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FULL PAPER

Ethnic and age differences in right-left breast asymmetry in a large population-based screening population

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Objective: Exposure to sex hormones is important in the pathogenesis of breast cancer and inability to tolerate such exposure may be reflected in increased asymmetrical growth of the breasts. This study aims to characterize, for the first time, asymmetry in breast volume (BV) and radiodense volume (DV) in a large ethnically diverse population.
Methods: Automated measurements from digital raw mammographic images of 54,591 cancer-free participants (aged 47–73) in a UK breast screening programme were used to calculate absolute (cm^3) and relative asymmetry in BV and DV. Logistic regression models were fitted to assess asymmetry associations with age and ethnicity.
Results: BV and DV absolute asymmetry were positively correlated with the corresponding volumetric dimension (BV or DV). BV absolute asymmetry increased, whilst DV absolute asymmetry decreased, with increasing age (P-for-linear-trend <0.001 for both). Relative to Whites, Blacks had statistically significantly higher, and Chinese lower, BV and DV absolute asymmetries. However, after adjustment for the corresponding underlying volumetric dimension the age and ethnic differences were greatly attenuated. Median relative (fluctuating) BV and DV asymmetry were 2.34 and 3.28% respectively.
Conclusion: After adjusting for the relevant volumetric dimension (BV or DV), age and ethnic differences in absolute breast asymmetry were largely resolved.
Advances in knowledge: Previous small studies have reported breast asymmetry—breast cancer associations. Automated measurements of asymmetry allow the conduct of large-scale studies to further investigate these associations.

INTRODUCTION

Exposure to endogenous and exogenous sex hormones are recognized to be important in breast development and in the pathogenesis of breast cancer,[1–5] with the effect of many reproductive factors on breast cancer risk, *e.g.* early age at menarche and late age at menopause, being mediated by circulating levels of these hormones.[6] There is also some evidence that prenatal exposure to high levels of sex hormones may increase the risk of breast cancer. Breast cancer risk is elevated in females who were exposed *in utero* to diethylstilboestrol given to their mothers to prevent pregnancy complications[7] and some studies have reported positive associations between breast cancer risk and birth size, pre-eclampsia and multiple births, all possible markers of raised, *in utero*, exposure to oestrogens.[8] It is also thought that an individual's ability to tolerate exposure to oestrogens, particularly during periods of growth, may be reflected in a higher degree of homeostasis and thus bilateral symmetrical development of paired organs such as the breasts.[9] Increased "fluctuating asymmetry," *i.e.* increased anthropometrical asymmetry in paired features, is a common response to increased stress during development[10] and is related to both fecundity and general health.[11–14] For example, studies of dermatoglyphics have shown that increased asymmetry in hand patterns is associated with increased risk of several diseases including breast cancer.[15] Also, females with high second digit to fourth digit ratio (2D:4D) (thought to be associated with lower exposure or sensitivity to prenatal testosterone and/or higher levels *in utero* oestrogen levels) had increased risk of breast cancer[16] and they presented with breast cancer at a younger age.[17,18] An association between left-handedness and increased risk

of breast cancer has also been reported.[19,20] Manning et al showed that increased breast FA was correlated not only with age, height and parenchymal type but also with reproductive factors such as parity, age at first birth and age at menopause.[9]

Only a few small-sized studies, mainly among Caucasians, have so far examined the association between breast size asymmetry and breast cancer risk. Their findings are consistent with asymmetry being associated with the presence of a breast cancer[21–24] as well as with a higher risk of having a breast cancer diagnosed in the short- and medium-term (mean interval between mammography and diagnosis 6.44 years).[25] Mammographic density captures the amount of radiodense tissue in the breast, and there is also some evidence that asymmetry in density might be associated with higher short-term likelihood of being diagnosed with breast cancer.[26–28] It has also been suggested that a slightly larger left breast, with a higher volume of radiodense tissue, may account for the slightly higher frequency of cancers in the left than the right breast although the mechanisms for this are poorly understood.[29–31] Overall, the findings from these studies suggest that asymmetry in breast size and density may reflect underlying biological mechanisms linked to the pathogenesis of breast cancer or may be early consequences of the presence of a tumour. Hence, asymmetry measurements have the potential to be used as risk predictors or diagnostic markers. To our knowledge there is, as yet, no large-scale study of the prevalence of breast volume asymmetry and breast density asymmetry from large population-based studies.

The recent introduction of full-field digital mammography has led to the development of automated algorithms which allow volumetric assessments of both breast size and mammographic density from two-dimensional digital mammographic images. Such automated methods make it feasible to conduct large-scale studies based on objective measurements of bilateral asymmetry in breast size and mammographic density. This study aims to quantify bilateral asymmetry in breast size and mammographic density volume in a very large, and ethnically diverse sample of over 54,000 females who participated in a population-based breast screening programme in England. The findings will provide the first population-based data on the distribution of breast asymmetry, and potential age and ethnic variations.

METHODS

Study participants

The study participants were females resident in one of five London boroughs—Wandsworth, Merton, Croydon, Sutton, Richmond and Kingston—who underwent routine 3-yearly screening mammography as part of the England and Wales National Health Service Breast Screening Programme (NHSBSP) at the South West London Breast Screening Service based in the St George's University Hospitals National Health Service (NHS) Foundation Trust. The NHSBSP is an organized population-based mammographic screening programme, with a call–recall system, which targets females aged 50–70 years and has a coverage of ~75%.[32] Also included were a small number of younger females (aged 29–45) who had been identified as having a higher risk of breast cancer and therefore were invited for screening on an annual basis,[33] plus any females over 73 years who had optionally contacted the service for a self-referred screening appointment. All females were asymptomatic at the time of screening. Participants were screened during the period 01 March 2013 to 18 August 2016. Data on ethnicity were collected as part of the standard screening protocol via a self-completed screening questionnaire. Ethnicity was categorized according to the Census classification and summarized 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."[34] Data for other known breast cancer risk factors (*e.g.* parity, duration of breast feeding, age at menarche, 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.

