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Original article

Estimation of the benefit and harms of including clinical breast examination in an organized breast screening program

Huan Jiang [a, c, *], Stephen D. Walter [b], Patrick Brown [c], Parminder Raina [b], Anna M. Chiarelli [a, c]

[a] Prevention and Cancer Control, Cancer Care Ontario, Canada
[b] Department of Health Research Methods, Evidence & Impact, McMaster University, Canada
[c] Dalla Lana School of Public Health, University of Toronto, Canada

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ABSTRACT

Background: There is controversy about the value of clinical breast examination (CBE) in addition to mammography for breast screening. The study investigates the associations between risk factors such as mammographic density, hormone therapy use and family history and the effectiveness of screening mammography with or without CBE.

Methods: The cohort consists of women 50–69 years old screened at the Ontario Breast Screening Program. The associations of the risk factors were investigated using a joint logistic regression model that accommodates the partially unobserved disease status, clustered data structures, individual risk factors, and the dependence between true and false detection.

Results: Having high mammographic density, a first degree relative with breast cancer and using hormone therapy generally increased a woman's probability of being referred correctly. For low risk group (defined as without dense breasts, family history, and not currently using hormone therapy), the average loss of specificity ranged from 3.6% to 5.7% and the gain of sensitivity was between 10.6% and 21.2% with the addition of CBE.

Conclusions: The addition of CBE to mammography would increase the overall sensitivity and decrease the specificity. CBE can be targeted to those women in which it has the highest net benefit.

1. Introduction

Although there are studies which have found that clinical breast examination (CBE) can detect cancers missed by mammography [1–4], the additional value of CBE in a breast screening program has not been thoroughly established. An earlier review by the International Agency for Research on Cancer (IARC) in 2002 showed there is inadequate evidence that screening with CBE, either alone or in addition to mammography, can reduce mortality from breast cancer, and their 2015 update suggested that new studies on CBE are warranted. IARC noted that CBE may be important in countries where there are insufficient resources for mammography and that it might increase the breast-cancer detection rate when combined with mammographic screening [5]. The recent American Cancer Society (ACS) guideline did not recommend CBE for breast cancer screening among average-risk women at any age [6]. However, they suggested that CBE might have a role in women at very high risk.

Therefore there is an emerging need to investigate the effectiveness of CBE in addition to mammography and to identify women who might benefit from it. Even though a complete assessment of screening has to be in terms of mortality, measures of screening accuracy such as sensitivity and specificity can be used as interim indicators of effectiveness so that screening methods can be evaluated and compared sooner. The cancer detection rate and screen sensitivity determine whether screening is effective in detecting women with breast cancer, while screen specificity is related to the efficiency, or the ability to identify women without breast cancer [12].

The contribution of CBE has varied significantly by study: the

Abbreviations: ACS, American Cancer Society; IARC, International Agency for Research on Cancer; CBE, clinical breast exam; OBSP, Ontario Breast Screening Program; OCR, Ontario Cancer Registry.

* Corresponding author. 505 University Avenue – 16th Floor, Toronto, ON M5G 1X3, Canada.
E-mail address: hedy.jiang@cancercare.on.ca (H. Jiang).

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contribution of CBE alone to breast cancer detection has ranged from 3% to 45% in randomized clinical trials [7–10]. Three studies conducted in community settings have looked at the contribution of CBE in addition to mammography for women 50–69 years of age. The additional cancers they identified ranged from 2.6 to 4 per 10,000 mammography screenings [11,12]. However, achieving these results comes at a cost as there would be an additional 219 false positives found per 10,000 women screened Ref. [13]. It has been suggested that the performance of CBE and mammography is influenced by age and mammographic breast density and varies according to factors such as duration of the examination, examiner experience, and the CBE technique used [3,14]. However, there was no strong evidence that greater patient volume or experience in interpreting mammograms is associated with better performance [15]. It is often difficult to estimate the contribution of CBE in an organized screening program since the screening techniques are performed by different examiners in different centers. The accuracy of mammography or CBE varies according to factors related to the women, examiners and centers. Statistical methodology need to be selected carefully to deal with this kind of clustered data structure.

Another difficulty in assessing the sensitivity of an exam with population-level screening data is that the true cancer status of the screening participants is often unknown. Ideally, a screening test would be compared to an accepted "reference standard", for instance, pathological classification of tissue biopsy for women having undergone a breast cancer screen. The ideal reference standard would correctly identify clinically important cancers that will progress if left untreated, rather than histopathological cancers that may include over-diagnosed cancers. However, it is infeasible to apply the reference standard to all individuals due to the limited resources, ethics or practicality issues, and therefore the true disease status at the time of screening is necessarily partially missing due to verification bias, which might lead to biased estimation of the performance measures of the screening program.

