

Breast Density and Risk of Interval Cancers: The Effect of Annual Versus Biennial Screening Mammography Policies in Canada

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Abstract

Regular screening mammography reduces breast cancer mortality. However, in women with dense breasts, the performance of screening mammography is reduced, which is reflected in higher interval cancer rates (ICR). In Canada, population-based screening mammography programs generally screen women biennially; however, some provinces and territories offer annual mammography for women with dense breast tissue routinely and/or on recommendation of the radiologist. This study compared the ICRs in those breast screening programs with a policy of annual vs. those with biennial screening for women with dense breasts. Among 148,575 women with dense breasts screened between 2008 to 2010, there were 288 invasive interval breast cancers; screening programs with policies offering annual screening for women with dense breasts had fewer interval cancers 63/70,814 (ICR 0.89/1000, 95% CI: 0.67-1.11) compared with those with policies of usual biennial screening 225/77,761 (ICR 1.45 /1000 (annualized), 95% CI: 1.19-1.72) i.e. 63% higher ($p = 0.0016$). In screening programs where radiologists' screening recommendations were able to be analyzed, a total of 76,103 women were screened, with 87 interval cancers; the ICR was lower for recommended annual (65/69,650, ICR 0.93/1000, 95% CI: 0.71, 1.16) versus recommended biennial screening (22/6,453, ICR 1.70/1000 (annualized), 95%CI: 0.70, 2.71)($p = 0.0605$). Screening program policies of annual as compared with biennial screening in women with dense breasts had the greatest impact on reducing interval cancer rates. We review our results in the context of current dense breast notification in Canada.

Résumé

La mammographie régulière de dépistage abaisse la mortalité par cancer du sein. Cependant, chez les femmes dont les seins sont denses, les performances de la mammographie de dépistage sont réduites, ce qui se manifeste par des taux de cancers dans l'intervalle (ICR) plus élevés. Au Canada, les programmes de mammographies de dépistage basés sur la population contactent habituellement les femmes tous les deux ans. Certaines provinces et des territoires proposent de façon régulière une mammographie annuelle aux femmes ayant un tissu mammaire dense et/ou sur recommandation du radiologiste. Cette étude a comparé les ICR chez les femmes ayant un tissu mammaire dense et participant à ces programmes de dépistage sur une base

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annuelle ou tous les deux ans. Parmi les 148 575 femmes ayant des seins denses examinées entre 2008 et 2010, il y a eu 288 cancers du sein invasifs dans l'intervalle. Les programmes de dépistage appliquant une politique d'examen annuel pour les femmes ayant des seins denses ont eu moins de cancers de l'intervalle (63/70 814, soit 0,89 ICR/1000, IC à 95 % : 0,67 à 1,11) que les programmes appliquant une politique d'examen tous les deux ans (225/77 761, 1,45 ICR/1000 [annualisés], IC à 95 % : 1,19 à 1,72), c.-à-d. 63 % de plus ($P > 0,0016$). Dans les programmes de dépistage où les recommandations des radiologistes ont pu être analysées, un total de 76 103 femmes a été examiné avec 87 cancers dans l'intervalle; l'ICR a été plus faible lorsque l'examen annuel était recommandé (65/69 650, 0,93 ICR/1000, IC à 95 % : 0,71 à 1,16) par rapport à la politique recommandée de dépistage tous les deux ans (22/6 453, 1,70 ICR/1000 [annualisés], IC à 95 % : 0,70 à 2,71) ($P > 0,0605$). Les politiques de programmes de dépistage annuel comparées aux politiques de dépistage tous les deux ans chez les femmes ayant un tissu mammaire dense ont eu le plus grand effet sur la réduction des taux de cancer dans l'intervalle. Nous revoyons nos résultats dans le contexte de la notification actuelle de seins denses au Canada.

Keywords

breast density, screening mammography, interval cancer, supplemental screening, MRI

Introduction

Breast cancer mortality is reduced by the detection of small, node-negative cancers.^{1,2} But, for women with dense breasts, the sensitivity of mammography is limited due to the masking effect of dense tissue.³ In addition, dense breast tissue is one of the strongest and most common independent risk factors for breast cancer.⁴⁻⁶ As such, it is critical to understand the significance of breast density as it directly affects performance of screening mammography and impacts patient outcomes. In Canada, a review of breast tissue density is important within the context of well-established population-based screening programs with overall high performance indicators. Both a reduced cancer detection rate (CDR) and lower reduction in breast cancer mortality have been demonstrated in screening mammography for women with dense breasts.⁷⁻⁹ Women with non-dense breasts screened regularly have a 41% mortality reduction from screening mammography, while women with dense breasts have a 13% mortality reduction.¹⁰ A higher rate of advanced breast cancers has been shown in women with dense breasts¹¹ (see Figure 1). Women with extremely dense breasts have a 4- to 5-fold greater risk of developing breast cancer compared to women with fatty breasts.^{3,6} Compared to women with scattered fibroglandular density (non-dense), women with heterogeneously dense and extremely dense breasts are 1.4-1.6 and 1.5-2.1 times more likely to develop breast cancer respectively.¹² Breast tissue density is considered a biomarker, defined as what is used to “detect or confirm presence of a disease or condition of interest or to identify individuals with a subtype of the disease.”¹³⁻¹⁶ Breast density can predict the effectiveness of various treatment interventions for breast cancer such as response to chemotherapy¹⁷ and surgery, with higher rates of locoregional recurrence in women with dense breasts.¹⁷⁻²⁰

