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FULL PAPER

Are mammography image acquisition factors, compression pressure and paddle tilt, associated with breast cancer detection in screening?

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Objectives: To assess the associations between objectively measured mammographic compression pressure and paddle tilt and breast cancer (BC) detected at the same ("contemporaneous") screen, subsequent screens, or in-between screens (interval cancers).
Methods: Automated pressure and paddle tilt estimates were derived for 80,495 mammographic examinations in a UK population-based screening programme. Adjusted logistic regression models were fitted to estimate the associations of compression parameters with BC detected at contemporaneous screen (777 cases). Nested case-control designs were used to estimate associations of pressure and tilt with: (a) interval cancer (148 cases/625 age-matched controls) and (b) subsequent screen-detected cancer (344/1436), via conditional logistic regression.
Results: Compression pressure was negatively associated with odds of BC at contemporaneous screen (odds ratio (OR) for top versus bottom third of the pressure distribution: 0.74; 95% CI 0.60, 0.92; P-for-linear-trend (Pt) = 0.007). There was weak evidence that moderate pressure at screening was associated with lower odds of interval cancer (OR for middle versus bottom third: 0.63; 95% CI 0.38, 1.05; p = 0.079), but no association was found between pressure and the odds of BC at subsequent screen. There was no evidence that paddle tilt was associated with the odds of contemporaneous, subsequent screen or interval cancer detection.
Conclusions: Findings are consistent with compression pressure, but not paddle tilt, affecting the performance of mammographic screening by interfering with its ability to detect cancers.
Advances in knowledge: Inadequate or excessive compression pressure at screening may contribute to a reduced ability to detect cancers, resulting in a greater number of interval cancer cases.

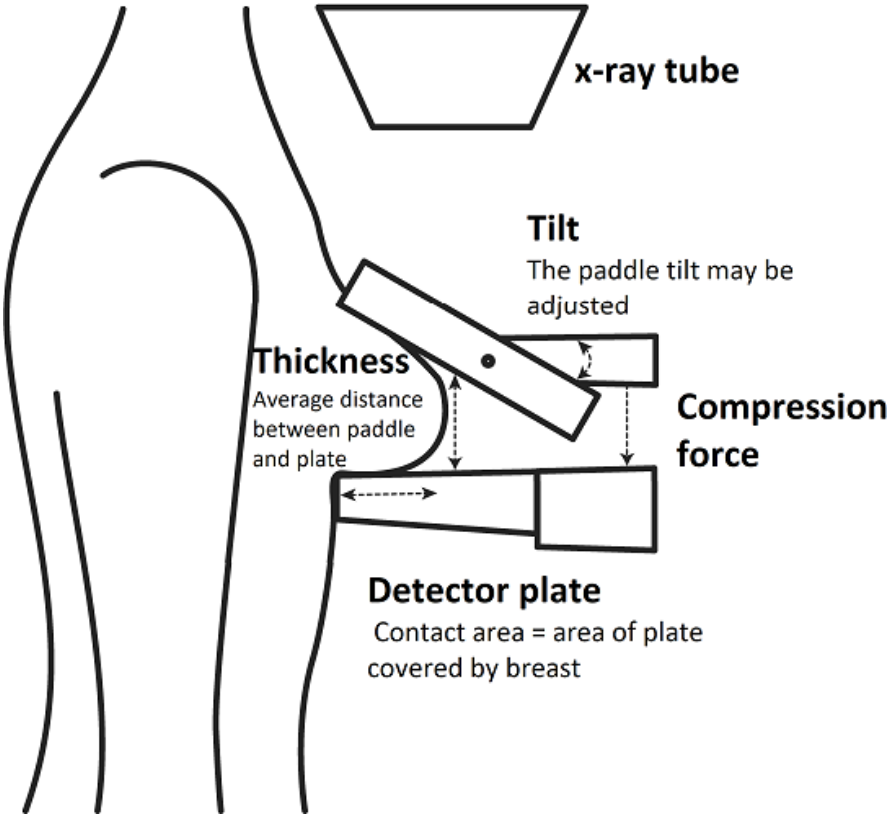
INTRODUCTION

Population-based mammographic screening programmes, such as the England and Wales Breast Screening Programme (NHSBSP), have been found to reduce mortality through detection of asymptomatic cases coupled with early treatment.[1] However, such programmes rely on the quality of the mammographic images to enable radiological detection of suspicious features in the breast.

Mammography involves compressing the breast between a detector plate and a transparent paddle such that the breast is immobilised, and the thickness of tissue minimised without causing unnecessary pain. The force applied to achieve this compression can be monitored by the practitioner. A tilting or hinging paddle may optionally be used to adjust the angle of the top paddle away from parallel to reflect the natural shape of the compressed breast (Figure 1).