This study aims to provide evidence to evaluate the benefits and harms of CBE in conjunction with mammography. It investigated and predicted the associations between risk factors such as mammographic density, hormone use and family history and the effectiveness of screening mammography with or without CBE. A joint mixed-effect logistic regression model developed by Ref. [16] is used to estimate these associations while taking into account the clustered nature of the data and the partly missing true cancer status.

2. Subjects and methods

2.1. Study Population

The study cohort consists of women 50–69 years of age screened at the Ontario Breast Screening Program (OBSP) between January 1, 2002 and December 31, 2003 and followed for up to 12 months after their last screening examination. Although women can self-refer, the majority are referred to OBSP by their family physician or other health care professional. The two types of screening protocols used are mammogram only or CBE in addition to mammogram. At centers with a nurse, the primary role of the nurses is to perform CBE at both the initial and subsequent screens. At OBSP centers that do not employ nurses, women do not receive a CBE. A woman may be referred by either the radiologist or the nurse. Referral information is collected in a standardized method on the screening report and recorded as "normal" or "recommended clinical assessment by physician" by the nurse and as "normal/benign" or "needs additional evaluation by imaging and/or surgical consultation" by the radiologist. The nurse makes an independent decision about whether the woman has an abnormality that requires further assessment based on standardized referral criteria for visual and palpable findings. The nurse informs the woman of any clinical abnormality at the time of the visit and refers the woman to her family physician for assessment. The radiologist makes his or her decision to refer the woman for diagnostic assessment regardless of the CBE findings recorded by the nurse and indicates his or her recommendations for assessment (eg, additional views, ultrasound, or a surgical consultation). Women with an abnormal mammogram and or CBE may then be referred for breast biopsy if indicated by diagnostic imaging or physician consultation. For women diagnosed with breast cancer (found at screening or after screening as interval cases), pathological confirmation is obtained from regional staff during the recall process or through record linkage with the Ontario Cancer Registry.

Of the 102 OBSP screening centers in operation during the study period, 68 (67%) offered CBE in addition to mammography. A complete description of the details of the operation of OBSP and the cohort has been published elsewhere [3,7]. During the study period, the OBSP provided 343,711 screens to 301,362 women who had complete follow-up. A total of 11,128 women were excluded to make the centers and the types of screening protocols consistent. Eight women were excluded as they attended an affiliate that screened less than 10 eligible women. The final sample size for analyses included 290,226 women. Performance measures for 234,177 women who were screened by mammography and CBE at the 68 centers that provided CBE were compared with those for 56,049 women who were screened by mammography alone at 34 centers that did not provide CBE.

2.2. Risk factors & performance measures

We have used the definitions of risk factors and screening visit characteristics as described by Ref. [13,17] except for the definitions of certain performance measures. "Cancer detection rate" was defined as the number of women detected with invasive or ductal carcinoma in situ cancer per 1000 women screened (True positive/Total Participants). For both types of screening protocols, sensitivity was defined as the proportion of women with a breast cancer who had a positive screening test (True positive/(True positive + False negative)). A true positive result or screen-detected cancer included breast cancers diagnosed within 12 months after a referral from a radiologist or a nurse. False negative results included breast cancers diagnosed after a negative mammogram when only mammogram was used; or a negative mammogram and a negative CBE when both tests were applied. Specificity was defined as the proportion of women without a breast cancer who had a negative screening test (True Negative/(True Negative + False Positive)). True negative results included women without a breast cancer diagnosis within 12 months after a normal mammogram and a normal CBE if applied. A false positive result included women without a breast cancer diagnosis after a positive mammogram or a positive CBE result.

3. Statistical model

The model from Ref. [16] considers three partially unobserved and latent processes: the cancer incidence for an individual; referral due to correct identification of a cancerous nodule as a result of mammography or CBE with the exclusion of "incidental" detection (termed a *referral with breast cancer detection*); and referral without having identified a nodule by mammography or CBE with the inclusion of "incidental" detection (termed a *referral without breast cancer detection*). Detections are considered "incidental" when the classification of a lesion as a true positive occurs by chance, rather than the underlying nodule actually being found

by examiners [18]. The "incidental" detection feature of the model allows for examiners to successfully identify cancers, even if their "true detection" probability is low. For example, a less skilled but cautious nurse might tend to refer as many patients as he/she could for further diagnostic exam without identifying a lesion based on real clinical findings. Ignoring "incidental" detection may lead to over-estimated sensitivity and underestimated specificity.

