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Heritability of mammographic breast density, density change, microcalcifications, and masses

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Title: Heritability of mammographic breast density, density change, microcalcifications, and masses

Running title: Heritability of mammographic features

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Keywords: heritability, microcalcifications, masses, breast density, density change

Abstract:

Background: Mammographic features influence breast cancer risk and are used in risk prediction models. Understanding how genetics influence mammographic features is important since the mechanisms through which they are associated with breast cancer are not well known.

Methods: Mammographic screening history and detailed questionnaire data for 56,820 women from the KARMA prospective cohort study were used. The heritability of mammographic features such as dense area (MD), microcalcifications, masses, and density change (MDC – cm^2/year) were estimated using 1,940 sister pairs. We investigated the association between a genetic predisposition to breast cancer and mammographic features, among women with family history of breast cancer information (N=49,674) and a polygenic risk score (PRS, N=9,365).

Results: Heritability was estimated at 58% (95% CI: 48%, 67%) for MD, 23% (2%, 45%) for microcalcifications, and 13% (1%, 25%) for masses. The estimated heritability for MDC was essentially null (2%, 95% CI: -8%, 12%). The association between a genetic predisposition to breast cancer (using PRS) and MD and microcalcifications was positive, while for masses this was borderline significant. In addition, for MDC, having a family history of breast cancer was associated with slightly greater MD reduction,

Conclusions: We confirmed previous findings of heritability in MD, and also found heritability of the number of microcalcifications and masses at baseline. Since these features are associated with breast cancer risk, and can improve detecting women at short-term risk of breast cancer, further investigation of common loci associated with mammographic features is warranted to better understand the etiology of breast cancer.

Introduction

Breast cancer screening reduces breast cancer mortality by an estimated 20-35%.[1-4] Mammography is the most used breast cancer screening imaging modality which, while relatively easily collected and primarily used for diagnostic purposes, in recent years is now also providing relevant information to assist in predicting breast cancer risk.[5-8] Mammographic breast density (MD), which represents the amount of fibro glandular tissue in the breast, is the most strongly established image-based risk factor for breast cancer.[6,8-10] MD declines with age,[11] and while MD is used in a number of risk prediction models, a lack of density reduction may also be an important risk factor.[12]

Microcalcifications are calcium deposits that can be found in breast ducts, stroma, or vessels.[13] Microcalcifications are markers of breast cancer and have been identified in 30-50% of screen-detected cancers.[14] Computer-aided detection (CAD), which is designed to support radiologists, can also reveal suspicious malignant microcalcifications and masses within the breast. Microcalcifications and masses (Supplementary Figure 1), together with MD, have been shown to identify women at high short-term risk of breast cancer,[5,15] and therefore provide potential to individualise screening and improve clinical care, by identifying women in need of additional examination procedures.

Understanding the genetic determinants of mammographic features is important, given that the exact mechanisms through which they are associated with breast cancer is not well known. A family history of breast cancer, in first-degree relatives, is associated with an almost two-fold increased risk of breast cancer.[16] The heritability of breast cancer ranges from 27% to 31%,[17,18] as explained by both common and rare genetic variants.[17,19] The combined effect of common genetic variants, such as single-nucleotide polymorphisms (SNPs), have been used to create disease-specific polygenic risk scores (PRS).[20] The most up-to-date and comprehensive breast cancer PRS, including 313 SNPs, estimates a 1.6 increased odds of breast cancer per 1 standard deviation of PRS.[20] Compared to breast cancer, the heritability of MD is

higher, at approximately 60%.[21-25] While it is known that MD shares some SNPs with breast cancer,[26-29] to our knowledge no studies report the heritability of microcalcifications, masses, or density change. By studying genetic variation in these features, additional important loci for breast cancer susceptibility can be identified, and hence improve the ability to detect women at increased risk of breast cancer.

We investigated the heritability of mammographic features, specifically i) MD (dense area); ii) mammographic density change (MDC - cm^2/year); iii) microcalcifications; and iv) masses. To further understand how the genetic contribution of mammographic features are related to a genetic susceptibility to breast cancer, we modelled their association with both family history of breast cancer and a breast cancer polygenic risk score (PRS). To our knowledge, this is the first study aimed at identiyfying genetic determinants of microcalcifications, masses, and MDC.

Methods

Study population

Ethical approval for The KARMA prospective cohort study was given by the ethical review board at Karolinska Institutet (Stockholm, Sweden – dnr 2010/958-31/1) and written informed consent was obtained from all participants. The study includes 70,871 women who attended mammography screening at one of four Swedish hospitals from January 2011 to March 2013 and were enrolled in the study, with mammograms collected continually. In Sweden, women aged 40-74 years are invited for mammography screening every 18-24 months. Women were followed for diagnosis of breast cancer; the mean follow-up time from baseline to the last update in October, 2017, was 5.2 years, SD 0.9. Participants completed a detailed questionnaire on lifestyle and other factors (at baseline and repeatedly thereafter), and consented to accessing data from Swedish health registers.[30] Participants also consented to continuous collection of mammograms at subsequent examinations. Sisters (n=5,238) within the KARMA cohort were identified through the Swedish Multigeneration register[31] using national Personal Identity Numbers.

We excluded women at baseline who: had a prior breast cancer diagnoisis (n=4,627), breast enlargement (n=1,419) or reduction (n=2,142), did not have a baseline density mammogram (n=5,106), and were younger than 40 (n=643) or older than 75 years (n=43) at first mammogram (Figure 1). Of the 56,820 women in the study population, 8% had one mammogram available, 24% had two, 55% had three, 12% had four, and 1% had 5 or more. Our sibling sub-population included 3,880 women, consisting of 1,739 full siblings, 127 maternal half-siblings, and 74 paternal half-siblings pairs. The sub-population estimating the association between family history of breast cancer and mammographic features was restricted to women with information on family history (N=49,674), while the PRS sub-population was restricted to women who were genotyped (N=9,365).

Measures

Mammographic images

Full-field digital mammograms (General Electric, Philips, Sectra, Hologic, Siemens, Fuji) from medio-lateral onlique (MLO) and cranio-caudal (CC) views of the left and right breasts at baseline and over the follow-up period were included. For each woman, the STRATUS algorithm[32] aligned the breast area in subsequent mammograms, and measured mammographic density (MD) in the left and right breast areas at each time point. Microcalcifications and masses were measured, in both the MLO and CC views, using the CAD (M-Vu CAD®, Nashua, USA) algorithm[32] an FDA approved software, class 3 device (PMA number P010038), with reproducibility being a part of the approval criteria.

Mammographic density at baseline and density change

Average MD was calculated as the mean of the left and right breast dense areas (cm^2) at each time point. Average percent MD (dense area divided by breast area) was calculated similarly. MD at baseline was log transformed for modelling, in order to approximate a normal distribution.

Average mammographic density change (MDC) per year (cm^2/year) over the follow-up period was estimated for each individual as a slope using linear regression based on age at each density measurement, as in our previous study.[33] This model uses full information for each woman, regardless of the number of mammograms, which varies for each woman. Adjusted models included age at first and last mammogram, accounting for the strong association between age and MD, as well as several breast cancer risk factors.

Microcalcifications and masses at baseline

Number of clusters (two or more microcalcifications) of microcalcifications were categorised into 0, 1, 2, ≥3. The average number of clusters was calculated as the mean number of left and right breasts at each time point, included in an algorithm based on individual risk of breast cancer. Microcalcifications and the number of masses at baseline (absolute) were both modelled as ordinal variables.

Genetic predisposition to breast cancer

Information on family history of breast cancer was retrieved from the self-reported questionnaire and categorised as a dichotomous exposure, indicating whether a first degree relative (biological parent, sibling, or child) had been diagnosed with breast cancer. Genotyping of a random sample of KARMA women without breast cancer was performed using a custom Illumina iSelect array (iCOGS)) or an Illumina Infinium Oncoarray (5,033 and 4,332 women, respectively) which was used for the genetic association between breast cancer risk and mammographic features sub-population.[34] A weighted overall breast cancer PRS was calculated for each genotyped woman using 313 genome-wide significant SNPs, with details of this calculation found elsewhere.[20] Higher PRS values indicate an increased risk of breast cancer, with this variable divided into quintiles.

Covariates

Self-reported information from the detailed KARMA questionnaire completed at baseline was used: body mass index (BMI: kg/m^2), previous benign breast disease (dichotomous), and use of hormone replacement

therapy (HRT) (dichotomous). Menopausal status was determined according to the following criteria: postmenopausal women had not menstruated in the past year, had previously had an oophorectomy, or were over age 50; while premenopausal women had menstruated in the past three months or were younger than age 50. Total number of children and age at the birth of the first child were combined to create a variable capturing reproductive history (no births; 1 child, <25 years; 1 child, ≥25 years; 2 children, <25 years; 2 children, ≥25 years; 3+ children, <25 years; 3+ children, ≥25 years). Age (years) at first mammogram (all analyses) and at last mammogram (analysis of MDC) were modelled as continuous variables. Other variables included for descriptive purposes include: height, age at menopause, and history of 'other cancer'. KARMA sisters were classified according to sibling type for the heritability analyses (full siblings, maternal half-siblings, and paternal half-siblings).