Breast compression is thought to be a key factor in the production of high-quality images because it helps to reduce movement (blur), separate overlying tissues and also reduce thickness, thereby improving tumour conspicuity.[2,3] Furthermore compression reduces the absorbed radiation dose during the screening procedure.[4] Tilting paddles were introduced with the aim of reducing pain during mammography, but a previous study, conducted within the same study population as the present investigation found that increased paddle tilt was associated with increased compression thickness; therefore, it is possible that tilting paddle use also affects cancer conspicuity.[5]

Figure 1. Compression of the breast during CC image acquisition schematic



Internationally, a wide variation in objectively measurable imaging parameters has been observed.[6–9] In the UK, although regular image audits take place, objective guidelines on optimal breast compression are currently limited to the guidance that force should not exceed 20daN.[10,11] Our previous study on the same population found that compression pressure and paddle tilt are not systematically adjusted in accordance with objective breast characteristics and consequently there is inconsistency in technique and compression outcomes.[5]

A limited number of studies have used objective mammographic acquisition measures to show that screening performance is associated with the degree of compression force and pressure used during image acquisition.[12,13] However, little is known, as yet, about the association between paddle tilt and cancer detection in screening programmes.

BC risk is increased in females with denser breasts, with females in the densest category having 4.6 times the risk of females in the fatty category.[14] Furthermore, breast density affects the effectiveness of mammographic screening because fibro-glandular tissue, that makes up breast density, can mask cancers, resulting in reduced sensitivity and a higher risk of interval cancers in denser breasts.[15–18] Studies have shown that mammographic acquisition measures are correlated with breast density.[19]

The aim of this study is to investigate the association between image acquisition pressure and paddle tilt, and the risk of being diagnosed with BC at the same or subsequent screens, or as an interval cancer between screens, among a large population-based sample of 94,408 examinations taken amongst 68,776 women who underwent mammographic screening on one or more occasion in South-West London, England, between March 2013 and June 2017.

METHODS

Study participants

Study participants underwent routine 3-yearly screening mammography at the South-West London Breast Screening Service (SWLBSS) based in the St George's University Hospitals NHS Foundation Trust. SWLBSS is a part of the NHSBSP, an organised population-based mammographic screening programme, which targets females aged 50–70. We also included females aged 47–49 and 71–73 screened as part of a national trial[20] plus any females over 73 years who had contacted the service for a self-referred screening appointment. A small number of females who are invited to annual screening due to higher familial risk, were also included. Participants were screened during the period 01/03/2013 to 20/06/2017. The subject's age at the time of screening was recorded. A self-completed questionnaire is routinely used at SWLBSS to gather ethnicity data according to the Census classification[21] and these data were further categorised into, "Asian" (Indian, Pakistani or Bangladeshi or other), "Black-African", "Black-British or Caribbean or other", "Chinese", "Mixed" (White and Black, White and Asian or any other mixed), "White" (British or Irish or other) and "Other". The NHSBSP does not systematically record data on

other known BC risk factors and thus we were unable to collect data on factors such as reproductive history, body mass index (BMI), family-history of breast cancer and menopause hormone therapy usage.

Exposure assessment

Each female was screened according to the NHSBSP standard, 2-view (cranio-caudal (CC) and medio-lateral-oblique view (MLO)) mammography of each breast.[22] Raw digital mammographic images were processed using an automated algorithm, i.e. Volpara® Density™ version 1.5.11 (Volpara), (Matakina Technology Limited, Wellington, New Zealand),[23] which provided estimates (in cm^3) of the volume of the breast (BV) and the volume of the radio-dense tissue (DV) plus an estimate contact area (cm^2) between breast and detector plate. Estimates were provided separately for each of the four (left/right CC and MLO) images and as an average across all four images. The algorithm also yielded estimates, separately for each image and also as an overall average, of non-dense volume (NDV) as BV-DV and of % dense volume as the ratio of DV to BV expressed as a percentage. In addition, the algorithm provided a density grade (DG) score of 1 to 4, corresponding to the BI-RADS (Breast Imaging Reporting and Data System fourth Edition) classification for mammographic density *i.e.* A: almost entirely fatty, B: scattered areas of fibroglandular density, C: heterogeneously dense, and D: extremely dense.

The Digital Imaging and Communications in Medicine (DICOM) image header provided additional data on compression force (in decaNewton, daN) and compression paddle tilt (in degrees from horizontal). The resulting pressure (in kiloPascals, kPa) was calculated by the algorithm from force*10/contact area. The anonymised identifiers of the mammographer taking the image and the type of screen (first (prevalent) versus subsequent (incident) screens) were also recorded.