Breast density refers to the amount of fibroglandular tissue relative to fat and is determined either visually or quantitatively on mammography. The BI-RADS[®] 5th edition includes 4 categories of breast density, reflecting the densest portion of the breast: A (fatty), B (scattered fibroglandular density), C

(heterogeneously dense) and D (extremely dense).²¹ The 2013 BI-RADS 5th ed. density classification is based on the masking effect of breast tissue density, while the 2003 BI-RADS 4th ed.²² was based on visually estimated percentage breast density; both are associated with high rates of inter- and intra-observer variability.^{23,24} There is less variability for women with extremely dense than with heterogeneously dense breast tissue.^{24,25} Dense breasts are normal and common: 43.3% of women 40 to 74 years of age have heterogeneously or extremely dense breasts, and the incidence decreases with age, particularly around menopause.²⁵ Only 7.4% of women have extremely dense breasts.²⁵ Knowledge of implications of breast density on the part of radiologists and referring physicians is essential. In addition, women want to be informed of their breast density.²⁶ Patient advocacy groups in Canada and across the world are lobbying to ensure density notification for all women.^{27,28} At the time of writing in Canada, Alberta, Manitoba, Nova Scotia, New Brunswick, British Columbia and Prince Edward Island formally notify screening participants of breast tissue density using BI-RADS 5th ed. categories in their results letters, while Ontario, Newfoundland and Saskatchewan notify screened women if they are in the densest category (i.e. extremely dense, category D, previously defined as visually $\geq 75\%$ dense). In addition to provincial variability regarding density notification, recommended age to begin screening is under the jurisdiction of each province/territory (Table 1)

The sensitivity of mammography decreases with increasing breast density with a range of 81-93% for fatty breasts, 84-90% for breasts with scattered fibroglandular density, 69-81% for heterogeneously dense breasts and 57-71% for extremely dense breasts in women 40-74 years of age³⁰ (see Figure 2). About 45% of invasive cancers have associated microcalcifications,³¹ and calcifications remain visible even in the densest breasts. The remaining 55% of noncalcified cancers manifest as masses or asymmetries which are only visible mammographically if there is some surrounding fat and/or associated architectural distortion.

