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FULL PAPER

Left-right breast asymmetry and risk of screen-detected and interval cancers in a large population-based screening population

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Objectives: To assess the associations between automated volumetric estimates of mammographic asymmetry and breast cancers detected at the same (“contemporaneous”) screen, at subsequent screens, or in between (interval cancers).

Methods: Automated measurements from mammographic images ($N = 79,731$) were used to estimate absolute asymmetry in breast volume (BV) and dense volume (DV) in a large ethnically diverse population of attendees of a UK breast screening programme. Logistic regression models were fitted to assess asymmetry associations with the odds of a breast cancer detected at contemporaneous screen (767 cases), adjusted for relevant confounders.

Nested case-control investigations were designed to examine associations between asymmetry and the odds of: (a) interval cancer (numbers of cases/age-matched controls: 153/646) and (b) subsequent screen-detected cancer (345/1438), via conditional logistic regression.

Results: DV, but not BV, asymmetry was positively associated with the odds of contemporaneous breast cancer (P -for-linear-trend (Pt) = 0.018). This association was stronger for first (prevalent) screens (Pt = 0.012). Both DV and BV asymmetry were positively associated with the odds of an interval cancer diagnosis (Pt = 0.060 and 0.030, respectively). Neither BV nor DV asymmetry were associated with the odds of having a subsequent screen-detected cancer.

Conclusions: Increased DV asymmetry was associated with the risk of a breast cancer diagnosis at a contemporaneous screen or as an interval cancer. BV asymmetry was positively associated with the risk of an interval cancer diagnosis.

Advances in knowledge: The findings suggest that DV and BV asymmetry may provide additional signals for detecting contemporaneous cancers and assessing the likelihood of interval cancers in population-based screening programmes.

INTRODUCTION

Breast cancer is the most common female cancer.¹ Mammographic screening programmes, such as the England and Wales Breast Screening Programme (NHSBSP), have been found to reduce mortality through earlier detection.² However, although increased amount of radio-dense tissue on a mammogram is associated with an increased risk of developing breast cancer,^{3–5} there is strong evidence that it also reduces the effectiveness of breast screening^{6–10} by decreasing mammographic sensitivity, as radio-dense tissue may hide cancers. Boyd et al found that females in the highest category of mammographic density (density in $\geq 75\%$ of mammogram) had greater odds of being diagnosed with cancer in the year following a “normal” mammogram than females in the lowest density

category (density in $<10\%$ of mammogram) (OR of 17.8 (95% CI 4.8–65.9)).⁶ Other research has focused on the texture or type of parenchymal pattern in breast tissue as a risk factor for breast cancer; a review of over 40 research papers concluded that automated analysis of quantitative features in mammographic images may be useful in breast cancer risk assessment and potential stratification for screening but that further research was necessary.¹¹

One little explored potential feature is mammographic asymmetry in the total size of the breast and in the size of the radio-dense tissue between the left and the right breasts. Increased “fluctuating asymmetry” (FA), that is, increased anthropometrical asymmetry in paired features, is related to both fecundity and general health.^{12–15} Furthermore,

breast FA appears to be related to many of the known reproductive breast cancer risk factors, such as parity, age at first birth and age at menopause.¹⁶ Findings to date are consistent with breast volume (BV) asymmetry being associated with the presence of breast cancer^{17–20} as well as with a higher risk of having a breast cancer diagnosed in the short- and medium-term.²¹ There is also limited evidence that asymmetry in mammographic density might be associated with higher short-term,^{22–24} and medium-term²⁵ risk of being diagnosed with breast cancer although the previous research used very specific bespoke algorithms to derive asymmetry scores based on comparing multiple bilateral mammographic density features.

Breast cancer subtypes, based on gene expression or receptor status, are clinically relevant because they are associated with differential treatment options and prognoses. Studies have shown that some hormonal risk factors associated with FA are also associated with particular breast cancer subtypes (*e.g.*, parity is inversely associated with FA¹⁶ and with the risk of luminal-like breast tumours^{26,27}).

The aim of this study is to investigate the association between left–right asymmetry in breast size and in the amount of radio-dense tissue, as ascertained by mammography, and the risk of being diagnosed with breast cancer (overall and by subtype) at the same or subsequent screens, or as an interval cancer, among a large population-based sample of 68,776 females who underwent mammographic screening in South West London, England, between March 2013 and June 2017.

METHODS

Study participants

The study participants were female residents in one of six London boroughs—Wandsworth, Merton, Croydon, Sutton, Richmond and Kingston—who underwent routine 3 yearly screening mammography as part of the NHSBSP at the South West London Breast Screening Service (SWLBSS) based in the St George's University Hospitals NHS Foundation Trust. The NHSBSP is an organised population-based mammographic screening programme, with a call–recall system, which targets females aged 50–70 years (with a trial for 50% of females aged 47–50 and 70–73) and has a coverage of approximately 75%.²⁸ Also included were small numbers of younger females who had been identified as having a higher risk of breast cancer and therefore invited for screening on an annual basis, plus any females over 73 years who had optionally contacted the service for a self-referred screening appointment. Participants were screened during the period 01 March 2013 to 20 June 2017.

Data on ethnicity were collected as part of the standard screening protocol via a self-completed screening questionnaire. Ethnicity was categorised according to the Census classification²⁹ and summarised as, “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.” Data for other known breast cancer risk factors (*e.g.*, reproductive history, body mass index (BMI), family-history of breast

cancer) are not collected in a systematic way across the NHSBSP screening programme and thus were unavailable. The type of screen (first (prevalent) versus subsequent (incident) screens) was recorded.

Exposure assessment

Each female underwent the NHSBSP standard, two-view (cranio-caudal (CC) and medio-lateral-oblique views (MLO)) mammography of each breast.³⁰ Raw digital mammographic images were processed via an automated algorithm, that is, Volpara® Density™ V.1.5.11, (Matakina Technology Limited, Wellington, New Zealand)³¹; this algorithm provided fully automated estimates (in cm³) of the volume of the BV and the volume of the radio-dense tissue (DV) separately for each of the four (left–right CC and MLO) images. The volume of non-dense volume (NDV) was calculated as the difference between BV and DV on the same image. The NHSBSP does not use mammographic density as a diagnostic aid, and participants are not informed on whether they have dense breasts.

For each participant, we estimated absolute measures of left–right asymmetry (in cm³), that is, the unsigned difference between left BV (or DV) and right BV (or DV). Absolute asymmetry was estimated from the CC images because this view is likely to capture the whole of the breast while being less affected than the MLO view by the inclusion of variable amounts of retro-glandular fat tissue near the chest wall.