Examination eligibility

Screening examinations where exposure measurements (*i.e.,* pressure and paddle tilt) and outcome ascertainment (screen-detected cancer) were collected concurrently, were regarded as "contemporaneous screens for the purposes of this study. A total of 94,408 contemporaneous screening examinations took place during the study period. Examinations were excluded from the analysis if: (i) the reason for the examination was not known (*i.e.,* screening episode type was missing) (n = 992); (ii) the females had a previous BC (n = 2,068) because this might have influenced the physical nature and compressibility of the breast; (iii) examinations were performed using non-Hologic systems (n = 836) because of potential differences between manufacturers (iv) if more, or less, than the four standard images were taken, because the automated algorithm is not designed to make estimates where non-standard imaging sets are taken[23] (n = 10,234). Thus, a total of 80,495 examinations (321,980 compressions) were eligible for inclusion in the analyses.

Some examinations were on females who were screened more than once in the study period; 13,489 women had two examinations, 439 women had three examinations and 157 women had four examinations or more. All valid screening examinations were included in the analysis.

"Subsequent" screens were screens that took place at ~3 years after the contemporaneous screen *i.e.* at the next screening invitation following on from a contemporaneous screen. ~20% of subsequent screens were examinations that were taken in the period 2013 to 2017 and were therefore also eligible for inclusion in the contemporaneous screen analysis.

Cancer ascertainment

For the purpose of this study "contemporaneous" screen detected cancers were classified as cancers detected at the same time that the compression exposures (*i.e.,* pressure and tilt) were estimated (Figure 2). "Interval cancers" were those diagnosed symptomatically in the 3-year period following the initial screen and exposure measurement but before the next screening invitation. Any cancers detected at the subsequent screen, were classified as "subsequent cancers". All screens in this study were double read. A third, arbitration read, was conducted and a consensus agreed for all abnormal reads.

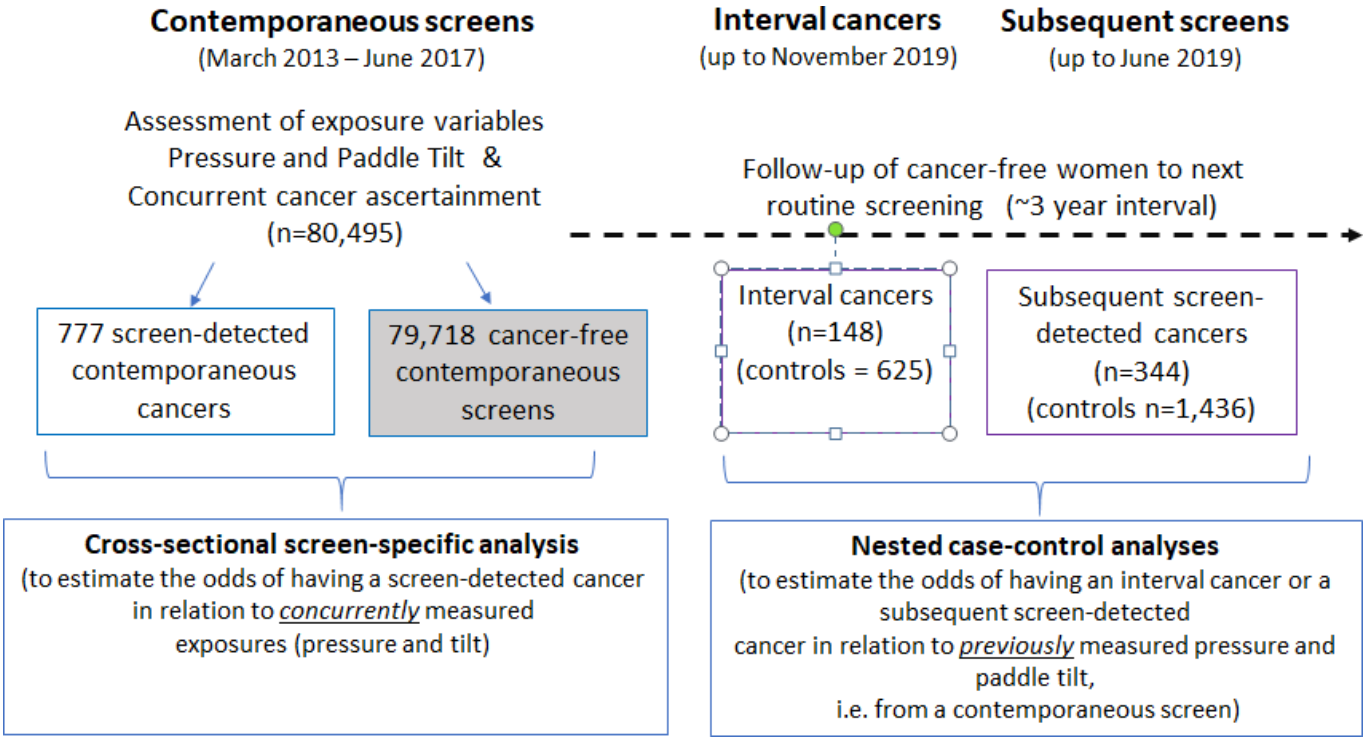
Screen detected cancers (contemporaneous or subsequent screen) were routinely recorded by the SWLBSS at the time of the relevant screening. Interval cancer cases were notified to SWLBSS through sharing of data between the Screening Quality Assurance Service and Cancer Registries and via direct contact between the screening services and local treating NHS Trusts and then recorded in the SWLBSS screening database. We included all subsequent screens up to June 2019 and all recorded interval cancers from the SWLBSS database as of 6/11/2019.