Statistical Analysis

Characteristics of the study population, and three sub- populations were compared using χ^2 tests for categorical variables and t-tests for continuous variables.

We estimated the additive genetic effects (representing heritability, A), dominance deviations (D), familial environmental effects (C), and unique environmenatl effects (E) of different mammographic features. We assumed that full-siblings share 0.5 of their segregating alleles, while maternal and paternal half-siblings share 0.25. Based on an assumption of shared rearing, a shared environment was only assumed for full-siblings and maternal half-siblings; during the time in which these women were growing up, children in Sweden traditionally lived with their mother after parental separation.[35]

Heritability estimation was performed using the structural equation modelling package 'OpenMx'[36] in R software, which uses full information maximum likelihood and is able to handle missing data. MD and MDC were modelled as continuous outcomes. For the ordinal outcomes (microcalcifications and masses),

we used a liability threshold approach, assuming a normal distribution and estimable correlations between these underlying distributions.

We first estimated heritability using the intra-class coefficient coefficient for each of the mammographic outcomes. We then modelled the observed data in a saturated model - where observed means, thresholds, and covariance matrices were estimated independently between sibling types (i.e., no shared parameters across the sibling groups). We then fitted quantitative genetic models for each outcome, where the proportion of total variance explained by combinations of A, D, C, and E were tested for statistically significant deterioration compared to the model including all sources (ADCE model), using likelihood ratio tests. We used the Akaikes Information Criteria (AIC) to assess goodness of fit of the ACE, ADE, and AE models, with lower values indicating a better model fit, while also favouring the most parsimonious model. Estimates for the unadjusted model are presented, as well as after adjustment. For the outcomes MD, microcalcifications, and masses, we adjusted for Model 1: age at mammogram, menopausal status, BMI; and Model 2: Model 1 + HRT use, previous benign breast disorder, and reproductive history. For analyses of MDC, we adjusted for Model 1: age at first mammogram, menopausal status, BMI, and age at last mammogram. Despite previous findings using the same data finding no association between reproductive factors and MDC,[33] for consistency with the other outcomes we also provide estimates from an additional model that adjusts for reproductive history (Model 2). For consistency with prior literature, we additionally ran sensitivity analyses using the outcome percent density at baseline. As further sensitivity analyses, we excluded sister pairs where at least one sister went on to develop breast cancer (134 women).

The associations between a genetic predisposition to breast cancer and both MD and MDC were modelled using linear regression, using family history of breast cancer ('no' as the reference category) and PRS (quintile 1, 0-20%, as the reference category). We estimated the association between a genetic predisposition to breast cancer and microcalcifications and masses in ordinal logistic regression models.

We tested for a linear trend over quintiles of PRS using a χ^2 test. For all outcomes, Model 1 is minimally adjusted for age at first mammogram, and for the exposure PRS, additionally genotyping platform (iCOGS or Oncoarray). Model 2 includes full adjustment as described above for the heritability modelling. As sensitivity analyses, we also present results i) using percent MD at baseline as the outcome; and for all outcomes ii) excluding women who went on to develop breast cancer; and iii) using both an estrogen receptor positive and estrogen receptor negative PRS as the exposure.

Aside from the heritability analyses, which used R version 3.6.1, all other analyses were completed in SAS version 9.4 (SAS Institute Inc., Cary, NC).

Results

The four populations included in the study did not differ to a large extent (Table 1). Women included in the family history sub-study had slightly higher MD than women in the PRS and sibling sub-populations. A higher proportion of women in the PRS sub-population were postmenopausal and had a previous benign breast disease (Table 1).

Correlations within sisters suggested a genetic influence on MD, microcalcifications, and masses at baseline (Table 2). For MD and masses, the correlation between maternal half-siblings (Model 2 correlation 0.21 and 0.16, respectively) was higher than between paternal half-siblings (Model 2 correlation 0.01 for both), potentially indicating a small component attributable to the shared environment. For MDC, the data suggests no correlation (Model 2 correlation in full siblings 0.01) (Table 2). For this outcome, the likelihood ratio tests (Table 3, $p<0.0001$) show that the adjusted quantitative genetic model fit the data statistically significantly worse than the saturated model, indicating deviations from modelling assumptions (the interchangeability of sibling one and two). Therefore, as sensitivity analyses, we performed all heritability analyses again using a sample where sisters had a re-randomized pair order.

Results remained unchanged, but the indicated problems with assumptions remained for the MDC-models (Supplementary Tables 1 and 2).

Table 3 shows the univariate model fitting, with the AE models not fitting the data statistically significantly worse than the saturated model for MD, microcalcifications, and masses at baseline; these models had the lowest AIC, fewest parameters estimated, and were the most parsimonious. Given this, the influence of the shared environment was set to zero. Based on AIC, the AE model was also the best fit for the outcome MDC, although it fit the data statistically significantly worse than the saturated model (Table 3, $p < 0.0001$).

Univariate estimates of heritability

Based on the preferred models, the proportion of variance explained by additive genetic (A) and individual/non-shared environment (E) components for the four outcomes are shown in Table 4. The heritability of MD was marginally attenuated after full adjustment, and estimated at 58% (95% CI: 48%, 67%), while the estimated heritability of MDC was essentially null (2%, 95% CI: -8%, 12%). After full adjustment, the heritability of microcalcifications was estimated at 23% (95% CI: 2%, 45%), and masses at 13% (1%, 25%). For all outcomes, the remaining variance was attributable to the individual/non-shared environment (E). Sensitivity analyses showed results remained essentially the same when i) estimating the heritability of percent MD (Supplementary Table 3); and ii) excluding women who went on to develop breast cancer (Supplementary Table 4).

Association between family history of breast cancer and mammographic features

Having a family history of breast cancer was positively associated with increased MD (β 0.07, 0.04 to 0.10), increased odds of microcalcifications (OR 1.14, 1.07 to 1.22), and slightly greater MD reduction (MDC β -0.12, -0.22 to -0.03) (Table 5, Model 2). There was no statistically significant association between family history of breast cancer and masses. In sensitivity analyses, these estimates were

essentially the same when i) using percent MD as the outcome (Supplementary Table 5); and ii) when we excluded women who went on to develop breast cancer (Supplementary Table 6).

Association between breast cancer polygenic risk score and mammographic features

There was a statistically significant association between PRS quintiles and MD and microcalcifications (Table 5, Model 2, $p < 0.0001$) and borderline significant association for masses at baseline (Table 5, Model 2, $p=0.0586$), with suggestion of a positive linear trend (Table 5, Model 2 – $p < 0.0001$ for MD and microcalcifications, $p=0.0394$ for masses). No association was found between PRS and MDC (Model 2, $p=0.1061$). Estimates remained similar when i) using percent MD as the outcome (Supplementary Table 5); and for all outcomes when we ii) excluded women who went on to develop breast cancer (Supplementary Table 6); and iii) used estrogen receptor-specific PRS as the exposure (Supplementary Table 7).

Discussion

Using a large prospective Swedish cohort, we found statistically significant heritability of MD, microcalcifications, and masses. In contrast, MDC did not seem to be inherited. Using the latest PRS, we found a statistically significant association between a genetic predisposition to breast cancer and MD, microcalcifications, and masses. Additionally, women with a family history of breast cancer had a slightly greater MD reduction. While our results confirm the heritability of MD, a well-studied mammographic feature, to our knowledge we are the first to show heritability estimates of microcalcifications, masses, and MDC.

This study focused on understanding the genetic involvement of different mammographic features, given that they are becoming recognised as strong factors associated with breast cancer. In order to better understand the mechanisms behind these features, we not only estimated their heritability, but also how they are associated with a genetic susceptibility to breast cancer.

Mammographic density

Using a refined method to measure density, we confirm previous studies showing approximately 60% heritability in MD,[21,22] using both dense area at baseline (main results) and percent density at baseline (sensitivity analysis). We also show a positive linear association between a genetic predisposition to breast cancer and MD, confirming that MD is a strong risk factor for breast cancer. The strong heritability of MD also highlights the importance of further investigating shared loci contributing to both MD and breast cancer, in order to better understand the etiology of the disease and mechanisms through which MD influences breast cancer risk.[26-29] Indeed, previous studies find that approximately one-fifth of breast cancer susceptibility variants are also associated with MD,[37] indicating a common genetic predisposition.[26,37-39] To date, there are approximately 170 breast cancer susceptibility loci identified, with the best-performing breast cancer PRS (used in this study) including 313 SNPs.[20] Further identification of new SNPs associated with breast cancer will also allow us to refine polygenic risk scores for the disease, with the combined effect of common breast cancer susceptibility variants being the best indicator of risk.[20] We found a positive association between family history of breast cancer and PRS with MD. It is estimated that 14% of breast cancer risk is attributable to percent MD,[40] with the combined effect of both MD and increased familial risk of breast cancer having a substantial influence on disease risk.