Subject eligibility

Screening events where exposure measurements (*i.e.*, breast asymmetry) and outcome ascertainment (screen-detected cancer) were done concurrently, were regarded as “contemporaneous screens” for the purposes of this study. In all, 93,416 contemporaneous screens took place during the study period. Screens were excluded from this analysis if: females had a previous history of breast cancer ($N = 2,068$); females had breast implants or where the standard set of four (*i.e.*, left–right CC and MLO) images was incomplete or exceeded ($N = 10,234$); and of these if one or both of the CC images was rejected by Volpara based on its internal consistency checks ($N = 1,383$). Thus, a total of 79,731 screens were eligible for inclusion in the analysis. Some females were screened more than once in the study period; 9,600 females had two screens; 221 females had three screens; 72 had four screens; and 3 females had five screens; all valid screens were included in the analysis. “Subsequent” screens were screens that took place, as a result of the next screening round invitation following on from a contemporaneous screen, at approximately 3 years after the contemporaneous screen. Approximately 20% of subsequent screens were also included in the contemporaneous screen study.

Cancer ascertainment

The images were double read with arbitration by consensus. In this study, cancers detected at the screen when breast asymmetry was estimated were called “contemporaneous screen detected cancers,” cancers diagnosed symptomatically in the 3-year period following this measurement and prior to the next screening invitation were regarded as “interval cancers” and

breast cancers detected at the subsequent screen were considered as being “subsequent cancers”.

Interval cancer case ascertainment was based on the 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. Each NHSBSP screening service is responsible for recording and reviewing all reported interval cancers. We included all recorded interval cancers from the SWLBSS database as of 06 November 2019.

Contemporaneous screen cancers were categorised according to histological subtype and laterality (left-side, right-side, bilateral tumour). Tumour subtypes are routinely differentiated in the NHSBSP by immunohistochemical (IHC) analysis of the oestrogen (ER) and progesterone (PR) hormone receptors and the human epidermal growth factor (HER2) (using IHC plus *in situ* hybridisation (ISH) molecular analysis). These tests are carried out on diagnostic or surgical biopsies. In the NHSBSP, ER testing is required for all invasive tumours and guidelines are used to ensure standard reporting of results across the screening programme.³² The results were used to approximately differentiate between the most clinically relevant subtypes based on the definitions proposed by Waks and Winer³³ as: Hormone+ (H+) cancers if ER +and/or PR+, HER2-; HER2 +cancers if ER ± PR+/-, HER2+; and triple negative cancers if ER-, PR- and HER2-. The size of tumours was estimated as maximum dimension of the whole tumour at surgical excision where such data were available. No data on receptor status or tumour size were available for interval cancers.

Study design

A cross-sectional screen-specific design was used to examine associations between left–right breast asymmetry and contemporaneous screen-detected cancers (Figure 1). Screens at which females were diagnosed with a first occurrence of breast cancer ($n = 767$) were defined as cases, and screens where no cancer was detected ($n = 78,964$) as non-cases. In all, 82 females had both a non-cancer contemporaneous screen and a later contemporaneous first screen-detected cancer; in the analysis, their

non-cancer screens were included as being non-cancer while their screen-detected cancers were included as cases.

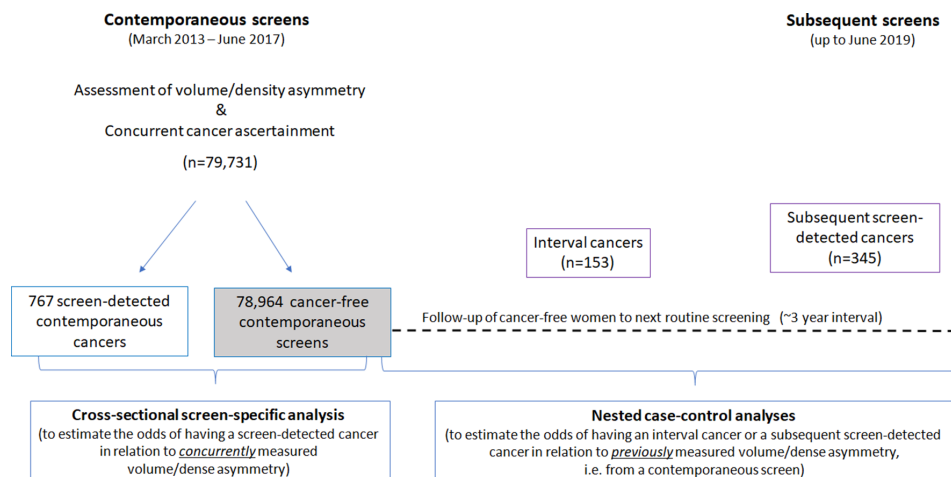
An incident-density-sampling (nested) case–control design was used to investigate the association between breast asymmetry and interval cancers (Figure 1). Cases were females who were diagnosed with an interval cancer after a normal contemporaneous screen. For each case, up to five controls were randomly selected among females who had a contemporaneous screen in the same year and month as the case and who had a verified “non-cancer” status (based on subsequent screening records) at the time that the case was diagnosed, matched to the case on age at contemporaneous screen (± 1 year). For cases aged >73 years at contemporaneous screen, controls were aged-matched within ± 5 years due to paucity of controls. A total of 153 interval cancer cases and 646 matched controls were identified corresponding to 87 cases with five controls each, 37 cases with four controls each, 14 cases with three controls each, seven cases with two controls each and seven cases with one control each; one case was excluded in the analysis because there were no valid matched controls.

A similar nested case–control approach was also used to assess the association between mammographic asymmetry and risk of being diagnosed with a breast cancer in a subsequent screen (Figure 1). This design was preferred to a cross-sectional analysis because subsequent screens had not yet been performed for around one-third of the study participants. Cases were females who had a normal contemporaneous screen but were diagnosed with breast cancer in the subsequent screening round ($n = 345$). Up to five age-matched controls per case were identified (a total of 1,438) using a similar approach to that outlined above for interval cancers, corresponding to 202 cases with five controls each, 58 cases with four controls each, 44 cases with three controls each, 25 cases with two controls each and 14 cases with one control each; two cases were excluded in the analysis because there were no eligible controls.

Statistical analyses

Tertiles of the distributions were used to categorise BV asymmetry and DV asymmetry into three equally sized categories (low,

Figure 1. Timing of mammography and cancer diagnosis



medium and high) based on the distributions in the non-cases/controls.

Logistic regression models were used to examine the strength of the associations between the exposures of interest, BV asymmetry and DV asymmetry, and the odds of being diagnosed with a contemporaneous screen-detected breast cancer (overall and by subtype). Robust standard errors (clustering by female) were used to account for the fact that some females had repeat screens over the 52-month study period. Similarly, separate conditional logistic regression models were used to examine the strength of the associations between BV asymmetry and DV asymmetry 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 and mean mammographic NDV (a valid proxy for BMI when data for the latter are not available³⁴) and additionally for mean BV (log transformed) in the BV asymmetry model and mean DV (log transformed) in the DV asymmetry model. DV was not added as a potential confounder in the BV asymmetry model because previous studies using this data showed that there was no association between DV and BV asymmetry.³⁵ Mean BV, NDV and DV values were calculated as averages of the corresponding fully automated readings obtained from each female's four contemporaneous CC and MLO images (all available image sets being used to derive the best estimate for these confounders). Trend tests for the association with the asymmetry measures were carried out fitting models with the ordinal values of each asymmetry measure and assessing their significance using Wald tests.

