Volumetric mammographic density: heritability and association with breast cancer susceptibility loci

Judith S. Brand [1], Keith Humphreys [1], Deborah J. Thompson [2], Jingmei Li [3], Mikael Eriksson [1], Per Hall [1], Kamila Czene [1]

[1] Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden.

[2] Department of Public Health and Primary Care, Centre for Cancer Genetic Epidemiology, Cambridge, United Kingdom.

[3] Human Genetics, Genome Institute of Singapore, Singapore, Singapore.

***Corresponding author:**

Judith S. Brand

Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Nobels Väg 12A, 171 77 Stockholm, Sweden.

Email: judith.brand@ki.se; Phone: 0046-8-524-82352; Fax: 0046-8-31 49 75

Key words: volumetric mammographic density, heritability and breast cancer susceptibility loci

Word count: 250 (abstract); 3245 (text excluding abstract)

Tables: 3

References: 50

ABSTRACT

Background: Mammographic density is a strong heritable trait, but data on its genetic component are limited to area-based and qualitative measures. We studied the heritability of volumetric mammographic density ascertained by a fully-automated method and the association with breast cancer susceptibility loci.

Methods: Heritability of volumetric mammographic density was estimated with a variance component model in a sib-pair sample (N pairs = 955) of a Swedish screening based cohort. Associations with 82 established breast cancer loci were assessed in an independent sample of the same cohort (N = 4,025 unrelated women) using linear models, adjusting for age, body mass index and menopausal status. All tests were two-sided, except for heritability analyses where one-sided tests were used.

Results: After multivariable adjustment, heritability estimates (standard error) for percent dense volume, absolute dense volume and absolute nondense volume were 0.63 (0.06) and 0.43 (0.06) and 0.61 (0.06) respectively (all $P < 0.001$). Percent and absolute dense volume were associated with rs10995190 (*ZNF365*; $P = 9.0 \times 10^{-6}$ and 8.9×10^{-7} respectively) and rs9485372 (*TAB2*; $P = 1.8 \times 10^{-5}$ and 1.8×10^{-3} respectively). We also observed associations of rs9383938 (*ESR1*) and rs2046210 (*ESR1*) with the absolute dense volume ($P = 2.6 \times 10^{-4}$ and 4.6×10^{-4} respectively), and rs6001930 (*MLK1*) and rs17356907 (*NTN4*) with the absolute nondense volume ($P = 6.7 \times 10^{-6}$ and 8.4×10^{-5} respectively).

Conclusions: Our results support the high heritability of mammographic density, though estimates are weaker for absolute than percent dense volume. We also demonstrate that the shared genetic component with breast cancer is not restricted to dense tissues only.

INTRODUCTION

Mammographic density which reflects the amount of fibroglandular or radio-dense tissue in the breast is a strong determinant of breast cancer risk (1). Although the exact mechanisms underlying the association between mammographic density and breast cancer are not completely understood, both traits share several risk factors including nulliparity, late age at first birth and hormone replacement therapy (HRT) (2,3). Apart from an overlap in environmental risk factors, there is also evidence of a shared genetic basis. Twin studies estimate that approximately 60% of the variation in mammographic density is genetically determined (4,5) and the polygenic mode of inheritance suggests that both traits share a large number of genetic variants (6). To date, five single nucleotide polymorphisms (SNPs) which have been reported to be associated with mammographic density [rs10995190 in *ZNF365*, rs2046210 at 6q25 near *ESR1* (7), rs3817198 in *LSP1*, rs10483813 in *RAD51L1* (8), rs13281615 at 8q24 (9)] had previously been identified as breast cancer susceptibility SNPs, whilst only one SNP [rs1265507 at 12q24 (10)] has been reported as being associated with mammographic density but not with breast cancer. Last year, 41 new breast cancer loci were discovered in a large collaborative effort (11), enlarging the pool of candidate SNPs for further analysis of mammographic density.

Thus far, all studies investigating the genetic basis of mammographic density have used either qualitative or semi-automated area-based measures (4,5,12-16). The main disadvantage of these measures is that they are reader-dependent and do not acknowledge the 3D structure of the breast. Fully-automated measures of volumetric mammographic density may provide more accurate measures as they incorporate information on breast thickness (17,18). Studies comparing volumetric to area-based measures show good agreement for percent mammographic density, but the correlation for the absolute dense tissue is weak (19-23). These data underscore the notion that both methods measure different aspects of the same underlying entity.

In the present study, we aimed to estimate the heritability of volumetric mammographic density and to explore the shared genetic component with breast cancer by analyzing associations with established breast cancer susceptibility loci.

METHODS

Study population

The KARolinska MAmmography project for risk prediction of breast cancer (KARMA) is a prospective cohort study initiated in January 2011 and comprises 70,866 women attending mammography screening or clinical mammography at four hospitals in Sweden (24). Upon study entry, participants responded to a web-based questionnaire, donated blood and gave permission for storage of raw full field digital mammograms.

We used two study populations to address our research questions. We used a sib-pair design for the heritability analysis including all full and half-sib pairs in KARMA. Since all women in Sweden have a unique national registration number, sister-relations can be retrieved through the Multiple Generation Register. We only considered female blood relatives for this analysis and excluded twins as their number was too small for having a meaningful contribution. We selected a separate independent sample for the breast cancer SNP analysis including unrelated women who were genotyped using the custom Illumina iSelect genotyping array (iCOGS, details described below).

The same selection criteria were applied to both samples. We included all women with raw digital mammograms who were in the age range for mammography screening in Sweden (40-74 years). We excluded women who had previous cancers other than non-melanoma skin cancer, women with breast enlargements/reductions/surgery and participants who were pregnant in the twelve months prior to study entry. We further excluded women with incomplete questionnaire data and missing information on age, BMI and menopausal status, as well as sisters with incomplete covariate data. This resulted in a study population of 955 sib-pairs (908 full-sib and 47 half-sib pairs) for the

heritability analysis and 4,025 unrelated women for the breast cancer SNP analysis. The study was approved by the ethical review committee at Karolinska Institutet and all participants provided written informed consent.

Mammographic density measures

Mammographic density was measured from the medio-lateral oblique (MLO) view using a fully automated volumetric method (Volpara^{TM}, version 1.4.3). Technical details of the software have been described elsewhere (17). In brief, the algorithm computes the thickness of dense tissue at each pixel using the X-ray attenuation of an entirely fatty region as an internal reference. The absolute dense volume (cm^3) is measured by integrating the dense thickness at each pixel over the whole mammogram and the total breast volume (cm^3) is derived by multiplying the breast area by the recorded breast thickness, with an appropriate correction for the breast edge. Percent dense volume (%) is obtained from the ratio of these two measures, and the absolute nondense volume (cm^3) from subtracting the absolute dense volume from the total breast volume.