Mammographic density change

Factors that influence MDC have not been studied to any large extent. We recently showed that, in contrast to MD, few established risk factors for breast cancer influence MDC;[33] only age, HRT, BMI, and physical activity influenced MDC. We found heritability in MD, which is most strongly predictive of breast cancer risk,[9,41,42] and although our study found that MDC is not genetically determined, further studies on factors determining MDC are warranted. While reproductive factors associated with breast cancer and MD are not associated with MDC,[33] it is possible that more immediate factors such as body mass index play a larger role for this outcome. Interestingly, though we did not find any heritability in MDC, having a family history of breast cancer was associated with slightly greater MD reduction, as

shown previously.[33] Given that we did not find any heritability in MDC, we speculate that in addition to genetics, other shared factors between breast cancer and MDC must be important, including hormonal factors.

Microcalcifications

We found 23% (fully adjusted) heritability in microcalcifications, and evidence of an association between a genetic predisposition to breast cancer and microcalcifications. Both PRS and family history were positively associated with microcalcifications, indicating a possible shared basis with breast cancer. A continued search for loci associated with microcalcifications, as has been done for MD,[37] may also reveal new SNPs related to breast cancer. It may also give us a better understanding of the biology behind epithelial-mesenchymal transition, a potentially malignant change in characteristics and properties of cells, as reflected in microcalcifications.[43] While modifiable lifestyle factors such as alcohol intake[44] and hormonal replacement therapy[45] are positively associated with MD, the association of lifestyle factors and genetics with microcalcifications is not well known.

Masses

While the heritability of masses was lower than for MD and microcalcifications, we did find a genetic contribution. Despite this, there was no statistically significant association between family history of breast cancer with the number of masses at baseline; while for PRS this association was borderline significant, with suggestion of a positive linear trend.

Some limitations should be considered. For MDC, having measures of longitudinal risk factors such as body weight would have been ideal; although given the short follow-up time, we do not believe this would result in considerable differences in BMI, and therefore any such bias would be non-differential. We also identified some problems with modelling assumptions of MDC, however sensitivity analyses indicated almost no heritability, so we believe the presented results are reliable.

The major strength of our study is the use of a large population-based cohort. We had detailed information on sibling status and breast cancer risk factors, as well as repeated mammographic measurements over time. Our study uses data processed using STRATUS[32] – an algorithm that incorporates and aligns multiple digital images from any vendor before density is measured and compared. Such image alignment is esssential when comparing changes over time, as it ensures that comparisons are made using the same part of the breast. We also used an FDA approved CAD tool for identifying suspicious malignant microcalcifications and masses. We also conducted a number of sensitivity analyses to check the robustness of our results- including re-randomising sibling order, using percent density at baseline instead of dense area at baseline, excluding women who went on to develop a breast cancer, and using estrogen receptor specific PRS. All results remained consistent.

In conclusion, using a large data set and a novel way of measuring MD and MDC, we confirmed that MD is inherited, while we did not find strong hereditary or genetic determinants for MDC. In addition, we found microcalcifications and masses to be heritable traits. Our results are important given that MD, microcalcifications, and masses are strongly associated with breast cancer. Furthermore, little is known of the biology behind any of these three traits. A better understanding of mammographic features might lead to further efforts aimed at improving how they are measured, and thus lead to improvements in breast cancer detection. Continued search for factors that influence their prevalence might shed light on the mechanism behind breast cancer.

Author contributions

NH, KC and RKH conceived and designed the study. ME extracted all mammographic features and developed methods for these measurements. NH, RKH, and KC performed statistical analysis and interpreted the data. NH drafted the manuscript. All authors critically reviewed the manuscript and approved the final manuscript.

Table 1. Characteristics of the KARMA study population* (N=56,820) and three sub-populations – KARMA siblings (N=3,880), family history of breast cancer (N=49,674), and PRS sub-populations (N=9,365).

	Study population* (N=56,820)		**Sibling sub-population (N=3,880)**		**Family history of breast cancer sub-population (N=49,674)**		**PRS sub-population (N=9,365)**	
	N	mean (median)	N	mean (median)	N	mean (median)	N	mean (median)
MD (cm^2)	55,871	28.25 (22.93)	3,825	27.64 (22.67)	49,674	28.50 (23.32)	9,365	25.85 (20.44)
% MD	55,871	22.79 (17.97)	3,825	22.19 (17.80)	49,674	23.14 (18.48)	9,365	20.65 (15.62)
Mammographic breast volume (cm^3)	56,390	847.15 (760.17)	3,866	865.79 (773.73)	49,566	830.17 (747.23)	9,329	859.39 (778.56)
MDC(cm^2)/year	52,339	-1.03 (-0.65)	3,679	-1.15 (-0.73)	49,674	-1.04 (-0.68)	9,365	-0.91 (-0.58)
		n (%)		n (%)		n (%)		n (%)
Number of clusters of microcalcifications								
0		46,512 (82.3)		3,215 (83.2)		41,112 (82.8)		7,514 (80.2)
1		5,523 (9.8)		351 (9.1)		4,771 (9.6)		1,016 (10.9)
2		2,320 (4.1)		174 (4.5)		1,990 (4.0)		447 (4.8)
3+		2,145 (3.8)		125 (3.2)		1,801 (3.6)		388 (4.1)
Number of masses								
0		20,634 (36.5)		1,403 (36.3)		18,051 (36.3)		3,343 (35.7)
1		18,187 (32.2)		1,233 (31.9)		16,092 (32.4)		3,072 (32.8)
2		10,306 (18.2)		698 (18.1)		9,064 (18.3)		1,731 (18.5)
3+		7,373 (13.1)		531 (13.7)		6,467 (13.0)		1,219 (13.0)
Polygenic risk score (quintiles)								
0-20%		2,458 (22.7)		184 (23.3)		2,104 (22.5)		2,104 (22.5)
20-40%		2,334 (21.6)		175 (22.1)		2,001 (21.4)		2,001 (21.4)
40-60%		2,187 (20.2)		142 (17.9)		1,906 (20.4)		1,906 (20.4)
60-80%		2,068 (19.1)		144 (18.2)		1,809 (19.3)		1,809 (19.3)
80-100%		1,765 (16.3)		146 (18.5)		1,545 (16.5)		1,545 (16.5)
Family history of breast cancer								
No		47,015 (85.9)		3,215 (85.4)		42,751 (86.1)		8,075 (86.2)
Yes		7,718 (14.1)		552 (14.6)		6,293 (13.9)		1,290 (13.8)
		mean (med.)		mean (med.)				mean (med.)
Age at first mammogram	56,820	54.59 (54.0)	3,880	54.41 (54.0)	49,674	54.07 (54.0)	9,365	56.63 (57.0)
Number of mammograms	56,820	2.74 (3.0)	3,880	2.91 (3.0)	49,674	2.89 (3.0)	9,365	3.03 (3.0)
Time between first and last mammogram (years)	52,126	3.65 (4.0)	3,656	3.82 (4.0)	49,475	3.66 (4.0)	9,317	3.90 (4.0)
Height (cm)	56,153	166.63 (167.0)	3,837	166.63 (167.0)	49,400	166.72 (167.0)	9,352	166.59 (167.0)
BMI (kg/m^2)	56,153	25.23 (24.5)	3,837	25.38 (24.6)	49,400	25.11 (24.4)	9,352	25.24 (24.5)
Age at menopause	28,256	50.04 (51.0)	1,901	49.71 (50.0)	24,212	50.04 (51.0)	5,333	50.24 (51.0)
Menopausal status		n (%)		n (%)				n (%)
Pre-menopausal		25,380 (44.7)		1,738 (44.8)		22,957 (46.2)		3,350 (35.8)
Postmenopausal		31,440 (55.3)		2,142 (55.2)		26,717 (53.8)		6,015 (64.2)
Hormone replacement therapy use								
No		50,074 (96.1)		3,440 (95.9)		44,221 (96.1)		8,219 (95.0)
Yes		2,052 (3.9)		146 (4.1)		1,815 (3.9)		429 (5.0)
Previous benign breast disorder								
No		45,984 (80.9)		3,038 (78.3)		40,085 (80.7)		7,230 (77.2)
Yes		10,836 (19.1)		842 (21.7)		9,589 (19.3)		2,135 (22.8)
Other cancer								
No		48,925 (88.7)		3,362 (89.0)		43,348 (89.2)		7,733 (87.8)
Yes		6,221 (11.3)		415 (11.0)		5,275 (10.8)		1,079 (12.2)
Age at first birth								
< 25 years		16,028 (33.1)		1,213 (36.3)		13,786 (32.1)		2, 920 (35.8)
25-29.99 years		17,227 (35.5)		1,257 (37.6)		15,378 (35.8)		3,079 (37.7)
≥ 30 years		15,237 (31.4)		870 (26.1)		13,809 (32.1)		2,165 (26.5)
Number of children								
0		7,090 (12.8)		465 (12.2)		6,119 (12.5)		1,093 (11.8)
1		8,029 (14.4)		494 (13.0)		7,011 (14.3)		1,339 (14.5)
2		26,701 (48.0)		1,802 (47.3)		23,844 (48.5)		4,462 (48.2)
3+		13,783 (24.8)		1,046 (27.5)		12,134 (24.7)		2,368 (25.5)

