would be to eligible individuals (general population), but for those at moderately increased risk annual screening may be acceptable. Due to a lack of capacity to screen everyone annually and the increased burden of additional tests (no cancer) annual screening is probably not acceptable to healthcare providers and policy makers. However, this varies based on risk and it may be acceptable for those at moderately increased risk. **Acceptability to Healthcare Providers** Screening for breast cancer is generally acceptable among healthcare providers in Canada, given its role in reducing cases of advanced breast cancer and related mortality. Patients who undergo screening for breast cancer often do so at the encouragement of their respective healthcare professionals. Qualitative studies suggest that healthcare providers are more likely to discuss the benefits of screening than the harms with their patients, suggesting further acceptability (229–231,233). However, concerns have been expressed among health care providers regarding the harms of breast cancer screening (236). In particular, there have been concerns about additional testing +/- biopsy (no cancer) results and overdiagnosed cases burdening healthcare systems through unnecessary testing and treatment (236). As such, acceptability of screening may be lower to some providers. A recommendation to begin screening at age 50 years represents the status quo. Lowering the recommendation to 40 years may be acceptable to healthcare providers. Canadian radiologists, as represented by the Canadian Association of Radiologists (237) and the Canadian Society of Breast Imaging (238), have argued that screening should begin at 40 years of age, in line with the USPSTF recommendation. However, qualitative studies interviewing Canadian healthcare providers highlights variations in views towards breast cancer screening in individuals aged 40 to 49 years (29–31,239). It is unknown what the acceptability of a reduced screening interval, or recommendation for different modalities as an additional screening modality would be to providers. Data from KQ2 and the model show an increase in additional tests (no cancer) with annual screening. The Canadian Association of Radiologists (237) and Canadian Society of Breast Imaging (238), support additional modalities and recommend: switching or upgrading digital mammography to tomosynthesis when it is time to replace end of life mammography to reduce abnormal recall rates and increase cancer detection rates as well as supplemental screening (MRI, contrast-enhanced mammography, ultrasound) in patients with dense breast tissue, or who are at high risk for breast cancer. **Acceptability to Governments** Screening for breast cancer is accepted and promoted by Canadian federal/provincial/territorial (FPT) governments. All Canadian provinces and territories (with the exception of Nunavut) have implemented organized breast cancer screening programs (9). Most provinces and territories are committed to increasing screening uptake among several underscreened populations through employing various strategies which include mobile screening clinics and culturally sensitive resources (9). Most provincial screening programs operate in line with CTFPHC recommendations for screening in individuals 50-74 years old. A recommendation to begin screening at age 50 years represents the status quo. Lowering the recommended age for initiation of breast cancer screening to 40 years may be acceptable to federal, provincial and territorial governments. Alberta and NWT recently lowered the recommended age for breast cancer screening to 45 years from 50 years of age (18,19). Patients in their 40s in BC, NS, PEI, and YT are able to self-refer to breast cancer screening (9). ON, NB and SK will also provide the self-referral breast cancer screening opportunity for the 40-49 age group in late 2024 - early 2025 (24–26). Patients aged 40 and above are eligible for breast cancer screening programs with referral from a healthcare provider in MB, NL, and QC (9). In 2023, the USPSTF lowered its recommended initiation age to 40 years from 50 years of age (240). It is unknown what the acceptability of a reduced screening interval or recommendation for different modalities as an additional screening modality would be to governments. Currently, some provinces (NS, PEI) screen ages 40-49 annually and others screen annually based on moderately increased risk (see right column). For those with dense breast, supplementary screening (e.g., ultrasound, MRI, tomosynthesis, contrast enhanced mammography) may improve cancer detection and the Health Technology Assessment found that it also leads to better outcome, but at an increased cost. Ontario Health, based on guidance from the Ontario Health Technology Advisory Committee, recommends publicly funding supplemental screening as an adjunct to mammography for people with extremely dense breasts (102,241). Resource (financial and human) implications for implementing these changes for all individuals 40+ could be considerable.	