For the association between breast asymmetry and the odds of having a contemporaneous screen-detected cancer, further analysis included stratification by type of screen (prevalent *vs* incident) and reanalyses restricted to each tumour subtype. Adjustment for ethnicity was omitted for the latter due to sparsity of data.

Spearman rank correlation coefficients (*r*) were estimated to investigate whether the magnitude of the breast asymmetry in BV and DV among contemporaneous screen-detected breast cancer cases was correlated with the size of the tumour. The proportion of cancers detected in the larger breast was also calculated.

In all the analyses, we considered statistical significance (two-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 when the screen did not lead to cancer detection and 60.4 years when it did. Mean time between contemporaneous screen and interval cancer diagnosis was 19.2 (range 0.14–36.0; 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.

The median values for BV and DV asymmetry were higher for contemporaneous cases (65.4 cm³ and 6.64 cm³, respectively) than non-cases (60.3 cm³ and 5.78 cm³, respectively; [Table 1](#)). Median values for BV asymmetry and DV asymmetry were also higher for interval cancer cases (71.9 cm³ and 8.90 cm³, respectively) than their matched controls (57.5 cm³ and 5.60 cm³, respectively; [Table 1](#)). A similar pattern was observed for subsequent cancers but with smaller case–control differences in median BV asymmetry and DV asymmetry ([Table 1](#)) ([Supplementary Table 1](#)).

Tumour subtype was known for 88% of all contemporaneous screen-detected cases. Of these 84% were HR+, 11% HER2+ and 4.8% triple-negative tumours ([Table 1](#)). The median BV and DV asymmetry values for the latter were markedly higher (110.4 cm³ and 11.66 cm³, respectively) than for the other subtypes (average 65.4 cm³ and 6.64 cm³, respectively) ([Supplementary Table 2](#)).

Associations between BV and DV asymmetry and contemporaneous screen-detected breast cancer

There was a possible positive, but weak (*p*-for-linear-trend (Pt) = 0.105), log-linear association between BV asymmetry and the odds of being diagnosed with cancer at the contemporaneous screen. Relative to females in the bottom third of the BV asymmetry distribution (<36.4 cm³), those in the top third (≥93.7 cm³) appeared to have 1.17 times greater odds (OR 1.17; 95% CI 0.97, 1.44) of having a screen-detected cancer, in the fully adjusted models. There was stronger evidence that DV asymmetry was positively associated with the odds of being diagnosed with a cancer at the contemporaneous screen; (Pt = 0.018) with females in the top third of the DV asymmetry (≥9.04 cm³) having 1.26 times greater odds (OR 1.26; 95% CI 1.04, 1.53) than those in the bottom third (<3.48 cm³) ([Figure 2](#)).

In stratified analyses by type of screen, BV asymmetry was not associated with the odds of a contemporaneous screen-detected cancer in either group. DV asymmetry was however positively associated with the odds of a contemporaneous screen-detected breast cancer among females who had a prevalent screen (OR 1.56; 95% CI 1.07, 2.27; Pt = 0.012) but not among those who had an incident screen (OR 1.15 (0.92, 1.45); Pt = 0.21; [Figure 3](#)).

No clear associations were found between BV asymmetry and any specific tumour subtype. DV asymmetry however was positively associated with both the odds of having a contemporaneous screen-detected HR +breast cancer and the odds of having a triple negative breast cancer, but no association was found with HER2 +cancers. Relative to females in the bottom third of the DV asymmetry distribution those in the top third were 3.7 times more likely to have a triple negative cancer (OR 3.72; 95% CI 1.11, 12.45) and 1.3 times more likely to have a HR +cancer (1.28; 1.05, 1.58; [Figure 4](#)).

Table 1. Characteristics of the study participants, their mammographic screens and their breast cancer

	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. females^a	n (%) n = 767	n (%) n = 68,776 ^a	n (%) n = 153	n (%) n = 646	n (%) n = 345	n (%) n = 1,438
Age at contemporaneous screening	Mean (SD)	Mean (SD) ^b	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
	60.39 (7.66)	58.42 (7.17)	59.52 (7.29)	60.10 (7.38)	59.93 (6.21)	59.74 (6.23)
Ethnicity	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
White ^c	526 (68.6%)	44,203 (64.3%)	114 (74.5%)	419 (64.9%)	252 (73.0%)	968 (67.3%)
Asian ^d	73 (9.5%)	6,422 (9.3%)	5 (3.3%)	78 (12.1%)	32 (9.3%)	132 (9.2%)
Black – Caribbean ^e	25 (3.3%)	3,265 (4.7%)	10 (6.5%)	25 (3.9%)	10 (2.9%)	78 (5.4%)
Black – African	22 (2.9%)	2,425 (3.5%)	3 (2.0%)	22 (3.4%)	1 (0.3%)	53 (3.7%)
Mixed	11 (1.4%)	1,311 (1.9%)	3 (2.0%)	16 (2.5%)	6 (1.7%)	24 (1.7%)
Chinese	8 (1.0%)	859 (1.2%)	1 (0.7%)	3 (0.5%)	7 (2.0%)	25 (1.7%)
Missing/not reported	102 (12.3%)	10,291 (15.0%)	17 (11.1%)	83 (12.9%)	37 (10.7%)	158 (11.0%)
No. Screens^f	n = 767	n = 78,964	n = 153	n = 646	n = 345	n = 1,438
Type of screen						
Prevalent	205	21,242				
Incident	562	57,722				
Breast Volumetric measurements^g	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)
Median BV, cm ³	778.8 (514.3–1149.9)	756.7 (493.4–1112.9)	920.2 (502.9–1225.9)	780.1 (536.5–1133.1)	794.8 (529.9–1156.4)	748.3 (493.6–1116.5)
Median DV, cm ³	50.9 (39.5–69.6)	49.3 (37.2–67.2)	56.9 (43.4–86.2)	48.3 (36.1–65.5)	50.8 (39.1–70.5)	47.7 (35.9–65.1)
Median NDV cm ³	726.1 (463.4–1082.5)	702.7 (443.1–1049.1)	847.2 (413.6–1133.6)	730.0 (484.1–1064.6)	732.6 (485.3–1089.2)	700.7 (438.5–1049.1)
Absolute Volumetric Asymmetry, cm^{3h}	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)
BV Bilateral Asymmetry	65.4 (28.1–127.4)	60.3 (26.4–117.6)	71.9 (32.7–130.8)	57.5 (25.5–117.2)	69.8 (27.1–133.3)	61.0 (28.7–122.2)
DV Bilateral Asymmetry	6.64 (2.90–13.29)	5.78 (2.51–11.43)	8.9 (3.9–15.3)	5.6 (2.1–10.9)	6.24 (2.95–11.51)	5.40 (2.38–11.20)
Asymmetry laterality	n (%)	n (%)	n/a	n/a	n/a	n/a
Right BV > Left BV	322 (41.98%)	31,169 (39.47%)				
Left BV > Right BV	445 (58.02%)	47,790 (60.52%)				
No difference ⁱ BV	0 (0%)	5 (0.01%)				
Right DV > Left DV	348 (45.37%)	35,693 (45.13%)				
Left DV > Right DV	418 (54.50%)	43,288 (54.82%)				
No difference ⁱ DV	1 (0.01%)	37 (0.05%)				
No. Cancers	n = 767		n = 153		n = 345	