MD - mammographic density, MDC –mammographic density change

*Study population inclusion criteria: no prior breast cancer before study entry, no breast enlargements/reductions, aged between 40-74.99 at baseline mammogram

Sibling sub-population: Sibling pairs remaining after extracting the sample population

Genetic breast cancer risk sub-populations: women with information on family history of breast cancer who also had information for baseline number of clusters of microcalcifications, number of masses, mammographic density (cm^2), mammographic density change; and women with a polygenic risk score

Table 2. Correlation of mammographic density at baseline, density change, number of clusters of microcalcifications at baseline, and number of masses at baseline among sisters in the KARMA cohort. Intra-class correlation coefficients presented with 95% confidence intervals. (N=3,880)

	Intra-class correlation coefficient (95% CI)											
	(log) Mammographic density (cm^2)			Mammographic density change (cm^2)/year			Microcalcifications			Masses		
Sibling type (pairs)	**Unadjusted**	**Model 1[a]**	**Model 2[b]**	**Unadjusted**	**Model 1[c]**	**Model 2[d]**	**Unadjusted**	**Model 1[a]**	**Model 2[b]**	**Unadjusted**	**Model 1[a]**	**Model 2[b]**
Full siblings (1,368)	0.33 (0.29 to 0.38)	0.27 (0.23 to 0.32)	0.29 (0.24 to 0.34)	0.00 (-0.04 to 0.05)	0.00 (-0.05 to 0.05)	0.01 (-0.05 to 0.06)	0.17 (0.07 to 0.26)	0.12 (0.02 to 0.22)	0.12 (0.01 to 0.23)	0.07 (0.01 to 0.12)	0.06 (0.00 to 0.12)	0.06 (0.00 to 0.12)
Maternal half-siblings (100)	0.08 (-0.10 to 0.25)	0.17 (0.00 to 0.34)	0.21 (0.03 to 0.39)	-0.04 (-0.22 to 0.14)	-0.01 (-0.19 to 0.17)	-0.02 (-0.21 to 0.18)	-0.07 (-0.50 to 0.35)	-0.12 (-0.54 to 0.31)	-0.15 (-0.58 to 0.28)	0.11 (-0.10 to 0.32)	0.13 (-0.08 to 0.34)	0.16 (-0.05 to 0.37)
Paternal half-siblings (52)	-0.01 (-0.23 to 0.22)	0.02 (-0.22 to 0.26)	0.01 (-0.24 to 0.25)	-0.03 (-0.27 to 0.20)	0.01 (-0.23 to 0.25)	0.00 (-0.25 to 0.26)	0.21 (-0.21 to 0.63)	0.16 (-0.27 to 0.59)	0.03 (-0.39 to 0.45)	0.00 (-0.27 to 0.27)	0.00 (-0.28 to 0.29)	0.01 (-0.29 to 0.30)

The baseline outcomes 'mammographic density', 'microcalcifications', and 'masses' were adjusted for:

Model 1[a]: age at mammmogram, menopausal status, BMI

Model 2[b]: age at mammmogram, menopausal status, BMI, hormone replacement therapy use, previous benign breast disorder, and reproductive history (parity x age at first birth)

The outcome 'mammographic density change/year' was adjusted for:

Model 1[c]: age at first mammogram, menopausal status, BMI, and age at last mammogram

Model 2[d]: age at first mammogram, menopausal status, BMI, age at last mammogram, hormone replacement therapy use, previous benign breast disorder, and reproductive history (parity x age at first birth)

Table 3. Model fitting from univariate analyses of mammographic density at baseline, mammographic density change/year, number of clusters of microcalcifications at baseline, and number of masses at baseline and among sisters in the KARMA cohort (N=3,880)

	AIC	-2LL	Diff-df	Diff-LL	p-value*
(log) Mammographic density (cm^2)					
Saturated Model	4715.58	12335.58	NA	NA	NA
ADE	4704.75	12346.75	11	11.17	0.429
ACE	4706.73	12348.73	11	13.15	0.283
AE	4705.00	12349.00	12	13.42	0.339
Model 1[a]	3648.50	11094.50	NA	NA	NA
ADE	3637.69	11105.69	11	11.19	0.427
ACE	3636.60	11104.60	11	10.10	0.521
AE[e]	3635.78	11105.78	12	11.28	0.505
Model 2[b]	3013.18	9415.18	NA	NA	NA
ADE	3006.60	9430.60	11	15.43	0.164
ACE	3005.03	9429.03	11	13.85	0.241
AE[e]	3004.62	9430.62	12	15.45	0.218
Mammographic density change (cm^2) /year					
Saturated Model	12037.19	19365.19	NA	NA	NA
ADE	12057.78	19407.78	11	42.59	<0.0001**
ACE	12057.80	19407.79	11	42.61	<0.0001**
AE	12055.80	19407.80	12	42.61	<0.0001**
Model 1[c]	11572.39	18650.39	NA	NA	NA
ADE	11599.97	18699.97	11	49.58	<0.0001
ACE	11599.97	18699.97	11	49.58	<0.0001
AE[e]	11597.97	18699.97	12	49.58	<0.0001
Model 2[d]	9989.49	16083.49	NA	NA	NA
ADE	10027.55	16143.55	11	60.05	<0.0001
ACE	10027.55	16143.55	11	60.05	<0.0001
AE[e]	10025.55	16143.55	12	60.05	<0.0001
Microcalcifications					
Saturated Model	-2915.06	4772.94	NA	NA	NA
ADE	-2927.35	4792.65	16	19.71	0.233
ACE	-2927.35	4792.65	16	19.71	0.233
AE	-2927.35	4792.65	17	19.71	0.289
Model 1[a]	-2950.34	4535.66	NA	NA	NA
ADE	-2962.50	4555.49	16	19.83	0.228
ACE	-2962.45	4555.55	16	19.89	0.225
AE[e]	-2964.45	4555.55	17	19.89	0.280
Model 2[b]	-2514.45	3927.55	NA	NA	NA
ADE	-2526.09	3947.90	16	20.36	0.205
ACE	-2525.83	3948.17	16	20.62	0.194
AE[e]	-2527.83	3948.17	17	20.62	0.244
Masses					
Saturated Model	2454.58	10142.58	NA	NA	NA
ADE	2432.02	10152.02	16	9.44	0.894
ACE	2431.57	10151.57	16	8.99	0.914
AE	2430.02	10152.02	17	9.44	0.925
Model 1[a]	2256.75	9742.75	NA	NA	NA
ADE	2230.67	9748.67	16	5.92	0.989
ACE	2230.18	9748.18	16	5.42	0.993
AE[e]	2228.67	9748.67	17	5.92	0.994
Model 2[b]	1965.69	8407.69	NA	NA	NA
ADE	1939.77	8413.77	16	6.07	0.987
ACE	1939.13	8413.13	16	5.43	0.993
AE[e]	1937.77	8413.77	17	6.07	0.9992

AIC- Akaike's information criteris; -2LL – minus 2 log-likelihood; Diff-df – difference in degrees of freedom; Diff-LL – difference in log-likelihood; p-value – testing whether each model if statistically significantly different from the saturated model

A- additive genetic factors; D – dominant genetic factors; C- shared environment; E - non-shared environmental factors

* p-value to test whether the nested model fits the data worse than the saturated model ($p < 0.05$ indicates a poorer fit)

** Given the statistically significant difference between the saturated model and the ADCE models for the outcome 'mammographic density change', we explored this in further detail. We found the issue to be among paternal half-siblings only, with further investigation revealing the difference between siblings to be in the variance and not the means. We tested whether re-randomisation of sibling order influenced the estimates from the ADCE models, and it did not (see Appendix 1 and 2)

[a] adjusted for: age at mammogram, menopausal status, BMI

[b] adjusted for: age at mammogram, menopausal status, BMI, hormone replacement therapy use, previous benign breast disorder, and reproductive history (parity x age at first birth)

[c] adjusted for: age at first mammogram, menopausal status, BMI, and age at last mammogram

[d] adjusted for: age at first mammogram, menopausal status, BMI, age at last mammogram, hormone replacement therapy use, previous benign breast disorder, and reproductive history (parity x age at first birth)

[e] The AE model was preferred, given that it has fewer parameters and did not fit the data statistically significantly worse than the ACE model

Table 4. Univariate estimates of additive genetic (A) and individual/non-shared environment (E) components[a] for mammographic density at baseline, mammographic density change/year, number of clusters of microcalcifications at baseline, and number of masses at baseline among sisters in the KARMA cohort (N=3,880). Estimates with 95% confidence intervals presented.

