November 22 2018

Script for Breast Cancer Screening Guideline Stakeholder Presentation

[Slide 1]

Recommendations on screening for breast cancer in women (2018)

[Slide 3]

Members of the breast cancer screening working group:

Task Force members

- Scott Klarenbach (Chair)
- Brett Thombs
- Harminder Singh
- Gaby Lewin
- Guylène Thériault
- Marcello Tonelli

Task Force spokespersons

- Ainsley Moore
- Donna Reynolds
- Guylène Thériault

Non-voting members

Public Health Agency of Canada

- Susan Courage
- Alejandra Jaramillo Garcia
- Nicki Sims-Jones

Evidence Review and Synthesis Centres

- (AB) Lisa Hartling, Jennifer Pillay, Robin Featherstone, Ben Vandermeer, Tara MacGregor
- (ON) David Moher, Julian Little, Pauline Barbeau, Adrienne Stevens, Andrew Beck, Becky Skidmore

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Overview of webinar

- **Presentation**
    - Background on breast cancer
    - Methods of the CTFPHC
    - Recommendations
    - Rationale for recommendations
    - Considerations for implementation
    - Conclusions
- **Questions and Answers**

November 22 2018

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Heading

Screening for Breast Cancer: Background

[Slide 6]

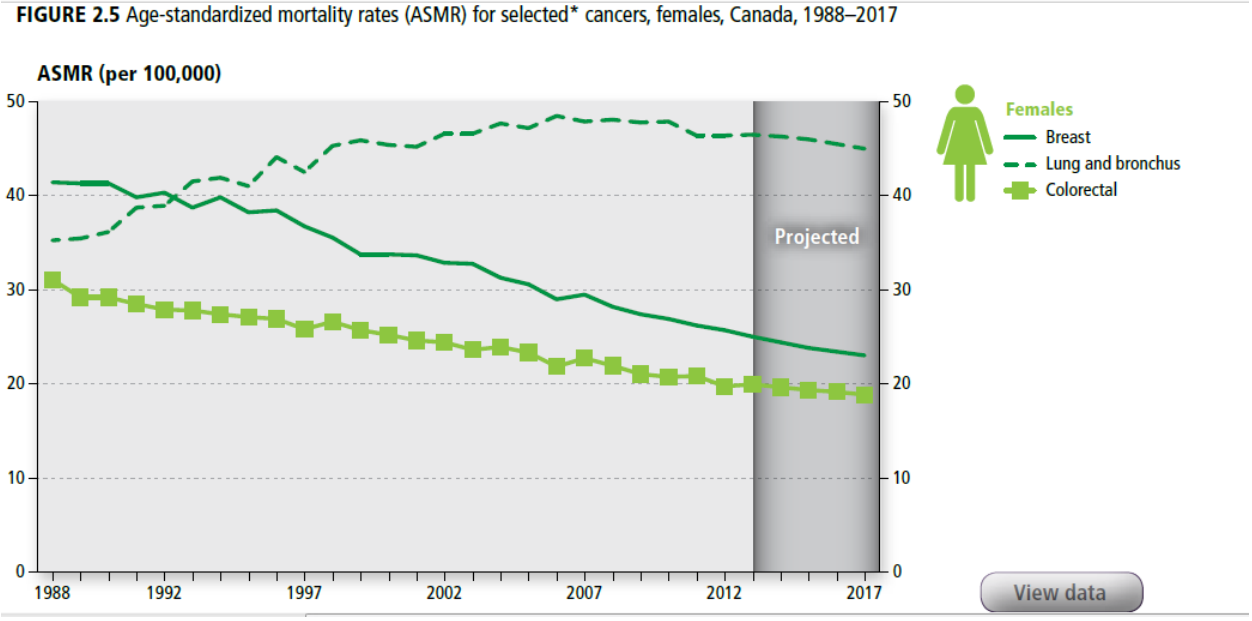
Breast cancer in Canada

- Second leading cause of cancer death among Canadian women
- Age-standardized incidence has remained stable since 2004
  - 130.1 per 100,000 women
- Declining breast cancer mortality rates among Canadian women
  - 41.7 per 100,000 women (1986)
  - 23.4 per 100,000 women (2016, projected)
- Possible factors:
  - Positive impact from breast cancer screening programs
  - More effective treatment for breast cancer
  - Both of the above
- Current uptake of screening
  - 54% of Canadian women aged 50 to 69 screened (2014; over 30 month period; within screening programs)
  - The number of women screened outside of a program is unknown

[Slide 7]

Age-standardized mortality rate female cancers 1988-2017

Graph of Canadian Age Standardized Mortality Rates of Female Cancers



Breast cancer mortality rates are declining in the context of relatively stable incidence rates indicating a positive impact from screening, treatment or both. However despite this progress, breast cancer remains a significant health issue for Canadian women. Hence the desire to revisit the 2011 task force breast cancer screening guideline.