Cancer screening outcomes are described with a random effects model, with observed data including referral results and cancer diagnoses and unobserved latent variables, including the individual's true disease status and "incidental" detection of a lesion. The stochastic dependence was examined between the estimates of sensitivity and specificity by allowing for multi-level correlation structures, covariates attached to patients, examiners and screening centers. The same models were applied separately to the populations screened with or without CBE. Inference on the mixed-effects logistic regression models was done using a Bayesian MCMC algorithm coded in the R statistical programming environment (www.r-project.org). The model was adjusted by factors related to the woman and to the screening center she attended. To control for clustering of women and providers within screening centers, all models included random effects for radiologists and centers.

To assess the performance of the two screening protocols, namely with and without CBE, we computed posterior distributions of sensitivities, specificities and predictive values through the referral probabilities (see Ref. [16] for computational details). Since the referral accuracies of mammography and CBE depend on the characteristics of the women screened, a better way of assessing the accuracy is to investigate case ascertainment when given the same pool of women. To do so, we applied the estimated parameters obtained from the existing cohort to predict performance measures on four groups of women: the first group of women varying by age at high risk (defined as women with mammographic density $\geq$75%, having at least one first degree relative with breast cancer and currently using hormone therapy); the second group of women at low risk (defined as women without high density, having at least one first degree relative with breast cancer or current hormone therapy); the third group of women with high density but without first degree relative with breast cancer or hormone therapy; the fourth group of women currently using hormone therapy but without first degree relative with breast cancer or high density. All groups were assumed to be examined by an average radiologist from an average center.

4. Results

Among the 290,226 women selected, 56,049 (19.3%) women had a mammogram only, among whom 3936 (7.0%) were referred to further clinical tests; 234,177 (80.7%) women had CBE and mammography, among whom 16,523 (7.0%) were referred. A total of 374 screen-detected cases (6.7 per 1000) and 52 (0.9 per 1000) interval cases were found in women screened with mammography alone, while 1822 screen-detected cases (7.7 per 1000) and 145 interval cases (0.6 per 1000) in women screened with both CBE and mammography.

Table 1 summarizes the screening referral in subgroups of women with different risk profiles. After adjusting for personal and center characteristics, women using hormone therapy who attended centers offering both mammogram and CBE had a significantly lower probability of being referred with breast cancer detection (OR = 0.73; 95% CL, 0.56–0.96) than women not using hormone therapy, but they had a significantly higher probability of being referred without breast cancer detection (OR = 1.26; 95% CL, 1.22–1.31) (Table 2). For both types of screening protocols, having high mammographic density and using hormone therapy significantly increased a woman's probability of being referred without breast cancer detection. When using mammography alone, high mammographic density was significantly associated with a decreased likelihood of being referred with breast cancer detection. However, the associations were not statistically significant when CBE was added in addition to the mammography.

There was more variation between the examiners than between the centers after adjusting for various personal and facility factors. At the radiologist's level, the probabilities of being referred with and without detection were negatively correlated (CORR = −0.52; 95% CL, −0.73 to −0.25), which means the more true detections a radiologist made, the less false detections he/she made. However, at the level of screening centers, referrals with breast cancer detection and without detection were not highly correlated (CORR = −0.13; 95% CL, −0.83 − 0.70) and the variation between centers was fairly small.

5. Estimation of performance measures at the first screen

5.1. Cancer detection rate

The estimated benefit of offering CBE in addition to mammography varied by age and risk group. For women at high risk being screened for the first time, the rate of cancer detection was reduced with the addition of CBE for women at younger ages, for example by 1.85 per 1000 for women at 50 years old (Fig. 1). The decreases narrowed with time and eventually it began to increase around the age of 60. However, for women at low risk being screened for the first time, the rate of cancer detection increased with the addition of CBE by 0.37–7.69 per 1,000, depending on their ages for the first screen (Fig. 1(c)). For the group taking hormone therapy but without first degree relative with breast cancer or high density, the increase of cancer detection rate ranged from 1.07 to 11.4 cancers per 1000 varying by ages (Fig. 1(c)). In addition, overall women at high risk and women with dense breast tissue benefited much less than women at low risk or women currently having hormone therapy when being screened for the first time.