	Additive genetic (A)	**Individual/non-shared environment (E)**
(log) Mammographic density (cm^2)		
Unadjusted	0.66 (0.57 to 0.74)	0.34 (0.26 to 0.43)
Model 1 – age at mammogram, menopausal status, BMI	0.54 (0.46 to 0.63)	0.46 (0.37 to 0.54)
Model 2 –age at mammogram, menopausal status, BMI, HRT use, previous benign breast disorder, reproductive history	0.58 (0.48 to 0.67)	0.42 (0.33 to 0.52)
Mammographic density change (cm^2)/year		
Unadjusted	0.01 (-0.09 to 0.10)	0.99 (0.90 to 1.09)
Model 1 – age at first mammogram, menopausal status, BMI, age at last mammogram	0.00 (0.00 to 0.00)	1.00 (1.00 to 1.00)
Model 2 – age at first mammogram, menopausal status, BMI, age at last mammogram, reproductive history	0.02 (-0.08 to 0.12)	0.98 (0.88 to 1.08)
Microcalcifications		
Unadjusted	0.33 (0.15 to 0.52)	0.67 (0.48 to 0.85)
Model 1 – age at mammogram, menopausal status, BMI	0.24 (0.05 to 0.43)	0.76 (0.57 to 0.95)
Model 2 –age at mammogram, menopausal status, BMI, HRT use, previous benign breast disorder, reproductive history	0.23 (0.02 to 0.44)	0.77 (0.56 to 0.98)
Masses		
Unadjusted	0.14 (0.03 to 0.25)	0.86 (0.75 to 0.97)
Model 1 – age at mammogram, menopausal status, BMI	0.12 (0.01 to 0.24)	0.88 (0.76 to 0.99)
Model 2 –age at mammogram, menopausal status, BMI, HRT use, previous benign breast disorder, reproductive history	0.13 (0.01 to 0.25)	0.87 (0.75 to 0.99)

[a] For all outcomes, the AE model was the best fit for the data (See Table 3)

Wald standard errors and confidence intervals were used, allowing confidence bounds of variances to be lower than zero.

Table 5. Association between a genetic predisposition to breast cancer (measured using family history of breast cancer and polygenic risk score) and mammographic density at baseline, mammographic density change/year, number of clusters of microcalcifications at baseline, and number of masses at baseline among women who had information on family history of breast cancer and all four outcomes (N=49,674). The breast cancer polygenic risk score (PRS) sub-population includes 9,365 women. Odds ratios (OR) and beta coefficients (β) presented with 95% confidence intervals, with p-values provided for tests of linear trends.

	(log) Mammographic density (cm^2)		**Mammographic density change (cm^2)/yr**		**Microcalcifications**		**Masses**	
	Model 1[a] β (95% CI)	Model 2[a] β (95% CI)	Model 1[b] β (95% CI)	Model 2[b] β (95% CI)	Model 1[a] OR (95% CI)	Model 2[a] OR (95% CI)	Model 1[a] OR (95% CI)	Model 2[a] OR (95% CI)
Family history of breast cancer								
No	0.00 (Ref)	0.00 (Ref)	0.00 (Ref)	0.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Yes	0.07 (0.04 to 0.10)	0.07 (0.04 to 0.10)	-0.12 (-0.22 to -0.03)	-0.12 (-0.22 to -0.03)	1.14 (1.07 to 1.23)	1.14 (1.07 to 1.22)	0.99 (0.95 to 1.04)	1.00 (0.95 to 1.05)
Overall breast cancer PRS - percentiles								
0-20%	0.00 (Ref)	0.00 (Ref)	0.00 (Ref)	0.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
20-40%	-0.03 (-0.11 to 0.04)	-0.01 (-0.08 to 0.06)	-0.02 (-0.22 to 0.19)	0.03 (-0.17 to 0.22)	1.07 (0.90 to 1.26)	1.08 (0.91 to 1.28)	0.89 (0.79 to 0.99)	0.88 (0.78 to 0.98)
40-60%	0.04 (-0.03 to 0.12)	0.06 (-0.01 to 0.13)	-0.18 (-0.39 to 0.03)	-0.13 (-0.33 to 0.07)	1.19 (1.01 to 1.41)	1.20 (1.02 to 1.42)	0.92 (0.82 to 1.03)	0.90 (0.80 to 1.01)
60-80%	0.07 (-0.01 to 0.15)	0.09 (0.02 to 0.16)	-0.03 (-0.24 to 0.18)	-0.03 (-0.23 to 0.17)	1.28 (1.08 to 1.51)	1.29 (1.09 to 1.53)	1.02 (0.90 to 1.14)	0.99 (0.88 to 1.12)
80-100%	0.14 (0.06 to 0.21)	0.15 (0.08 to 0.23)	-0.17 (-0.39 to 0.05)	-0.13 (-0.34 to 0.08)	1.55 (1.31 to 1.84)	1.58 (1.33 to 1.87)	1.10 (0.98 to 1.25)	1.10 (0.97 to 1.24)
p-value linear	<0.0001	<0.0001	0.2300	0.2515	<0.0001	<0.0001	0.0337	0.0586
PRS (standardised continuous)								
	0.06 (0.03 to 0.08)	0.06 (0.04 to 0.08)	-0.05 (-0.11 to 0.02)	-0.05 (-0.12 to 0.01)	1.16 (1.10 to 1.22)	1.16 (1.10 to 1.23)	1.05 (1.01 to 1.09)	1.04 (1.00 to 1.08)
p-value linear	<0.0001	<0.0001	0.1624	0.1061	<0.0001	<0.0001	0.0170	0.0394

Model 1[a] - adjusted for age at mammogram Model 2[a]– Model 1 + adjusted for postmenopausal (no; yes), BMI, HRT status (former/non; current), previous benign breast disorder (no, yes), reproductive history (parity x age at first birth)
Model 1[b] - adjusted for sampling type and age at first mammogram Model 2[b]– Model 1 + adjusted for postmenopausal (no; yes), BMI, age at last mammogram