Each participant underwent the NHSBSP standard 2-view [craniocaudal (CC) and mediolateral-oblique views (MLO)] mammography of each breast,[35] with the set of four digital raw images being stored on the South West London Breast Screening Service Picture Archiving and Communication system. The images were double read with arbitration by consensus. When participants had multiple screening episodes during the study period, only images from the earliest screen episode were included in the analysis. Raw digital mammographic images were processed via the automated algorithm Volpara® Density™ v. 1.5.11 (Volpara), (Matakina Technology Limited, Wellington, New Zealand)[36]; this algorithm provided fully automated estimates (in cm^3) of the volume of the breast (BV) and the volume of the radiodense tissue (DV) separately for each of the four [left (L) and right (R) breasts/CC and MLO views] images. The screening programme does not use mammographic density as a diagnostic aid, and participants are not informed on whether they have dense breasts.

In all, 66,176 females were screened during the study period. Females were excluded from this analysis if cancer was detected by the current screen (N = 530); if they had a previous history of breast cancer (N = 438); if their screen images were classified as "technical recall," *i.e.* were considered by the reader not to be of high enough quality for diagnosis (N = 26); if they had breast implants; if their standard set of four images (*i.e.* L/R CC and MLO images) was incomplete (N = 9823); and if at least one of the two CC images was rejected by Volpara based on its internal consistency checks (N = 7338). Exclusions were not mutually exclusive, leaving a total of 54,591 females who were eligible for inclusion in the analysis.

Ethical approval

This retrospective study was carried out on fully anonymous, routinely collected data only, held in accordance with the 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 methods

For each participant the BV and DV was calculated as the average of the readings obtained from the same side CC and MLO images (*i.e.* CC and MLO views were used to obtain an overall average). Both absolute and relative measures of left-right asymmetry were calculated: *absolute* asymmetry (in cm^3), *i.e.* the unsigned difference between left BV (or DV) and right BV (or DV), and *relative* asymmetry as (|L-R|)/ (*L* + R)/2 expressed as a percentage. Absolute and relative asymmetry were estimated from the CC images only because this view is likely to capture the whole of the breast whilst being less affected than the MLO view by the inclusion of variable amounts of retroglandular fat tissue near the chest wall.[36] (For comparison the equivalent asymmetry measures were also calculated using the MLO views only).

The distributions of absolute and relative asymmetry values were plotted. Natural-log transformations were applied to normalize the distributions of absolute and relative BV and DV asymmetry and quintiles were used to categorize BV and DV into five equally sized categories.

To examine whether age-related variations in breast volume and breast asymmetry differ across the various ethnic groups, medians, 25th and 75th centiles of the distributions of untransformed BV, DV and absolute asymmetry measures were also calculated and plotted separately by 5 year age categories and ethnicity. These were also calculated for each single year of age and plotted after smoothing using a Lowess function (values based on fewer than 20 observations were omitted from the plots). Scatter plots and Spearman correlation coefficients were used to examine the correlations between asymmetry measures and the corresponding volumetric dimension. In order to assess whether allometry is a feature of this relationship (as identified by Manning et al[9]) we regressed log of asymmetry on log of the corresponding volumetric measure.

Linear regression models were used to examine the strength of the associations between each exposure variable—age and ethnicity—and the outcome variables, BV or DV absolute asymmetry, controlling for their respective average volume (BV or DV). Because of the log-transformation, regression coefficients represent the relative change (RC) in absolute asymmetry per one unit change in the exposure category. In all the analyses, we considered statistical significance (two-sided) at p-value < 0.05. All analyses were conducted in Stata (IC 14).[37]

RESULTS

Study participants

The characteristics of the 54,591 participants are shown in Table 1. The majority (~87%) of participants were within the ages of 50–70 years, the age-group targeted by the NHSBSP. Among the 85% of the participants who reported their ethnicity,~76% were White but there were also high numbers of females of Black and Asian ethnicity.

Breast volume, dense volume and absolute asymmetry by age and ethnicity

The median (25th, 75th centiles) BV and DV values for the whole study sample were 757 (496, 1112) cm^3 and 48.9 (36.8, 66.5) cm^3, respectively (Table 1). There was, however, evidence of bilateral asymmetry in BV and DV, with a median (25th, 75th centiles) absolute difference in BV and DV between the two breasts of 60.6 (26.6, 117.8) cm^3 and 5.71 (2.49, 11.27) cm^3, respectively, with the wide interquartile range (IQR) indicating considerable between-woman variation in bilateral asymmetry (Table 1). This difference was seen in every age and ethnic group, albeit with some variations with the smallest median absolute differences seen among Chinese females.

The distributions of BV and DV absolute asymmetry estimates were right skewed and, hence, a log-normal transformation was used to normalize them (Figure 1). The transformed BV and DV asymmetry distributions approximated a normal distribution although both were leptokurtic (kurtosis coefficient: 5.60 and 4.76, respectively) and slightly skewed (skewness coefficient: −1.12 and −0.96, respectively).

Further analyses by age-group show that, on average, BV increased slightly with increasing age up to ages 55–59, declining thereafter (Figure 2). Ethnic variations in BV were much more marked than those observed with age (Figure 3), with BV being, on average, highest among Black Caribbean (median: 956 cm^3) and Black African (960 cm^3) females and lowest among Chinese females (394 cm^3) but with wide between-woman variability being present within each ethnic group. Absolute BV asymmetry showed similar age and ethnicity patterns to those observed for BV (Figures 2 and 3).

In contrast to BV, DV decreased, on average, with increasing age-group from <45 to 70+ years but, similarly to BV, DV was highest among Black Caribbean (median: 58.3 cm^3) and Black African females (56.0 cm^3) and lowest among Chinese females (41.0 cm^3). Absolute DV asymmetry followed a similar pattern to DV, *i.e.* lower values across successive age-groups, and higher among Black African and Black Caribbean females (Figures 2 and 3).