	Supplementary MRI **Eligible population, (Moderately increased risk)** ○ No ○ Probably no ○ Probably yes ○ Yes X Varies ○ Don't know **Healthcare providers and policy makers (Moderately increased risk)** ○ No X Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know		
FEASIBILITY	**Is the intervention feasible to implement?** **40-74 (General population or moderately increased risk)** ○ No ○ Probably no **X** Probably yes ○ Yes ○ Varies ○ Don't know **75+ (General population or moderately increased risk)** ○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies X Don't know **Annual (General population risk)** ○ No X Probably no ○ Probably yes ○ Yes	**FEASIBILITY** **SUMMARY JUDGEMENT – FEASIBILITY** **A recommendation for screening in ages 50 to 74 using mammography is feasible, as it represents the status quo regarding the CTFPHC recommendations and aligns with screening policies and practice of most provinces and territories.** **A recommendation for lowering the age of screening initiation to age 40 is probably feasible to implement throughout Canada, given that self-referral policies are already in place (or plan to be in place) in many provinces. Additionally, we are aware of workforce challenges in carrying out screening across Canada according to the current recommendation. As such, there could be considerable challenges to implement screening at an early age, but the time required to address these challenges is uncertain. Therefore such recommendations may have varied impacts feasibility if provinces and territories have screening capacity issues. Feasibility of implementing organized program (i.e., with invitations) for those 40-49 is unknown.** **It was unknown whether it is feasible to increase the age to 75+, although some provinces allow self-referral if already in place.** **A recommendation for screening every 2 or 3 years is feasible, as it represents the status quo regarding the Task Force recommendations and aligns with screening policies and practice of most provinces and territories. The Task Force indicated that a recommendation for screening the general population every year was not or probably not feasible. However, a recommendation for screening moderately increased risk individuals may have varied impacts on feasibility if provinces and territories have different screening capacity issues. It may also have decreased feasibility for individuals with difficulties in accessing screening (e.g. disability or geographical location). However, screening annually within moderately increased risk populations is already occurring in many provinces (see right column).** **A recommendation for screening with tomosynthesis may have varied impacts on feasibility if provinces and territories have different capacities in providing screening using those tests.** **Screening moderately increased risk individuals with supplemental ultrasound was thought to be probably feasible but it was not feasible or probably not feasible to add supplemental MRI (see WG feedback in right column).** The feasibility of screening for breast cancer in Canada (ages 50-74) has been shown through the successful implementation of organized breast screening programs in all provinces and territories (excluding Nunavut)(9). The first Canadian organized breast screening program was established within British Columbia in 1988 and was quickly	Provincial screening policies (9,242): <u>40-49</u> NS (22) and PEI (21) recommend annual screening <u>Moderate family history</u> BC, AB, SK, ON, NS, PEI, NL and YK refer all patients with moderate family history for annual screening. MB and NWT refer based on radiologist recommendation (e.g., 1-2 years) (242). <u>Dense breasts</u> AB and ON, refer all patients with extremely dense breasts (BIRADS D) for annual screening. YT, NT, NU, SK, PE, and NL recommend *more frequent screening* but does not indicate the interval and NB, NS base this on radiologist recommendations. Ontario Health recommends supplemental ultrasound, MRI or DBT for extremely dense breasts (BIRADS D) be publicly funded (243). WG feedback - Similar to acceptability, the cost and resource required for a new modality might limit feasibility. - In isolation and not considering benefits or