5.2. Sensitivities

For all women aged 50 to 70, the sensitivity increased when CBE was provided in addition to mammography (Fig. 2). It appeared that CBE generally improved sensitivity more for women at high risk and women currently using hormone therapy. For women receiving hormone therapy being screened for the first time, the sensitivity when both exams were applied ranged from 82.2% to 93.0%, comparing with a range of 50.8%–74.0% with mammography only. For the women at low risk being screened for the first time, the sensitivity of mammography with CBE ranged from 84.0% to 93.8% while that of mammography alone ranged from 62.8% to 83.2%. (Fig. 2(a) (b)). Women with dense breast tissue benefited least among the four groups, with an average increment of 8.21%–15.3% varying by their age at the first screen (Fig. 2(c)).

5.3. Specificity

Specificity was estimated to decline when CBE was used in conjunction with mammography, and this decrement was more pronounced in women at high risk ((Fig. 3)). For the high risk group screened for the first time, the estimated average loss of specificity ranged from 8.18% to 11.4% for women ages 50 to 70, comparing with the gain of sensitivity ranged from 16.2% to 26.7%. For the low risk group at first screen, the average loss of specificity ranged from 3.64% to 5.67% and the gain of sensitivity was between 10.6% and 21.2%. The differences between specificities of high risk and low risk

Table 1
Summary of breast cancer outcomes and characteristics of women.

	Centers without CBE				Centers with CBE			
	n = 56,049				n = 234,177			
	N (%)	Referred (%)	Breast Cancer	Interval Cancer	N (%)	Referred (%)	Breast Cancer	Interval Cancer
First degree relative with breast cancer								
No	50,501 (90.1)	3559 (90.4)	316	45	205,639 (87.8)	14,488 (87.7)	1517	116
Yes	5548 (9.9)	377 (9.6)	58	7	28,538 (12.2)	2035 (12.3)	305	29
Breast density								
<75%	49,657 (88.6)	3388 (86.1)	331	11	220,456 (94.1)	15,376 (93.1)	1664	118
≥75%	6392 (11.4)	548 (13.9)	43	41	13,721 (5.9)	1147 (6.9)	158	27
Rescreen								
First	30,532 (54.5)	2446 (62.1)	229	28	65,936 (28.2)	6676 (40.4)	586	38
Subsequent	25,517 (45.5)	1490 (37.9)	145	24	168,241 (71.8)	9847 (59.6)	1236	107
Current use of hormone therapy								
No	42,424 (75.7)	2942 (74.7)	270	32	163,650 (69.9)	10,932 (66.2)	1170	82
Yes	12,458 (22.2)	913 (23.2)	95	19	69,370 (29.6)	5499 (33.3)	640	63
Unknown	1167 (2.1)	81 (2.1)	9	1	1157 (0.5)	92 (0.6)	12	0

Table 2
Adjusted odds ratios (OR) with 95% confidence intervals and estimated variation in risk of being referred with breast cancer detection and without detection (The variables age at last screen, centers' annual screen volume and radiologists' year of experience were standardized by subtracting their means then dividing by their standard deviations).

	Mammogram	Mammogram and CBE
	OR (95% CI)	OR (95% CI)
Referral with breast cancer detection (W)		
mammographic density (<75% or ≥ 75%)	1.20 (0.44, 3.65)	0.31 (0.20, 0.48)
age at last screen	1.41 (1.02, 1.98)	1.28 (1.11, 1.48)
family history (y/n)	1.18 (0.47, 3.26)	1.14 (0.78, 1.65)
current hormone use (y/n)	0.55 (0.28, 1.09)	0.73 (0.56, 0.96)
rescreen (y/n)	0.85 (0.42, 1.73)	0.88 (0.65, 1.18)
radiologists' year of experience	0.97 (0.52, 1.79)	0.79 (0.59, 1.08)
centers' annual screen volume	0.99 (0.67, 1.41)	1.00 (0.92, 1.08)
Referral without breast cancer detection (V)		
mammographic density (<75% or ≥ 75%)	1.41 (1.28, 1.57)	1.32 (1.23, 1.43)
age at last screen	0.97 (0.94, 1.00)	0.93 (0.91, 0.95)
family history (y/n)	1.02 (0.90, 1.14)	1.04 (0.99, 1.10)
current hormone use (y/n)	1.15 (1.05, 1.25)	1.26 (1.22, 1.31)
rescreen (y/n)	0.55 (0.52, 0.60)	0.55 (0.54, 0.57)
Radiologists' year of experience	1.04 (0.59, 1.84)	1.20 (0.87, 1.64)
centers' annual screen volume	1.01 (0.80, 1.28)	1.00 (0.95, 1.06)
Standard errors in radiologists' level		
in W	1.77 (1.60, 1.94)	1.52 (1.42, 1.63)
in V	1.80 (1.68, 1.94)	1.59 (1.51, 1.68)
correlation between W and V	−0.52 (−0.73, −0.25)	−0.74 (−0.85, −0.60)
Standard errors in centers' level		
in W	0.97 (0.61,1.34)	0.49 (0.30, 0.70)
in V	0.78 (0.54, 1.04)	0.42 (0.28, 0.59)
correlation between W and V	−0.13 (−0.83, 0.70)	−0.15 (−0.89, 0.73)