[Slide 8]

Guideline scope:

- This guideline *updates* the task force's previous recommendations (2011) for primary care providers on breast cancer screening for women aged 40 to 74 years **not at increased risk** of breast cancer.
- Characteristics of women at **increased** risk include;
  - personal or family history of breast cancer;
  - carriers of gene mutations such as BRCA1 or BRCA2 or who have a first-degree relative with these gene mutations;
  - chest radiation therapy before 30 years of age or within the past eight years.

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Heading

Screening for Breast Cancer: Methods

[Slide 10]

Canadian Task Force on Preventive Health Care

- Independent body of up to 15 clinicians and methodologists
- Mandate:
  - develop evidence-based clinical practice guidelines that support primary care providers in the delivery of preventive healthcare
- Ultimately the goal of the task force is to improve the health of Canadians by making sure that primary care providers have access to clinical prevention guidelines which are based on the best available evidence.

[Slide 11]

Evidence Review and Synthesis Centres

- Undertake a systematic review of the literature based on the analytical framework
- Prepare a systematic review of the evidence with GRADE tables
- Participate in working group and CTFPHC meetings

[Slide 12]

Task Force Review Process

- **Internal review process involving**:
  - Guideline working group and other CTFPHC members
- **External review undertaken at key stages**:
  - Protocol, systematic review(s) and guideline
- **External stakeholder reviewer groups:**
  - Generalist and disease specific stakeholders
  - Federal and Provincial/Territorial stakeholders
  - Academic peer reviewers

— **CMAJ undertakes an independent peer review process** to review guidelines before accepting for publication

[Slide 13]

Breast cancer screening recommendations based on two reviews:

<u>Part A</u>: An Evidence report to inform an update of the Canadian Task Force on Preventive Health Care 2011 guideline

Barbeau P, Stevens A, Beck A, Skidmore B, Arnaout A, Brackstone M, et al.

(Prepared by the Knowledge Synthesis Group, Ottawa Methods Centre, Ottawa Hospital Research Institute for the Canadian Task Force on Preventive Health Care under contract by the Public Health Agency of Canada). CTFPHC; October 2017.

<u>Part B</u>. Systematic review on women's values and preferences to inform an update of the Canadian Task Force on Preventive Health Care 2011 guideline.

Pillay J, MacGregor T, Hartling L, Featherstone R.

(Prepared by the Alberta Evidence Review Synthesis Centre for the Canadian Task Force on Preventive Health Care under contract by the Public Health Agency of Canada). CTFPHC; October, 2017.

Both will be available on the task force website: www.canadiantaskforce.ca

The first is an overview of reviews on outcomes of screening while the second explores women's values and preferences around breast cancer screening. They will be posted on the task force website when the guideline is published.

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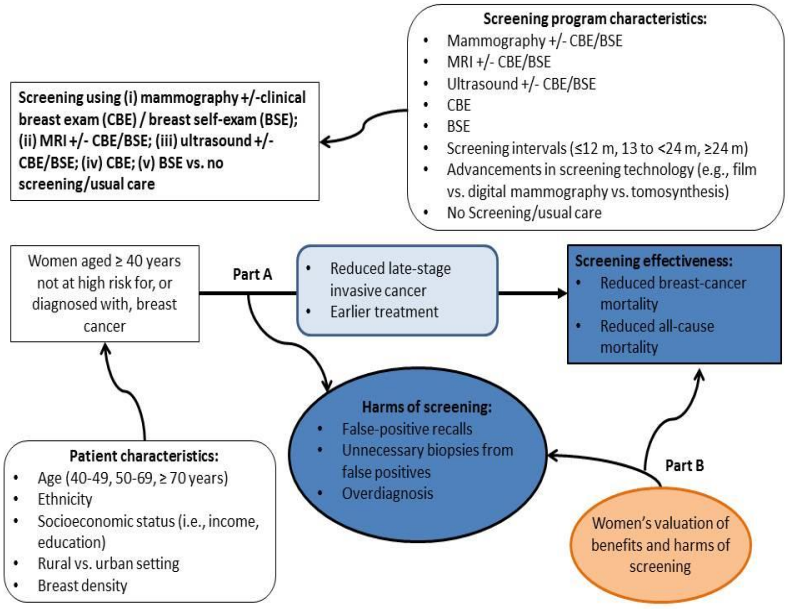
Analytic Framework



Part A: Benefit and harm outcomes
Part B: Women's value and preferences

This analytic framework guided the two evidence reviews conducted for the guideline.