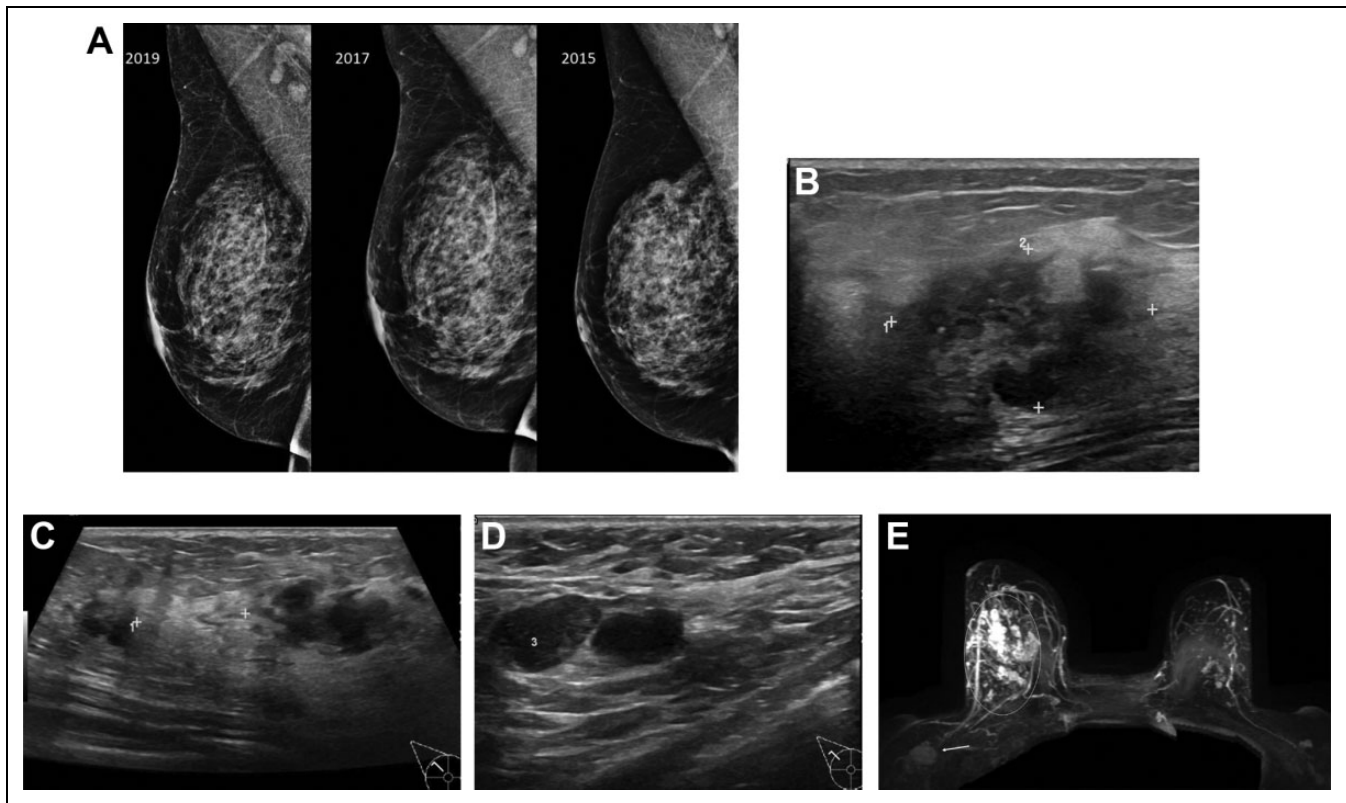


Figure 1. 60-year-old woman with no family history of breast cancer undergoing regular screening mammography every 2 years, with heterogeneously dense breasts (BI-RADS Category C). Two months after her last normal screening mammogram, she presented with a new right palpable breast mass at 12 o'clock in her right breast. A, Demonstrates mediolateral oblique (MLO) views from her screening mammograms from 2019, 2017 and 2015, all normal. Breast tissue density masked the tumors found 2 months later with ultrasound. B, A right breast ultrasound performed for evaluation of the palpable mass shows a 3×1.8 cm irregular heterogeneous mass at the site of the palpable mass. C, additional 2.5 cm mass was found at 11:00, 1.8 cm away from the clinical finding. D, Axillary ultrasound shows the 2 enlarged axillary lymph nodes, both of which were proven malignant. E, Axial maximum intensity projection (MIP) image of the breast on contrast-enhanced breast MRI shows the multicentric enhancing tumors involving most of the right breast (circle) with right axillary lymphadenopathy (arrow), in keeping with locally advanced right breast cancer. Final pathology was invasive ductal carcinoma, ER and PR negative, HER2 neu positive, T3N2M0. The patient was treated with neoadjuvant chemotherapy and subsequent right mastectomy and targeted localized sentinel lymph node dissection.

Because dense tissue masks some cancers on mammographic screening, breast cancers are more likely to present with symptoms in the interval between recommended screens in women with dense breasts. Interval cancers are cancers found during the interval after a normal screening mammogram and before the next screen is due.²⁹ Some interval cancers are newly developed biologically aggressive tumors (e.g. triple negative or HER2 neu positive cancers), while others are those missed on screening mammography. Women with dense breasts experience more interval cancers, likely related to the masking effect of density.^{32,33} Interval cancers are 13-31 times more likely in extremely dense breasts as compared with fatty breasts.^{3,34,35} Such interval cancers are often more aggressive and in several studies are more likely to be larger and to have spread to axillary nodes at presentation than are cancers detected on screening.^{33,36-40} Interval cancers are associated with a 2-3 times greater mortality rate in women with dense breasts.^{7,41}

One measure of the effectiveness of a screening program is the interval cancer rate (ICR), typically for invasive cancers, also referred to as post-invasive cancer rate.^{29,42} The ICR

reflects the sensitivity of a screening program and depends on cancer incidence within a population. An ICR exceeding 1 per 1000 screened women per year within a population with a cancer incidence of 4/1000 or sensitivity < 75% suggests an ineffective screening strategy.³⁰ In Canada, screening programs demonstrate overall high sensitivity of 84.3%⁴³ and an incidence of 3.7 invasive cancers per 1000 women screened; the targets for ICR are < 0.6 per 1000 for annual screening and < 1.2 per 1000 for 12 to 24 months after screening.²⁹ Houssami et al³⁷ evaluated screening programs worldwide and showed that biennial and triennial screening increase ICR, with many interval cancers found in the second or third years, and an average ICR of < 0.8 per 1000 with annual screening.

Although annual screening mammography is performed in the USA and parts of Canada, and every 18 months for women age 40-54 in some counties in Sweden, most population-based screening mammography is performed biennially.^{27,29} While a few studies have predicted a reduction in interval cancers of 36% to 50% when going from triennial to annual screening,^{8,44} to date, there are little trial or observational data on the

Table 1. Organized Screening Programs in Canada and Density Notification.

Province/Territory	Accepts average risk 40-49 year-old women with referral**	Screening interval for 40-49 year-old women (years)**	Screening interval for 50-74 year-old women (years)	Annual Screening mammography policy for dense breasts	Current Dense Breast Notification (results letters, as of 2021)
Data Included for Women					
Age 40-74					
New Brunswick	Yes	NA	2	No	Yes
Northwest Territories	Yes	1	2	Yes	Yes*
Data Included for Women					
Age ≥50-74					
Newfoundland and Labrador	No	NA	2	Yes	Yes*
Ontario	No	NA	2 ^{^ ^}	Yes	Yes*
Québec	No	NA	2	No	No
Manitoba	No	NA	2	No	Yes
Not included in analysis					
Alberta	Yes	1	2	No	Yes
British Columbia	Yes	2 [^]	2	No	Yes
Nova Scotia	Yes	1	2	No	Yes
Prince Edward Island	Yes	1	2	Yes	Yes
Saskatchewan	No	NA	2	Yes	Yes*
Yukon Territory	Yes	1	2 ^{^ ^ ^}	No	No

Note that Nunavut has no organized screening program.