Volpara has been validated against breast magnetic resonance imaging (MRI) data and the method appears to be robust to changes in imaging conditions (17). Moreover, we have recently shown that Volpara performs well in a high-throughput setting with both percent and absolute dense volume being associated with established density determinants and breast cancer risk (25).

Covariates

Participants filled out a detailed web-based questionnaire including information on reproductive history, use of hormone replacement therapy (HRT) and previous benign breast disease. Menopausal status was defined according to information on menstruation status, previous oophorectomy and age at study entry. Postmenopausal women were defined as those who had no periods during the last year, a history of oophorectomy, or age 55 or older. Women were considered premenopausal when they reported having periods during the past 3 months or age < 46 years if they had missing data on

menstruation status. Body mass index (BMI) was calculated based on self-reported height and weight. We also collected information on body size at age 7 and 18 years by means of a nine-level somatotype, a method that has previously been validated against BMI data (26).

Genotyped and imputed SNP data

Genotyping was performed using the iCOGS array. This array comprises 211,155 SNPs which were primarily selected for replication of loci putatively associated with breast, ovarian or prostate cancer (11). Standard SNP quality control was performed in Plink (version 1.07) (27) and SNPs with call rates < 95% and/or deviation from Hardy–Weinberg equilibrium (HWE) at $P < 1x10^{-5}$ were excluded.
For the breast cancer SNP analysis, we considered all common variants linked to breast cancer at a genome-wide significance level ($P < 5 \times 10^{-8}$) in COGS (11,28) or previous genome-wide association studies (GWAS) as identified through the GWAS catalog (29). We also included SNPs that were identified in recent fine-mapping studies of the TERT and 11q13 regions (30,31). In total 82 established breast cancer SNPs were identified. All variants were genotyped directly, except for 6 (rs11242675, rs2180341, rs9485372, rs11814448, rs2284378 and rs13393577) which were imputed using IMPUTE v2 using the 1000 Genomes Project March 2012 release as a reference.
(32). All imputed SNPs passed quality control (INFO-score > 0.80).

Statistical analysis

All mammographic measures were log-transformed prior to analyses to approximate the normal distribution. We first estimated full and half sib-pair correlations by calculating intra-class correlation coefficients (ICCs) between the residuals of each mammographic measure. Three models were used to study the influence of potential confounders. We started with a model adjusting for age and menopausal status, after which BMI was added in a second model. Age at menarche, HRT, history of benign breast disease, parity and age at first birth were then added to the final multivariable adjusted model. We also performed a sensitivity analysis with additional adjustment for height and

body size at age 7 and 18 years. Previous studies have shown that adjustment for all relevant covariates is important, not only to account for potential overestimation of genetic influences by shared environmental factors, but also to reduce noise as covariates can influence the variability of the trait (16).

Heritability was estimated by fitting variance-component models as implemented in the Sequential Oligogenic Linkage Analysis Routines package (SOLAR, version 7.2.5.) (33,34). This approach is based on maximum likelihood estimation of a linear mixed-effects model incorporating fixed covariate effects, additive genetic effects and residual error. According to this model, each mammographic value P_i for individual *i* can be written as a linear function of the following form:

$$P_i = \mu + \sum_{j=1}^{M} \beta_j v_{ij} + g_i + e_i$$

where μ is the overall mean and β_j is the regression coefficient of the *j*th individual specific covariate which takes value v_{ij} for the *i*th individual. The values of g_i and e_i represent deviations from μ that are due to additive genetic effects and residual error respectively, and are assumed to be independently normally distributed. Heritability (h^2) in this case is narrow sense heritability, defined as the ratio of the variance of the additive genetic effects to the total (residual) variance in mammographic density.

Breast cancer SNP analyses were performed using tests for genotype trend effects in linear regression models with mammographic density as outcome and adjusting for age, BMI and menopausal status. For imputed SNPs, allele dosages were used in place of genotype calls. We also estimated the proportion of variance explained by all breast cancer SNPs.

Statistical tests for heritability were necessarily one-sided (H1: ICC > 0 and H1: $h^2 > 0$), while tests for breast cancer SNP associations were all two-sided. A Bonferroni correction was applied in the breast cancer SNP analysis to account for multiple testing with the threshold of statistical significance being defined as $P = 6.10 \times 10^{-4}$ (= 0.05 divided by 82). We also calculated a more conservative threshold of

$P = 2.03 \times 10^{-4}$ [0.05 / (82 x 3)] based on further correction for the three different (albeit) related outcomes and we carefully interpreted SNPs with P values between 6.10×10^{-4} and 2.03×10^{-4}.

RESULTS

Participant characteristics are summarized in **Table 1.** Both populations had a mean age at study entry of 54 years and a mean BMI of 25 kg/m^2. Geometric means (95% CI) of percent dense volume, absolute dense volume and absolute nondense volume were 7.8 (4.5-11.2), 57 (54-60) and 662 (658-666) respectively in the KARMA sisters. The corresponding values were 8.4 (5.1-11.7), 60 (57-63) and 646 (642-649) in the sample of unrelated women with SNP data. The majority of KARMA sisters were full-sisters, with only a small proportion being half-sib (4.9%).

Sister-pair correlations and heritability of volumetric mammographic density

Overall, sib-pair correlations were stronger for percent than absolute dense volume. In full sisters, age and menopause adjusted ICCs (SE) for percent dense volume and absolute dense volume were 0.30 (0.03) and 0.21 (0.03) respectively (all $P < 0.001$). The full-sib correlation for the absolute nondense volume was similar to the ICC for percent dense volume [0.31 (0.03)]. Adjustment for BMI and other covariates did not influence the sib-pair correlations **(Table 2)**. Although ICCs were less precise in half-sibs due to the small number of pairs, the multivariable adjusted ICC (SE) for percent dense volume [0.16 (0.14)] and absolute dense volume [0.11 (SE 0.14)] were approximately half of those found in full-sibs. Heritability analyses showed similar results, with stronger heritability estimates for percent than absolute dense volume. After multivariable adjustment heritability estimates (SE) for percent dense volume, absolute dense volume and absolute nondense volume were 0.63 (0.06), 0.43 (0.06) and 0.61 (0.06) respectively **(Table 2)**. Results remained unchanged after additional adjustment for height and body size at age 7 and 18 years (data not shown).