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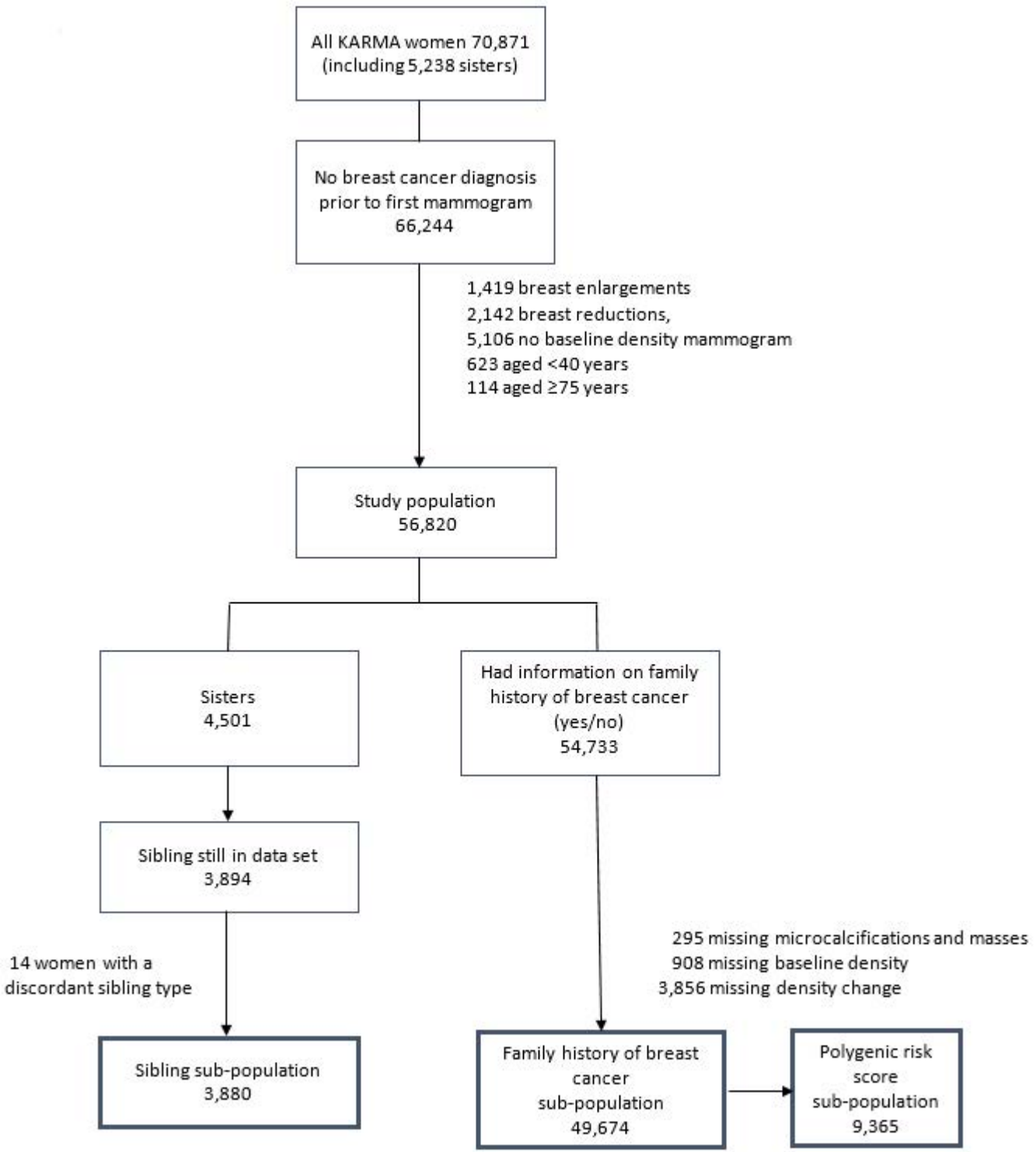
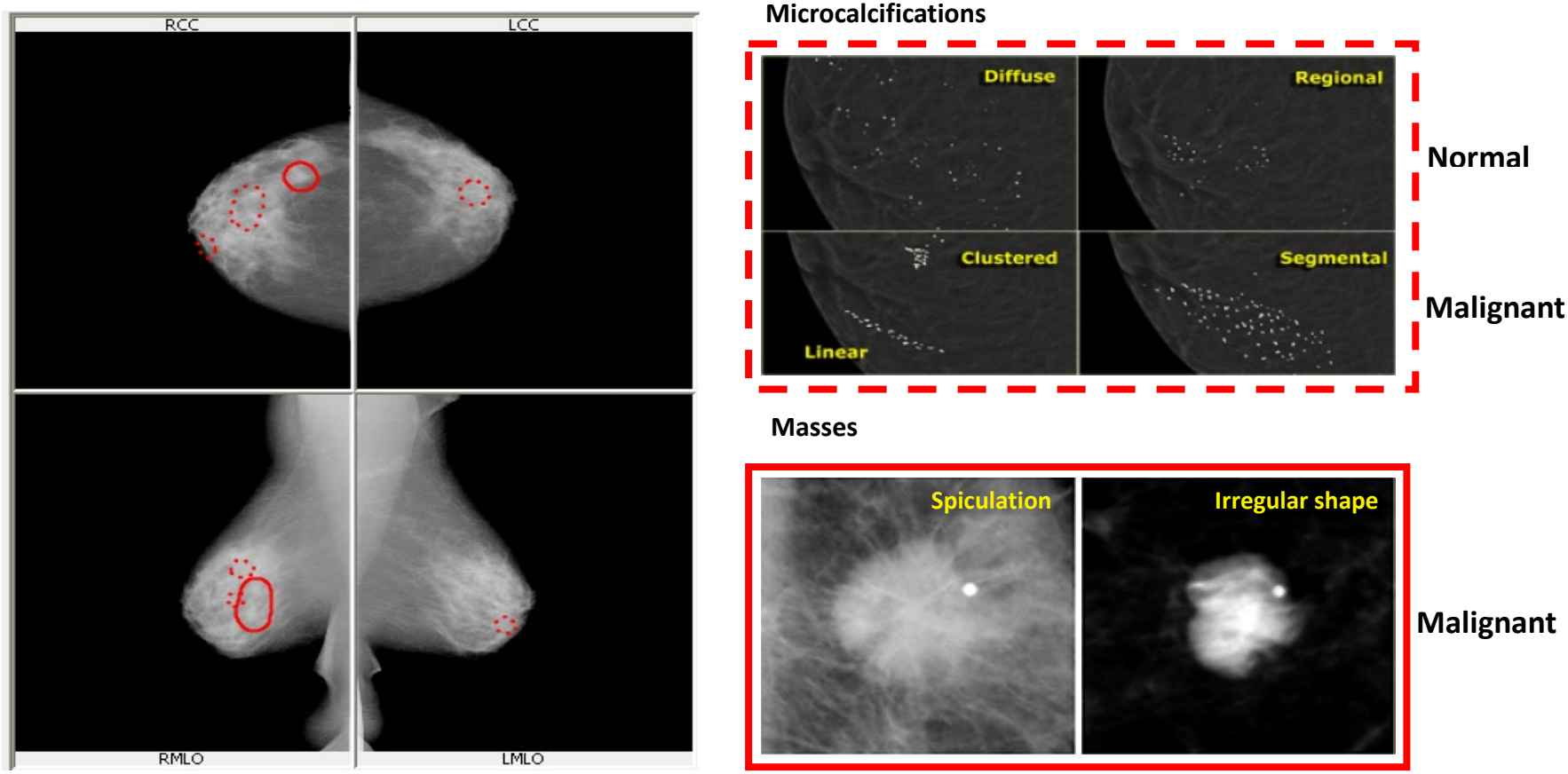


Figure 1. Sample attrition and study populations used for analyses

Supplementary Figure 1. Illustration of microcalcifications and masses within the breast



Supplementary Table 1. Model fitting from univariate analyses of baseline information on mammographic density at baseline, mammographic density change/year, number of clusters of microcalcifications at baseline, and number of masses at baseline among sisters in the KARMA cohort (N=3,880). Re-randomisation of siblings for all analyses due to issues with paternal half siblings having differing variances for the outcome 'mammographic density change'

	AIC	-2LL	Diff-df	Diff-LL	p-value*
(log) Mammographic density (cm^2)					
Saturated Model	4653.13	12197.13	NA	NA	NA
ADE	4646.09	12212.09	11	14.96	0.184
ACE	4648.19	12214.19	11	17.06	0.106
AE	4646.42	12214.42	12	17.29	0.139
Model 1[a]	3515.06	10697.06	NA	NA	NA
ADE	3505.46	10709.46	11	12.39	0.334
ACE	3504.59	10708.59	11	11.53	0.399
AE[e]	3503.68	10709.68	12	12.62	0.397
Model 2[b]	2891.67	9061.67	NA	NA	NA
ADE	2886.41	9078.41	11	16.73	0.116
ACE	2884.98	9076.98	11	15.31	0.169
AE[e]	2884.51	9078.51	12	16.84	0.156
Mammographic density change (cm^2) /year					
Saturated Model	12010.79	19344.79	NA	NA	NA
ADE	12022.95	19378.95	11	34.16	0.0003
ACE	12022.96	19378.96	11	34.17	0.0003
AE	12020.97	19378.97	12	34.18	0.0006
Model 1[c]	11370.78	18322.78	NA	NA	NA
ADE	11384.15	18358.15	11	35.37	0.0002
ACE	11384.15	18358.15	11	35.37	0.0002
AE[e]	11382.15	18358.15	12	35.37	0.0004
Model 2[d]	9799.22	15771.21	NA	NA	NA
ADE	9825.63	15819.63	11	48.41	<0.0001
ACE	9825.61	15819.61	11	48.39	<0.0001
AE[e]	9823.64	15819.64	12	48.42	<0.0001
Microcalcifications					
Saturated Model	-2800.37	4887.63	NA	NA	NA
ADE	-2754.12	4965.88	16	78.25	<0.0001
ACE	-2754.12	4965.88	16	78.25	<0.0001
AE	-2754.12	4965.88	17	78.25	<0.0001
Model 1[a]	-2916.99	4433.01	NA	NA	NA
ADE	-2926.98	4455.02	16	22.02	0.143
ACE	-2926.98	4455.02	16	22.02	0.143
AE[e]	-2928.98	4455.02	17	22.02	0.184
Model 2[b]	-2480.79	3829.21	NA	NA	NA
ADE	-2492.43	3849.57	16	20.36	0.204
ACE	-2492.43	3849.57	16	20.36	0.204
AE[e]	-2494.43	3849.57	17	20.36	0.256
Masses					
Saturated Model	2454.58	10142.58	NA	NA	NA
ADE	2432.02	10152.02	11	9.44	0.894
ACE	2431.57	10151.57	11	8.99	0.914
AE	2430.02	10152.02	12	9.44	0.925
Model 1[a]	2256.78	9742.75	NA	NA	NA
ADE	2230.67	9748.67	16	5.92	0.989
ACE	2230.17	9748.18	16	5.42	0.993
AE[e]	2228.67	9748.67	17	5.92	0.993
Model 2[b]	1965.69	8407.69	NA	NA	NA
ADE	1939.77	8413.77	16	6.07	0.987
ACE	1939.13	8413.13	16	5.44	0.993
AE[e]	1937.77	8413.77	17	6.07	0.992

AIC- Akaike's information criteris; -2LL – minus 2 log-likelihood; Diff-df – difference in degrees of freedom; Diff-LL – difference in log-likelihood; p-value – testing whether each model if statistically significantly different from the saturated model