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Heading

The "GRADE" System: Grading of Recommendations, Assessment, Development & Evaluation

[Slide 16]

GRADE Process (1) Defining the question and collecting evidence

- Define questions in terms of populations, alternative management strategies and patient-important outcomes.
- Characterise outcomes as critical or important to developing recommendations.
- Systematic search for relevant studies by ERSC(s).
- Based on pre-defined criteria for eligible studies generate best estimate of the effect of the intervention on each critical and important outcome
- Assess certainty of evidence associated with that effect estimate.

[Slide 17]

GRADE Process (2) – rating certainty of evidence

In GRADE Approach:

- RCTs start as high-certainty evidence and observational studies as low-certainty evidence
- RCT data prioritized over observational
- Rating of certainty is modified downward for each outcome across studies in relation to:
  - Study limitations (Risk of Bias)
  - Imprecision
  - Inconsistency of results
  - Indirectness of evidence
  - Publication bias likely (part of the upgrading criteria below)
- Rating of certainty is modified upward for each outcome across studies in relation to:
  - Publication bias (undetected)
  - Large magnitude of effect
  - Dose response
  - No evidence for plausible confounders likely minimizing the effect

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GRADE Process (3) Rating certainty of evidence and grading recommendations

What are we grading?

1. Certainty of Evidence

Degree of confidence that the available evidence **correctly reflects the theoretical true effect** of the intervention or service

High, moderate, low, very low

2. Strength of Recommendation

The balance between the **certainty of supporting evidence**; the certainty about the **balance between desirable and undesirable** effects; the certainty/variability in **values and preferences** of individuals; and the certainty about whether the intervention represents a **wise use of resources**

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Heading

Screening for Breast Cancer: Recommendations

[Slide 20]

Recommendations for breast cancer screening for women aged 40 to 74 years not at increased risk:

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 two to three 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 two to three 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)*

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Recommendations on other screening modalities, apart from mammography, for breast cancer screening:

- *We recommend not using MRI, tomosynthesis or ultrasound to screen for breast cancer in women 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)*

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Outcomes of breast cancer screening

Benefits

- All-case mortality
  - Evidence from trials indicates no significant difference in all-cause mortality as a result of screening.
- Breast cancer mortality
  - Results of breast cancer mortality reported in subsequent slides.

Harms

- Overdiagnosis with adverse sequelae from unnecessary treatment
- Consequences of false positives (including biopsies)

- Results of harms reported in subsequent slides.

[Slide 23]

Evidence on benefits of breast cancer screening (Barbeau et al, 2017)

- Eight RCTs or quasi-RCTs identified with information on benefits of breast cancer screening using mammography
  - Initiated from 1963 to 1991 in Sweden, Canada, US and UK.
  - Between 18,000 to 160,000 women were randomized in the trials with a mean follow-up from 18 to 30 years.
  - Screening intervals between 12 and 33 months.
  - Duration of the screening period was from 3 to 12 years (median 7 years).
  - Participation rates of 65% to 88%.
- Certainty of the evidence from these trials assessed as being lower than in the review from 2011 due to *very serious* concerns around risk of bias.

These are the same trials used in the earlier guideline and they remain the best evidence available on the benefits of breast cancer screening. Examples of risks of bias are failure to conceal allocation, failure to blind, loss to follow-up and failure to consider intention-to-treat.

[Slide 24]

Benefit of screening: Breast cancer mortality (Barbeau et al, 2017)

Age	Relative Risk (95% CI)**	Absolute effect per 1,000 (95% CI)	Number needed to screen (95% CI)	GRADE Rating of Certainty of Evidence
40-49	0.85 (0.78 to 0.93)	0.58 fewer (0.27 fewer to 0.85 fewer)	1,724 (1,176 to 3,704)	⊕⊕OO LOW[A]
50-59	0.85 (0.78 to 0.93)	0.75 fewer (from 0.35 fewer to 1.10 fewer	1,333 (909 to 2,857)	⊕OOO VERY LOW[B]
60-69	0.85 (0.78 to 0.93)	0.92 fewer (from 0.43 fewer to 1.35 fewer)	1,087 (741 to 2,326)	⊕⊕OO LOW[A]
70-74	0.85 (0.78 to 0.93)	1.55 fewer (from 0.72 fewer to 2.27 fewer)	645 (441 to 1,389)	⊕OOO VERY LOW[C]

** A subgroup analysis of relative risk by age was assessed based on published methodology (31, 32). No difference in relative risk among subgroups was detected and true differences due to age were deemed unlikely. The use of the all ages relative risk data rather than focusing on each age decade aligns with this assessment. (Calculations provided in Appendix IV).