	○ Varies ○ Don't know **Annual (Moderately increased risk)** ○ No ○ Probably no ○ Probably yes ○ Yes **X** Varies ○ Don't know **Tomosynthesis (General population or moderately increased risk)** ○ No ○ Probably no ○ Probably yes ○ Yes **X** Varies ○ Don't know **Supplementary ultrasound (Moderately increased risk)** ○ No ○ Probably no **X** Probably yes ○ Yes ○ Varies ○ Don't know **Supplementary MRI (Moderately increased risk)** X No X Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	followed by the rest of the provinces throughout the 1990s. By 2003, all provinces and most territories had implemented organized breast screening programs (244). As of 2024, these programs are still in effect, implying that infrastructure exists to ensure long-term feasibility of breast cancer screening in Canada. The feasibility of self-referral breast cancer screening of 40-49 age group has been shown in Nova Scotia, Yukon, British Columbia, and PEI (20–23). Ontario, Saskatchewan, and New Brunswick plan to lower the screening age to 40 in late 2024 (24–26). A recommendation for screening with other tests than digital mammography may have varied impacts on feasibility if provinces and territories have different capacities in providing screening using those tests. For example, Alberta has begun using tomosynthesis as a primary screening tool and some provinces recommend supplementary screening (e.g., ultrasound, MRI, tomosynthesis, contrast enhanced mammography) for those with extremely dense breasts (241,245–247). The cost and access considerations for MRI are greater than for ultrasound (248). Several factors contributing to health inequities may also affect the feasibility of breast cancer screening in Canada. For example, travel and accommodation costs can negatively impact feasibility of breast cancer screening for those living far away from screening centers. Moreover, patients who cannot afford to take days off from work or cover the costs of childcare to attend screening appointments may find screening less feasible (249). As primary care providers play a key role in several Canadian organized breast screening programs, those with limited access to them may also find screening for breast cancer less feasible, unless they have the option to self-refer. Ethnic minorities may also find screening for breast cancer less feasible with a lack of translated materials to navigate screening programs. However, several provinces and territories have employed strategies to mitigate these barriers, thus improving the feasibility of breast cancer screening in their respective jurisdictions (9). For example, several provinces and territories deploy mobile screening units to remote areas, match primary care providers to those without designated personnel, and distribute translated resources tailored to ethnic minorities (9). Lowering the initiation age of breast cancer screening from 50 years to 40 years, or lowering the interval of screening, will result in more patients who are eligible for screening, which will increase the quantity of healthcare resources required to support testing. The CTFPHC is aware of health workforce challenges related to breast cancer screening (e.g., availability of technologists) being experienced in many provinces. In jurisdictions where screening under the current recommendation of 50-74 is a challenge, lowering the age or interval of screening may not be feasible currently. However, we are uncertain as to how long these challenges may last, and published information on the feasibility of lowering the initiation age of breast cancer screening in Canada is limited. Thus, we cannot assess with certainty the positive and negative impacts of lowering the screening initiation age on feasibility of breast cancer screening. <u>Preliminary Model Results – Number of screens:</u> **Age group** | **Interval** | **Number of screens, per 1000 people** 40 - 74 | Annual | 31602.8 40 - 79 | Annual | 35218.4 45 - 74 | Annual | 27616.3 45 - 79 | Annual | 31231.8 50 - 74 | Annual | 23714.1 50 - 79 | Annual | 27329.6 40 - 74 | Biennial | 19130.9 40 - 79 | Biennial | 20712.9 45 - 74 | Biennial | 16817.5 45 - 79 | Biennial | 18997.7 50 - 74 | Biennial | 15171.6 50 - 79 | Biennial | 16753.6 40 - 74 | Hybrid | 23062.5 40 - 79 | Hybrid | 24644.3 45 - 74 | Hybrid | 19075.4 45 - 79 | Hybrid | 20657.3	harms, supplemental ultrasound seems like an easy modality and feasible, but expertise is required. - While MRI is less reliant on the technologists' ability to perform the test as compared to ultrasound, it is expensive. - We should not add a modality if benefits are not proven. - Access is already very difficult and we would need equal access for a new modality. - It also may not be feasible to start screening at 40 as there is already poor access for those with symptoms. Nevertheless, the feasibility is a small problem in comparison to the impact on the health care due to the cost of a mastectomy vs a mammogram and the provinces who start screening at age 40 have managed to support such a program. - Recommendations could be followed by increased funding from government to improve access to screening in underserved areas.