Study design

A cross-sectional screen-specific design was used to examine associations between the pressure and tilt used in the mammography examination and contemporaneous screen-detected cancers (Figure 2). Examinations at which females were diagnosed with BC (n = 777) were defined as cases, and examinations where no cancer was detected (n = 79,718) as non-cases.

An incident-density-sampling (nested) case-control design was used to investigate the association between mammography technique (pressure and tilt) and interval cancers (Figure 2). Cases were examinations where females were diagnosed with an interval cancer after a previous negative contemporaneous screen. Up to five matching controls were randomly selected for each case from females of the same age (± 1 year) who had a contemporaneous screen in the same year and month as the case with a verified 'non-cancer' status at the time that the case was diagnosed (based on subsequent screening records). For cases aged >73 years at contemporaneous screen controls were aged-matched within ± 5 years due to lack of qualifying controls. A total of 148 interval cancer cases and 625 matched controls were identified, corresponding to 86 cases with five controls each, 29 cases with four controls each, 20 cases with three controls

Figure 2. Timing of mammography and cancer diagnosis



each, 6 cases with two controls each and 7 cases with one control each; one case was excluded in the analysis because there were no valid matched controls.

A nested case-control approach was also used to assess the association between mammographic technique and risk of being diagnosed with a BC at a subsequent screen (Figure 2). This design was preferred to a cross-sectional analysis because at the time that the data was available, subsequent screens had only been performed for around 65% of study participants. Cases were examinations where females had a negative contemporaneous screen and no interval cancer diagnosis but were then diagnosed with breast cancer in the subsequent screening round (n = 344). Up to five age-matched controls per case were identified (a total of 1,436) using a similar approach to that outlined above for interval cancers.

Ethical approval

This retrospective study was carried out on fully anonymous, routinely collected data only, held in accordance with the National Health Service (NHS) Cancer Screening Programmes Confidentiality and Disclosure Policy 2011. The NHSBSP has section 251 support under the NHS Act 2006. The study was approved by all relevant ethics committees (Research Ethics Committees from St George's University Hospitals NHS Foundation Trust, and the London School of Hygiene and Tropical Medicine).

Statistical analyses

Mean compression pressure and mean paddle tilt used for an examination were calculated using all compressions from both views (MLO, CC) and each side; the distributions of these variables were approximately normal, and we further categorised them into thirds (low, medium and high) using as cut-off points the tertiles of the distributions in the non-cases/controls. The mean acquisition pressure and tilt for MLO and CC views separately were also calculated and thirds defined using tertiles as above.

Separate logistic regression models were used to examine the strength of the associations between the categorical exposures of interest, pressure and tilt, and the odds of being diagnosed with a contemporaneous screen-detected BC. Robust standard errors (clustering by female screened) were used to account for the fact that some females may have been screened more than once during the period. Similarly, separate conditional logistic regression models were used to examine the strength of the associations between pressure and tilt and the odds of an interval cancer and the odds of a subsequent screen-detected cancer.

All regression models were adjusted for a priori potential confounders: age at screening, ethnicity, DG (as estimated by the Volpara algorithmn) and additionally, in the tilt models only, for mammographic NDV (a valid proxy for BMI when data for the latter are not available[24]). NDV was not included as a potential confounder in the pressure model because of collinearity between pressure and NDV (data not shown). Linear trend tests for the association with the exposures of interest were carried out fitting models with the ordinal values of each categorical measure, assessing their significance using Wald tests. To allow comparison to other studies an alternative pressure model was fitted to replicate Moshina's Norwegian model,[12] adjusting for absolute DV rather than the relative density measure DG.

In all contemporaneous screening models we additionally adjusted for type of screen, (incident or prevalent) since a female undergoing her first (prevalent) screen is more likely to be recalled for additional tests and a higher cancer detection rate is normally observed.[25]

In all the analyses, we considered statistical significance (2-sided) at p-value < 0.05. All analyses were conducted in Stata (IC 14) [33].

RESULTS

Study participants

The characteristics of the participants, and of their screens, are shown in Table 1. The majority of the participants were White. The mean age, at contemporaneous screening, was 58.4 years in non-cases and 60.4 years in BC cases. Mean time between contemporaneous screen and interval cancer diagnosis was 19.2 (range 1.7–36.0; SD = 9.1) months. Mean time between contemporaneous screen and subsequent screen diagnosis was 36.4 (range 9.6–70.8; SD = 8.2) months by design, since the screening programme aims to invite females at ~36 monthly intervals

The median values for pressure and tilt were lower for contemporaneous cases (8.41 kPa and 2.59 degrees, respectively) than non-cases (8.65 kPa and 2.69 degrees, respectively; Table 1). In contrast median value for exposure pressure used in the original mammogram was higher for interval and subsequent screen cancer cases (8.54 kPa and 8.55 kpa, respectively) than their matched controls (8.28 kPa and 8.50 kpa, respectively; Table 1). This difference mainly reflects differences in pressure used during the CC compressions with smaller case-control differences observed in the MLO view (Table 1).