A- additive genetic factors; D – dominant genetic; C- shared environment; E - non-shared environmental factors

* p-value to test whether the nested model fits the data worse than the saturated model ($p < 0.05$ indicates a poorer fit)

[a] adjusted for: age at mammogram, menopausal status, BMI

[b] adjusted for: age at mammogram, menopausal status, BMI, hormone replacement therapy use, previous benign breast disorder, and reproductive history (parity x age at first birth)

[c] adjusted for: age at first mammogram, menopausal status, BMI, and age at last mammogram

[d] adjusted for: age at first mammogram, menopausal status, BMI, age at last mammogram, hormone replacement therapy use, previous benign breast disorder, and reproductive history (parity x age at first birth)

[e] The AE model was preferred, given that it has fewer parameters and did not fit the data statistically significantly worse than the ACE model (result not shown)

Supplementary Table 2. Univariate estimates of additive genetic (A), shared environment (C), and individual/non-shared environment (E) components mammographic density at baseline, mammographic density change/year, number of clusters of microcalcifications at baseline, and number of masses at baseline among sisters in the KARMA cohort (N=3,880). Estimates with 95% confidence intervals presented. Re-randomisation of siblings for all analyses due to issues with paternal half siblings having differing variances for the outcome 'mammographic density change'

	Additive genetic (A)	**Individual/non-shared environment (E)**
(log) Mammographic density (cm^2)[a]		
Unadjusted	0.65 (0.57 to 0.74)	0.35 (0.26 to 0.43)
Model 1 – age at mammogram, menopausal status, BMI	0.55 (0.46 to 0.64)	0.45 (0.36 to 0.54)
Model 2 –age at mammogram, menopausal status, BMI, HRT use, previous benign breast disorder, reproductive history	0.58 (0.49 to 0.68)	0.42 (0.32 to 0.51)
Mammographic density change (cm^2)/year[a]		
Unadjusted	0.01 (-0.09 to 0.10)	0.99 (0.90 to 1.09)
Model 1 – age at first mammogram, menopausal status, BMI, age at last mammogram	0.00 (0.00 to 0.00)	1.00 (1.00 to 1.00)
Model 2 – age at first mammogram, menopausal status, BMI, age at last mammogram, reproductive history	0.01 (-0.08 to 0.11)	0.99 (0.89 to 1.08)
Microcalcifications[b]		
Unadjusted	0.43 (0.24 to 0.61)	0.57 (0.39 to 0.76)
Model 1 – age at mammogram, menopausal status, BMI	0.25 (0.06 to 0.44)	0.75 (0.56 to 0.94)
Model 2 –age at mammogram, menopausal status, BMI, HRT use, previous benign breast disorder, reproductive history	0.24 (0.03 to 0.45)	0.76 (0.55 to 0.97)
Masses[a]		
Unadjusted	0.14 (0.03 to 0.25)	0.86 (0.75 to 0.97)
Model 1 – age at mammogram, menopausal status, BMI	0.12 (0.01 to 0.24)	0.88 (0.76 to 0.99)
Model 2 –age at mammogram, menopausal status, BMI, HRT use, previous benign breast disorder, reproductive history	0.13 (0.01 to 0.25)	0.87 (0.75 to 0.99)

[a] the AE model was the best fit for the data [b]the ACE model was the best fit for the data

Wald standard errors and confidence intervals were used, allowing confidence bounds of variances to be lower than zero.

Supplementary Table 3. Univariate estimates of additive genetic (A) and individual/non-shared environment (E) components[a] for mammographic % density at baseline among sisters in the KARMA cohort (N=3,880). Estimates with 95% confidence intervals presented.

	Additive genetic (A)	**Individual/non-shared environment (E)**
(log) Mammographic density (%)		
Unadjusted	0.68 (0.59 to 0.76)	0.32 (0.24 to 0.41)
Model 1 – age at mammogram, menopausal status, BMI	0.54 (0.45 to 0.63)	0.46 (0.37 to 0.55)
Model 2 –age at mammogram, menopausal status, BMI, HRT use, previous benign breast disorder, reproductive history	0.57 (0.47 to 0.67)	0.43 (0.33 to 0.53)

[a] For all outcomes, the AE model was the best fit for the data

Wald standard errors and confidence intervals were used, allowing confidence bounds of variances to be lower than zero.

Supplementary Table 4. Univariate estimates of additive genetic (A), shared environment (C), and individual/non-shared environment (E) components mammographic density at baseline, mammographic density change/year, number of clusters of microcalcifications at baseline, and number of masses at baseline among sisters in the KARMA cohort who did not develop a breast cancer during follow-up (N=3,746). Estimates with 95% confidence intervals presented.

	Additive genetic (A)	**Individual/non-shared environment (E)**
(log) Mammographic density (cm^2)[a]		
Unadjusted	0.66 (0.58 to 0.75)	0.34 (0.25 to 0.42)
Model 1 – age at mammogram, menopausal status, BMI	0.55 (0.46 to 0.64)	0.45 (0.36 to 0.54)
Model 2 –age at mammogram, menopausal status, BMI, HRT use, previous benign breast disorder, reproductive history	0.58 (0.49 to 0.68)	0.42 (0.32 to 0.51)
Mammographic density change (cm^2)/year[a]		
Unadjusted	0.02 (-0.07 to 0.12)	0.98 (0.88 to 1.07)
Model 1 – age at first mammogram, menopausal status, BMI, age at last mammogram	0.01 (-0.09 to 0.11)	0.99 (0.89 to 1.09)
Model 2 – age at first mammogram, menopausal status, BMI, age at last mammogram, reproductive history	0.04 (-0.07 to 0.14)	0.96 (0.86 to 1.07)
Microcalcifications[b]		
Unadjusted	0.37 (0.18 to 0.55)	0.63 (0.45 to 0.82)
Model 1 – age at mammogram, menopausal status, BMI	0.27 (0.08 to 0.47)	0.73 (0.53 to 0.92)
Model 2 –age at mammogram, menopausal status, BMI, HRT use, previous benign breast disorder, reproductive history	0.27 (0.05 to 0.48)	0.73 (0.52 to 0.95)
Masses[a]		
Unadjusted	0.14 (0.03 to 0.25)	0.86 (0.75 to 0.97)
Model 1 – age at mammogram, menopausal status, BMI	0.12 (0.01 to 0.23)	0.88 (0.77 to 0.99)
Model 2 –age at mammogram, menopausal status, BMI, HRT use, previous benign breast disorder, reproductive history	0.12 (0.00 to 0.24)	0.88 (0.76 to 1.00)

[a] the AE model was the best fit for the data [b]the ACE model was the best fit for the data

Wald standard errors and confidence intervals were used, allowing confidence bounds of variances to be lower than zero.

Supplementary Table 5. Association between a genetic predisposition to breast cancer (measured using family history of breast cancer and polygenic risk score) and percent mammographic density at baseline among women who had information on family history of breast cancer and all four outcomes (N=49,674). The breast cancer polygenic risk score (PRS) sub-population includes 9,365 women. Odds ratios (OR) and beta coefficients (β) presented with 95% confidence intervals, with p-values provided for tests of linear trends.

	(log) Mammographic density (%)	
	Model 1[a] β (95% CI)	Model 2[a] β (95% CI)
Family history of breast cancer		
No	0.00 (Ref)	0.00 (Ref)
Yes	0.08 (0.04 to 0.11)	0.08 (0.05 to 0.11)
Overall breast cancer PRS - percentiles		
0-20%	0.00 (Ref)	0.00 (Ref)
20-40%	-0.05 (-0.13 to 0.03)	-0.01 (-0.08 to 0.06)
40-60%	0.02 (-0.07 to 0.10)	0.05 (-0.03 to 0.12)
60-80%	0.05 (-0.03 to 0.14)	0.08 (0.01 to 0.15)
80-100%	0.12 (0.03 to 0.21)	0.14 (0.07 to 0.22)
p-value linear	0.0001	0.0001
PRS (standardised continuous)	0.05 (0.03 to 0.08)	0.05 (0.03 to 0.08)
p-value linear	0.0002	<0.0001

Model 1[a] - adjusted for age at mammogram
Model 2[a]– Model 1 + adjusted for postmenopausal (no; yes), BMI, HRT status (former/non; current), previous benign breast disorder (no, yes), reproductive history (parity x age at first birth)

Supplementary Table 6. Association between a genetic predisposition to breast cancer (measured using family history of breast cancer and polygenic risk score) and mammographic density at baseline, mammographic density change/year, number of clusters of microcalcifications at baseline, and number of masses at baseline among women who did not go on to develop breast cancer, who also had information on family history of breast cancer and all four outcomes (N=48,654). The breast cancer polygenic risk score (PRS) sub-population includes 8,765 women. Odds ratios (OR) and beta coefficients (β) presented with 95% confidence intervals, with p-values provided for tests of linear trends.