Summary of judgements

	JUDGEMENT (BY AGE GROUP – GENERAL POPULATION OR MODERATELY INCREASED RISK)					IMPLICATIONS
KQ1	**40-49**	**50-59**	**60-69**	**70-74**	**75+**	
PROBLEM	Yes	Yes	Yes	Yes	Yes	
DESIRABLE EFFECTS	Small	Small	Small	Small	Little to none	

	JUDGEMENT (BY AGE GROUP – GENERAL POPULATION OR MODERATELY INCREASED RISK)					IMPLICATIONS
UNDESIRABLE EFFECTS	Small	Small	Small	Small	Small	
CERTAINTY OF EVIDENCE	Very low	Very low	Very low	Very low	Very low	
VARIABILITY IN PVP	Possibly important variability	Possibly important variability	Possibly important variability	Possibly important variability	Possibly important variability	
UNCERTAINTY IN PVP	Possibly important uncertainty	Possibly important uncertainty	Possibly important uncertainty	Possibly important uncertainty	Possibly important uncertainty	
BALANCE OF EFFECTS	TBD	TBD	TBD	TBD	TBD	
RESOURCES REQUIRED	Moderate costs	Status quo	Status quo	Status quo	Moderate costs	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	No SR and model not graded for cost	No SR and model not graded for cost	No SR and model not graded for cost	No SR and model not graded for cost	No SR and model not graded for cost	
COST EFFECTIVENESS	Probably favours the intervention	Probably favours the intervention	Probably favours the intervention	Probably favours the intervention	Probably favours the intervention	
EQUITY	• Rec. for: Varies • Rec. against: Varies	• Rec. for: Probably no impact • Rec. against: Probably reduced	• Rec. for: Probably no impact • Rec. against: Probably reduced	• Rec. for: Probably no impact • Rec. against: Probably reduced	• Rec. for: Varies • Rec. against: Don't know	
ACCEPTABILITY	• Eligible population, healthcare providers & policy makers: Probably yes	• Eligible population: Probably yes • Healthcare providers & policy makers: Yes	• Eligible population: Probably yes • Healthcare providers & policy makers: Yes	• Eligible population, healthcare providers and policy makers: Probably yes	• Eligible population: Probably yes • Healthcare providers and policy makers: Don't know	
FEASIBILITY	Probably yes	Probably yes	Probably yes	Probably yes	Don't know	

- All judgements apply to general population (gen pop) and moderately increased risk (mod risk) groups (family history or dense breasts).

	JUDGEMENT (BY AGE GROUP – GENERAL POPULATION OR MODERATELY INCREASED RISK)				IMPLICATIONS
KQ2	**Annual screening (40+, general population or moderately increased risk) vs biennial or triennial**	**DBT (40+, general population or moderately increased risk) vs digital mammography (DM)**	**Supplementary ultrasound (40+, moderately increased risk) vs DM alone**	**Supplementary MRI (40+, moderately increased risk) vs DM alone**	
PROBLEM	Yes	Yes	Yes	Yes	
DESIRABLE EFFECTS	Little to none	Little to none	Don't know	Don't know	
UNDESIRABLE EFFECTS	Very small	Little to none	Very small to Small	Don't know	
CERTAINTY OF EVIDENCE	Very low	Very low	Very low	Very low	
VARIABILITY IN PVP	N/A	N/A	N/A	N/A	
UNCERTAINTY IN PVP	N/A	N/A	N/A	N/A	
BALANCE OF EFFECTS	TBD	TBD	TBD	TBD	
RESOURCES REQUIRED	Moderate costs	No data	No data	No data	

	JUDGEMENT (BY AGE GROUP – GENERAL POPULATION OR MODERATELY INCREASED RISK)				IMPLICATIONS
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	No SR and model not graded for cost	No data	No data	No data	
COST EFFECTIVENESS	Probably favours the intervention	No data	No data	No data	
EQUITY	• Rec. for or against: Don't know	• Rec. for or against: Don't know	• Rec. for or against: Don't know	• Rec. for or against: Don't know	
ACCEPTABILITY	• Gen. pop: Don't know • Mod. Risk: Probably yes • Healthcare providers and policy makers (gen. pop): Probably no • Healthcare providers and policy makers (mod. risk): Varies	• Eligible population, Healthcare providers and Policy makers: Probably yes (with some variation)	• Eligible population, Healthcare providers and Policy makers: Probably yes (with some variation)	• Eligible population, (mod risk): Varies • Healthcare providers, and policy makers: Probably no	
FEASIBILITY	• Annual (gen pop): Probably no • Annual (Mod risk): Varies	Varies	Probably yes	No – Probably no	