(Continued)

Table 1. (Continued)

Cancer Laterality	n (%)	n (%)	n (%)	n (%)
Bilateral	20 (2.6%)	3 (2.0%)		0
Left breast	380 (49.5%)	42 (27.5%)		165 (47.8%)
Right breast	364 (47.5%)	40 (26.1%)		180 (52.2%)
Unknown	3	68 (44.4%)		0
Tumour subtype	n (%)	n/a		n/a
HR+ (ER + and/or PR+, HER2-)	566 (84.2%)			
HER2+ (ER+/-, PR+/-, HER2+)	74 (11.0%)			
Triple negative (ER-, PR-, HER2-)	32 (4.8%)			
Unknown or non-invasive	95 (12.4%)			
Tumour size mm¹	Median (IQR)			
Left breast (n = 245)	19 (17 -21)			
Right breast (n = 249)	20 (18-22)			

BV, breast volume; DV, volume of radio-dense tissue on a mammogram; ER, oestrogen receptor; HER2, human epidermal growth factor; HR, hormone receptor; IQR, inter quartile range; NDV, volume of non-radio-dense (fatty) tissue on a mammogram; PR, progesterone receptor; SD, standard deviation; J, No measurable difference in volumes; n/a, not available.

^a9,814 females have more than one contemporaneous screen.

^bWhere females have more than one contemporaneous screen the average of their age at screen is taken.

^cWhite includes: British/Irish and other

^dAsian includes: British Indian, Pakistani, Bangladeshi and other

^eBlack includes: British, Caribbean and other (non-African)

^fScreens included must have at exactly four images taken, only screening images are included, excluded are images that were rejected as outliers by the Volpara algorithm. Screens for females known to have previous breast cancer were also excluded.

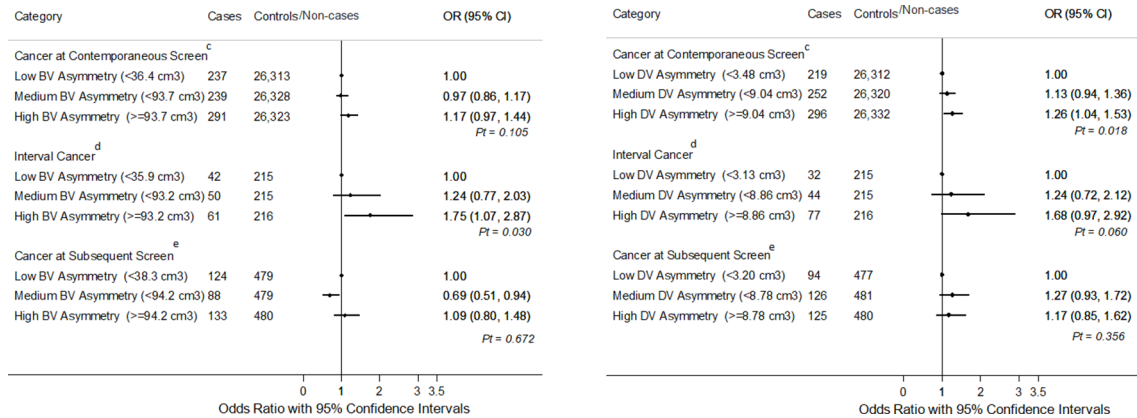
^gMedian values are calculated using all available images from the relevant view (MLO and CC from each side) at a contemporaneous screen

^hMedian value of maximum dimension in mm for unilateral cancers where size has been reported

ⁱCalculated as absolute difference between left CC image and right CC image

^jNo measurable difference in volumes

Figure 2. Associations^a between breast volume (BV) asymmetry^b and mammographic density volume (DV) asymmetry with the odds of having a breast cancer detected at the contemporaneous screen (a) Adjusted for age, ethnicity, NDV (volume of non-dense mammographic tissue, as a proxy for BMI), and log BV for BV asymmetry or log DV for DV asymmetry (b) Automated BV and DV asymmetry measures from the CC (cranio-caudal view) images categorised according thirds of the distribution in non-cases (c) Contemporaneous screen corresponds to the same screen whose images were used to estimate BV and DV asymmetry (d) Interval Cancers were cancers diagnosed within 3 years of the contemporaneous screen, but before a subsequent screen (e) Cancers at subsequent screen were those diagnosed at next the routine screening round after the contemporaneous screen



Associations between BV and DV asymmetry and interval cancer

BV asymmetry was positively associated with the odds of having an interval cancer; relative to females in the bottom third of the BV asymmetry distribution those in the top third had significantly higher odds of being diagnosed with an interval cancer (adjusted OR 1.75; 95% CI 1.07, 2.87). Similarly, there was a positive, but weak (*P*-trend = 0.060), log-linear association between DV asymmetry and the odds of being diagnosed with a subsequent interval cancer (OR for females in the top third of the DV asymmetry distribution versus those in the bottom third: 1.68; 95% CI 0.97, 2.92). (Figure 2)

Associations between BV and DV asymmetry and a subsequent screen-detected cancer

There were no clear associations between BV or DV asymmetry and the odds of having a cancer detected at the next screening round. (Figure 2)

Cancer laterality

The cancer was detected in the breast with larger BV in approximately 52% of all cases and in the breast with larger DV in approximately 54% of cases. These proportions were similar irrespective of whether the cancer was detected at the contemporaneous screen (*i.e.*, from the same images that were used to measure BV/DV asymmetry) or whether it was an interval cancer or a cancer detected at a subsequent screen (Table 2).