Associations with established breast cancer susceptibility loci

Results from the breast cancer SNP analysis are shown in **Table 3**. Four breast cancer SNPs were found to be associated with volumetric mammographic density. The strongest association was observed for rs10995190 in the *ZNF365* gene, with betas (SE) per minor allele increase being -0.05 (0.01) for percent dense volume ($P = 9.0 \times 10^{-6}$) and -0.07 (0.01) for absolute dense volume ($P = 8.9 \times 10^{-7}$). We also found associations of rs9485372 in the *TAB2* gene with percent dense volume ($P = 1.8 \times 10^{-5}$) and absolute dense volume ($P = 1.8 \times 10^{-3}$), although the latter association was not statistically significant. The corresponding betas (SE) per minor allele increase were -0.09 (0.02) and -0.08 (0.03) respectively. Furthermore, two SNPs (rs9383938 in the *ESR1* gene and rs2046210 upstream of *ESR1*) were associated with the absolute dense volume, but not with percent dense volume: beta (SE) per minor allele increase = 0.07 (0.02) for rs9383938 ($P = 2.6 \times 10^{-4}$) and 0.04 (0.01) for rs2046210 ($P = 4.6 \times 10^{-4}$).

We also explored associations with the absolute nondense volume and found associations with rs6001930 in the *MKL1* gene ($P = 6.7 \times 10^{-6}$) and rs17356907 near the *NTN4* ($P = 8.4 \times 10^{-5}$).

All breast cancer SNP associations exceeded the primary and more conservative *P* value threshold, except for rs9383938 and rs2046210 which were only statistically significant at the primary *P* value threshold.

When fitted together, the established breast cancer SNPs explained 4.3% of the variance in absolute dense volume. This percentage was lower for percent dense volume and the absolute nondense volume (2.2% and 1.6% respectively).

DISCUSSION

We observed high heritability values for volumetric mammographic density, though estimates were weaker for absolute than percent dense volume. We could replicate previously observed associations of rs10995190 (*ZNF365*) and rs2046210 (*ESR1*) with mammographic density, and identified novel associations with breast cancer SNPs in 6q25: rs9485372 (*TAB2)* and rs9383938 (*ESR1)*. We also found evidence of breast cancer SNP associations with the absolute nondense volume: rs6001930 (*MKL1*) and rs17356907 (*NTN4*).

Previous studies using area-based mammographic measures (4,5,12,14,16,35) have shown comparable estimates for percent and absolute mammographic density. In the Sisters in Breast Screening Study (SIBS) h^2 values of 0.63 and 0.66 were observed for percent and absolute dense area respectively (35). In our study using volumetric measures, we found a similar heritability estimate for percent dense volume (h^2 = 0.63), but a weaker estimate for the absolute dense volume (h^2 = 0.43). This difference in heritability between absolute dense area and absolute dense volume is not totally unexpected and complements previous data showing good agreement between area-based and volumetric methods for percent density, but weaker correlations for the absolute dense tissue (19-23). In fact, both measures represent different aspects of mammographic density, as area-based methods reduce mammographic density to projected areas where pixels represent either dense or non-dense tissue, while volumetric methods account for breast thickness by estimating the relative amount of density in each individual pixel. The incorporation of breast thickness is also reflected in the differential association with BMI. BMI is inversely related to the absolute dense area, but shows a positive association with the absolute dense volume (19,21-23). Altogether these results suggest that absolute dense area and volume have unique features, not only regarding the association with BMI but also in terms of heritability.

Results of our breast cancer SNP analyses are partly in line with those previously reported for area-based measures. The minor allele of rs10995190 in the *ZNF365* gene was found to be associated with

a lower percent dense area in the first GWAS of mammographic density (7); accordingly, we found the minor allele to be associated with lower percent and absolute dense volume. In addition, the minor allele of rs2046210 on chromosome 6q25 (upstream of the *ESR1* gene) is known to be associated with higher percent and absolute dense area (7); we found it to be associated with higher absolute dense volume, but saw no association with percent dense volume (P = 0.27). Furthermore, no associations were observed with other SNPs that have previously been linked to area-based density in non-GWAS approaches (i.e. rs3817198 in the *LSP1* gene, rs13281615 at chromosome 8q24 and rs10483813 in the *RAD51L1* gene) (7-9). There are several possible explanations for the differences between our findings and those obtained using area-based measures. Firstly, it is important to bear in mind that whilst both mammographic dense area and dense volume attempt to capture the same information about breast composition, they are distinct measures of mammographic density. An alternative explanation may lie in differences between study populations. Recent data show that the effect of breast cancer SNPs varies according to other environmental factors (36) and this kind of heterogeneity may explain the lack of an overall association found in this study. A third explanation is the statistical power of the different studies. Our study had 90% power to detect a 1% absolute difference in percent dense volume between homozygous carriers and non-carriers of a SNP with a minor allele frequency (MAF) of 0.16 e.g. rs10995190 (*ZNF365*). We had higher statistical power to detect similar effects for more common SNPs. However, our study could have been underpowered when the effect sizes of the SNPs are much smaller than the effect of the *ZNF365* SNP.

Interestingly, we found evidence of two novel breast cancer SNP associations with mammographic density at 6q25: rs9383938 and rs9485372. Rs9383938 is located in the *ESR1* gene and despite being in close proximity to rs2046210, both SNPs are not strongly correlated (R^2 = 0.12). Rs9485372 is located in the TGF-beta activated kinase 1/MAP3K7 binding protein 2 (*TAB2*) gene and has been associated with breast cancer risk in Asian women (39). The underlying biology of this association remains to be determined, but the TGF-beta pathway plays an important role in early tumorigenesis

and metastasis (40,41) as well as mammary development (42). The TAB2 protein also interacts directly with the N-terminal domain of ESR1 and has been implicated in pro-inflammatory induced re-activation of repressed estrogen receptor signalling pathways (43,44).

For all SNPs described above, associations were in the same direction as their effect on breast cancer risk (11,39,45). In addition, we found two breast cancer SNP associations for the absolute nondense volume: rs17356907 near the *NTN4* gene and rs6001930 in the *MKL1* gene. Both SNPs have previously been associated with an area-based measure of breast size (46), but not specifically with the nondense volume. The direction of both associations is opposite to those reported for breast cancer (11), supporting the idea that the absolute nondense volume exerts a protective effect on breast cancer risk (47,48).