TYPE OF RECOMMENDATION	Strong recommendation against the intervention ○	**40-49, 75+, annual screening interval, Supplementary ultrasound or MRI** Conditional recommendation against the intervention X	**Tomosynthesis vs Digital mammography (50-74)** Conditional recommendation for either the intervention or the comparison X	**50-74** Conditional recommendation for the intervention X	Strong recommendation for the intervention ○
RECOMMENDATION	**<u>Recommendations</u>** Breast cancer screening is a personal choice. **Women[17] 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.** This information should be accessible and shared in absolute numbers[18]. 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, modeling 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). *<u>Benefits and harms</u>:* In ages 40 to 49, we found that the harms may outweigh the benefits. *<u>Patient values and preferences</u>:* 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. *<u>Race and ethnicity</u>:* 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.				

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

[18] 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 treatment. 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 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 or ethnically diverse populations. **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 or 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[19] 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.
JUSTIFICATION	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 (250). 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, recognizing 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 (251). 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 (224). 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

[19]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)

unknown(252). 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 (105). 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 (2), and age-specific incidence has increased for some groups, age-standardized mortality due to breast cancer has declined by approximately 47% since 1984 (41.7 deaths per 100,000 in 1989 to an estimated rate of 22.1 deaths per 100,000 in 2023)(3,8). 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) (253).

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 race and ethnicity (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.
SUBGROUP CONSIDERATIONS	Moderate family history and increased breast density: 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. • There is no direct evidence to estimate the benefits and harms of screening. To calculate a moderately increased risk group, we used an estimate from Engmann et al. (52) 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. We considered harms to be the same as they could not be estimated. Breast cancer deaths prevented in 1000 women screened over 10 years. • The benefit for 40-49 is estimated to be “0.44-1.51” (vs “0.27-0.94” for average risk) • The benefit for 50-59 is estimated to be “0.79-2.76” (vs “0.50-1.72” for average risk) • The benefit for 60-69 is estimated to be “1.04-3.59” (vs “0.65-2.24” for average risk) • The benefit for 70-74 is estimated to be “1.47-5.10” (vs “0.92-3.17” for average risk) Moderately increased risk due to a breast density is defined as category C (heterogeneously dense) or D (extremely dense) (254). • There is no direct evidence to estimate the benefits and harms of screening. To calculate a moderately increased risk group due to dense breasts, we used an estimate from the Swedish mammography trial (48) which suggested those with high breast density have a relative increased lifetime risk of 1.9. We considered harms to be the same as they could not be estimated. Breast cancer deaths prevented in 1000 women screened over 10 years. • The benefit for 40-49 is estimated to be “0.53-1.82” (vs “0.27-0.94” for average risk) • The benefit for 50-59 is estimated to be “0.95-3.28” (vs “0.50-1.72” for average risk) • The benefit for 60-69 is estimated to be “1.23-4.26” (vs “0.65-2.24” for average risk) • The benefit for 70-74 is estimated to be “1.74-6.03” (vs “0.92-3.17” for average risk) • While dense breasts can make cancer harder to identify, there is a lack of evidence on patient-important outcomes (e.g., mortality, stage at diagnosis) for additional screening (e.g., ultrasound, MRI). For women with moderately increased risk due to high breast density (Category C and D) or due to family history, 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. Race and ethnicity There’s not enough evidence for the Task Force to provide race- and ethnicity- specific screening recommendations. However, preliminary unpublished data (5) 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). Breast cancer incidence rates vary by race and ethnicity. • The median age at diagnosis for non-White women is younger (52 to 60 years) than for White women (63 years).