women were slightly narrower at older ages when CBE was provided in addition to mammography: for example, for the first screen, the gap decreased from 5.71% in women aged 50 to 4.50% in women aged 70. Women receiving hormone therapy lost specificity the second most: the average loss ranges from 3.49% to 5.58% varying by age. Women having dense breasts lost specificity almost as much as women receiving hormone therapy did.

6. Discussion

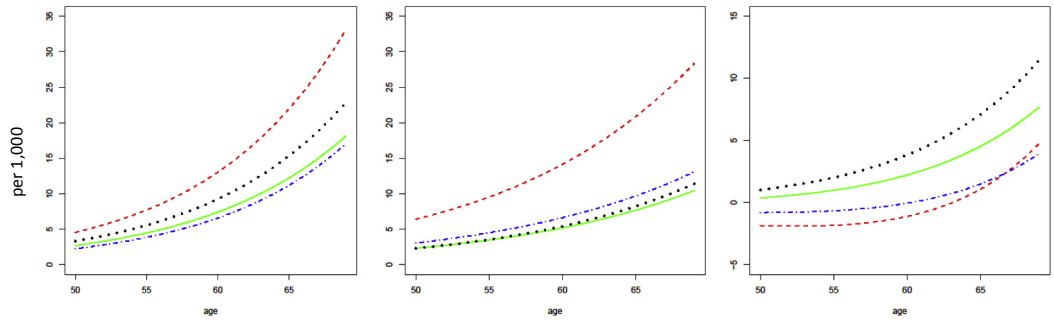
This study found a number of individual-level risk factors affected screening results for both screening protocols. For both screening protocols, having high mammographic density and using hormone therapy significantly increased a woman's probability of being referred incorrectly. Our finding agrees with several studies that have shown that current use of hormone therapy substantially lowered the rate of cancer detection while increasing the probability of false detection compared to non-use [19–22].

The addition of CBE to mammography did not always improve detection rates for women receiving both tests after adjusting for various provider and facility characteristics. For women with high mammographic density, a first degree relative with breast cancer and using hormone therapy, the addition of CBE might reduce the overall detection rate. A similar effect can also be found in women with high mammographic density but without family history and hormone therapy. For women ages 50 to 59, the proportion of cancers detected by including CBE was estimated to be between −1.85 and 11.44 per thousand, very different from previous studies which have found incremental benefits in the range of 3.3%–44.7% [14,23,24]. This is largely due to some of those reports were based on less sensitive mammographic technology, as well the differences in the statistical models, and the fact that most of the previous studies were not in community settings.

The addition of CBE to mammography would increase the overall sensitivities and decrease the specificity, but the changes are different among the four group women we examined. The results suggest that CBE has greater incremental benefit in women at low risk or currently using hormone therapy. These two groups of women have improved detection rates and sensitivity while lost less specificity when CBE was applied in addition to mammography, especially for women older than 60. Accordingly, CBE could usefully be targeted to the groups in which it has the highest net benefit, for example, women older than 60 and receiving hormone therapy. Our model shows that women with dense breast tissue is the group which benefits least from increased tumor ascertainment when CBE is added to a screening program; also this group experiences the second most harm from CBE due to false-positive results among our four risk groups. This finding differs from the belief that CBE generally adds incrementally more to sensitivity among women with dense breasts [14].

There is considerable variation between examiners' referral probabilities, even after adjusting for various factors, and this variation is not accounted for by years of experience or variation between screening centers. However, the small number of cancers in the dataset and the consequent lack of information on cancer detection rates for women not being referred might limit the reliability of the estimated true positive rates.