Figure 3. Associations^a between breast volume (BV) asymmetry^b, and mammographic density volume (DV) asymmetry^b, and the odds of having a breast cancer detected at the contemporaneous screen^c, by type of screen^d. (a) Adjusted for age, ethnicity, NDV (volume of non-dense mammographic tissue, as a proxy for BMI) and log BV for BV asymmetry or log DV for DV asymmetry. (b) Automated BV and DV asymmetry measures from the CC (cranio-caudal view) images categorised according thirds of the distribution in non-cases. (c) Contemporaneous screen corresponds to the same screen whose images were used to estimate BV and DV asymmetry. (d) Prevalent screen if the contemporaneous screen was the first screen a female had ever had; incident screen if the female had at least one screen prior to the contemporaneous screen.

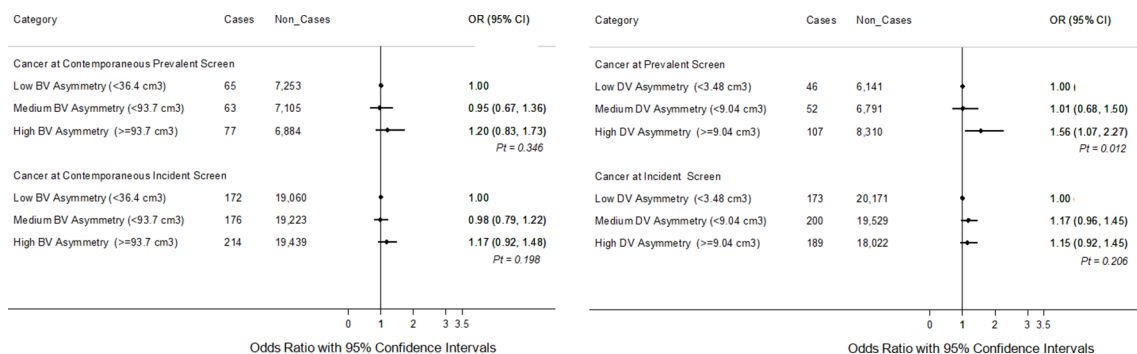
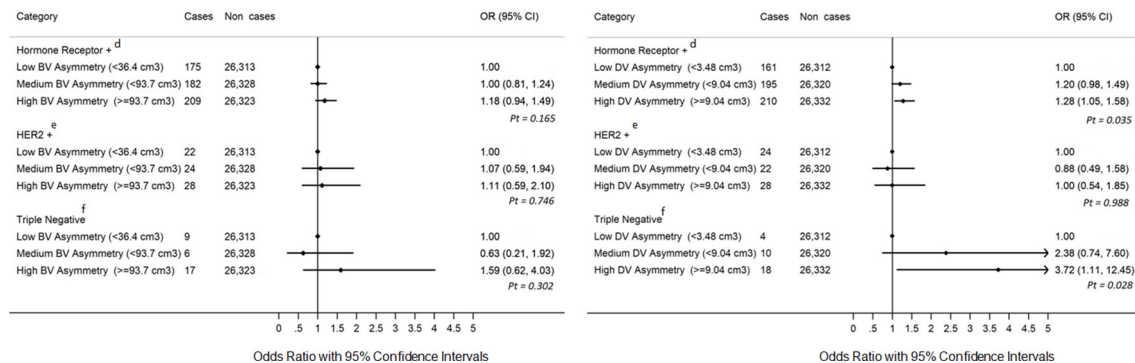


Figure 4. Associations^a between breast volume (BV) asymmetry^b, and mammographic density volume (DV) asymmetry^b, and the odds of having a breast cancer detected at the contemporaneous screen, by tumour subtype^c. (a) Adjusted for age, ethnicity, NDV (volume of non-dense mammographic tissue, as a proxy for BMI), and log BV for BV asymmetry or log DV for DV asymmetry (b) Automated BV and DV asymmetry measures from the CC (cranio-caudal view) images categorised according to thirds of the distribution in non-cases (c) 95 cases with unknown sub-type excluded from this figure (d) Hormone receptor positive (HR+) includes oestrogen receptor positive (ER+) and/or progesterone receptor positive (PR+) (e) HER2+ includes tumours with over-expression or amplification of human epidermal growth factor 2 (ER+/-, PR+/-) (f) Triple negative tumours correspond to those which were HER2-, PR- and ER-.



Correlations between contemporaneous screen tumour size and absolute asymmetry

Tumour size, as measured at surgical excision (available for 494 (64%) tumours), was not correlated with the degree of mammographic BV asymmetry ($r = 0.01$ ($p = 0.82$) and $r = 0.03$ ($p = 0.60$) for tumours located, respectively, in the left and right breasts). Similarly, there was only a very weak correlation between tumour size and DV asymmetry ($r = 0.12$ ($p = 0.06$)) for cancers located in the left breast and ($r = -0.12$ ($p = 0.06$)) for cancers located in the right breast).

The median percentage of BV occupied by the largest tumour was 0.57% (IQR; 0.14–2.15%). For DV, the median percentage of tumour size to overall breast DV was 8.04% (IQR; 1.9–29.48%).

Figure 5 shows that the distribution of tumour size versus signed difference in volume between the left and right breasts and tumour size was broadly similar irrespective of laterality of the tumour.

DISCUSSION

Main findings

The present study found positive associations between automatically estimated mammographic DV asymmetry and the odds of having a breast cancer diagnosed at a contemporaneous screen

and as an interval cancer. Increasing BV asymmetry was also strongly associated with increasing odds of having an interval cancer but only weakly associated with higher odds of a contemporaneous screen cancer. Neither BV nor DV asymmetry were associated with the odds of a subsequent screen-detected cancer in our study.

Our findings are similar to previous smaller studies by Scutt *et al* who used visually assessed mammographic breast size (BV) asymmetry estimates (~250 cases; ~250 age-matched controls) to show that absolute BV asymmetry was positively associated with contemporaneously detected cancer.¹⁷ Our larger study using automated measurements also found a positive association between BV asymmetry and the odds of a breast cancer diagnosis at the contemporaneous screen (although with borderline significance). Unlike our study, Scutt *et al* also found an association between BV asymmetry and medium-term risk of breast cancer diagnosis (mean time to diagnosis 6.44 years) after adjustment for known-risk factors and absolute breast size.²¹ As in our study, Scutt *et al* found no correlation between tumour size and BV asymmetry and they noted that approximately 50% of the tumours were found in the smaller breast by BV. Eltonsy *et al* used a computerised algorithm to estimate BV asymmetry from screening mammographic images (280 screen-detected cancer cases; 82 controls). They found that mean absolute BV