The observed absolute asymmetry in BV and DV reflected that fact that, on average, females had a larger left breast with a larger amount of radiodense tissue. The only exception was that DV was higher in the right breast among Chinese females.

Figure 4, which depicts median single-year-of-age volumetric and asymmetry values by ethnicity, shows that age-related changes in BV varied across the different ethnic groups. Among Asian, Black African and White females, BV increased progressively up to age ~60 years but declined thereafter whilst among Black Caribbean females, BV continued to increase up to age 70 years. In contrast, DV decreased with age in all ethnic groups. There was, however, a marked levelling out after age ~55. BV and DV absolute asymmetry follow the same general pattern as their corresponding underlying volumetric dimension.

Relative asymmetry by age and ethnicity

The magnitude of relative BV asymmetry was similar across all age groups (median overall relative BV asymmetry for all study participants: 2.43% [25th, 75th centiles: (1.15%, 4.19%); Table 1] except that it was slightly higher in the youngest age band

Table 1. Characteristics of the study participants

			Median (25th and 75th centiles)					
	No.	**Percent**	**BV (cm^3)[a]**	**DV (cm^3) [a]**	**BV absolute CC asymmetry[b] (cm^3)**	**DV absolute CC asymmetry[b] (cm^3)**	**BV relative CC asymmetry (%)[c]**	**DV relative CC asymmetry (%)[c]**
Age at screening (yrs)								
<45	234	0.4	563 (353, 950)	63.8 (47.4, 94.7)	56.7 (24.7, 105.6)	7.79 (3.86, 16.18)	2.87 (1.48, 4.56)	3.26 (1.87, 5.74)
45–49	3297	6.0	727 (450, 1135)	62.0 (45.4, 85.3)	57.5 (24.7, 112.8)	7.46 (3.39, 14.46)	2.42 (1.11, 4.06)	3.40 (1.62, 5.83)
50–54	15,405	28.2	762 (485, 1138)	54.3 (40.6, 75.5)	59.2 (25.8, 115.4)	6.45 (2.79, 12.69)	2.36 (1.12, 4.09)	3.33 (1.54, 5.87)
55–59	12,408	22.7	770 (498, 1148)	48.5 (36.6, 64.6)	61.8 (26.8, 120.4)	5.59 (2.45, 10.86)	2.43 (1.15, 4.21)	3.26 (1.53, 5.82)
60–64	10,440	19.1	767 (515, 1109)	46.1 (35.1, 61.0)	60.1 (26.9, 117.1)	5.21 (2.26, 10.24)	2.41 (1.14, 4.13)	3.18 (1.47, 5.65)
65–69	9483	17.4	751 (506, 1063)	44.0 (33.9, 57.7)	62.5 (27.5, 120.9)	5.04 (2.19, 10.04)	2.50 (1.17, 4.33)	3.23 (1.47, 5.78)
70+	3297	6.0	723 (499, 1014)	42.9 (33.5, 56.1)	63.6 (28.3, 118.9)	5.25 (2.27, 10.10)	2.66 (1.24, 4.52)	3.28 (1.52, 5.79)
Missing	27	0.1						
Ethnic group								
White—British, Irish, Other	35,443	64.9	747 (485, 1098)	47.9 (36.1, 64.9)	59.3 (25.8, 115.5)	5.60 (2.44, 11.13)	2.42 (1.13, 4.18)	3.30 (1.53, 5.84)
Asian[d]	4829	8.9	718 (508, 1005)	44.8 (34.8, 59.6)	59.4 (27.2, 111.8)	5.02 (2.10, 9.91)	2.43 (1.19, 4.24)	3.17 (1.40, 5.52)
Black—British, Caribbean	2705	5.0	956 (610, 1381)	58.3 (44.6, 77.8)	71.6 (31.1, 136.4)	6.59 (3.02, 12.17)	2.26 (1.04, 4.02)	3.17 (1.50, 5.49)
Black—African	1999	3.7	960 (672, 1347)	56.0 (42.1, 74.0)	81.1 (35.7, 155.5)	6.39 (2.95, 12.65)	2.50 (1.20, 4.14)	3.23 (1.50, 5.64)
Mixed[e]	1029	1.9	800 (535, 1176)	53.0 (39.4, 71.5)	64.5 (28.4, 124.5)	6.12 (2.71, 11.66)	2.36 (1.13, 4.21)	3.28 (1.50, 5.54)
Chinese	654	1.2	394 (258, 552)	41.0 (29.6, 60.7)	35.1 (16.2, 67.7)	5.03 (2.28, 9.67)	2.71 (1.38, 4.68)	3.38 (1.60, 6.52)
Missing or not reported	7932	14.5	751 (499, 1121)	51.2 (38.5, 70.8)	61.6 (27.5, 119.5)	6.20 (2.71, 12.05)	2.48 (1.19, 4.21)	3.35 (1.56, 5.91)
All females	54,591		757 (496, 1112)	48.9 (36.8, 66.5)	60.6 (26.6, 117.8)	5.71 (2.49, 11.27)	2.43 (1.15, 4.19)	3.28 (1.52, 5.79)

BV, breast volume; CC, craniocaudal; DV, dense volume; MLO, mediolateral oblique.

[a]Calculated from the average BV (or DV) value from the four images: left CC image, right CC image, left MLO image, right MLO image.