In each category (contemporaneous, interval and subsequent round screens) the DV, DG and NDV were higher in cases than non-cases/controls, (Table 1).

Associations between image acquisition pressure and tilt and contemporaneous screen-detected breast cancer

There was a negative association between compression pressure and the odds of being diagnosed with BC at the contemporaneous screen (Figure 3) (p-for-linear-trend (Pt) = 0.007). Relative to females in the bottom third of the pressure distribution (<6.7 kPa), those in the top third (>9.3 kPa) had 26% lower odds (OR 0.74; 95% CI 0.60, 0.92) of having a screen detected cancer in the fully-adjusted models (Figure 3 and Supplementary Table 1). There was a possible negative association between paddle tilt and odds of breast cancer detected at contemporaneous screen, but trends were non-significant (Pt = 0.119), (Figure 3). In all models age and breast density were strongly positively associated with increased risk of BC (Supplementary Tables 1 and 2).

Associations between image acquisition pressure and tilt and interval cancer

After adjustment for relative breast density, age and ethnicity, compression pressure was weakly negatively associated with the odds of having an interval cancer; females in the top third of the pressure distribution had odds, similar to, but somewhat lower than, those in the bottom third (adjusted OR 0.87; 95% CI 0.53, 1.43; Figure 3). However, females in the middle third had lowest odds of being diagnosed with an interval cancer relative to those in the lowest third of the pressure distribution (adjusted OR 0.63; 95% CI 0.38, 1.05; Figure 3). These results were however of borderline significance p = 0.079 (Supplementary Table 1). This association was stronger but also non-significant, in the CC compressions (adjusted OR 0.64; 95% CI 0.36, 1.14) than the MLO (adjusted OR 0.88; 95% CI 0.49, 1.56) compressions (Supplementary Table 3).

The odds of being diagnosed with an interval cancer were higher for greater degrees of paddle tilt but these estimates were very imprecise as reflected by the wider confidence intervals (Figure 3).

Associations between image acquisition pressure and tilt and a subsequent screen-detected cancer

There were no clear associations between pressure and the odds of being diagnosed with cancer at the subsequent screen (Figure 3). Nor were there associations between paddle tilt and the odds of having a cancer detected at the next screening round (Figure 3).

DISCUSSION

Main findings

Females who received the highest-pressure compressions were less likely to have a contemporaneous screen detected cancer. The findings for interval cancers show no clear trend but females in the middle third of the pressure distribution had lower odds of an interval cancer diagnosis than females in the lowest and highest pressure thirds of the distribution (but with borderline significance). We found no evidence of an association between pressure and the odds of a BC diagnosis at the subsequent routine screen. Increasing compression paddle tilt was not strongly associated with increasing odds of having an interval cancer or a subsequent routine-screen cancer in our study.

Our findings on pressure partly support those from a similar study by Holland et al who used the same computer algorithm and controlled for similar confounders, but used MLO views only, from over 100,000 women invited for screening in the Netherlands breast screening programme.[13] Mean BV was higher in the Dutch study than in our study (974 cm^3 and 850 cm^3 respectively) and average pressure for the MLO view was also higher than in our study (10.5 kPa and 7.4 kPa respectively). Holland et al found that screening sensitivity (based on interval cancers) was significantly lower in the highest pressure compression quintiles but higher in the middle pressure quintile of the distribution. We also found that odds of interval cancer were lowest in the middle pressure third of the pressure distribution. In our study the association between pressure and interval cancer was stronger for CC compressions than for MLO compressions. This may be related to the higher mean compression pressures that are used for CC views, which only include breast tissue and are not limited by inclusion of the pectoral muscle.

Table 1. Characteristics of the study participants, their mammographic examinations and cancers detected