Our study has several strengths and weaknesses. We used a fully automated density method which is expected to be less prone to measurement errors. Furthermore, SNP analyses were performed in cancer-free women, reducing the likelihood of artificial associations due to confounding by breast cancer (49,50). The heritability analysis was confined to full and half-sisters only. We could not retrieve cousin relations in our cohort, as this would require three generation pedigree information which is not available in the Multiple Generation Register. Also, we did not consider mother-daughter relations for our analysis, as this number would be very small given the age range for mammography screening. Further, it should be noted that genetic correlations among sisters could be affected by shared environmental effects. Heritability estimates were not materially different after adjusting for known determinants of mammographic density. Thus, inflation of our estimates due to these factors is unlikely, although we cannot rule out potential inflation by unmeasured shared environmental factors.

In conclusion, our results confirm the high heritability of mammographic density, though estimates are weaker for absolute than percent dense volume. These data support the notion that mammographic density is a risk factor under strong genetic influence that may partially explain the familial aggregation of breast cancer. The breast cancer SNPs that have been identified to date

explain only little of the variation in mammographic density, but the observed associations with individual SNPs are relevant as they provide more insight into the biological mechanisms leading to breast cancer in women with high dense breasts. In addition, the observed breast cancer SNP associations with the absolute nondense volume indicate that the shared genetic component with breast cancer is not restricted to dense tissues only.

FUNDING

This work was supported by the Swedish Research Council (grant no: 521-2011-3187) and Swedish Cancer Society (grant no: CAN 2013/469). The KARMA study was supported by Märit and Hans Rausing's Initiative Against Breast Cancer and the Cancer and Risk Prediction Center, a Linneus Centre (Contract ID 70867902) financed by the Swedish Research Council. KH is supported by the Swedish Research Counsil [grant no: 521-2011-3205] and JL is a UNESCO-L'OREAL International Fellow.

NOTES

The study sponsors had no role in the design of the study, the collection, analysis and interpretation of the data, the writing of the manuscript or the decision to submit the manuscript for publication.

ACKNOWLEDGEMENTS

We would like to thank Ralph Highnam for providing access and technical support to the Volpara software.

REFERENCES

1. McCormack VA, dos Santos Silva I. Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. *Cancer Epidemiol Biomarkers Prev*. 2006;15(6):1159-1169.

2. Assi V, Warwick J, Cuzick J, Duffy SW. Clinical and epidemiological issues in mammographic density. *Nat Rev Clin Oncol*. 2011;9(1):33-40.

3. Vachon CM, Kuni CC, Anderson K, Anderson VE, Sellers TA. Association of mammographically defined percent breast density with epidemiologic risk factors for breast cancer (United States). *Cancer Causes Control*. 2000;11(7):653-662.

4. Boyd NF, Dite GS, Stone J, et al. Heritability of mammographic density, a risk factor for breast cancer. *N Engl J Med*. 2002;347(12):886-894.

5. Stone J, Dite GS, Gunasekara A, et al. The heritability of mammographically dense and nondense breast tissue. *Cancer Epidemiol Biomarkers Prev*. 2006;15(4):612-617.

6. Varghese JS, Thompson DJ, Michailidou K, et al. Mammographic breast density and breast cancer: evidence of a shared genetic basis. *Cancer Res*. 2012;72(6):1478-1484.

7. Lindstrom S, Vachon CM, Li J, et al. Common variants in ZNF365 are associated with both mammographic density and breast cancer risk. *Nat Genet*. 2011;43(3):185-187.

8. Vachon CM, Scott CG, Fasching PA, et al. Common breast cancer susceptibility variants in LSP1 and RAD51L1 are associated with mammographic density measures that predict breast cancer risk. *Cancer Epidemiol Biomarkers Prev*. 2012;21(7):1156-1166.

9. Odefrey F, Stone J, Gurrin LC, et al. Common genetic variants associated with breast cancer and mammographic density measures that predict disease. *Cancer Res*. 2010;70(4):1449-1458.

10. Stevens KN, Lindstrom S, Scott CG, et al. Identification of a novel percent mammographic density locus at 12q24. *Hum Mol Genet*. 2012;21(14):3299-3305.

11. Michailidou K, Hall P, Gonzalez-Neira A, et al. Large-scale genotyping identifies 41 new loci associated with breast cancer risk. *Nat Genet*. 2013;45(4):353-61, 361e1-2.

12. Nguyen TL, Schmidt DF, Makalic E, et al. Explaining variance in the cumulus mammographic measures that predict breast cancer risk: a twins and sisters study. *Cancer Epidemiol Biomarkers Prev*. 2013;22(12):2395-2403.

13. Sung J, Song YM, Stone J, Lee K, Jeong JI, Kim SS. Genetic influences on mammographic density in Korean twin and family: the Healthy Twin study. *Breast Cancer Res Treat*. 2010;124(2):467-474.

14. Kataoka M, Antoniou A, Warren R, et al. Genetic models for the familial aggregation of mammographic breast density. *Cancer Epidemiol Biomarkers Prev*. 2009;18(4):1277-1284.

15. Ursin G, Lillie EO, Lee E, et al. The relative importance of genetics and environment on mammographic density. *Cancer Epidemiol Biomarkers Prev*. 2009;18(1):102-112.

16. Pankow JS, Vachon CM, Kuni CC, et al. Genetic analysis of mammographic breast density in adult women: evidence of a gene effect. *J Natl Cancer Inst*. 1997;89(8):549-556.

17. Highnam R, Brady M, Yaffe M, Karssemeijer N, Harvey J. Robust breast composition measurement - Volpara™. *Lectures Notes in Computer Science*. 2010;6136:342-349.

18. Ciatto S, Bernardi D, Calabrese M, et al. A first evaluation of breast radiological density assessment by QUANTRA software as compared to visual classification. *Breast*. 2012;21(4):503-506.

19. McCormack VA, Highnam R, Perry N, dos Santos Silva I. Comparison of a new and existing method of mammographic density measurement: intramethod reliability and associations with known risk factors. *Cancer Epidemiol Biomarkers Prev*. 2007;16(6):1148-1154.

20. Boyd N, Martin L, Gunasekara A, et al. Mammographic density and breast cancer risk: evaluation of a novel method of measuring breast tissue volumes. *Cancer Epidemiol Biomarkers Prev*. 2009;18(6):1754-1762.