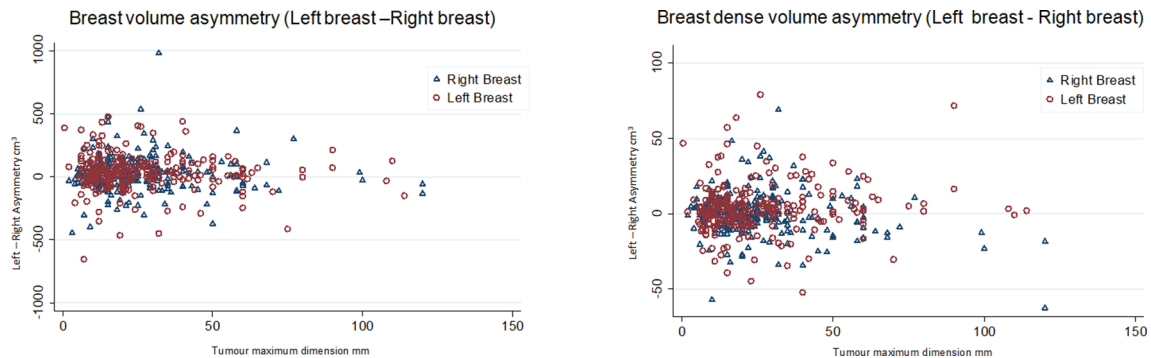
Table 2. Proportion of tumours occurring in the larger breast^{a b}

Point of diagnosis	Cancer in larger breast by BV cm ³	Cancer in larger breast by DV cm ³
Contemporaneous screen cancers	377/744 (50.7%)	413/744 (55.5%)
Interval cancers	45/83 (54.2%)	46/83 (55.4%)
Subsequent screen cancers	181/345 (52.5%)	180/345 (52.2%)
All cancers	603/1172 (51.5%)	639/1172 (54.5%)

^aExcludes bilateral cases

^bCalculated as the signed difference in cm³ between the BV (or DV) value from the left CC image and the BV (or DV) value from the right CC image.

Figure 5. Tumour size and Left breast – Right breast asymmetry^a by cancer laterality^b (a) Calculated as the signed difference in cm³ between the BV (or DV) value from the left CC image and the BV (or DV) value from the right CC image. (b) Excludes bilateral cases



asymmetry, adjusting for BV, was significantly higher in cancer patients.¹⁸ Only limited research has looked at the association between BV asymmetry and interval cancers. Kayar et al used physical breast measurements (251 cases; 466 controls) from a Turkish outpatient (non-screening) clinic, to identify a “pathological breast asymmetry ratio.”²⁰ They found that approximately 50% of the tumours were located in the smaller breast but that left breast:right breast BV ratio of $\geq 20\%$ was associated with an increased risk of breast cancer being diagnosed within 1 year of the examination.²⁰ Similarly, we found a significant positive association between BV asymmetry at the original screening and interval cancer risk (mean time to diagnosis 1.6 years). Our findings are in line with Cheong et al who studied 87 breast cancer patients referred for breast reconstruction and found that only approximately 0.2% of the BV was occupied by the actual tumour. They found no association between tumour size and BV asymmetry.³⁶

Our study also broadly agrees with the findings of a previous small case-control study, which used a bespoke algorithm for estimating mammographic density percentage (%MD) asymmetry in 230 cases found clear of cancer at the time the image was taken but who were subsequently diagnosed with breast cancer and 230 matched cancer-free controls.^{22,25} Increasing %MD asymmetry was positively associated with the odds of cancer at the subsequent screen (1–3 years later) after adjusting for age and subjective breast density category (BIRADS),^{22,25} in line with our findings.

DV asymmetry was more strongly associated with contemporaneous cancer detection in prevalent than in incident screens. Asymmetries might be more likely to be identified and investigated in the first (prevalent) screen when prior screening images are not normally available for comparison.³⁷

To our knowledge, this is the first study to look at the association between breast asymmetry (DV or BV) and cancer subtypes. A systematic review by Antoni et al.^{38,38} showed that the density-breast cancer association did not differ by cancer subtype. Our analysis, albeit based on small numbers, suggests that the DV

asymmetry association with breast cancer may be particularly strong for triple-negative cancers.

The findings that neither BV nor DV asymmetry were associated with the odds of a subsequent screen-detected cancer is possibly a result of the relatively small number of subsequent breast cancer cases; both BV and DV asymmetry showed positive associations with the odds of subsequent screen cancer but not at the 95% CI level. Larger studies will be required to investigate this fully.

The pathways through which asymmetry in BV and DV may affect the risk of being diagnosed with breast cancer (in the short or longer term) are poorly understood. If asymmetry is simply attributable to the presence of a tumour in the breast, then a higher correlation between tumour size and asymmetry would be expected together with a closer correspondence between tumour laterality and the breast with larger volume/density (in our study only ~55% of unilateral screen detected tumours were located in the breast with higher DV/BV) and previous studies found no evidence that the tumour was associated with the larger BV.^{20,21,36} In our study, there was some evidence of a weak positive correlation between DV asymmetry and tumour size, but overall little of the observed asymmetry in our study can simply be explained by the presence of a tumour in the larger breast. We therefore conclude that asymmetry cannot be explained by the presence of a tumour alone but may be a biomarker of increased genetic/early life susceptibility to breast cancer.

Radiologists are able to identify abnormal signals from mammograms extremely quickly by extracting the “gist” of the image in fractions of a second³⁹ but they may also find it more difficult to read bilateral mammograms that display greater asymmetry between the breasts,^{40,41} due to the “obfuscation” effect of increased asymmetry. The “masking effect” of DV has been recognised for some time^{6,7} and this study suggests that the masking effect is enhanced where DV is asymmetrical. This association may however be subtle since Evans et al⁴² found that, although asymmetry may be part of what signals an abnormal mammogram, there is still above-chance performance from

clinicians when presented with artificial asymmetric conditions (e.g., where the contralateral breast was from a different female).

Strengths and limitations

Strengths of this study include its population-based design, large sample size, ethnic mix, and availability of information on receptor status. The images for both breasts were collected at the same point in time, and under similar technical conditions therefore within-woman left:right breast comparisons are unlikely to have been biased by anthropometric, reproductive and lifestyle characteristics or the equipment used. The study used an automated method to estimate BVs, therefore measurements were free from subject or observer biases.

The algorithm (Volpara Density) used gives reliable volumetric BV and DV estimates.^{43–45} There is no published data specifically on the reliability of *asymmetry* measures derived from the Volpara volumetric measurements but examination of data from a subset of 464 females in our study, who had two sequential screens, using Bland Altman plots showed no systematic bias although the limits of agreement were large (unpublished).

A limitation of this study was the lack of data on potential reproductive confounders (e.g., parity, age at menarche, menopausal status) which have been shown to be associated with breast asymmetry,¹⁶ (these data are not routinely collected at screening in the UK). Our adjustment and matching for age (at least partly) dealt with the potential confounding effect of menopausal status; however, too little is known of the direction and strength of the cumulative effects of other reproductive variables to speculate on the direction of the potential residual confounding bias affecting the reported estimates. The number of interval cancers recorded was relatively small, partly reflecting the lag time between diagnosis and notification to the screening services. Information on tumour subtypes was limited and there was insufficient power to analyse asymmetry associations with the rarer tumour subtypes.