	Contemporaneous screen-detected analysis		Subsequent interval cancer analysis		Subsequent screen-detected cancer analysis	
	Contemporaneous screen-detected cancer cases	Non-cancer at contemporaneous screen	Interval cancer cases	Controls	Subsequent screen-detected cancer cases	Controls
No. examinations[a]	*n* = 777	*n* = 79,718 a	*n* = 148	*n* = 625	*n* = 344	*n* = 1,436
Age at contemporaneous screening	**Mean (SD)**	**Mean (SD)** [b]	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
	60.35 (7.69)	58.40 (7.18)	59.19 (7.16)	59.59 (7.05)	59.90 (6.18)	59.74 (6.21)
Ethnicity	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
White [c]	530 (68.2%)	51,931 (65.1%)	113 (76.4%)	405 (64.8%)	252 (73.3%)	965 (67.2%)
Asian [d]	75 (9.7%)	7,536 (9.5%)	5 (3.4%)	75 (12.0%)	32 (9.3%)	135 (9.4%)
Black – Caribbean [e]	25 (3.2%)	3,720 (4.7%)	9 (6.1%)	26 (4.2%)	10 (2.9%)	75 (5.2%)
Black – African	22 (2.8%)	2,703 (3.4%)	2 (1.4%)	20 (3.2%)	1 (0.3%)	53 (3.7%)
Mixed	11 (1.4%)	1,515 (1.9%)	3 (2.0%)	16 (2.6%)	6 (1.7%)	24 (1.7%)
Chinese	10 (1.3%)	1,052 (1.3%)	1 (0.7%)	3 (0.5%)	7 (2.0%)	24 (1.7%)
Missing/not reported	104 (13.4%)	11,261 (14.1%)	15 (10.1%)	80 (12.8%)	36 (10.5%)	160 (11.1%)
Type of screen	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Prevalent	212 (27.3%)	21,558 (27.0%)	36 (24.3%)	130 (20.8%)	61 (17.7%)	262 (18.2%)
Incident	565 (72.7%)	58,160 (73.0%)	112 (75.7%)	495 (79.2%)	283 (82.3%)	1,174 (81.8%)
Imaging parameters average for MLO and CC views [g] Mean pressure, kPa Mean positive paddle tilt, degrees	**Mean (SD)** 8.41 (3.47) 2.59 (1.01)	**Mean (SD)** 8.65 (3.54) 2.69 (1.06)	**Mean (SD)** 8.54 (3.29) 2.47 (1.01)	**Mean (SD)** 8.28 (3.16) 2.59 (1.01)	**Mean (SD)** 8.55 (3.28) 2.53 (0.96)	**Mean (SD)** 8.50 (3.33) 2.62 (1.04)
Imaging parameters for MLO [g] Mean pressure, kPa Mean positive paddle tilt, degrees	7.24 (2.43) 2.77 (1.23)	7.36 (2.51) 2.87 (1.28)	7.24 (2.35) 2.59 (1.25)	7.24 (2.48) 2.79 (1.21)	7.45 (2.37) 2.68 (1.16)	7.31 (2.38) 2.80 (1.26)
Imaging parameters for CC [g] Mean pressure, kPa Mean positive paddle tilt, degrees	9.63 (4.93) 2.34 (1.12)	9.98 (4.96) 2.43 (1.16)	9.95 (4.72) 2.28 (1.10)	9.44 (4.38) 2.32 (1.10)	9.92 (4.74) 2.29 (1.07)	9.82 (4.79) 2.35 (1.16)

(Continued)

Table 1. (Continued)

	Contemporaneous screen-detected analysis		Subsequent interval cancer analysis		Subsequent screen-detected cancer analysis	
Breast Volumetric measurements[h]	**Median**	**Median**	**Median**	**Median**	**Median**	**Median**
Breast dense volume,[i] cm^3	51.1 (39.9–69.6)	49.3 (37.2–67.3)	57.1 (43.0–89.4)	48.1 (36.0–65.5)	50.3 (43.0–89.4)	47.7 (36.0–65.1)
Breast non-dense volume, cm^3	725.7 (462.3–1075.5)	698.8 (438.0–1046.4)	838.7 (386.0–1144.3)	728.7 (484.1–1074.5)	727.65 (447.5–1085.4)	697.8 (437.5–1048.3)
Volpara Density Grade (n, %)[j]	**n** (%)	**n** (%)	**n** (%)	**n** (%)	**n** (%)	**n** (%)
Category 1	132 (16.99%)	17,512 (21.97%)	20 (13.51%)	146 (23.36%)	70 (20.35%)	356 (24.79%)
Category 2	303 (39.00%)	29,771 (37.35%)	47 (31.76%)	258 (41.28%)	122 (35.47%)	531 (36.98%)
Category 3	278 (35.78%)	23,270 (29.19%)	55 (37.16%)	169 (27.04%)	121 (35.17%)	418 (29.11%)
Category 4	64 (8.24%)	9,165 (11.50%)	26 (17.57%)	52 (8.32%)	31 (9.01%)	131 (9.12%)