NB – absolute effect per 1,000 women screened over median of 7 years (range 3-12).

NB – no differences in all-cause mortality.

[Slide 25]

Evidence on harms of breast cancer screening
(Barbeau et al, 2017)

- ***Overdiagnosis:*** cancer that would not have become apparent in a woman's lifetime or caused harm if not detected through screening
  - New evidence from a Canadian RCT (*moderate* risk of bias) (Baines, To & Miller, 2016)
  - Calculated the difference between the cumulative numbers of invasive and in situ breast cancers in the *screened* arm and the *control* arm of the CNBSS over time
  - More on overdiagnosis in next slide.
- ***False positives:*** positive screen in women who do not have breast cancer
  - leads to repeat testing and in some cases biopsy
  - Calculated from CPAC data

[Slide 26]

Overdiagnosis and breast cancer screening

- Concern around overdiagnosis in breast cancer screening supported by:
  - Where screening has been introduced, increases in breast cancer incidence are not met by a corresponding decline in the number of advanced cancers diagnosed
  - The number of breast cancers diagnosed in populations of women being screened remains higher than those unscreened over decades – this difference should reduce over time in the absence of overdiagnosis as cancers are assessed in other ways or become symptomatic
- US and UK national guideline developers estimate that for every woman who avoids a breast cancer death, between 2 to 3 are overdiagnosed and suffer adverse sequelae from unnecessary treatment (surgery, radiation chemotherapy, hormone therapy).

[Slide 27]

Harm of screening: Estimated proportion of breast cancers overdiagnosed from screening

		Percentage of Breast Cancers Estimated as Overdiagnosed	
Age of Women at Initial Screen	**Years Post Screen**	**Invasive and In Situ Cancers**	**Invasive Cancers**
40 to 49	5	41%	32%
	20	55%	48%
50 to 59	5	25%	16%
	20	16%	5%

Notes:

- Overdiagnosis by age estimated using this calculation: *The numerator is the difference in numbers of cancers in the mammography arm less those in the control arm; and the denominator is the number of screen-detected cancers in the mammography arm* (34).
- Only the findings from the estimate on overdiagnosis from a Canadian RCT (34) are included because it provided an estimate by age and was appraised as being at *moderate* risk of bias (15).

[Slide 28]

Harm of screening: False positives and unnecessary biopsies from an estimated cohort of 1,000 women

False Positives and Unnecessary Biopsies from an Estimated Cohort of Women in a Breast Screening Program[1]				
	40-49 years	50-59 years	60-69 years	70-74 years
Per 1,000 women screened (3 cycles of screening for which women are screened every 2-3 years, for a total of 6-9 years of a screening period) [2]				
FP Mammography	294	294	256	219
Biopsies on FP	43	37	35	30
	40-49 years	50-59 years (M)	60-69 years	70-74 years
Per one breast cancer death prevented				
FP Mammography (based on 3 cycles of screening)[2]	508	392	278	141
Biopsies on FP (based on 3 cycles of screening) [2]	74	50	38	19

* As the median duration of screening trials was 7 years (range 3-12 years), the impact of this duration of screening on benefits and harms was used

M: Calculated using the Moderate baseline risk for this age group (15)

[1]The data is used to approximate a cohort of women entering the screening program. Although assumed, but not confirmed, the 'initial screen' in the CPAC report is the first screen documented in the database, and may not necessarily be the first 'true' screen of a woman. This is especially true for data originating from Alberta.

[2]Calculation: Initial screening cycle + 2 (subsequent screening cycle) to estimate harms occurring with 7 years of screening.