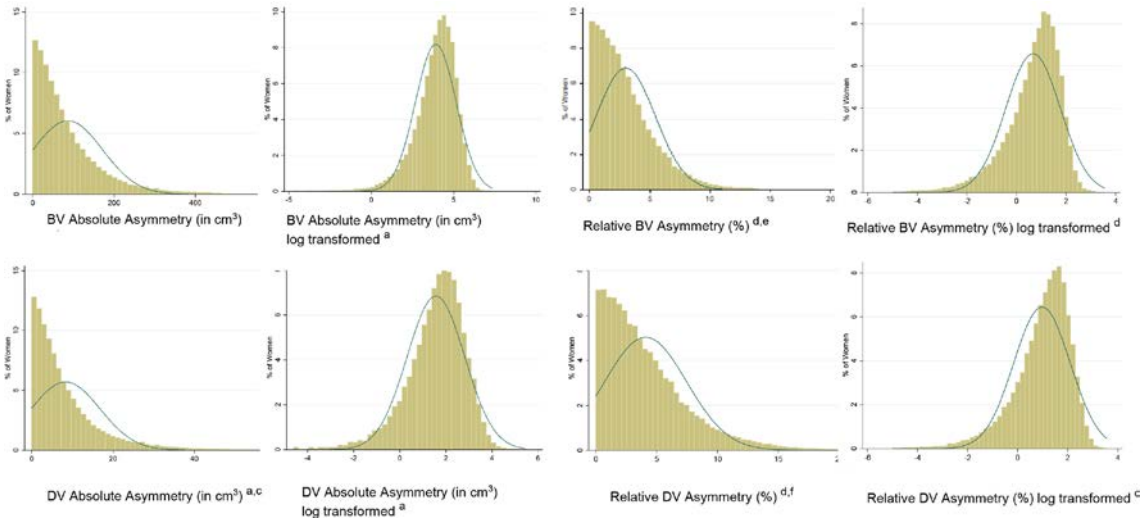
[b]Calculated as the absolute difference between the BV (or DV) value from the left CC image and the BV (or DV) value from the right CC image.

[c]Relative asymmetry estimated as (|L-R|)/ (*L* + R)/2*100, where L and R are volumes from the left and right breasts estimates from the CC views.

[d]Asian includes: British Indian, Pakistani, Bangladeshi, Other Asian excluding Chinese

[e]Mixed includes: White and Black, White and Asian or any other mixed

Figure 1. Distribution of breast tissue absolute and relative asymmetry measurements. (a) Absolute asymmetry derived from absolute difference left and right CC views. (b) Outliers where absolute BV asymmetry >610 cm^3 (10 *mean value) have been omitted to aid clarity (*n* = 109). (c) Outliers where absolute DV asymmetry >57cm3 (10 * mean value) have been omitted to aid clarity (*n* = 252). (d) Relative symmetry % derived from (|L-R|)/ (*L* + R)/2*100, where L and R represent the volumes of the left and right breasts as estimated from the CC views. (e) Outliers where relative BV asymmetry >20% have been omitted to aid clarity (*n* = 51). (f) Outliers where relative DV asymmetry >20% have been omitted to aid clarity (*n* = 139). BV,breast volume; CC, craniocaudal; DV, dense volume.



[median 2.87% (1.48%, 4.56%)]. The magnitude of relative BV asymmetry was also similar irrespective of the ethnicity of the participants although slightly higher in the Chinese ethnic group [2.71% (1.38%, 4.68%)].

The magnitude of relative DV asymmetry was similar across all age groups and ethnicities [median overall relative DV asymmetry for all study participants: 3.28% (1.52%, 5.79%)]. Overall age and ethnic variations in relative BV and DV asymmetry were much less marked than those observed for absolute BV asymmetry and absolute DV asymmetry (Figures 2 and 3).

Correlations between absolute asymmetry and volumetric measures

BV and DV absolute asymmetry were moderately positively associated with their corresponding underlying volumetric measure (Spearman correlation coefficient (r): 0.45 and 0.43, respectively; $p < 0.0001$ for both). Regressing log BV asymmetry on log BV revealed negative allometry [coefficient: 0.84; 95% confidence interval 0.83, 0.85)] whilst regressing log DV on log DV revealed slight positive allometry (1.09; 1.07, 1.12). There were no statistically significant differences in the magnitude of these allometry coefficients across the different ethnic groups (data not shown).

Associations between absolute asymmetry and age and ethnicity

The fitted linear regression models showed that BV absolute asymmetry increased with increasing age (in 5 year categories, P for trend (Pt) <0.001; Table 2), and that this trend persisted after adjustment for BV (Pt <0.001). In contrast, DV absolute asymmetry decreased with increasing age (Pt <0.001), but this trend was attenuated upon adjustment for DV (Pt = 0.14; Table 2). Further adjustment for ethnicity affected little the magnitude of the BV or DV absolute asymmetry associations with age (Table 2).