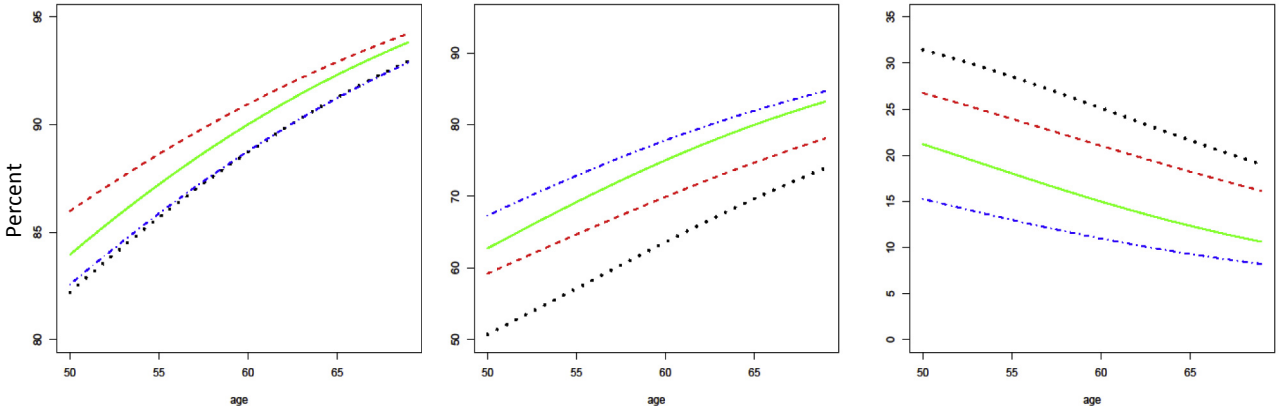
This study had several strengths. First, it accounted for the effects of provider experience and facility characteristics on the



(a) with both mammography and CBE (b) with mammography alone (c) The difference between (a) and (b)

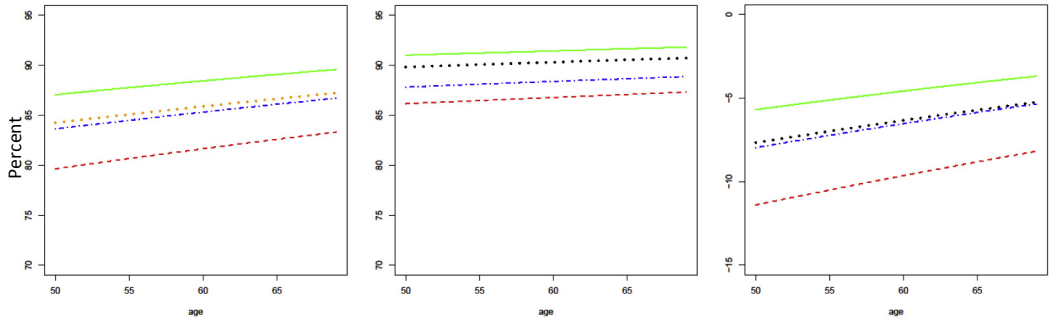
Fig. 1. The detection rate for the first screen: low risk women with low density without family history (solid lines), high risk women with high mammographic density and a family history of cancer (dashed lines), women currently use hormone therapy (dotted line), and women with high density breast (dotdash line).

accuracy of an exam. Secondly, by applying advanced statistical models, possible biases created by missing cancers due to incomplete case ascertainment in OBSP and the cancers detected by chance have been taken into account. An earlier study of the same population found that women referred by CBE alone were significantly more likely to have incomplete follow-up information in the OBSP [13]. It would lead to underestimated accuracy measures if missed cancers were not taken into account. Lastly, the study estimates the effect of CBE on diagnostic accuracy mammography by directly comparing two screening protocols,



(a) with both mammography and CBE (b) with mammography alone (c) The difference between (a) and (b)

Fig. 2. The gain in sensitivity when including CBE for the first screen: low risk women with low density without family history (solid lines), high risk women with high mammographic density and a family history of cancer (dashed lines), women currently use hormone therapy (dotted line), and women with high density breast (dotdash line).



(a) with both mammography and CBE (b) with mammography alone (c) The difference between (a) and (b)

Fig. 3. The gain in specificity when including CBE for the first screen: low risk women with low density without family history (solid lines), high risk women with high mammographic density and a family history of cancer (dashed lines), women currently use hormone therapy (dotted line), and women with high density breast (dotdash line).

with CBE and without instead of comparing CBE and mammography, and sensitivity of mammography may be overestimated as CBE results are available to the radiologist.

As some of the characteristics of the women such as family history and hormone therapy use were based on self-report, misclassification may have occurred. Although accuracy of reporting breast cancer in first degree relatives or hormone therapy use was relatively high [13] and ascertainment of information was similar between groups, any misclassification may have been non-differential and could have attenuated our estimates. Effect sizes of risk factors related to false positive probabilities were much better estimated than those related to cancer detection, likely due to the much greater number of women without cancer than those with cancer in the dataset; also, the lack of significance for these variables with respect to cancer detection may be due to low power.