[Slide 29]

Evidence on Other Breast Cancer Screening Modalities (Barbeau et al 2017)

- Breast self examination
  - No difference in breast cancer mortality
- Clinical breast examination
  - No evidence meeting criteria of effectiveness for breast cancer screening
- Other screening modalities (including tomosynthesis, MRI and ultrasound)
  - No evidence meeting criteria of effectiveness for breast cancer screening

[Slide 30]

Heading

Patient Values and Preferences on Breast Cancer Screening

[Slide 31]

Patient values and preferences on breast cancer screening (Pillay et al 2017)

- Identified 29 studies
- Assessed the **relative importance** women placed on anticipated **benefits** and **harms** from breast cancer screening
- Assessed how these valuations may have influenced screening decisions:
  - Published between 2000 and 2017 (most after 2010).
  - Conducted in 11 different countries (one in Canada)
  - 5 qualitative studies, 9 RCTs, one single-arm trial 8 cross-sectional surveys 3 three uncontrolled pre-post studies 2 stated preference studies and a single deliberative jury.

- Studies varied widely in how information on benefits and harms was presented
  - in general provided high benefit-to-harm ratio information

[Slide 32]

Patient values and preferences (cont.) (Pillay et al, 2017)

After receiving information on absolute benefits and harms

Women aged 40 to 49 years:
- Substantial proportion of women chose not to be screened

Women aged 50 to 69 years:
- Many, but not all, chose to be screened
  - Reductions in breast cancer mortality from screening strongly valued by women
  - Compared with breast cancer mortality harms (overdiagnosis, false positives) weigh considerably less in decision of women to screen.

Women aged 70 years and older:
- Many, but not all, chose to be screened
  - Acceptance of continuing to be screened quite high.

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Heading

Screening for Breast Cancer: Rationale for recommendations

[Slide 34]

Key points :

- Low-certainty evidence indicates that screening for breast cancer with mammography results in a modest reduction in breast cancer mortality for women aged 40 to 74 years
  - the absolute benefit is lowest for women less than 50 years of age
- Screening leads to overdiagnosis resulting in unnecessary treatment of cancer
- Screening leads to false positive results that can lead to both physical and psychological consequences.
  - Overdiagnosis and false positives with related biopsies are more common in younger women.

NB: Low-certainty evidence for all women aged 40 to 74 years (Barbeau et al 2017).

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Key points (cont.)

- Evidence on women's values and preferences about screening suggests when informed of outcomes for their age group:
  - A substantial proportion of women aged 40 to 49 years would not choose to be screened
  - Older women often choose screening given the more favourable balance of benefits and harms

In light of:

  - low-certainty evidence for benefits and harms from breast cancer screening
  - variability in patient preferences

- **Shared decision-making** with a care provider should occur:
  - all women aged 50 to 74 years
  - support them to make an informed choice on screening
  - informed and based on individual values and preferences.

[Slide 36]

Women aged 40 to 49 years not at increased risk

- Very small and uncertain reduction in breast cancer mortality.
- Higher risk of overdiagnosis with resulting unnecessary treatment and consequences of false positive than for older women.
- Values and preferences of women this age indicate many would not want to be screened.

Risk/benefit analysis, and patient preferences, lead to a recommendation against screening women of this age although;

- This recommendation is conditional as some women may wish to be screened based on their values and preferences.
- Health care providers should engage in shared decision-making with women of this age who express an interest in being screened.

[Slide 37]

Women aged 50 to 69 years not at increased risk

- Modest reduction in breast cancer mortality.
- While lower than for younger women, risks of overdiagnosis resulting in unnecessary treatment and consequences from false positive results remain.
- Women of this age value the reduction in breast cancer mortality which results from screening, despite risk of harms.

Risk/benefit analysis, and patient preferences, lead to a recommendation in favour of screening women of this age, however:

- Health care providers should engage these women in shared decision-making 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.

[Slide 38]

Women aged 70 to 74 years not at increased risk

- Modest reduction in breast cancer mortality.
- While lower than for younger women, risks of overdiagnosis resulting in unnecessary treatment and consequences from false positive results remain.
- Women of this age see value in continuing to be screening, despite risk of harms.

Risk/benefit analysis, and patient preferences, lead to a recommendation in favour of screening women of this age, however:

- Health care providers should engage in shared decision-making with these women 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.

[Slide 39]

Heading

Screening for breast cancer: Considerations for implementation.

[Slide 40]

<u>Conditional</u> recommendations:

- Used when
  - desirable effects *probably* outweigh the undesirable effects or
  - undesirable effects *probably* outweigh the desirable effects but appreciable uncertainty exists.
- Variety of reasons why a recommendation may be 'conditional'
  - Balance of benefits and harms very close
  - Low certainty in estimates of effect
  - Variability or uncertainty of patient values and preferences
- Recommendations highlight considerations that are important to operationalize at the provider-patient level
  - Range of values and preference in women will influence whether they chose to be screened, or not.
  - Important to engage in shared decision-making with some patients
    - Recognize that different choices will be appropriate for individual patients
    - Assist each person to make a decision consistent with their values and preferences

The task force used to use the term 'weak' to describe recommendations where some uncertainty existed – unfortunately, clinicians sometimes thought that recommendations described as 'weak' were less important. The use of the term conditional makes our intent clearer.