*Notification only for ≥ 75% dense (BI-RADS D, extremely dense); density notification commenced in British Columbia in 2018.

NA = not applicable.

[^] accepted within 18 months, and for a woman with a first degree relative with breast cancer, is accepted within 12 months.

^{^ ^} accepted after 11 months with self-referral.

^{^ ^ ^} accepted after 12 months with self-referral.

**²⁹

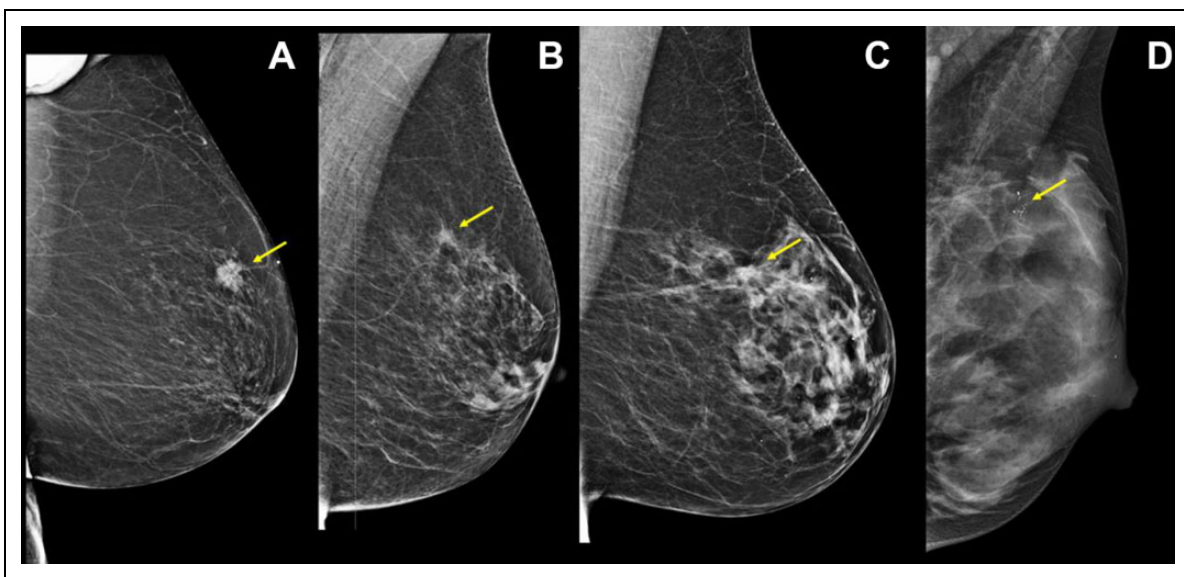


Figure 2. Malignancies in 4 women with each of 4 categories of breast tissue density, BI-RADS categories A (fatty replaced), B (scattered fibroglandular density), C (heterogeneously dense), and D (extremely dense), in 4 different patients. Each patient has a cancer in their upper breast (arrows). As density increases, the detection of the cancer becomes more challenging and only the presence of calcifications allows detection of a 1.5 cm cancer, the extent otherwise masked by the dense breast tissue in a patient with category D, with axillary nodal metastases also present.

potential stage shift and mortality reduction associated with higher frequency screening in women with dense breasts.⁴⁵

The purpose of our study was to evaluate the impact of population-based annual screening versus biennial screening policy on the ICR for women with dense breasts.

Materials and Methods

Patient Population

We used information available from the Canadian Breast Cancer Screening Database (CBCSD), which is operated and

maintained by the Public Health Agency of Canada (PHAC) on behalf of the Canadian Breast Cancer Screening Network.^{29,46} New Brunswick (NB) data for this analysis was contributed by the NB Cancer Network (NBCN). Data were included from provincial screening programs that provided information on breast density (BI-RADS 4th ed.), interval cancers, family history, and jurisdictional policy on supplemental screening for all women (aged ≥ 40) with extremely dense breasts (defined as visually $\geq 75\%$ glandular, unless the classification method necessitated use of $\geq 50\%$, as defined in NB), only results from women with no first-degree family history, known recommended screening interval and not referred for follow-up testing were included. Records with missing data were excluded. Screening programs from Quebec (QC), Ontario (ON) and Newfoundland (NL) included in the analysis did not submit screening information for women younger than 50 years old.²⁹ Six jurisdictions : Manitoba (MB), QC, ON, NL, Northwest Territories (NT) and New Brunswick (NB) contributed data with the necessary information; 4 jurisdictions (MB, ON, NL and NT) also included the radiologists' screening interval recommendation (as radiologists may recommend an earlier return visit than the general policy if they deem it indicated).^{29,46} Radiologists' recommendations for annual screening are based on their assessment that included clinical impression, breast density, and personal/family risk factors.