21. Lokate M, Kallenberg MG, Karssemeijer N, Van den Bosch MA, Peeters PH, Van Gils CH. Volumetric breast density from full-field digital mammograms and its association with breast cancer risk factors: a comparison with a threshold method. *Cancer Epidemiol Biomarkers Prev*. 2010;19(12):3096-3105.

22. Aitken Z, McCormack VA, Highnam RP, et al. Screen-film mammographic density and breast cancer risk: a comparison of the volumetric standard mammogram form and the interactive threshold measurement methods. *Cancer Epidemiol Biomarkers Prev*. 2010;19(2):418-428.

23. Jeffreys M, Harvey F, Highnam R. Comparing a new volumetric breast density method (VolparaTM) to Cumulus. *Lectures Notes in Computer Science*. 2010;6136:408-413.

24. The KARMA study. http://karmastudy.org/. Accessed January, 2014.

25. Brand JS, Czene K, Shepherd JA et al. Automated measurement of volumetric mammographic density: a tool for widespread breast cancer risk assessment. *Cancer Epidemiol Biomarkers Prev*. 2014.

26. Magnusson C, Baron J, Persson I, et al. Body size in different periods of life and breast cancer risk in post-menopausal women. *Int J Cancer*. 1998;76(1):29-34.

27. Purcell S, Neale B, Todd-Brown K, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am J Hum Genet*. 2007;81(3):559-575.

28. Garcia-Closas M, Couch FJ, Lindstrom S, et al. Genome-wide association studies identify four ER negative-specific breast cancer risk loci. *Nat Genet*. 2013;45(4):392-8, 398e1-2.

29. Hindorff LA, MacArthur J (European Bioinformatics Institute), Morales J (European Bioinformatics Institute), Junkins HA, Hall PN, Klemm AK, and Manolio TA. A Catalog of Published Genome-Wide Association Studies. www.genome.gov/gwastudies. Accessed January, 2014.

30. Bojesen SE, Pooley KA, Johnatty SE, et al. Multiple independent variants at the TERT locus are associated with telomere length and risks of breast and ovarian cancer. *Nat Genet*. 2013;45(4):371-84, 384e1-2.

31. French JD, Ghoussaini M, Edwards SL, et al. Functional variants at the 11q13 risk locus for breast cancer regulate cyclin D1 expression through long-range enhancers. *Am J Hum Genet*. 2013;92(4):489-503.

32. Howie BN, Donnelly P, Marchini J. A flexible and accurate genotype imputation method for the next generation of genome-wide association studies. *PLoS Genet*. 2009;5(6):e1000529.

33. Almasy L, Blangero J. Multipoint quantitative-trait linkage analysis in general pedigrees. *Am J Hum Genet*. 1998;62(5):1198-1211.

34. Broeckel U, Maresso K, Martin LJ. Linkage analysis for complex diseases using variance component analysis: SOLAR. *Methods Mol Med*. 2006;128:91-100.

35. Varghese JS, Smith PL, Folkerd E, et al. The heritability of mammographic breast density and circulating sex-hormone levels: two independent breast cancer risk factors. *Cancer Epidemiol Biomarkers Prev*. 2012;21(12):2167-2175.

36. Nickels S, Truong T, Hein R, et al. Evidence of gene-environment interactions between common breast cancer susceptibility loci and established environmental risk factors. *PLoS Genet*. 2013;9(3):e1003284.

37. Tamimi RM, Cox D, Kraft P, Colditz GA, Hankinson SE, Hunter DJ. Breast cancer susceptibility loci and mammographic density. *Breast Cancer Res*. 2008;10(4):R66.

38. Woolcott CG, Maskarinec G, Haiman CA, et al. Association between breast cancer susceptibility loci and mammographic density: the Multiethnic Cohort. *Breast Cancer Res*. 2009;11(1):R10.

39. Long J, Cai Q, Sung H, et al. Genome-wide association study in east Asians identifies novel susceptibility loci for breast cancer. *PLoS Genet*. 2012;8(2):e1002532.

40. Benson JR. Role of transforming growth factor beta in breast carcinogenesis. *Lancet Oncol*. 2004;5(4):229-239.

41. Barcellos-Hoff MH, Akhurst RJ. Transforming growth factor-beta in breast cancer: too much, too late. *Breast Cancer Res*. 2009;11(1):202.

42. Lee E, Van Den Berg D, Hsu C, et al. Genetic variation in transforming growth factor beta 1 and mammographic density in Singapore Chinese women. *Cancer Res*. 2013;73(6):1876-1882.

43. Zhu P, Baek SH, Bourk EM, et al. Macrophage/cancer cell interactions mediate hormone resistance by a nuclear receptor derepression pathway. *Cell*. 2006;124(3):615-629.

44. Cutrupi S, Reineri S, Panetto A, et al. Targeting of the adaptor protein Tab2 as a novel approach to revert tamoxifen resistance in breast cancer cells. *Oncogene*. 2012;31(40):4353-4361.

45. Fletcher O, Johnson N, Orr N, et al. Novel breast cancer susceptibility locus at 9q31.2: results of a genome-wide association study. *J Natl Cancer Inst*. 2011;103(5):425-435.

46. Li J, Foo JN, Schoof N, et al. Large-scale genotyping identifies a new locus at 22q13.2 associated with female breast size. *J Med Genet*. 2013;50(10):666-673.

47. Pettersson A, Graff RE, Ursin G, et al. Mammographic Density Phenotypes and Risk of Breast Cancer: A Meta-analysis. *J Natl Cancer Inst*. 2014;106(5):dju078.

48. Pettersson A, Hankinson SE, Willett WC, Lagiou P, Trichopoulos D, Tamimi RM. Nondense mammographic area and risk of breast cancer. *Breast Cancer Res*. 2011;13(5):R100.

49. Monsees GM, Tamimi RM, Kraft P. Genome-wide association scans for secondary traits using case-control samples. *Genet Epidemiol*. 2009;33(8):717-728.

50. Richardson DB, Rzehak P, Klenk J, Weiland SK. Analyses of case-control data for additional outcomes. *Epidemiology*. 2007;18(4):441-445.

Table 1. Characteristics of the study populations.