IMPLICATIONS

This study suggests that increasing left:right asymmetry in BV and DV may be of relevance when interpreting mammographic

screening images as a signal of the likely presence of a cancer on a contemporaneous screen and the likelihood of being diagnosed with an interval cancer before the next screen. Further studies are needed to confirm these findings and, if confirmed, to assess how they may affect the performance of the screening programme. Nevertheless, the availability of automated algorithms, which allow volumetric assessment of BV and density in real-time from two-dimensional mammographic images, means that such studies can now be conducted on a large-scale as objective measurements of bilateral asymmetry can be easily obtained for all females screened.

AUTHORS' INFORMATION

LSW was previously Director of the South West London Breast Screening Service, SWLBSS, UK

AUTHORS' CONTRIBUTIONS

SMH and IdSS designed the study; LSW organised the collection of participants' data and provided clinical guidance on the design; SMH performed the statistical analysis with guidance from BDS; SMH wrote the first draft of the manuscript. All authors (SMH, LSW, BDS, IdSS) contributed to the interpretation of the results and critically reviewed the draft of the manuscript; they all read and approved the final version of the manuscript, and they all agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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).

REFERENCES

1. Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Piñeros M, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *Int J Cancer* 2019; **144**: 1941–53. doi: <https://doi.org/10.1002/ijc.31937>
2. Independent UK Panel on Breast Cancer Screening. The benefits and harms of breast cancer screening: an independent review. *Lancet* 2012; **380**: 1778–86. doi: [https://doi.org/10.1016/S0140-6736\(12\)61611-0](https://doi.org/10.1016/S0140-6736(12)61611-0)
3. McCormack VA, dos Santos Silva I, Silva dosS I. Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. *Cancer Epidemiol Biomarkers Prev* 2006; **15**: 1159–69. doi: <https://doi.org/10.1158/1055-9965.EPI-06-0034>
4. Boyd NF, Martin LJ, Bronskill M, Yaffe MJ, Duric N, Minkin S. Breast tissue composition and susceptibility to breast cancer. *J Natl Cancer Inst* 2010; **102**: 1224–37. doi: <https://doi.org/10.1093/jnci/djq239>
5. Huo CW, Chew GL, Britt KL, Ingman WV, Henderson MA, Hopper JL, et al. Mammographic density—a review on the current understanding of its association with breast cancer. *Breast Cancer Res Treat* 2014; **144**: 479–502. doi: <https://doi.org/10.1007/s10549-014-2901-2>
6. Boyd NF, Guo H, Martin LJ, Sun L, Stone J, Fishell E, et al. Mammographic density and the risk and detection of breast cancer. *N Engl J Med* 2007; **356**: 227–36. doi: <https://doi.org/10.1056/NEJMoa062790>
7. Pisano ED, Hendrick RE, Yaffe MJ, Baum JK, Acharyya S, Cormack JB, et al. Diagnostic accuracy of digital versus film mammography: exploratory analysis of selected population subgroups in DMIST. *Radiology* 2008; **246**: 376–83. doi: <https://doi.org/10.1148/radiol.2461070200>