Screen years 2008-2010 were selected as the most recent screens available with interval cancer information. During 2008-2010 inclusively, all the breast screening programs used two-view, mostly analog mammography, provided at designated centers with a single radiologist interpretation. During this period in Canada, the proportion of mammograms performed on film decreased from 71.5% in 2008 to 41.0% in 2010, and in the 6 jurisdictions studied, 57% of mammograms were film, 22% digital radiography (DR) and 21% digital computed radiology (CR).²⁹ Entry to all programs was based upon self-referral except in the jurisdictions that required referral for women age 40-49, with jurisdiction-wide geographic access provided using a mixture of clinics and mobile services. Depending on time period and jurisdiction, women might have received personalized invitation letters to participate in screening prior to enrollment. After enrollment, women received periodic reminder letters for screening at 1 or 2 years, based on the screening interval policy or radiologist recommendation. In all jurisdictions, breast cancer care for women, including those participating in screening, was managed through family physicians who received results of diagnostic tests and who then managed referral to tertiary services or managed via direct referral from the screening centers.

Analysis

The main outcome examined was the frequency of invasive interval cancers among women with the densest breasts. Interval cancers were defined as cancers occurring between regular screening visits, after a negative or benign mammographic assessment, i.e. within 1-2 years of the last screen. ICRs for

biennial (24 month) screening interval are presented as averaged annual rates (annualized) to facilitate comparison with the annual (12 month) screening. Comparison was performed using the chi-square test based on per 1000/year results. Screening programs were combined according to the interval policy or radiologist recommendation to facilitate analysis.

Results

A total of 148,575 women were included in the analysis that compared the impact of jurisdictional policies in women with the densest breasts. This represents approximately 17.5% (148,575/864,386) of all women screened in these jurisdictions in 1 year (2009).⁴⁷ Of these, 288 women were diagnosed with interval cancers (Table 2). Of the 6 screening programs included, 3 offered routine annual mammography screening for women with dense breasts, and 3 did not. In the jurisdictions routinely providing annual screening, the rate of interval cancers was 0.89/1000 women screened/year (95% CI: 0.67-1.11) and for those providing biennial screening, the annualized ICR was 1.45/1000 women (95% CI: 1.19-1.72) screened/year, or 63% greater ($p = 0.0016$). When screening interval policy and radiologists recommendations were combined, there were 76,103 screened women eligible for the analysis, 87 of whom had invasive interval cancers: 65 of the 69,650 screened with annual recommendations had ICR 0.93/1000 (95% CI: 0.71-1.16) and 22 of 6453 screened with biennial recommendations had a higher annualized ICR 1.70/1000 (95% CI: 0.70-2.71) ($p = 0.0605$).

Discussion

In our study, women with dense breasts who received a screening recommendation by jurisdictional policy for biennial screening had an annualized ICR of 1.45 per 1000 as compared to 0.89 per 1000 for annual screening policy, 1.63 times higher ($p = .0016$). Those who had a radiologist's recommendation of biennial screening had an annualized rate of interval cancers that was almost twice that of women receiving an annual screening recommendation (1.7 vs 0.93 per 1000 women screened/year, $p = 0.0605$) trending to significance. By comparison, in Canada, 2009-2010, for all screened women age 50-69 years, including all categories of breast tissue densities, the ICR (post-screen invasive cancer rate) was 0.74/1000 within 12 months and 1.27/1000 between 12 and 24 months of a normal screen.²⁹ Although it would have been optimal to compare the ICR of women with dense to non-dense breasts, these data were not available within the jurisdictions studied. To our knowledge, this is the first study that has shown the impact of annual vs biennial screening policies on ICRs in women with dense breast tissue. These results suggest the need to prospectively assess the impact of annual screening in dense breasts.

ICR has become an important method of assessing the effectiveness of a screening program. Interval cancers represent a shortcoming in mammographic screening because of unfavorable tumor characteristics compared with screen-detected

Table 2. Impact of Screening Interval on Invasive Interval Cancers for Women with Dense Breasts Screened Between 2008 and 2010.

	Total number of women screened (2008-2010)	Total number of women with interval cancers	Invasive interval cancer rate/1000 women screened	Interval invasive cancer rate per 1000 women screened/yr** (Annualized) (95% CI)	p value*
Recommendations by screening program policy (6 jurisdictions)					
Annual screening	70,814	63	0.89	0.89 (0.67, 1.11)	0.0016
Biennial screening	77,761	225	2.89	1.45 (1.19, 1.72)	
Total	148,575	288			
Recommendations by radiologist and screening program policy (4 jurisdictions)					
Annual screening	69,650	65	0.93	0.93 (0.71, 1.16)	0.0605
Biennial screening	6,453	22	3.41	1.70 (0.70, 2.71)	
Total	76,103	87			

**Interval rates for the biennial (24 month) screening interval are presented as averaged annual rates to facilitate comparison with the annual (12 month) recommendation.