[Slide 41]

Other national breast cancer screening recommendations:

- United States Preventive Services Task Force, 2016
  - Recommends biennial screening mammography for women aged 50 to 74 years
  - Individual decision based on values for women 40 to 49
  - Current evidence *insufficient* to assess benefits and harms of digital breast tomosynthesis as a primary screening method.
  - Current evidence *insufficient* to assess the balance of benefits and harms of adjunctive screening for breast cancer following a negative mammogram in women with dense breasts.
- More on screening women with dense breast tissue on subsequent slide.

The current guidelines conform to those of other national guideline developers; some specialist cancer organizations may have differing recommendations. There is agreement that women aged 50 to 70 years of age are more likely to benefit from being screened than younger women.

[Slide 42]

Screening women with dense breast tissue

Summary of information from USPSTF guideline (2016):

- Approximately 43% of women aged 40 to 74 years living in the US classified as having dense breasts.
- Compared with women with average breast density these women have an RR of 1.23 to 1.30 of developing breast cancer depending on age.

- Women with dense breast tissue do not have an increased risk of dying following diagnosis of breast cancer according to data from the US.
- Reclassification of breast density status from year to year complicates a woman's assessment of her underlying breast cancer risk.
- Adjunctive screening following a negative mammogram results in:
  - Unknown health benefits
  - Most positive results are false positives leading to increased recalls and biopsy rates
  - Unknown effects on overdiagnosis rates

No screening guidelines from other jurisdictions recommend adjunctive screening of women with dense breast tissue following a negative screening mammogram.

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Other national breast cancer screening recommendations (cont)

- National Health Services, United Kingdom, 2016
  - Recommends that all eligible women aged 50 to 70 be invited to breast cancer screening every three years.
- Cancer Australia, 2015
  - Recommends that women aged 50–74 years attend the Breast Screen Australia Program for free two-yearly screening mammograms having considered the benefits and downsides
  - Individual choice for younger and older women – not invited to screening

[Slide 44]

Knowledge gaps

- Greater certainty in true benefits of breast cancer screening
  - Particularly <50 and >70 year age groups
  - AgeX cluster RCT in younger and older women in UK (results 2026)
- High quality evidence on alternate modalities
  - Tomosynthesis, MRI, U/S
  - To characterize benefits and **harms** (significant concern of overdiagnosis and false positives)
- Breast density:
  - Definition and approach to classification
  - Rigorous comparative studies to determine patient-important outcomes of supplemental screening
- Greater understanding of the risk of overdiagnosis from screening
- Additional studies on women's values and preferences for screening
  - Canadian populations – particularly national
  - Accurate estimates of both benefits and harms.
- Better estimates of the costs of breast cancer screening

Slide 45

Knowledge translation (KT) tools

- A KT tool has been developed to **help clinicians and women understand** the breast cancer screening guideline

- After the public release, this tool will be **freely available** for download in both **French** and **English** on the website: http://canadiantaskforce.ca

[Slide 46]

Other considerations for implementation

- Mammography vs. other modalities for screening:
  - No evidence on patient-important outcomes of screening with other modalities
- Screening intervals:
  - Every two to three years because intervals in the trials ranged from 12 to 33 months with similar benefits
- Women with dense breast tissue:
  - Current evidence insufficient to assess the balance of benefits and harms of adjunctive screening for breast cancer following a negative mammogram in women with dense breasts.

[Slide 47]

Heading

Screening for Breast Cancer: Conclusions

[Slide 48]

Conclusions

- Recommendations for screening women for breast cancer remain similar to 2011.
- Breast cancer screening has the *potential* to reduce breast cancer mortality; it increases risk of harms.
- Assessment of values and preferences of women
  - Support direction of recommendations
  - Indicate not all women should undergo screening depending on their values and preferences.
- Emphasis on shared decision making
  - Women should be supported to make an informed decision on screening that fits with their values and preferences .

[Slide 49]

More information

For more information on the details of this guideline please see:

- Canadian Task Force for Preventive Health Care website: http://canadiantaskforce.ca

[Slide 50]

Thank you