Our study found that CBE may benefit older low-risk women and women receiving hormone therapy when offered in addition to mammography. However, the benefit in effectiveness must take into account potential harms and costs of further follow-up including greater number of biopsies due to false positive results and anxiety from additional diagnostic evaluations. These harms and benefits may differ by characteristics of the women such as a higher mammographic density or family history, so women should be informed of the risks and benefits of having a CBE in addition to mammography for breast screening. In addition, the accuracy of mammography and CBE varies significantly by examiners and this variation is not accounted for by years of experience or variation between screening centers. Further investigation is required to determine the factors causing the difference in screening accuracy among examiners.

Declarations

The authors contributed equally to this work and declare that there is no conflict of interest.

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The datasets generated and/or analyzed during the current study are not publicly available due to ethics and data protection.

Appendix

A.1. Model details

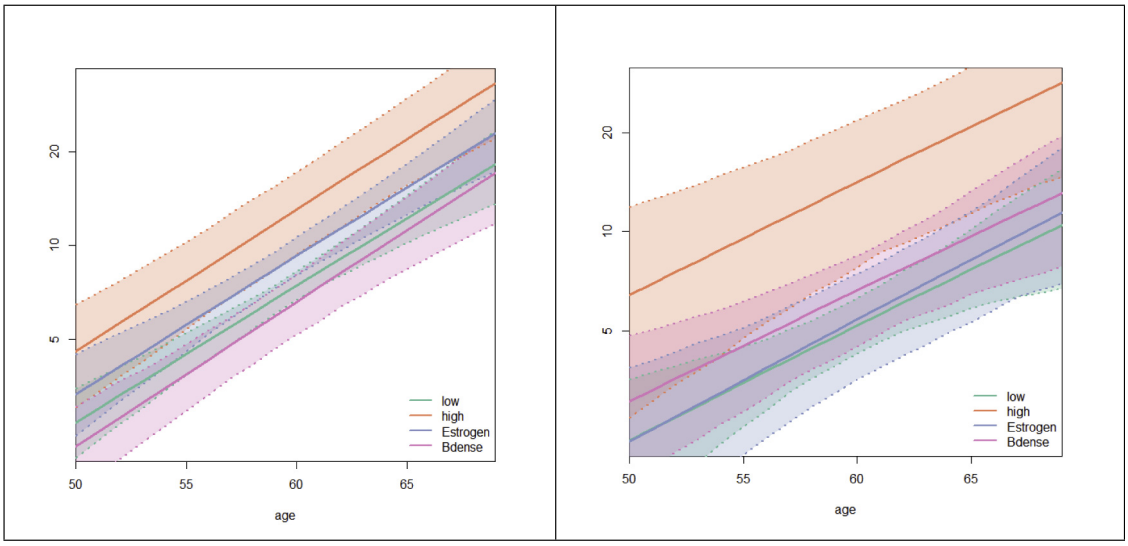
In our earlier work [16], we considered only data from individuals having undergone mammography without CBE, so here the methodology must be extended to allow for multiple exams per individual. As with [16], random effect terms are included in the model for the probabilities of referral from the W and V processes to allow for variation between different radiologists' and nurses' abilities to detect lesions and distinguish lesions from benign artifacts. Further, random effects are included at the screening site level to allow for possible variations between policies and cultures at different health facilities. Each radiologist or nurse has two random effects, one each for the W and V processes. Allowing for possible correlation between these random effects would, for instance, take into account any tendency for nurses with strong cancer detection abilities to be less likely to refer women when cancer is not present. Each screening site has four random effects, an effect on the W and V process for each of radiologist referrals and nurse referrals. Correlations between all four of these effects are allowed for.

In the case of multiple exams, for example mammography and CBE, the model was further extended by assuming the exams were independent conditional on real disease status C. That is:

Referral with detection: pr (W1, W2|C) = pr (W1|C) * pr (W2|C)
Referral without detection: pr (V1, V2|C) = pr (V1|C) * pr (V2|C)

The subscripts 1 and 2 are used to represent two different exams on same women, namely mammography and CBE here.