*Chi-square test based on annualized rates, per 1000/year results.

cancers.⁴⁸⁻⁵³ Specifically, interval cancers are more likely to be larger and node positive at the time of diagnosis, with more advanced stage; these factors result in poorer outcomes.^{33,36,37} More advanced tumors require more aggressive therapy with respect to both surgery and either neoadjuvant or adjuvant therapy.⁵⁴ A wide range of 17 to 30% of breast cancers detected in women in European population-based screening programs are interval cancers, the highest occurring in programs that screen triennially.^{37,55} A doubling of the ICR with biennial vs annual screening is well recognized, with a larger proportion occurring in the second year³⁷; a recent study found that two thirds of the interval cancers occurred in the second year.⁵⁵ The majority of population-based screening programs are biennial and report a range of ICRs of 0.84 to 2.11 per 1000.^{37,56} In Canada, between 2003 and 2010, the interval cancer rate among women with incident (subsequent) screens was between 1.25 and 1.28 per 1000 women within 12-24 months of their screen. The national target of < 1.2 per 1000 screened women was only met in the years 2004, 2005 and 2007.²⁹ During this period, the rate of invasive cancer detection was relatively stable at approximately 3.7 per 1000 women-screens.

In our study, the annualized ICR for biennial screening was significantly higher than the suggested target of less than 1 per 1000 for an effective screening program. Depending on the screening interval policy for jurisdictional policy or radiologist recommendation, the annualized ICR ranged from 1.45-1.7 per 1000 for biennial screening and was lower at 0.89-0.93 per 1000 with annual screening, within the suggested target. This suggests that annual screening mammography is a more effective screening strategy for women with dense breasts to meet suggested benchmarks for ICRs.

Despite the significantly lower ICR with annual screening for women with dense breasts, ICR still exceeded the Canadian benchmark of < 0.6 per 1000 women within 12 months of screening. The negative impact of breast density on

mammographic screening, mainly due to masking, highlights the need for more effective screening in women with dense breasts to ensure equal benefit from early cancer detection.

Dense breast tissue by both visual assessment and quantitative breast density software (such as Volpara[®] and Cumulus[®]) correlates with reduced mammographic sensitivity and increased ICR.^{26,27,28,30} While there is growing recognition of the importance of modifying breast cancer risk factors within the control of women, including avoiding alcohol, regularly exercising, modifying diet and maintaining a healthy body weight, there remain non-modifiable risk factors including genetics, family history, early menarche/late menopause, nulliparity, chest wall radiation, previous atypia, and dense breast tissue. Risk assessment tools such as the Tyrer-Cuzick Breast Cancer Risk Model, version 8, which includes breast density^{26,27} and emerging mammography-based deep learning models facilitate more accurate lifetime risk prediction of breast cancer.³² Dense breast tissue remains an obstacle to early cancer detection.

Supplemental screening options have been evaluated and show further reductions in ICR in women with dense breasts. Observed results using various supplemental screening modalities are summarized in Table 3. Incremental cancer detection in dense breasts has been demonstrated with multiple studies of supplemental screening with tomosynthesis,⁵⁷⁻⁶⁰ breast ultrasound,⁶¹ breast MRI,⁶²⁻⁶⁵ and more recently, with contrast-enhanced mammography^{66,67} and molecular breast Imaging (MBI)⁶⁸⁻⁷⁰ (Figure 3). The highest sustained incremental cancer detection rates (ICDR) are observed with breast MRI, with average ICDR of 14-20 per 1000 women in prevalence studies^{62,64,65} with sustained yield with incident rounds averaging ICDR of 5.8-8.6 per 1000 women screened.^{64,71} ICRs have been shown to be reduced with supplemental screening with ultrasound,^{62,72,73} breast MRI^{64,65} and most recently, with tomosynthesis⁷⁴ (Figure 4). In the J-START randomized controlled study of supplemental screening ultrasound in women

Table 3. Incremental Cancer Detection with Various Supplemental Screening Modalities and Impact on Reduction of Interval Cancer Rates in Women with Dense Breasts.*

Screening modality	Number of women reported	Incremental CDR per 1000 women screened	Incremental invasive CDR per 1000 women screened	Incremental recall rate per 100 women screened	Reduced interval cancers
MRI ^{62,64,65}	9256	16.0	12.1	10.4	Yes
MRI after DBT ⁶³	1444	9.7	6.9	21.5	Not yet evaluated
CEM ^{66,67}	1311	10.7	8.4	15	Not yet evaluated
Ultrasound ^{61,62,75}	452,743	2.0-2.7	1.8-2.3	7.6-10.6	Yes
DBT ^{57,59,60,76}	103,245	1.7	1.4	-2	Yes ⁷⁴

Abbreviations: CDR, cancer detection rate; DBT, digital breast tomosynthesis; CEM, contrast-enhanced mammography.