Participant characteristic	Karma sisters (N = 1,910)	Karma iCOGS (N = 4,025)
Age (years)	54.3 (9.1)	54.6 (9.4)
Body mass index (kg/m^2)	25.5 (4.5)	25.3 (4.2)
Age at menarche (years)	13.2 (1.5)	13.1 (1.4)
Age at first birth (years)	26.5 (4.9)	27.0 (5.0)
Number of births, % (N)		
0	11.7 (224)	12.9 (518)
1	12.3 (234)	14.6 (587)
2	47.0 (898)	46.2 (1,860)
≥ 3	29.0 (554)	24.7 (996)
Missing	0 (0)	1.6 (64)
Menopausal status, % (N)		
premenopausal	44.9 (858)	49.0 (1,971)
postmenopausal	55.1 (1,052)	51.0 (2,054)
Hormone replacement therapy, % (N)		
never	79.7 (1,523)	68.9 (2,772)
former	15.9 (303)	20.8 (837)
current	4.4 (84)	5.0 (201)
missing	0 (0)	5.3 (215)
Benign breast disease, % (N)		
no	78.7 (1,503)	76.5 (3,080)
yes	21.3 (407)	21.3 (857)
missing	0 (0)	2.2 (88)
Percent dense volume (%) *	7.8 (4.5-11.2)	8.4 (5.1-11.7)
Absolute dense volume (cm^3) *	57 (54-60)	60 (57-63)
Absolute nondense volume (cm^3) *	662 (658-666)	646 (642-649)
Sister relatedness, % (N)		
Full-sibling	95.1 (1,816)	
Half-sibling	4.9 (94)	

Values are expressed as mean (SD), unless stated otherwise. *Geometric mean (95% CI). Study populations; Karma sisters = Karma sib-pair sample; Karma iCOGS = Karma sample of unrelated women genotyped on the custom Illumina iSelect genotyping (iCOGS) array.

Table 2. Intraclass correlation coefficients (ICC) and heritability estimates (h^2) for volumetric mammographic measures.

Sib-pair	N pairs			
		ICC (SE)		
Full-sisters	908	Percent dense volume	Absolute dense volume	Absolute nondense volume
Model 1		0.30 (0.03)	0.21 (0.03)	0.31 (0.03)
Model 2		0.30 (0.03)	0.22 (0.03)	0.30 (0.03)
Model 3		0.31 (0.03)	0.21 (0.03)	0.30 (0.03)
Half-sisters	47			
Model 1		0.19 (0.14)	0.10 (0.14)	0.08 (0.14)
Model 2		0.17 (0.14)	0.09 (0.14)	0.08 (0.14)
Model 3		0.16 (0.14)	0.11 (0.14)	0.07 (0.14)
		h^2 (SE)		
Full and half-sister pairs	955	Percent dense volume	Absolute dense volume	Absolute nondense volume
Model 1		0.62 (0.06)	0.43 (0.06)	0.61 (0.06)
Model 2		0.60 (0.06)	0.43 (0.06)	0.61 (0.06)
Model 3		0.63 (0.06)	0.43 (0.06)	0.61 (0.06)

Abbreviations: ICC = intraclass correlation coefficient; h^2 = heritability estimate; SE = standard error.
All mammographic measures were log-transformed prior to analyses to approximate the normal distribution.
Model 1: adjusted for age (years) and menopausal status (postmenopausal vs. premenopausal)
Model 2: adjusted for age (years), menopausal status (postmenopausal vs. premenopausal) and BMI (kg/m^2)
Model 3: adjusted for age (years), menopausal status (postmenopausal vs. premenopausal), BMI (kg/m^2), age at menarche (years), number of births and age at first birth (nulliparous, 1 child age at first birth < 25 years, 1 child age at first birth ≥ 25 years, 2 children age at first birth < 25 years, 2 children age at first birth ≥ 25 years, ≥ 3 children age at first birth < 25 years, ≥ 3 children age at first birth ≥ 25 years), HRT status (never, former, current) and benign breast disease (yes vs. no).

Table 3. Associations between breast cancer single nucleotide polymorphisms and volumetric mammographic measures (N = 4,025)

CHR	Locus	SNP	Alleles *	MAF	Percent dense volume		Absolute dense volume		Absolute nondense volume	
					Beta (SE)	*P*	Beta (SE)	*P*	Beta (SE)	*P*
1	*PEX14*	rs616488	G/A	0.32	0.01 (0.01)	0.26	-0.01 (0.01)	0.29	-0.02 (0.01)	0.02
1	1p13.2	rs11552449	T/C	0.17	-0.01 (0.01)	0.55	-0.02 (0.01)	0.07	-0.02 (0.01)	0.17
1	1p11.2	rs11249433	G/A	0.39	-0.01 (0.01)	0.24	0.01 (0.01)	0.31	0.02 (0.01)	0.02
1	*LGR6*	rs6678914	A/G	0.43	0.00 (0.01)	0.98	0.00 (0.01)	0.64	0.00 (0.01)	0.73
1	*MDM4*	rs4245739	C/A	0.24	0.01 (0.01)	0.13	0.01 (0.01)	0.50	-0.01 (0.01)	0.42
2	2p24.1	rs12710696	T/C	0.35	0.01 (0.01)	0.42	0.00 (0.01)	0.71	-0.01 (0.01)	0.24
2	2q14	rs4849887	T/C	0.09	0.01 (0.01)	0.52	0.04 (0.02)	0.01	0.03 (0.02)	0.04
2	2q31.1	rs2016394	A/G	0.48	0.00 (0.01)	0.91	0.01 (0.01)	0.12	0.02 (0.01)	0.07
2	*CDCA7*	rs1550623	G/A	0.15	0.00 (0.01)	0.93	-0.01 (0.01)	0.51	-0.01 (0.01)	0.46
2	*ERBB4*	rs13393577 †	C/T	0.11	0.03 (0.03)	0.23	0.04 (0.04)	0.25	0.00 (0.03)	0.98
2	2q35	rs13387042	A/G	0.49	-0.01 (0.01)	0.17	-0.01 (0.01)	0.32	0.00 (0.01)	0.73
2	*DIRC3*	rs16857609	T/C	0.28	0.01 (0.01)	0.23	0.03 (0.01)	0.01	0.01 (0.01)	0.15
3	*ITPR1*	rs6762644	G/A	0.42	-0.01 (0.01)	0.43	0.01 (0.01)	0.54	0.01 (0.01)	0.13
3	*SLC4A7*	rs4973768	T/C	0.45	0.00 (0.01)	0.93	0.00 (0.01)	0.81	0.00 (0.01)	0.84
3	*TGFBR2*	rs12493607	C/G	0.37	0.00 (0.01)	0.76	0.00 (0.01)	0.88	0.00 (0.01)	0.68
4	*TET2*	rs9790517	T/C	0.25	0.03 (0.01)	0.01	0.03 (0.01)	4.9×10^{-3}	0.00 (0.01)	0.76
4	*ADAM29*	rs6828523	A/C	0.12	0.00 (0.01)	0.87	-0.01 (0.02)	0.45	-0.01 (0.01)	0.53
5	*TERT*	rs10069690	T/C	0.27	-0.01 (0.01)	0.60	0.01 (0.01)	0.42	0.01 (0.01)	0.16
5	*TERT*	rs2736108	T/C	0.29	-0.01 (0.01)	0.46	-0.01 (0.01)	0.17	-0.01 (0.01)	0.47
5	5p12	rs4415084	T/C	0.40	0.01 (0.01)	0.54	0.00 (0.01)	0.70	-0.01 (0.01)	0.27
5	5p12	rs10941679	G/A	0.25	0.01 (0.01)	0.30	0.00 (0.01)	0.87	-0.01 (0.01)	0.18
5	*MAP3K1*	rs889312	C/A	0.28	-0.02 (0.01)	0.08	-0.01 (0.01)	0.31	0.01 (0.01)	0.46
5	*RAB3C*	rs10472076	C/T	0.38	0.01 (0.01)	0.18	0.02 (0.01)	0.03	0.01 (0.01)	0.43
5	*PDE4D*	rs1353747	G/T	0.09	0.00 (0.02)	0.88	-0.03 (0.02)	0.07	-0.03 (0.02)	0.07
5	*EBF1*	rs1432679	C/T	0.44	0.02 (0.01)	0.01	0.03 (0.01)	0.01	0.00 (0.01)	0.87
6	*FOXQ1*	rs11242675 †	C/T	0.41	-0.02 (0.02)	0.23	0.00 (0.02)	0.98	0.02 (0.02)	0.19
6	*RANBP9*	rs204247	G/A	0.44	0.01 (0.01)	0.49	0.01 (0.01)	0.16	0.01 (0.01)	0.38
6	6q14.1	rs17530068	C/T	0.25	-0.01 (0.01)	0.44	0.00 (0.01)	0.95	0.01 (0.01)	0.43