SD, standard deviation ; n/a, not available.
[a]14,085 of the screens were on females who had two or more contemporaneous screen. Each examination is included independently.
[b]Where females have more than one contemporaneous screen the average of their age at screen is taken.
[c]White includes: British/Irish and other
[d]Asian includes: British Indian, Pakistani, Bangladeshi and other
[e]Black includes: British, Caribbean and other (non-African)
[f]Mean values are calculated using all available images from the relevant view (MLO and CC from each breast side) at a contemporaneous screen
[g]Mean and Median values are calculated using all available images (MLO and CC from each side) at a contemporaneous screen. Median (with 25th and 75th centile values) are shown.
[h]Screens included must have exactly four images taken, only screening images are included. Screens for females known to have previous breast cancer were also excluded.
[i]Mean (SD) Breast Volume for all contemporaneous screens was 850.1cm^3 (489.6), median 753.2 cm^3 (488.8–1110.1). Data included for comparative purposes with other studies.
[j]Density grade as calculated by the Volpara algorithm using relative % of dense and non-dense areas on the image. Estimates correspond to BIRADS fourth Edition. Images taken at the contemporaneous screen

A similar Norwegian study by Moshina et al using pressure estimates based on averaged MLO and CC views, yielded by the same algorithm (~339 interval cases; ~83,000 non-cases), found that compression pressure was positively associated with interval cancer.[12] The Norwegian screening programme participants were of similar average age as the participants in our study, but their median breast volume was somewhat greater (814.7 cm^3 and 776.8 cm^3 respectively). A key difference in the Norwegian study was that it controlled for absolute breast DV whilst, like Holland et al,[13] we adjusted for a relative measure of density to reflect breast composition and compressibility. When we replicated the Norwegian model by adjusting for DV rather than DG we found the adjusted ORs (high pressure third versus low pressure third) at interval cancer to be rather similar (OR 1.86 (95% CI 1.41, 2.45) in the Norwegian study, versus OR 2.03 (95% CI 1.21, 3.37) our study (Supplementary Table 4). Controlling for an absolute measure of breast dense volume, as in the Norwegian model, increased the magnitude of our findings, possibly because in our study population compression force was not altered adequately for breast size during mammography and hence smaller, denser breasts received higher average compression pressure (see previous study on the same study population[5]). On the other hand, it is possible that controlling for a relative measure of density attenuates the associations with pressure because relative density is relative to breast volume. Despite these difficulties it is clear from our study that the association between pressure and odds of interval cancer is not linear, and it is possible that moderate levels of pressure are associated with lower risk of interval cancer.

A recent UK study by Hill et al, which used a different design, appears to contradict these findings. They compared interval cancers with age and Volpara density grade matched screen detected cancer controls and found that pressure measured at initial screen was a significant predictor of interval versus screen detected cancers, with higher pressure being associated with a lower risk of interval cancers.[26] The results of Hill's study are not directly comparable to ours but suggest that the exact nature of the relationship between pressure and cancer detection is still not clear.

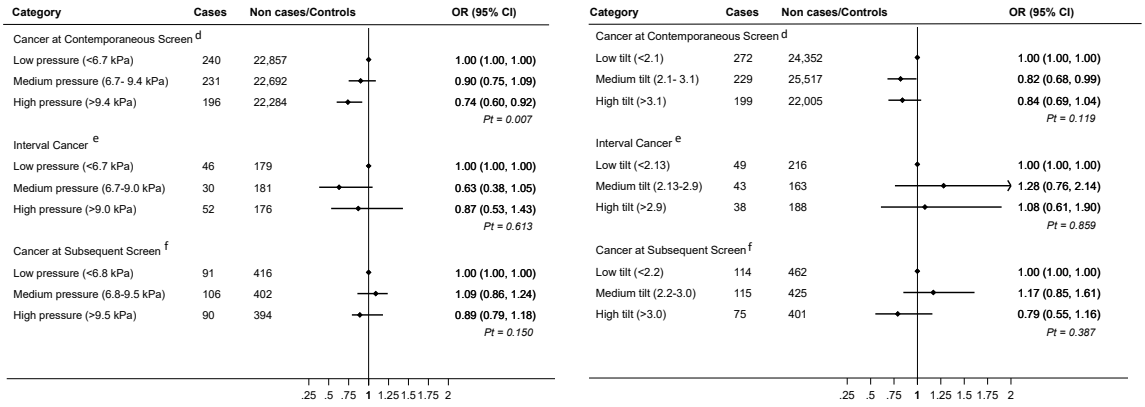
To our knowledge ours is the first study to look at the association between paddle tilt and cancer detection. Our findings, albeit non-significant at the 5% significance level suggest that fewer interval cancers may be associated with the lowest paddle tilt, but further studies are required to clarify this association.