	• 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). Breast cancer mortality rates vary by race and ethnicity • The median age at death for non-White women is younger (55 to 71 years) than for White women (71 years). • 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* . • 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. Additionally, some non-White populations show a higher proportion of aggressive subtypes of breast cancer, 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%). There were 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 II or IV (13.1%) for Chinese women. Breast cancer risk estimates also may not be consistent across an ethnicity as it can vary among specific countries of the same ethnicity (196). There may also be variations in disparity of screening for specific population such as Indigenous populations, rural or remote populations, underserved populations (e.g., racial or ethnic minorities, low income, immigrants, and refugees), and individuals who identify as LGBTQ2S+ (4,194-196,202–205,209-211). Preliminary data suggests cancer diagnosis may gradually converge to Canadian-born levels after years lived in Canada (198). However, there is insufficient data to understand if differences related to race and ethnicity may be influenced by immigration status (i.e., Canadian born vs. immigrants) and/or time lived in Canada. Healthcare providers and individuals should be aware of the increased risk experienced by different racial or ethnic groups and consider them when balancing the benefits and harms of screening.
IMPLEMENTATION CONSIDERATIONS	This guideline is intended to inform primary care practitioners (general practitioners (family doctors), nurse practitioners), or other health professionals who provide accessible, continued, comprehensive, coordinated care and who are a patient's first health system contact (e.g., obstetrician-gynecologist). 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.

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

Inequities in the uptake of breast cancer screening exist in Canada. Inequities can be attributed to factors such as real and perceived barriers: geographical, cultural, stigma, cost to patients, and inadequate health literacy. Compounding the issue, several underscreened populations intersect and share multiple barriers. Recently, the COVID-19 pandemic has further exacerbated inequities, leading to delays in screening, diagnosis, and treatment.

Barriers to screening related to geographical factors (rural and remote areas) include proximity to screening centres and travel costs. Barriers related to socioeconomic factors (low socioeconomic status and living in low-income neighborhoods) include lack of a healthcare provider, lack of transportation, conflicts with work, and low health literacy around the importance of screening (4,202). Strategies used to promote breast screening uptake that address geographical and socioeconomic barriers include patient navigation, media and outreach educational campaigns, extended program hours, direct mailing of invitations, and offering services to those without a healthcare provider (9).

Barriers to individuals who identify as LGBTQ2S include discomfort around mammograms and potential for discrimination by healthcare professionals. (217–219) Strategies in place to increase screening uptake among individuals who identify as LGBTQ2S in Canada are focused on developing educational materials with inclusive language and providing guidelines specific to LGBTQ2S patients (9).

Key barriers to screening among Indigenous populations include lack of access and a strained relationship with the Canadian healthcare system due to past government policies regarding assimilation and a lack of cultural competency. (202,205) Interventions to increase screening uptake among First Nations, Inuit, and Metis communities include working with these communities to develop culturally appropriate resources to strengthen patient-provider relations. Strategies already being used in Canada include tailored education programs, culturally safe resources, patient navigation, and cultural competency training for healthcare providers. Transportation to screening clinics and mobile screening (9).

Barriers to screening among immigrant and ethno-racial populations across Canada include limited access to a healthcare provider, language barriers, limited health literacy, perceived conflicts with modesty, and limited trust in the healthcare system. (96,208,209) Strategies to increase screening uptake in these populations include providing translated and culturally safe resources, education sessions for new immigrants and cultural groups, and cultural competency training for healthcare providers (9).

Barriers to screening may also include differences in views between patients and healthcare providers. Healthcare providers must be aware of the increased risks due to family history, breast density and race and ethnicity (e.g., Black, Indigenous, Filipina) and include this when discussing the benefits and harms. Additionally, shared decision-making involves an accurate and balanced discussion of the benefits and harms which respects the views of the patient. Strategies to resolve these issues include using clear and explicit language in the recommendations and communications, along with tools to facilitate discussions. In light of the various benefits and harms of screening for breast cancer, patients agree that it is important for them to have access to information (i.e., benefits and risks of screening) that will enable them to make an informed decision regarding breast cancer screening. (91,92,94) Patients also value importance of screening being framed as a choice (92,94). Framing screening for breast cancer as a choice is especially important given variations in screening beliefs, access to screening, and personal values among patients (92,94).

	Breast cancer screening should only be considered for people with a reasonable life expectancy and in good enough health to undergo tests and treatments.
MONITORING AND EVALUATION	The Task Force will perform annual surveillance review of new systematic review and randomized controlled trials using the Prevention Plus platform. Additionally, there will be a comprehensive guideline review at 5 years.
RESEARCH PRIORITIES	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 and 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. 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.

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