*Reproduced with permission from.⁷⁵

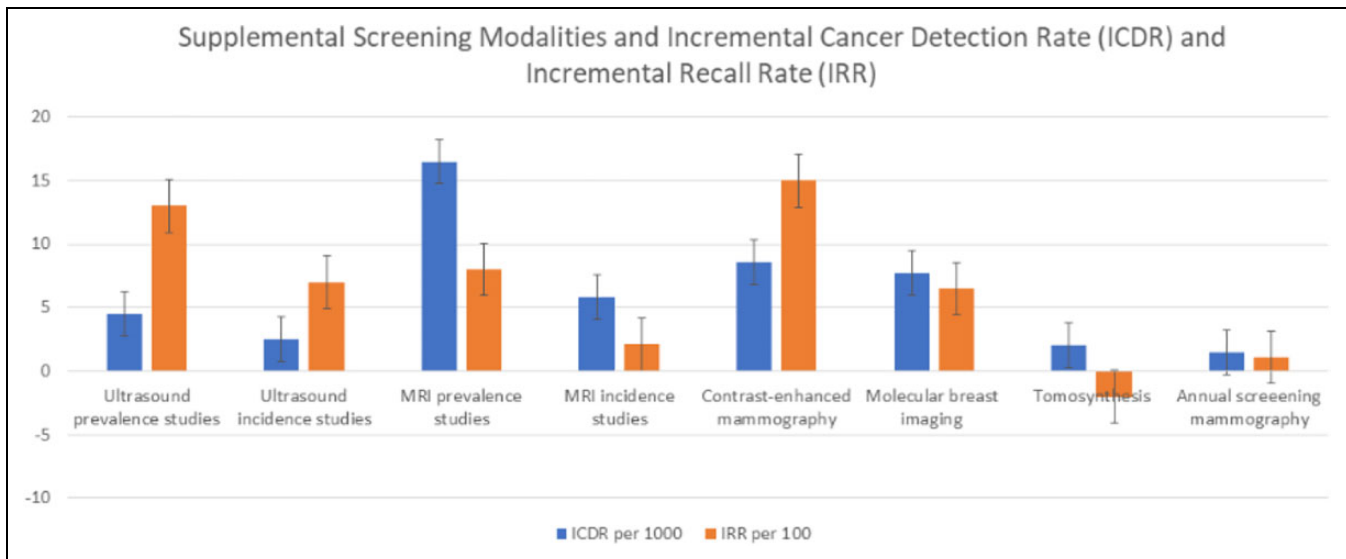


Figure 3. Bar graph demonstrating the different incremental cancer detection and recall rates for various supplemental screening modalities.

of all breast densities, interval cancers accounted for 0.05% of cancers detected with ultrasound as compared with 0.10% of cancers in the control group.⁷² In a retrospective prevalence study, Corsetti et al found that supplemental breast ultrasound had an ICR in women with dense breasts of 1.1 per 1000 screened women, which was similar to the ICR for women with non-dense breasts.⁷³ In the ACRIN 6666 trial, Berg et al showed ICR of 1.2 per 1000 after combined mammography and supplemental US screening in women with dense breasts.⁶² In the DENSE trial, a prospective Dutch randomized trial of women with extremely dense breasts, the ICR in women who received supplemental breast MRI was 0.8 per 1000 as compared with 5 per 1000 in those who did not.⁶⁵ The ability to maintain reduced ICRs in multiple rounds of screening with MRI is still unknown.³⁵ The most recent screening tomosynthesis study of a 5-year period found an ICR of 1.6 per 1000 screened women, compared with 2.8 per 1000 screened women in the control group.⁷⁴ Recalls are highest in prevalence scans for any modality, and with supplemental US, recalls reported at 15.1%, decreased to 7.4% in subsequent scans.⁶² Similarly with supplemental MRI screening, there were higher recalls of 9.5%

in the DENSE trial in the prevalence scans which decreased to 3.2% on incidence screening.⁶⁵

Limitations

Screening interval policy and even radiologists’ recommendations did not necessarily translate into patient behavior and so not all women eligible for an annual mammogram would have received it. Unfortunately, we do not have access to data on compliance, so this might underestimate the value of performing annual screening in women with dense breasts. Furthermore, the recommendations for offering more frequent screening for women with dense breast tissue varied, with 3 jurisdictions offering annual screening by program policy and 1 offering biennial screening that could be modified based on radiologist recommendations. Another limitation is that reasons for the radiologists’ recommendation of annual screening were not captured and could have included abnormal findings. Most Canadian screening programs defined “dense” breast tissue as $\geq 75\%$ density (i.e. extremely dense), according to the BI-RADS 4th edition, while NB defined it as $\geq 50\%$ (which