The pathways through which variations in pressure and tilt applied at imaging may influence cancer conspicuity and hence the likelihood of an interval cancer are poorly understood. Our findings also suggest that the association between compression thickness and tumour conspicuity may be more subtle in real-life than when simulated lesions in breast phantoms are used.[2]

Our study suggests that applying a moderate level of pressure may reduce the odds of cancers being missed at screening (albeit with non-significant findings). Under compression is likely to lead to increased thickness and more possibility of image blur

Figure 3. Regression analysis, fully adjusted [a, b], of associations between pressure [c] and tilt [c] measured at the contemporaneous screen and breast cancer. Footnotes a Adjusted associations: Age, Ethnicity and Volpara Density Grade (4th Edition) which corresponds to the breast imaging reporting & data system (BI-RADS) density category. All exposures measured at the contemporaneous screen. b Tilt model additionally adjusted for NDV (as a proxy for BMI), which was omitted in the pressure model due to collinearity; NDV was strongly negatively correlated with compression pressure (Pearson correlation coefficient <-0.70). c Automated pressure and tilt measures from the mean values from CC (cranio-caudal view) and MLO (medio-lateral oblique) images categorised according thirds of the distribution in non-cases. d Contemporaneous models additionally adjusted for incident or prevalent screening. e Interval Cancers – diagnosed during 3-year period since contemporaneous screen but before a subsequent screen. f Cancers at subsequent screen - diagnosed at next routine screening event after contemporaneous screen.

Fig 3 Regression analysis, fully adjusted [a, b], of associations between pressure [c] and tilt [c] measured at the contemporaneous screen and breast cancer



associated with movement, but higher pressure than strictly necessary may also be detrimental to the screening process. In practice film readers suggest that conspicuity depends on the relative density of fat and lesion and whereas fat is compressible and displaced from the image, the fibroglandular tissue and lesion are less compressible. At high levels of compression therefore the relative difference between fat and dense tissue may be reduced, hence reducing tumour conspicuity. It has also been suggested that reduced conspicuity may be the result of high compression pressure spreading tumour tissue and thereby diminishing the contrast required to identify the lesion.[27] An alternative explanation for possible reduced sensitivity at higher levels of compression pressure, was proposed by Hauge et al who found that the paddle moved for a significant period after the mammographer stopped increasing the compression force[28] and Ma et al also noted that the settling period was longer when higher compression force was used.[29] It is possible therefore, that at higher pressures, blurring can occur if the image is taken too soon after compression ceases *i.e.* whilst the breast is still undergoing settling movement. Others have suggested that the fact that fluids, including blood, are forced out of the breast during compression, whilst necessary for exposing some tumours may diminish the increased blood flow into a mass that can be a clue to identifying invasive cancers.[30]

The term "pressure" to describe force/contact area is not strictly correct since fluids, such as breast tissues, cannot be compressed, nevertheless it is a useful shorthand to describe the stretching of the breast. It is possible that models based on compression force adjusted for BV, may be better for understanding the association between relative force and cancer conspicuity because they take into account the entirety of the breast tissue undergoing compression and it is easier to control for breast density; however, unlike the compression pressure, it cannot easily be estimated in real-time and therefore has more limited use in practical settings.

Our study is inconclusive with respect to the association of paddle tilt and cancer detection although there is a possibility that lower tilt is associated with better screening outcomes. This could be related to the finding, in qualitative studies, that images taken with tilting paddles tend to show less tissue and have reduced contrast compared to rigid paddles.[31]

Strengths and limitations

Strengths of this study include its population-based design, large sample size, ethnic mix, and unbiased exposure measurements.

The algorithm (Volpara Density) used, also gives objective and reliable volumetric BV, plate contact area and DV estimates[32–34] which were used to calculate the exposure measures of interest as well as potential confounders. Force and tilt measurements are calibrated by the machine manufacturers and therefore the raw objective exposure variables are reliable and unbiased as they are independent of the outcome status of the participants (*i.e.,* their current or subsequent cancer status).

A limitation of this study was its low power to detect true associations, resulting from relatively few interval cancers being recorded, partly because of the lag time between diagnosis and notification to the screening services. Similarly, the number of subsequent round screen detected cancers was relatively low after excluding all the image sets that did not meet our inclusion criteria.

Implications

This study suggests that breast screening mammography technique, reflected in mammographer's discretionary decision making about positioning, force and paddle tilt, although poorly understood, has an impact on screening programme outcomes. Mammography is not a perfect screening tool and although cancer is successfully detected in almost 0.9% of females screened in the UK,[35] around 0.3% of females screened, actually present as interval cancers. Interval cancers tend to have a poorer prognosis than screen-detected cancers[36] therefore any improvements that increase the proportion of cancers that are detected at screening, will potentially save lives. Simple guidelines such as 'higher pressure is better' are unlikely to be helpful since there is evidence to suggest that outcomes (in terms of interval cancers) at medium-pressure levels may be better. As Ekpo et al pointed out 'errors in mammography cannot be solved through technology alone'[37] however by further improving our knowledge, and by challenging current assumptions incremental improvements may be made. The availability of automated image analysis could be used to increase the scope of routine image audits and enable more objective measures such as pressure or relative force to be incorporated into the audit process.

Further studies are required to compare outcomes where mammographers rely on their own discretion, with those where stricter pressure or force guidelines are adhered to. Research is also required to investigate whether the use of tilting or flexible paddles is associated with better or worse screening outcomes.

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