	(log) Mammographic density (cm^2)		**Mammographic density change (cm^2)/yr**		**Microcalcifications**		**Masses**	
	Model 1[a] β (95% CI)	Model 2[a] β (95% CI)	Model 1[b] β (95% CI)	Model 2[b] β (95% CI)	Model 1[a] OR (95% CI)	Model 2[a] OR (95% CI)	Model 1[a] OR (95% CI)	Model 2[a] OR (95% CI)
Family history of breast cancer								
No	0.00 (Ref)	0.00 (Ref)	0.00 (Ref)	0.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Yes	0.07 (0.04 to 0.10)	0.07 (0.04 to 0.10)	-0.12 (-0.22 to -0.03)	-0.12 (-0.22 to -0.02)	1.14 (1.06 to 1.22)	1.14 (1.06 to 1.22)	0.99 (0.94 to 1.04)	0.99 (0.95 to 1.04)
Overall breast cancer PRS -percentiles								
0-20%	0.00 (Ref)	0.00 (Ref)	0.00 (Ref)	0.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
20-40%	-0.04 (-0.12 to 0.03)	-0.02 (-0.09 to 0.05)	-0.02 (-0.22 to 0.18)	0.03 (-0.16 to 0.22)	1.05 (0.88 to 1.25)	1.06 (0.89 to 1.27)	0.88 (0.78 to 0.99)	0.87 (0.77 to 0.98)
40-60%	0.03 (-0.05 to 0.11)	0.05 (-0.02 to 0.12)	-0.19 (-0.39 to 0.02)	-0.14 (-0.34 to 0.05)	1.16 (0.97 to 1.38)	1.17 (0.98 to 1.39)	0.89 (0.79 to 1.00)	0.87 (0.77 to 0.98)
60-80%	0.06 (-0.02 to 0.14)	0.07 (-0.01 to 0.14)	0.03 (-0.17 to 0.24)	0.06 (-0.14 to 0.26)	1.22 (1.02 to 1.46)	1.23 (1.03 to 1.47)	0.99 (0.88 to 1.12)	0.98 (0.86 to 1.10)
80-100%	0.12 (0.04 to 0.21)	0.13 (0.06 to 0.21)	-0.07 (-0.29 to 0.15)	-0.01 (-0.22 to 0.21)	1.48 (1.23 to 1.77)	1.49 (1.24 to 1.79)	1.03 (0.90 to 1.17)	1.02 (0.89 to 1.16)
p-value linear	<0.0001	<0.0001	0.9729	0.9044	<0.0001	<0.0001	0.3541	0.4384
PRS (Standardised continuous)								
	0.05 (0.03 to 0.08)	0.05 (0.03 to 0.08)	-0.01 (-0.07 to 0.06)	-0.01 (-0.07 to 0.06)	1.13 (1.06 to 1.19)	1.13 (1.07 to 1.20)	1.03 (0.99 to 1.07)	1.02 (0.98 to 1.06)
p-value linear	<0.0001	<0.0001	0.9487	0.8205	<0.0001	<0.0001	0.2271	0.3443

Model 1[a] - adjusted for age at mammogram

Model 2[a]– Model 1 + adjusted for postmenopausal (no; yes), BMI, HRT status (former/non; current), previous benign breast disorder (no, yes), reproductive history (parity x age at first birth)

Model 1[b] - adjusted for sampling type and age at first mammogram

Model 2[b]– Model 1 + adjusted for postmenopausal (no; yes), BMI, age at last mammogram

Supplementary Table 7. Association between a genetic predisposition to breast cancer (separately measured using estrogen receptor negative and positive polygenic risk scores (PRS)) and mammographic density at baseline, mammographic density change/year, number of clusters of microcalcifications at baseline, and number of masses at baseline among women without breast cancer, who had information a polygenic risk score calculated (N=8,765). Odds ratios (OR) and beta coefficients (β) presented with 95% confidence intervals, with p-values provided for tests of linear trends.

	(log) Mammographic density (cm^2)		**Mammographic density change (cm^2)/yr**		**Microcalcifications**		**Masses**	
	Model 1[a] β (95% CI)	Model 2[a] β (95% CI)	Model 1[b] β (95% CI)	Model 2[b] β (95% CI)	Model 1[a] OR (95% CI)	Model 2[a] OR (95% CI)	Model 1[a] OR (95% CI)	Model 2[a] OR (95% CI)
Estrogen Receptor Positive PRS - percentiles								
0-20%	0.00 (Ref)	0.00 (Ref)	0.00 (Ref)	0.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
20-40%	-0.04 (-0.12 to 0.03)	-0.01 (-0.08 to 0.06)	-0.14 (-0.34 to 0.06)	-0.11 (-0.30 to 0.09)	1.05 (0.88 to 1.24)	1.06 (0.89 to 1.25)	0.92 (0.82 to 1.03)	0.89 (0.79 to 1.01)
40-60%	0.03 (-0.04 to 0.11)	0.07 (0.01 to 0.14)	-0.11 (-0.32 to 0.09)	-0.11 (-0.31 to 0.09)	1.16 (0.98 to 1.37)	1.17 (0.99 to 1.39)	0.93 (0.83 to 1.05)	0.90 (0.80 to 1.01)
60-80%	0.08 (0.01 to 0.15)	0.10 (0.03 to 0.17)	-0.03 (-0.24 to 0.17)	-0.03 (-0.24 to 0.17)	1.23 (1.04 to 1.46)	1.24 (1.05 to 1.47)	1.05 (0.93 to 1.18)	1.03 (0.91 to 1.16)
80-100%	0.11 (0.03 to 0.19)	0.14 (0.06 to 0.21)	-0.22 (-0.44 to -0.01)	-0.20 (-0.41 to 0.01)	1.51 (1.27 to 1.79)	1.54 (1.29 to 1.82)	1.11 (0.98 to 1.26)	1.10 (0.97 to 1.24)
p-value linear	0.0002	0.0001	0.486	0.522	<0.0001	<0.0001	0.021	0.0425
PRS (Standardised continuous)								
	0.05 (0.03 to 0.07)	0.05 (0.03 to 0.08)	-0.04 (-0.11 to 0.02)	-0.05 (-0.11 to 0.01)	1.15 (1.09 to 1.21)	1.16 (1.09 to 1.22)	1.05 (1.01 to 1.09)	1.04 (1.00 to 1.08)
p-value linear	<0.0001	<0.0001	0.2017	0.1273	<0.0001	<0.0001	0.0162	0.0405
Estrogen Receptor Negative PRS - percentiles								
0-20%	0.00 (Ref)	0.00 (Ref)	0.00 (Ref)	0.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
20-40%	0.09 (0.02 to 0.17)	0.08 (0.01 to 0.15)	-0.10 (-0.31 to 0.11)	-0.08 (-0.28 to 0.12)	1.10 (0.93 to 1.30)	1.11 (0.93 to 1.31)	0.96 (0.85 to 1.08)	0.97 (0.86 to 1.09)
40-60%	0.06 (-0.02 to 0.13)	0.03 (-0.04 to 0.10)	-0.08 (-0.29 to 0.13)	-0.03 (-0.23 to 0.17)	1.19 (1.01 to 1.41)	1.19 (1.01 to 1.41)	0.95 (0.85 to 1.07)	0.96 (0.85 to 1.08)
60-80%	0.13 (0.06 to 0.21)	0.14 (0.07 to 0.22)	-0.17 (-0.38 to 0.05)	-0.10 (-0.30 to 0.10)	1.34 (1.13 to 1.59)	1.34 (1.13 to 1.59)	1.02 (0.90 to 1.15)	1.01 (0.89 to 1.14)
80-100%	0.24 (0.16 to 0.31)	0.23 (0.16 to 0.30)	-0.20 (-0.41 to 0.02)	-0.15 (-0.36 to 0.05)	1.41 (1.19 to 1.67)	1.42 (1.20 to 1.69)	1.11 (0.98 to 1.25)	1.11 (0.98 to 1.25)
p-value linear	<0.0001	<0.0001	0.4413	0.3842	<0.0001	<0.0001	0.0788	0.1016
PRS (Standardised continuous)								
	0.08 (0.05 to 0.10)	0.08 (0.05 to 0.10)	-0.04 (-0.11 to 0.02)	-0.04 (-0.11 to 0.02)	1.13 (1.08 to 1.20)	1.14 (1.08 to 1.20)	1.04 (0.99 to 1.08)	1.03 (0.99 to 1.07)
p-value linear	<0.0001	<0.0001	0.2037	0.1859	<0.0001	<0.0001	0.0693	0.0963

Model 1[a] - adjusted for age at mammogram
Model 2[a]– Model 1 + adjusted for postmenopausal (no; yes), BMI, HRT status (former/non; current), previous benign breast disorder (no, yes), reproductive history (parity x age at first birth)
Model 1[b] - adjusted for sampling type and age at first mammogram
Model 2[b]– Model 1 + adjusted for postmenopausal (no; yes), BMI, age at last mammogram