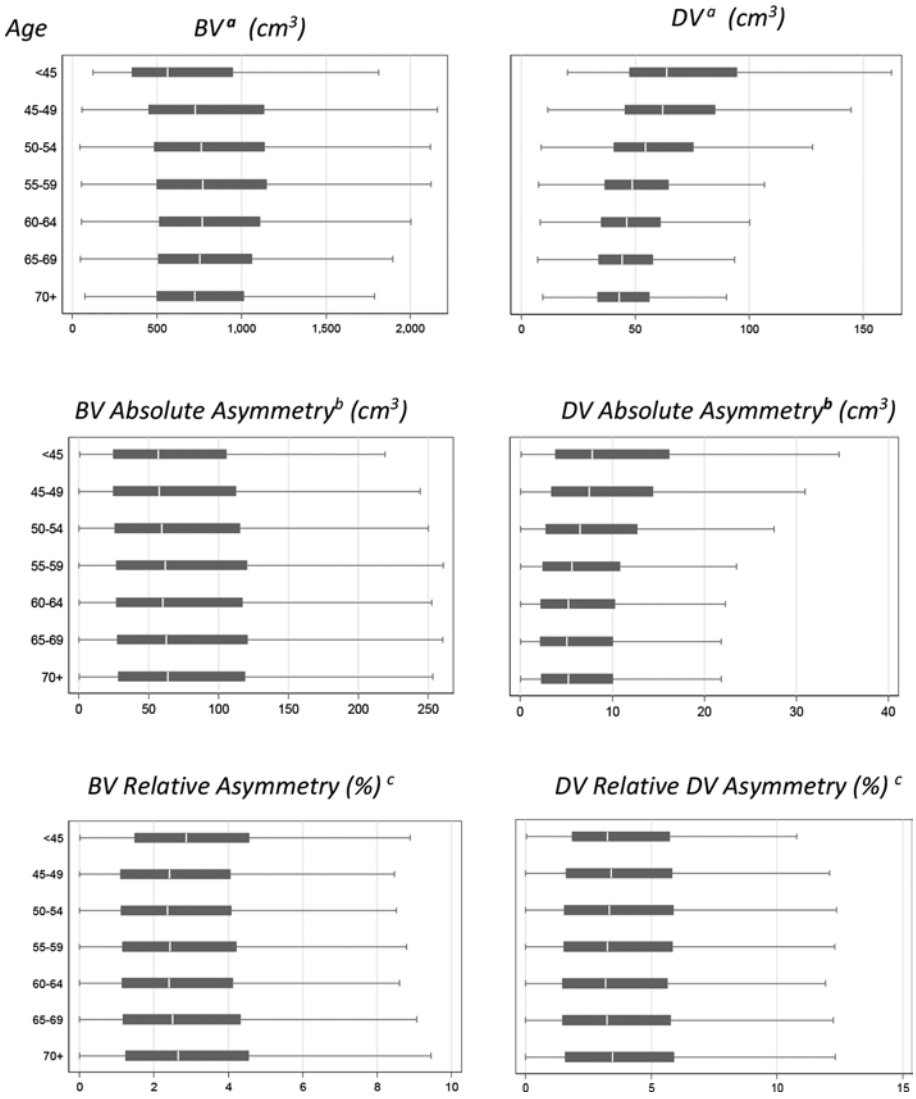
When considering ethnicity on its own, relative to White females (reference group) those of Black Caribbean, Black African and Mixed ethnicity had statistically significantly higher, whilst those of Chinese ethnicity had statistically significant lower, BV absolute asymmetry (Table 2). However, upon adjustment for BV the magnitude of these ethnic differentials was markedly reduced, remaining statistically significant only in Black African females (RC 1.13; 95% CI 1.07, 1.19), while there was borderline evidence of higher BV absolute asymmetry for Asian females (1.04; 1.00, 1.07; Table 2). Similarly, and still relative to White females, DV absolute asymmetry was found to be significantly higher among Black Caribbean and Black African females and significantly lower among Asian and Chinese females in unadjusted analyses. However, these differences remained significant after, adjustment for DV, only for Asian females (0.94; 0.91, 0.98; Table 2). There was no evidence of interaction between age and ethnicity in their effects on BV or DV absolute symmetry ($p = 0.69$ and $p = 0.53$, respectively).

DISCUSSION

Main findings

This study of >54,000 females clarifies the associations between absolute breast asymmetry and breast volume, with the findings being broadly consistent with those from a smaller study (*n* = 500 younger females) by Manning et al which showed that simple linear regression of BV absolute asymmetry (log transformed) on BV gives a significant positive association (our study $r^2 = 0.15$, $p < 0.001$; Manning $r^2 = 0.13$, $p < 0.001$).[9] We also found that absolute DV asymmetry is positively associated with DV. Thus,

Figure 2. Breast tissue volumes and asymmetry measurements by age, medians and IQR. (a) BV and DV are average values estimated from the four mammographic images: left CC image, right CC image, left MLO image, right MLO image. (b) Absolute asymmetry estimated from absolute difference between volume estimates derived from the left and right CC views. (c) Relative asymmetry estimated as (|L-R|)/ (*L* + R)/2*100, where L and R are volume estimates derived from the left and right CC views. Whiskers are calculated as lower adjacent value (*i.e.* smallest observed value ≥ lower quartile +1.5 IQR) and upper adjacent value (*i.e.,* largest observed value ≤ upper quartile +1.5 IQR). BV,breast volume; CC, craniocaudal; DV, dense volume; IQR, interquartile range; MLO,mediolateral oblique.