Table 3. Continued.

CHR	Locus	SNP	Alleles *	MAF	Percent dense volume		Absolute dense volume		Absolute nondense volume	
					Beta (SE)	*P*	Beta (SE)	*P*	Beta (SE)	*P*
6	6q22.33	rs2180341 †	G/A	0.24	-0.01 (0.02)	0.77	-0.02 (0.02)	0.49	-0.01 (0.02)	0.60
6	***TAB2***	**rs9485372 †**	A/G	0.18	**-0.09 (0.02)**	**$1.8x10^{-5}$**	-0.08 (0.03)	$1.8x10^{-3}$	0.02 (0.02)	0.28
6	*CCDC170*	rs3757318	A/G	0.06	0.03 (0.02)	0.11	0.06 (0.02)	$1.9x10^{-3}$	0.03 (0.02)	0.11
6	***ESR1***	**rs2046210**	A/G	0.33	0.01 (0.01)	0.27	**0.04 (0.01)**	**$4.6x10^{-4}$**	0.02 (0.01)	0.01
6	***ESR1***	**rs9383938**	T/G	0.07	0.02 (0.02)	0.20	**0.07 (0.02)**	**$2.6x10^{-4}$**	0.04 (0.02)	0.01
7	7q35	rs720475	A/G	0.23	0.01 (0.01)	0.28	0.01 (0.01)	0.21	0.00 (0.01)	0.87
8	8p21.1	rs9693444	A/C	0.32	0.02 (0.01)	0.04	0.00 (0.01)	0.87	-0.02 (0.01)	0.05
8	8q21.11	rs6472903	G/T	0.18	0.01 (0.01)	0.57	0.00 (0.01)	0.90	-0.01 (0.01)	0.46
8	*HNF4G*	rs2943559	G/A	0.07	0.01 (0.02)	0.51	0.00 (0.02)	0.84	-0.02 (0.02)	0.36
8	8q24	rs13281615	G/A	0.39	0.00 (0.01)	0.93	0.01 (0.01)	0.56	0.01 (0.01)	0.59
8	8q24	rs1562430	C/T	0.45	0.00 (0.01)	0.65	0.01 (0.01)	0.39	0.00 (0.01)	0.64
8	*MIR1208*	rs11780156	T/C	0.13	0.01 (0.01)	0.50	0.02 (0.01)	0.14	0.01 (0.01)	0.35
9	*CDKN2A/B*	rs1011970	T/G	0.17	0.00 (0.01)	0.69	-0.01 (0.01)	0.46	0.00 (0.01)	0.77
9	9q31.2	rs10759243	A/C	0.28	0.00 (0.01)	0.93	0.00 (0.01)	0.83	0.00 (0.01)	0.87
9	9q31	rs865686	G/T	0.39	0.01 (0.01)	0.44	0.00 (0.01)	0.86	-0.01 (0.01)	0.32
10	*MLLT10*	rs7072776	A/G	0.28	0.01 (0.01)	0.16	0.02 (0.01)	0.05	0.01 (0.01)	0.50
10	*DNAJC1*	rs11814448 †	C/A	0.02	-0.06 (0.06)	0.33	0.03 (0.07)	0.64	0.07 (0.05)	0.14
10	*ZNF365*	rs10822013	C/T	0.47	-0.03 (0.01)	$1.5x10^{-3}$	-0.02 (0.01)	0.07	0.01 (0.01)	0.20
10	***ZNF365***	**rs10995190**	A/G	0.16	**-0.05 (0.01)**	**$9.0x10^{-6}$**	**-0.07 (0.01)**	**$8.9x10^{-7}$**	-0.01 (0.01)	0.48
10	*ZMIZ1*	rs704010	T/C	0.37	0.01 (0.01)	0.56	0.00 (0.01)	0.82	-0.01 (0.01)	0.38
10	*TCF7L2*	rs7904519	G/A	0.44	-0.01 (0.01)	0.09	-0.01 (0.01)	0.20	0.00 (0.01)	0.72
10	10q26.12	rs11199914	T/C	0.32	0.00 (0.01)	0.87	0.00 (0.01)	0.90	0.00 (0.01)	0.78
10	*FGFR2*	rs2981579	A/G	0.39	0.00 (0.01)	0.69	0.00 (0.01)	0.86	-0.01 (0.01)	0.52
11	*LSP1*	rs3817198	C/T	0.30	0.00 (0.01)	0.81	0.01 (0.01)	0.61	0.00 (0.01)	0.66
11	11q13.1	rs3903072	T/G	0.47	0.00 (0.01)	0.59	0.01 (0.01)	0.35	0.00 (0.01)	0.64
11	11q13	rs614367	T/C	0.15	-0.01 (0.01)	0.61	-0.01 (0.01)	0.32	-0.01 (0.01)	0.59
11	11q13	rs78540526	T/C	0.08	-0.04 (0.03)	0.21	-0.01 (0.04)	0.77	0.02 (0.03)	0.41
11	11q13	rs75915166	A/C	0.06	0.00 (0.02)	0.96	-0.01 (0.02)	0.76	-0.01 (0.02)	0.66

Table 3. Continued.