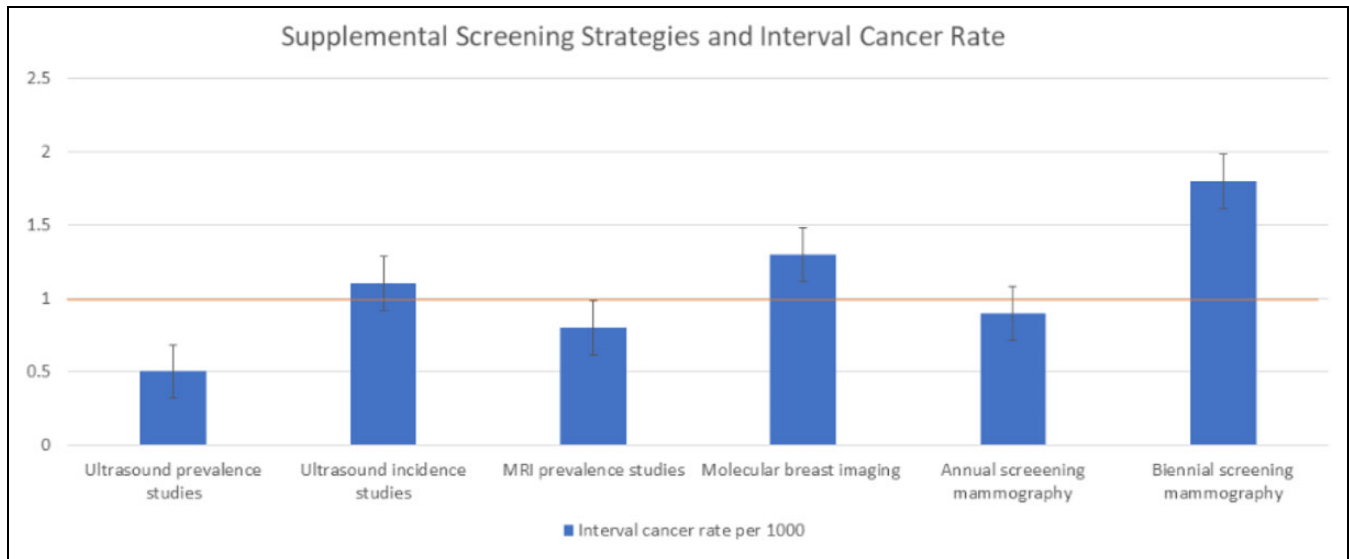


Figure 4. Bar graph demonstrating the different interval cancer rates for various supplemental screening modalities. * The red line indicates the threshold of interval cancer rate for an effective screening program that should not exceed 1 per 1000/women screened/year, for a sensitivity of >75% within a population with a cancer incidence of 4/1000.

would include heterogeneously dense breasts). If provinces and territories had recalled all women with dense breasts (i.e. categories C and D) annually, the ICR would likely have been even lower. The current definition of dense breasts, according to the BI-RADS 5th edition, which includes both heterogeneously dense and extremely dense categories, avoids density percentages and is based on a subjective visual assessment. None of the screening programs used quantitative methods of determining breast tissue density. This study primarily pertains to patients with the densest breast tissue, BI-RADS category D, extremely dense, which applies to only about 7% of all screened women. In addition, the study was not able to explore whether the increased ICR translated into worse outcomes for women with dense breasts as stage of cancers and survival could not be assessed. However, previous studies have shown a survival benefit of 1-year over 2-year screening intervals.⁷⁷ It was not possible to assess for potential lower specificity and increased recalls that may occur with annual screening mammography with this study. Chiarelli et al found that specificity decreased with annual screening with increasing breast tissue density.⁷⁸ Annual mammographic screening was not compared with other screening regimens using supplemental screening modalities, which is of increasing relevance in other countries where there is far greater uptake of supplemental ultrasound screening for women with dense breasts, such as the USA, France, Austria, and a few other European countries.^{27,75,79}

Currently, in Canada, access to supplemental screening with additional modalities varies according to jurisdiction. MRI supplemental screening for women with dense breasts is recommended in several countries but currently there is limited access to breast MRI in Canada to promote this as a population-based strategy. The European Commission Initiative for Breast Cancer Screening and Diagnosis guidelines suggest

not implementing tailored screening (with ultrasonography or MRI) in women with dense breast tissue.⁸⁰ Nickel et al have raised concerns about breast tissue density notification and concluded that evidence on whether benefit outweighs harm is required to inform future screening practice.⁸¹ Consensus on the balance of benefits versus harms has not yet been established. Although evidence is rapidly emerging, more studies are underway to evaluate sustainability and cost effectiveness. Lastly, the study evaluated women that were screened in 2008-2010 to permit assessment of subsequent cancers diagnosed; however, this study does not reflect improvements in technology such as more widespread use of digital mammography and even tomosynthesis. It is noted that although tomosynthesis increases CDR in all breast densities, the greatest increases are in categories B and C, with very few additional cancers found in category D.^{76,82,83} There is considerable uncertainty about the cost effectiveness of annual mammography.⁸⁴ Research on the effectiveness of screening strategies has been suggested.

This study is the first to demonstrate a reduced ICR with annual screening policies for women with dense breast tissue participating in a population-based screening program. Women with dense breast tissue (particularly those with densest breasts) may benefit from annual screening, as evidenced by a lower ICR compared to biennial screening. Potential further benefits and harms of supplemental screening modalities need to be considered in the context of ICRs and screening interval. Ultimately, all women deserve an equal opportunity for early cancer detection regardless of breast density.

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