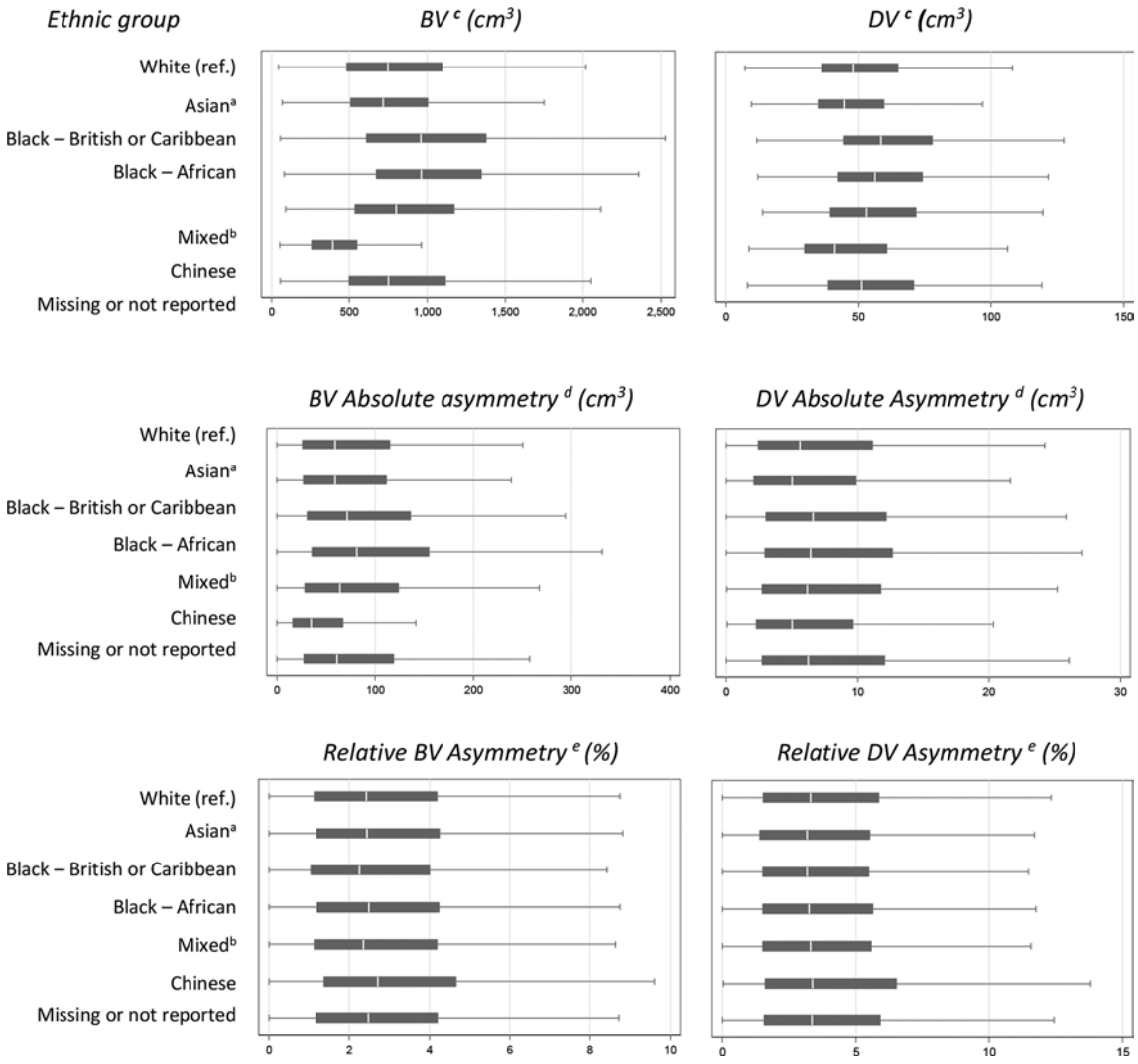


the larger BV (or DV) the higher the magnitude of BV (or DV) absolute asymmetry. This explained, at least in part, the higher levels of BV and DV asymmetry observed in females of Black ancestry as they also had, on average, higher BV and DV. After adjusting for the relevant breast volumetric measure (*i.e.* BV for BV asymmetry, DV for DV asymmetry), the ethnic differences in absolute breast asymmetry observed in the unadjusted analysis were attenuated, indicating that they were largely driven by ethnic differences in breast and dense tissue volumes.

Similar to the findings of Manning et al,[9] our findings showed that the BV absolute asymmetry/BV relationship was negatively allometric across all main ethnic groups, indicating that females with large breasts had a smaller fluctuating asymmetry than expected for their volume. There was, however, evidence that the DV absolute asymmetry/DV relationship was positively allometric.

Like Manning et al we found, using simple linear regression, that BV asymmetry is only weakly positively associated with age (our study $r^2 = 0.004$, $p < 0.001$, Manning $r^2 = 0.019$, $p = 0.02$).[9] The differences in the strength of the association might be explained by the fact that the females in our study were considerably older than those in the study by Manning et al[9] (mean ages 58.57 and 39.85 respectively). We found that DV absolute asymmetry is weakly but negatively associated with age, with these associations being attenuated upon adjustment for DV, indicating that these associations are largely driven by decreasing DV with age.

Figure 3. Breast tissue volumes and asymmetry measurements by ethnicity, medians and IQR. (a) Asian = British Indian, Pakistani, Bangladeshi or other Asian excluding Chinese. (b) Mixed = Mixed White and Black, White and Asian and any other Mixed. (c) BV and DV are average values estimated from the four mammographic images: left CC image, right CC image, left MLO image, right MLO image. (d) Absolute asymmetry estimated from absolute difference between volume estimates derived from the left and right CC views. (e) Relative asymmetry derived from (|L-R|)/ (*L* + R)/2*100, where L and R are volumes from Left and Right CC views. Whiskers are calculated as lower adjacent value (*i.e.* smallest observed value ≥ lower quartile +1.5 IQR) and upper adjacent value (*i.e.* largest observed value ≤ upper quartile +1.5 IQR)



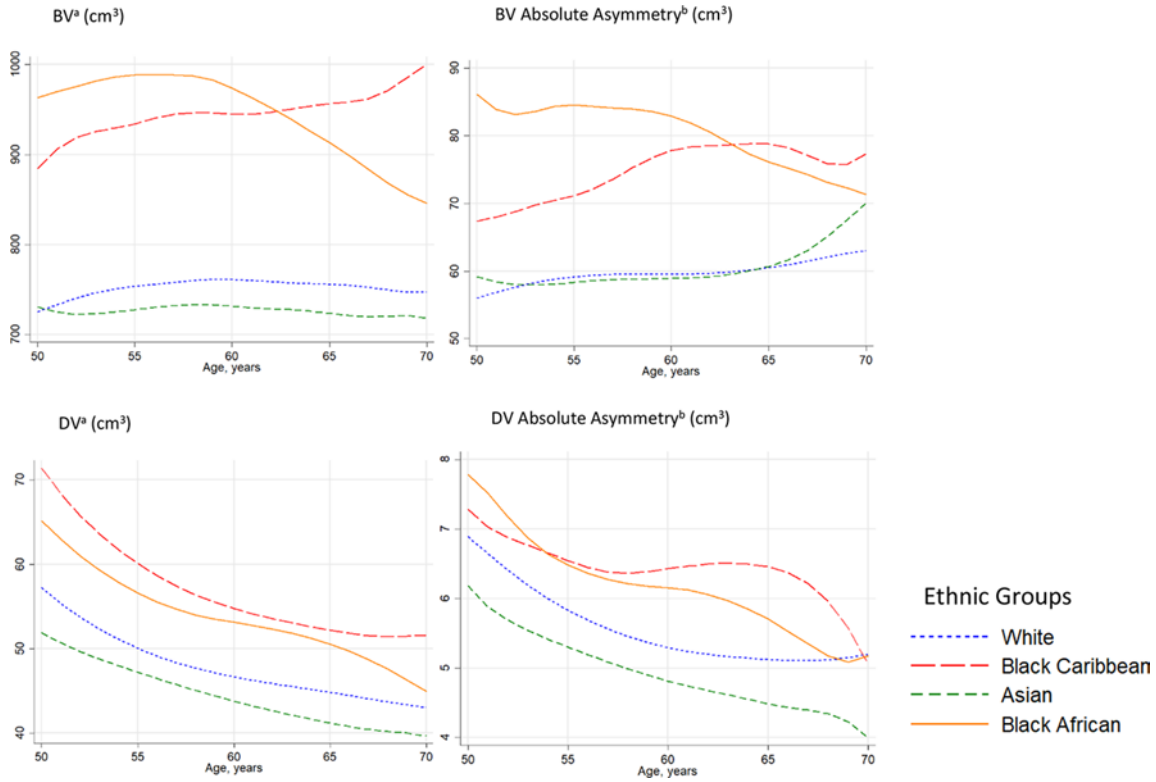
Two earlier studies, one in the USA ($n = 980$)[38] and the other in Switzerland ($n = 87$),[39] focused on the left:right ratio (L:R) in BV. Although such L:R ratio cannot be regarded as a measure of relative asymmetry, it is nevertheless worth noting that their findings are consistent with our finding that, on average, the left BV exceed the right BV by ~4% across the whole breast screening population irrespective of ethnicity and age. There was, however, marked between-woman variability in breast asymmetry among cancer-free, screened females.