CHR	Locus	SNP	Alleles *	MAF	Percent dense volume		Absolute dense volume		Absolute nondense volume	
					Beta (SE)	*P*	Beta (SE)	*P*	Beta (SE)	*P*
11	11q24.3	rs11820646	T/C	0.43	-0.01 (0.01)	0.46	0.00 (0.01)	0.78	0.01 (0.01)	0.29
12	12p13.1	rs12422552	C/G	0.25	0.01 (0.01)	0.42	0.02 (0.01)	0.17	0.01 (0.01)	0.53
12	*PTHLH*	rs10771399	G/A	0.13	0.00 (0.01)	0.91	-0.02 (0.01)	0.17	-0.02 (0.01)	0.12
12	***NTN4***	**rs17356907**	G/A	0.29	-0.02 (0.01)	0.01	0.01 (0.01)	0.24	**0.04 (0.01)**	**8.4×10^{-5}**
12	12q24	rs1292011	G/A	0.44	0.00 (0.01)	0.90	0.00 (0.01)	0.98	0.00 (0.01)	0.87
13	BRCA2	rs11571833	T/A	0.008	-0.11 (0.10)	0.25	-0.05 (0.12)	0.67	0.07 (0.08)	0.43
14	*PAX9*	rs2236007	A/G	0.21	0.00 (0.01)	0.97	0.00 (0.01)	0.75	0.00 (0.01)	0.77
14	*RAD51L1*	rs2588809	T/C	0.15	-0.01 (0.01)	0.25	-0.01 (0.01)	0.38	0.00 (0.01)	0.86
14	*RAD51L1*	rs999737	T/C	0.22	-0.01 (0.01)	0.38	-0.01 (0.01)	0.51	0.00 (0.01)	0.83
14	*CCDC88C*	rs941764	G/A	0.33	0.00 (0.01)	0.87	-0.01 (0.01)	0.26	-0.01 (0.01)	0.25
16	*TOX3*	rs3803662	A/G	0.25	0.00 (0.01)	0.71	0.01 (0.01)	0.38	0.01 (0.01)	0.18
16	*TOX3*	rs3112612	A/G	0.37	0.00 (0.01)	0.77	0.01 (0.01)	0.98	0.00 (0.01)	0.69
16	*FTO*	rs17817449	G/T	0.41	-0.01 (0.01)	0.37	-0.02 (0.01)	0.02	-0.01 (0.01)	0.13
16	*FTO*	rs11075995	A/T	0.26	0.00 (0.01)	0.63	0.00 (0.01)	0.66	-0.01 (0.01)	0.34
16	*CDYL2*	rs13329835	G/A	0.21	0.00 (0.01)	0.95	0.00 (0.01)	0.75	0.00 (0.01)	0.77
17	*COX11*	rs6504950	A/G	0.26	-0.03 (0.01)	2.8×10^{-3}	-0.02 (0.01)	0.11	0.01 (0.01)	0.16
18	18q11.2	rs527616	C/G	0.40	0.00 (0.01)	0.71	0.01 (0.01)	0.52	0.01 (0.01)	0.27
18	*CHST9*	rs1436904	G/T	0.41	0.02 (0.01)	0.03	0.00 (0.01)	0.64	-0.02 (0.01)	0.08
19	*MERIT40*	rs8170	A/G	0.19	0.01 (0.01)	0.50	0.02 (0.01)	0.21	0.01 (0.01)	0.56
19	*ANKLE1*	rs8100241	G/A	0.47	-0.01 (0.01)	0.50	-0.01 (0.01)	0.41	0.00 (0.01)	0.79
19	*ELL*	rs4808801	G/A	0.35	-0.02 (0.01)	0.06	-0.02 (0.01)	0.08	0.00 (0.01)	0.94
19	19q13.31	rs3760982	A/G	0.45	-0.01 (0.01)	0.16	-0.02 (0.01)	0.09	0.00 (0.01)	0.71
20	*RALY*	rs2284378 †	T/C	0.30	-0.01 (0.02)	0.64	-0.01 (0.02)	0.64	0.00 (0.02)	0.98
21	*NRIP1*	rs2823093	A/G	0.27	0.00 (0.01)	0.81	0.01 (0.01)	0.52	0.01 (0.01)	0.62
22	*EMID1*	rs132390	C/T	0.04	-0.05 (0.04)	0.20	-0.07 (0.05)	0.21	0.00 (0.04)	0.99
22	***MKL1***	**rs6001930**	C/T	0.12	0.01 (0.01)	0.34	-0.05 (0.02)	9.0×10^{-4}	**-0.06 (0.01)**	**6.7×10^{-6}**

Abbreviations: CHR = chromosome; MAF = minor allele frequency: SE = standard error. * Alleles: minor/major allele. † Imputed SNPs with info-score > 0.80. All SNP association tests were performed under the additive model with betas representing the per-minor allele increase in log volumetric mammographic measures, adjusted for age (years), body mass index (kg/m^2) and menopausal status (postmenopausal vs. premenopausal). Statistically significant associations in bold. SNP rs10483813 in *RAD51L1* was replaced by rs999737, as this is the index SNP identified by iCOGS (11). Linked SNPs: TERT: rs10069690 and rs2736108 r^2=0.13; 5p12: rs4415084 and rs10941679 r2=0.60; ESR1: rs3757318 and rs2046210 r^2=0.07; rs3757318 and rs9383938 r^2=0.44; rs2046210 and rs9383938 r^2=0.12; 8q24: rs13281615 and rs1562430 r2=0.47; ZNF365: rs10995190 and rs10822013 r^2=0.15; 11q13: rs614367 and rs78540526 r2=0.38; rs614367 and rs75915166 r^2=0.37; rs78540526 and rs75915166 r^2=0.58; TOX3: rs3803662 and rs3112612 r^2=0.15.