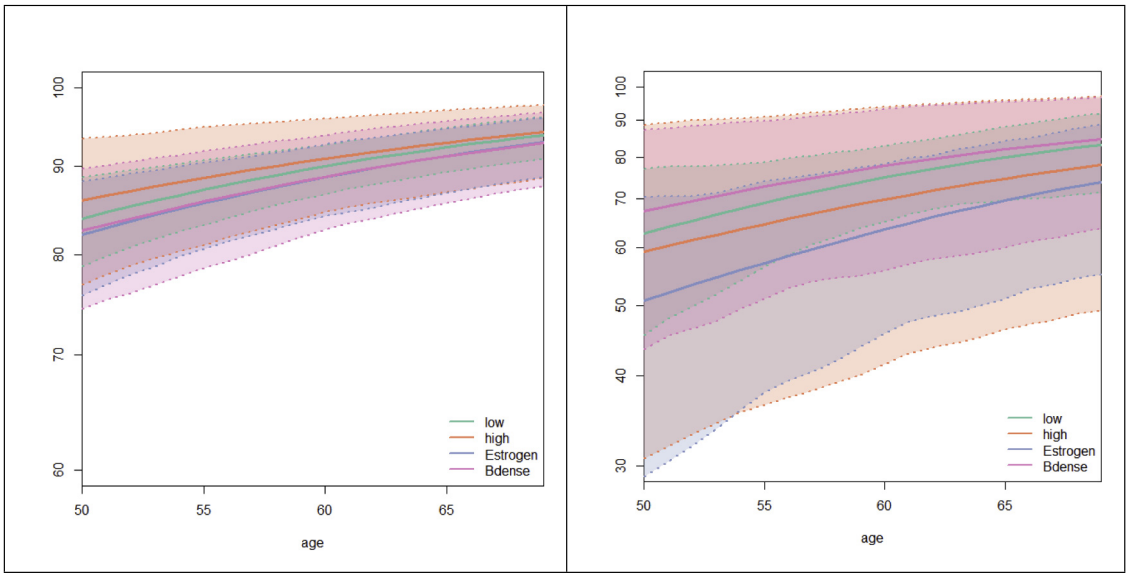
A.2. The detection rate estimates (Fig. 1) with their 95% confidence interval: low risk women with low density without family history (in green), high risk women with high mammographic density and a family history of cancer (in orange), women currently use hormone therapy(in blue), and women with high density breast(in purple).



(a) with both mammography and CBE

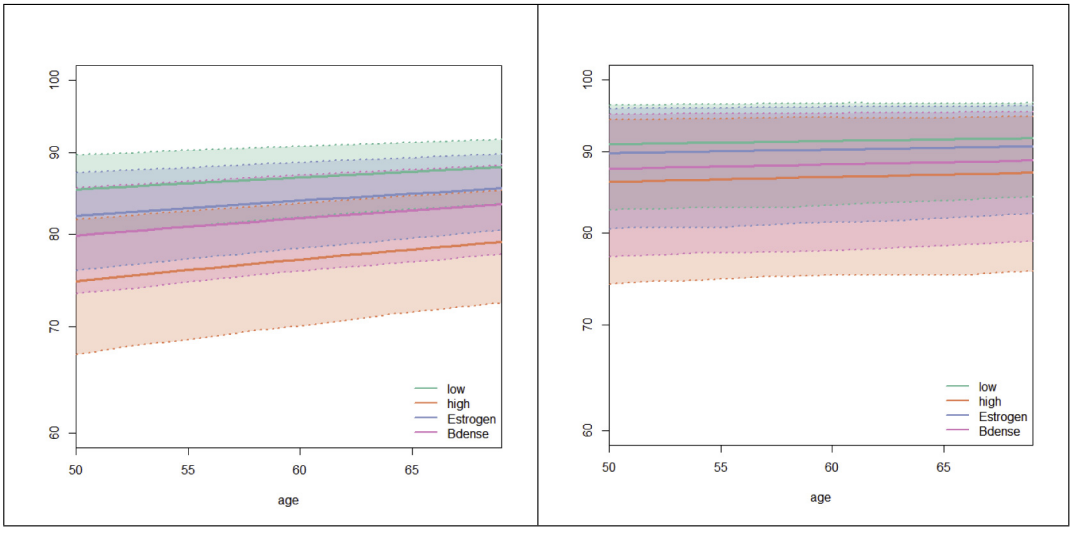
(b) with mammography alone

A.3. The estimated sensitivities (Fig. 2) with their 95% confidence interval: low risk women with low density without family history (in green), high risk women with high mammographic density and a family history of cancer (in orange), women currently use hormone therapy(in blue), and women with high density breast(in purple).



(a) with both mammography and CBE (b) with mammography alone

A.4. The estimated specificities (Fig. 3) with their 95% confidence interval: low risk women with low density without family history (in green), high risk women with high mammographic density and a family history of cancer (in orange), women currently use hormone therapy(in blue), and women with high density breast(in purple).



(a) with both mammography and CBE (b) with mammography alone

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