Literature on the prevalence of DV asymmetry is limited. Consistent with our findings Lee et al, in a study of 860 South Korean females, found that the L:R ratio in DV was less than one indicating a greater DV in the right breast,[40] thus challenging the view that the laterality of DV ratio is similar across all ethnic groups. Chen et al[41] on a small sample of 24 Taiwanese females also found that DV, as measured by MRI, was higher in the right than in the left breast.

Strengths and limitations

Strengths of this study include its population-based design, the very large sample size relative to previous studies, and the wide ethnic mix. As the images for both breasts were collected at the same point in time, and under similar technical conditions, within-woman L:R breast comparisons are unlikely to have been biased by anthropometric, reproductive and lifestyle characteristics (*e.g.* BMI, menopausal status) or by differences in image acquisition (*e.g.* differences in mammographic equipment) as these would have affected both breasts similarly. This does not exclude, however, the possibility that the findings may have been affected by within-woman differences

Figure 4. Breast composition and breast composition asymmetry by age and ethnicity. Median volume, absolute asymmetry in cm^3 in each year band smoothed using Stata Lowess function. [a]BV and DV are average values from the four images: left CC image, right CC image, left MLO image, right MLO image. [b]Asymmetry derived from absolute difference left and right CC views. Year group excluded if fewer than 20 observations in that age group Asian = British Indian, Pakistani, Bangladeshi or other Asian excluding Chinese Chinese ethnicity omitted due to sparsity of data in older females. BV,breast volume; CC, craniocaudal; DV, dense volume; MLO, mediolateral oblique.



in the way the left and right breasts were examined (*e.g.* differences in a female's positioning during mammography). The study relied on an automated method to estimate the volumes of the left and right breasts and the amounts of their radiodense tissues, and thus such objective measurements were not influenced by subject or observer biases. Although the volumetric estimates were derived from two-dimensional images and, hence, may have been affected by errors, these would have affected both breasts similarly.

The study included mostly females of screening age and reflected a mix of ethnic groups living in England. The proportion (15%) of females for whom ethnicity data were missing was relatively low and typical for NHSBSP screening services where collection of self-reported ethnicity data is undertaken.[42] Females with a previous history of breast cancer, or who were diagnosed with cancer at the time of screening, as well as those with breasts implants, were excluded from the study; however, females with other conditions that might have affected their breast size (*e.g.* surgery for non-malignant conditions) could not be excluded as information on these conditions is not routinely collected by the NHSBSP.

A limitation of this study was the lack of data on potential confounders or mediators (*e.g.* BMI, reproductive history) of the age/ethnicity associations with BV and DV asymmetry. Menstrual cyclic variations in breast width asymmetry (measured from CC mammograms) were reported by Manning et al,[43] based on mammograms from 280 premenopausal females, with lowest breast asymmetry occurring around the middle of the cycle (which Scutt & Manning later attributed to ovulation[44]). Although the present study was unable to consider cyclical changes in asymmetry as information on the day of menstrual cycle when the mammogram was taken is not routinely collected by the NSHBSP, the large majority of females screened by the NHSBSP are of post-menopausal age. Nevertheless, future studies of pre-menopausal females should examine cyclic variations in asymmetry and, in particular, whether such variations should be taken into account when assessing asymmetry—breast cancer risk associations.

The study was conducted using one specific algorithm for estimating volumetric breast size and volumetric density. There is no published data specifically on the reliability of asymmetry measures derived from the Volpara volumetric measurements, but the latter have been found to be reliable and repeatable.[45–47] Nevertheless, it would be worthwhile to assess breast asymmetry using other automated methods. Our estimates of BV and DV asymmetry were derived from the CC views of the left and right breasts; however, MLO views produced similar breast asymmetry estimates *[e.g.,* median (IQR) for BV and DV absolute asymmetry for all participants was 60.6 (26.6, 117.8) cm^3 and 5.71 (2.5, 11.3) cm^3, respectively, if derived from the CC views and 65.1 (28.7, 127.0) cm^3 and

Table 2. Linear regression analysis of associations between BC risk factors and asymmetry measures