8. Destounis S, Johnston L, Highnam R, Arieno A, Morgan R, Chan A. Using volumetric breast density to quantify the potential masking risk of mammographic density. *AJR Am J Roentgenol* 2017; **208**: 222–7. doi: <https://doi.org/10.2214/AJR.16.16489>
9. Wanders JOP, Holland K, Karssemeijer N, Peeters PHM, Veldhuis WB, Mann RM, et al. The effect of volumetric breast density on the risk of screen-detected and interval breast cancers: a cohort study. *Breast Cancer Res* 2017; **19**: 67. doi: <https://doi.org/10.1186/s13058-017-0859-9>
10. Moshina N, Sebuødegård S, Lee CI, Akslen LA, Tsuruda KM, Elmøre JG, et al. Automated volumetric analysis of mammographic density in a screening setting: worse outcomes for women with dense breasts. *Radiology* 2018; **288**: 343–52. doi: <https://doi.org/10.1148/radiol.2018172972>
11. Gastouniotti A, Conant EF, Kontos D. Beyond breast density: a review on the advancing role of parenchymal texture analysis in breast cancer risk assessment. *Breast Cancer Research* 2016; **18**: 1–12. doi: <https://doi.org/10.1186/s13058-016-0755-8>
12. Moller A, Soler M, Thornhill R. Breast asymmetry, sexual selection, and human reproductive success. 1995;: 207–19p.
13. Thornhill R, Moller AP, stability D. Disease and medicine. *Biological Reviews of the Cambridge Philosophical Society* 1997; **72**: 497–548.
14. Jasienska G, Lipson SF, Ellison PT, Thune I, Ziolkiewicz A. Symmetrical women have higher potential fertility. *Evolution and Human Behavior* 2006; **27**: 390–400. doi: <https://doi.org/10.1016/j.evolhumbehav.2006.01.001>
15. Milne BJ, Belsky J, Poulton R, Thomson WM, Caspi A, Kieser J. Fluctuating asymmetry and physical health among young adults. *Evolution and Human Behavior* 2003; **24**: 53–63. doi: [https://doi.org/10.1016/S1090-5138\(02\)00120-4](https://doi.org/10.1016/S1090-5138(02)00120-4)
16. Manning JT, Scutt D, Whitehouse GH, Leinster SJ. Breast asymmetry and phenotypic quality in women. *Evolution and Human Behavior* 1997; **18**: 223–36. doi: [https://doi.org/10.1016/S0162-3095\(97\)00002-0](https://doi.org/10.1016/S0162-3095(97)00002-0)
17. Scutt D, Manning JT, Whitehouse GH, Leinster SJ, Massey CP. The relationship between breast asymmetry, breast size and the occurrence of breast cancer. *Br J Radiol* 1997; **70**(OCT): 1017–21. doi: <https://doi.org/10.1259/bjr.70.838.9404205>
18. Eltonsy HN, Elmaghraby A, Tourassi G. Bilateral breast volume asymmetry in screening mammograms as a potential marker of breast cancer: preliminary experience. 2007;V-5 p.
19. Williams AC, Hitt A, Voisin S, Tourassi G, editors. Automated assessment of bilateral breast volume asymmetry as a breast cancer biomarker during mammographic screening. *International Society for Optics and Photonics*. 2013; SPIE Medical Imaging; 2013.
20. Kayar R, Çilengiroğlu Özgül V. Breast volume asymmetry value, ratio, and cancer risk. *Breast Cancer* 2015; **9**: 87–92. doi: <https://doi.org/10.4137/BCBCR.S32789>
21. Scutt D, Lancaster GA, Manning JT. Breast asymmetry and predisposition to breast cancer. *Breast Cancer Res* 2006; **8**: R14. doi: <https://doi.org/10.1186/bcr1388>
22. Zheng B, Sumkin JH, Zuley ML, Wang X, Klym AH, Gur D. Bilateral mammographic density asymmetry and breast cancer risk: a preliminary assessment. *Eur J Radiol* 2012; **81**: 3222–8. doi: <https://doi.org/10.1016/j.ejrad.2012.04.018>
23. Tan M, Zheng B, Ramalingam P, Gur D. Prediction of near-term breast cancer risk based on bilateral mammographic feature asymmetry. *Acad Radiol* 2013; **20**: 1542–50. doi: <https://doi.org/10.1016/j.acra.2013.08.020>
24. Sun W, Zheng B, Lure F, Wu T, Zhang J, Wang BY, et al. Prediction of near-term risk of developing breast cancer using computerized features from bilateral mammograms. *Comput Med Imaging Graph* 2014; **38**: 348–57. doi: <https://doi.org/10.1016/j.compmedimag.2014.03.001>
25. Zheng B, Tan M, Ramalingam P, Gur D. Association between computed tissue density asymmetry in bilateral mammograms and near-term breast cancer risk. *Breast J* 2014; **20**: 249–57. doi: <https://doi.org/10.1111/tbj.12255>
26. Ellingjord-Dale M, Vos L, Tretli S, Hofvind S, Dos-Santos-Silva I, Ursin G, Parity UG. Parity, hormones and breast cancer subtypes - results from a large nested case-control study in a national screening program. *Breast Cancer Res* 2017; **19**: 10. doi: <https://doi.org/10.1186/s13058-016-0798-x>
27. Lambertini M, Santoro L, Del Mastro L, Nguyen B, Livraghi L, Ugolini D, et al. Reproductive behaviors and risk of developing breast cancer according to tumor subtype: a systematic review and meta-analysis of epidemiological studies. *Cancer Treat Rev* 2016; **49**: 65–76. doi: <https://doi.org/10.1016/j.ctrv.2016.07.006>
28. Health and Social Care Centre Breast screening programme England. ; 2018;4/4/20182016-2017. UK: NHS Digital.
29. Office for National Statistics (ONS)2011 Census Guidance and Methodology 2015 [Overview of methods and codes used for 2011 census].. Available from: <https://www.ons.gov.uk/census/2011census/2011censusdata/2011censususerguide/variablesandclassifications>.
30. The Royal College of Radiologists *Guidance on screening and symptomatic breast imaging* 2013 London
31. Matakina Technology Ltd VolparaDensity™ User Manual Version 1.5.11. [User Manual Volpara Software. *In press* 2014;.
32. TRCo P. *Pathology reporting of breast disease in surgical excision specimens incorporating the dataset for histological reporting of breast cancer*. London: The Royal College of Pathologists; 2016.
33. Waks AG, Winer EP. Breast cancer treatment: a review. *JAMA* 2019; **321**: 288–300. doi: <https://doi.org/10.1001/jama.2018.19323>
34. Hudson S, Hjerkind KV, Vinnicombe S, Allen S, Trewin C, Ursin G, et al. Adjusting for BMI in analyses of volumetric mammographic density and breast cancer risk. 2018;.
35. Hudson SM, Wilkinson LS, Denholm R, De Stavola BL, Dos-Santos-Silva I. Ethnic and age differences in right-left breast asymmetry in a large population-based screening population. *Br J Radiol* 2020; **93**:: 201903280(0). doi: <https://doi.org/10.1259/bjr.20190328>
36. Cheong AL, Liu J, Reece GP, Nicklaus KM, Catherine Bordes M, Hanson SE, et al. Natural breast symmetry in preoperative breast cancer patients. *Plast Reconstr Surg Glob Open* 2019; **7**: e2297. doi: <https://doi.org/10.1097/GOX.0000000000002297>
37. Roelofs AAJ, Karssemeijer N, Wedekind N, Beck C, van Woudenberg S, Snoeren PR, et al. Importance of comparison of current and prior mammograms in breast cancer screening. *Radiology* 2007; **242**: 70–7. doi: <https://doi.org/10.1148/radiol.2421050684>
38. Antoni S, Sascó AJ, dos Santos Silva I, McCormack V. Is mammographic density differentially associated with breast cancer according to receptor status? A meta-analysis. *Breast Cancer Res Treat* 2013; **137**: 337–47. doi: <https://doi.org/10.1007/s10549-012-2362-4>
39. Evans KK, Georgian-Smith D, Tambouret R, Birdwell RL, Wolfe JM. The GIST of the abnormal: above-chance medical decision making in the blink of an eye. *Psychon Bull Rev* 2013; **20**: 1170–5. doi: <https://doi.org/10.3758/s13423-013-0459-3>
40. Lee HN, Sohn Y-M, Han KH. Comparison of mammographic density estimation by Volpara software with radiologists' visual assessment: analysis of clinical-radiologic

- factors affecting discrepancy between them. *Acta Radiol* 2015; **56**: 1061–8. doi: <https://doi.org/10.1177/0284185114554674>
41. Onega T, Smith M, Miglioretti DL, Carney PA, Geller BA, Kerlikowske K, et al. Radiologist agreement for mammographic recall by case difficulty and finding type. *J Am Coll Radiol* 2012; **9**: 788–94. doi: <https://doi.org/10.1016/j.jacr.2012.05.020>
42. Evans KK, Haygood TM, Cooper J, Culpan A-M, Wolfe JM. A half-second glimpse often LETS radiologists identify breast cancer cases even when viewing the mammogram of the opposite breast. *Proc Natl Acad Sci U S A* 2016; **113**: 10292–7. doi: <https://doi.org/10.1073/pnas.1606187113>
43. Brand JS, Czene K, Shepherd JA, Leifland K, Hedddson B, Sundbom A, et al. Automated measurement of volumetric mammographic density: a tool for widespread breast cancer risk assessment. *Cancer Epidemiol Biomarkers Prev* 2014; **23**: 1764–72. doi: <https://doi.org/10.1158/1055-9965.EPI-13-1219>
44. Alonzo-Proulx O, Mawdsley GE, Patrie JT, Yaffe MJ, Harvey JA. Reliability of automated breast density measurements. *Radiology* 2015; **275**: 366–76. doi: <https://doi.org/10.1148/radiol.15141686>
45. Holland K, van Zelst J, den Heeten GJ, Imhof-Tas M, Mann RM, van Gils CH, et al. Consistency of breast density categories in serial screening mammograms: a comparison between automated and human assessment. *Breast* 2016; **29**: 49–54. doi: <https://doi.org/10.1016/j.breast.2016.06.020>