	BV absolute asymmetry[a] (*N* = 54,591)			DV absolute asymmetry[a] (*N* = 54,591)		
	Unadjusted	Adjusted for BV[b]	Mutually adjusted[c]	Unadjusted	Adjusted for DV[b]	Mutually adjusted[c]
Variable	**RC (95% CI)**	**RC (95% CI)**	**RC (95% CI)**	**RC (95% CI)**	**RC (95% CI)**	**RC (95% CI)**
BV / DV (per quintile)	1.41 (1.40, 1.42)		1.41 (1.40, 1.42)	1.40 (1.39, 141)		1.39 (1.38, 1.40)
	p < 0.001		*<0.001*	*<0.001*		*<0.001*
	$r^2 = 0.15$			$r^2 = 0.14$		
Age[d] (years)						
<45	0.90 (0.76, 1.05)	1.07 (0.92, 1.24)	1.08 (0.93, 1.25)	1.32 (1.12, 1.55)	1.13 (0.97, 1.31)	1.13 (0.91, 1.31)
45–49	0.98 (0.94, 1.03)	1.01 (0.97,1.06)	1.01 (0.93, 1.06)	1.16 (1.10, 1.21)	1.04 (0.99,1.08)	1.03 (0.99,1.08)
50–54 (ref)	1.00	1.00	1.00	1.00	1.00	1.00
55–59	1.04 (1.01, 1.07)	1.03 (1.00,1.05)	1.03 (1.00,1.06)	0.87 (0.84, 0.89)	0.98 (0.95,1.00)	0.98 (0.95,1.01)
60–64	1.04 (1.01, 1.08)	1.03 (1.00,1.06)	1.04 (1.00,1.07)	0.80 (0.78, 0.83)	0.95 (0.93,0.98)	0.96 (0.93,0.99)
65–69	1.04 (1.01, 1.08)	1.06 (1.03,1.09)	1.06 (1.03,1.10)	0.78 (0.76, 0.81)	0.98 (0.05,1.00)	0.98 (0.95,1.01)
70+	1.08 (1.03, 1.13)	1.12 (1.08,1.17)	1.14 (1.09,1.19)	0.82 (0.79, 0.86)	1.05 (1.01,1.10)	1.05 (1.01,1.10)
P for homogeneity	*0.01*	*0.01*	*<0.001*	*<0.001*	*<0.001*	*<0.001*
P trend	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*0.14*	0.20
	$r^2 = 0.004$			$r^2 = 0.009$		
Ethnicity						
White (ref.)	1	1	1	1	1	1
Asian[e]	1.01 (0.97, 1.05)	1.04 (1.00, 1.07)	1.04 (1.01, 1.08)	0.89 (0.85, 0.92)	0.94 (0.91, 0.98)	0.95 (0.91, 0.98)
Black—British/Caribbean	1.20 (1.14, 1.26)	1.00 (0.96,1.05)	1.01 (0.97, 1.06)	1.16 (1.11, 1.22)	0.95 (0.91,1.00)	0.95 (0.91, 1.00)
Black—African	1.39 (1.31, 1.47)	1.13 (1.07,1.19)	1.14 (1.08,1.20)	1.14 (1.08,1.21)	0.98 (0.93,1.03)	0.98 (0.93, 1.03)
Mixed[f]	1.01 (1.02, 1.19)	1.04 (0.97,1.12)	1.04 (0.97,1.12)	1.05 (0.97, 1.14)	0.96 (0.89,1.03)	0.96 (0.89, 1.03)
Chinese	0.60 (0.55, 0.66)	0.94 (0.86,1.03)	0.95 (0.87, 1.04)	0.90 (0.81, 0.99)	1.01 (0.93,1.11)	1.02 (0.93, 1.11)
P for homogeneity	*<0.001*	*<0.01*	*<0.01*	*<0.001*	*0.54*	*0.55*

BC, breast cancer; BV, breast volume; CC, craniocaudal; DV, dense volume.
[a]Absolute breast asymmetry measures are absolute CC asymmetry volumes log transformed.
[b]Adjusted associations: BV asymmetry adjusted by BV category, FG asymmetry by FGV category. Volumetric categories are quintiles of respective volumes.
[c]Mutually adjusted also adjusted for either Age or Ethnicity as appropriate.
[d]Age in 5 year age bands
[e]Asian = British Indian, Pakistani, Bangladeshi
[f]Mixed = mixed White and Black, White and Asian or any other mixed

7.2 (3.2, 14.1) cm^3, respectively, if derived from the MLO views]. Similar associations of these measures with age and ethnicity were also found (data not shown).

Implications

So far, only a few small, studies have examined the relation of breast asymmetry measures with breast cancer. Scutt et al used area-based mammographic breast size (BV) asymmetry measurements from ~250 breast cancer cases and ~250 matched controls, while adjusting for known risk factors and absolute breast size, to show that absolute BV asymmetry at baseline screen was associated, with cancer diagnosis at the baseline screen[21] and also medium-term risk.[22] In a preliminary study, Eltonsy et al examined data from 280 breast cancer cases and 82 controls and found that the mean absolute BV asymmetry, adjusting for BV, was significantly higher in cancer patients.[19] Kayar et al used non-mammographic breast measurements (from Grossman-Rounder Discs) on 251 breast cancer cases and 466 controls from a Turkish outpatient clinic, to propose a 'pathological breast asymmetry ratio', suggesting that a L:R BV ratio of >±20% was associated with an increased risk of breast cancer being diagnosed within one year of the examination.[20]

Zheng et al investigated the relationship between mammographic density percentage (%MD) asymmetry and breast cancer using a bespoke algorithm on mammograms from 230 females with interval cancers (cancers diagnosed between screens) and 230 controls and suggested that as %MD increases there was an increased risk of cancer at both current screen and in the medium term (1–3 years). These models adjusted for subjective breast density category (BIRADS), but not for absolute breast density.[23,24]

The limited available literature suggests that BV and DV asymmetry may have potential value as markers of either the presence of a cancer (diagnostic marker) or the risk of developing cancer in the future (risk predictor). Proper examination of the potential value of these breast asymmetry measures as diagnostic or predictor markers will require the conduct of large-scale and longitudinal studies with objective measurements of breast asymmetry. Objective breast tissue asymmetry estimates can now be obtained using existing fully-automated mammographic volumetric analysis tools and thus can be provided, without additional investigations, for all females attending screening. The availability of such data will facilitate further research into the association between asymmetry and breast cancer, both at the current screen and subsequently, and may potentially provide a practical additional tool for stratifying the screening population in terms of likelihood of having, or risk of developing, breast cancer.

AUTHORS' CONTRIBUTIONS

SMH, IdSS and RD, designed the study; LSW organized 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, RD, 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.

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