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REVIEW

Mammographic Density Phenotypes and Risk of Breast Cancer: A Meta-analysis

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Background Fibroglandular breast tissue appears dense on mammogram, whereas fat appears nondense. It is unclear whether absolute or percentage dense area more strongly predicts breast cancer risk and whether absolute nondense area is independently associated with risk.

Methods We conducted a meta-analysis of 13 case–control studies providing results from logistic regressions for associations between one standard deviation (SD) increments in mammographic density phenotypes and breast cancer risk. We used random-effects models to calculate pooled odds ratios and 95% confidence intervals (CIs). All tests were two-sided with *P* less than .05 considered to be statistically significant.

Results Among premenopausal women (n = 1776 case patients; n = 2834 control subjects), summary odds ratios were 1.37 (95% CI = 1.29 to 1.47) for absolute dense area, 0.78 (95% CI = 0.71 to 0.86) for absolute nondense area, and 1.52 (95% CI = 1.39 to 1.66) for percentage dense area when pooling estimates adjusted for age, body mass index, and parity. Corresponding odds ratios among postmenopausal women (n = 6643 case patients; n = 11 187 control subjects) were 1.38 (95% CI = 1.31 to 1.44), 0.79 (95% CI = 0.73 to 0.85), and 1.53 (95% CI = 1.44 to 1.64). After additional adjustment for absolute dense area, associations between absolute nondense area and breast cancer became attenuated or null in several studies and summary odds ratios became 0.82 (95% CI = 0.71 to 0.94; $P_{heterogeneity}$ = .02) for premenopausal and 0.85 (95% CI = 0.75 to 0.96; $P_{heterogeneity}$ < .01) for postmenopausal women.

Conclusions The results suggest that percentage dense area is a stronger breast cancer risk factor than absolute dense area. Absolute nondense area was inversely associated with breast cancer risk, but it is unclear whether the association is independent of absolute dense area.

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Fibroglandular breast tissue (epithelial cells, fibroblasts, and connective tissue) appears radio-dense on a mammogram, whereas breast fat appears transparent or nondense. Dense mammographic tissue, quantified as either the absolute or percentage dense area on a mammogram, is a strong risk factor for breast cancer. According to one meta-analysis, women with 75% or more dense area are at a 4.6-fold increased risk of breast cancer relative to women with less than 5% dense area (1).

It is possible that women with high mammographic density are at increased risk of breast cancer because they have large amounts of fibroglandular breast tissue at risk (2). In line with this hypothesis, some studies have reported greater magnitudes of breast cancer risk for absolute dense area than percentage dense area (3). Several other studies, however, have reported greater magnitudes of risk for percentage than absolute dense area (1,4). The latter findings suggest that the ratio of fibroglandular to fatty tissue is a stronger breast cancer risk factor, implying that either the ratio itself reflects an underlying biological mechanism associated with breast cancer risk or that absolute nondense area, which contributes to the denominator of percentage dense area, is inversely associated with breast cancer risk. Two recent nested case–control studies examining the association between absolute nondense area and breast cancer risk yielded conflicting results (5,6). In statistical models including both absolute dense and nondense area, in one study (5) there was a statistically significant lower risk of breast cancer with increasing absolute nondense area, whereas in the other study (6) there was a statistically significant increased risk of breast cancer.

It is critical to establish the relationship between the different mammographic density phenotypes (absolute dense area, absolute nondense area, and percentage dense area) and breast cancer risk to

uncover underlying biological mechanisms and to improve upon breast cancer risk prediction modeling. We thus conducted a meta-analysis of 13 case–control studies that examined the associations between mammographic density phenotypes and risk of breast cancer; we benefitted from a reanalysis of each individual study for the purpose of this meta-analysis such that the study-specific associations were consistently analyzed using the same adjustments and categorizations.

Methods

Invited Studies, Inclusion Criteria, and Participating Studies

Eligible studies for this meta-analysis included those partaking in the DENSNP consortium (7), an international collaboration of 19 epidemiological studies with data on breast cancer susceptibility genetic variants and mammographic density, as well as any others led by DENSNP consortium principal investigators. To be eligible for inclusion in the meta-analysis, we required that studies used a case–control design (nested or not) and had digitized prediagnostic film mammograms, mammographic density assessed using a computer-assisted thresholding technique, and relevant covariable data measured at the time (within a few years) of mammography. In total, 13 studies provided data for the meta-analysis (Table 1) (5,6,8–17). Twelve were case–control studies nested within existing prospective cohorts, trials, or fully enumerated registries, and one was a population-based case–control study.

Mammographic density studies within the AGE Trial were approved by the UK South East Research Ethics Committee (REC 05/MRE01/77). Approval for the Cancer and Hormones Replacement Study (CAHRES) study was given by the ethical review boards in the respective regions in which the subjects were based in Sweden. The Canadian Breast Density Study (CBDS) study was approved by the ethics committees at the University of Toronto, the University Health Network (Toronto), the Ontario Breast Screening Program (OBSP), and the University of British Columbia. The European Prospective Investigation into Cancer and Nutrition study--Netherlands (EPIC-NL) study was approved by the institutional review board of the University Medical Centre Utrecht. The Melbourne Collaborative Cohort Study (MCCS) study was approved by the Cancer Council Victoria's human research ethics committee. The Mayo Clinic Mammography Study (MCMAM) and Mayo Mammography Health Study (MMHS) studies were approved by the Mayo Clinic Institutional Review Board. The Multiethnic Cohort (MEC) study was approved by the Committee on Human Studies at the University of Hawaii. The Nurses' Health Study 1 (NHS1) and Nurses' Health Study 2 (NHS2) studies were approved by the Committee on the Use of Human Subjects in Research at Brigham and Women's Hospital. The Singapore Breast Cancer Screening Project (SBSP) study was approved by the National University of Singapore Institutional Review Board. The Norwich & Cambridge, UK National Health Service Breast Cancer Screening Program (UK-NHS) study was approved by the Norfolk Local Research Ethics Committee. The University of Southern California (USC) study was approved by the institutional review board at the University of Southern California. Participants of all studies except the UK-NHS provided informed consent. The UK-NHS was a medical records study, so direct consent from the patients was not required.

Mammographic Density Measures

All studies had prediagnostic film mammograms of the craniocaudal (CC; n = 9 studies) or mediolateral oblique (MLO; n = 4 studies) view (Table 1). [The MCMAM study provided data for both the CC and MLO views; data from the CC view were used in all analyses unless otherwise specified because they have been used in previous publications (16).] Mammographic density was measured using the computer-assisted thresholding technique Cumulus (18) (n = 12 studies) or Madena (19) (n = 1 study). Using these techniques, two grayscale thresholds are selected on the digitized mammograms. One threshold separates the breast from the background (or alternatively the breast edge is manually delimited), and the other classifies the breast tissue into dense and nondense area. The percentage dense area is calculated as 100 × (absolute dense area / (absolute dense area + absolute nondense area)). Trained readers blinded to case–control status read the mammograms and selected the thresholds in all studies.

Statistical Analysis

Study Level. Each study provided study-specific parameter estimates (βs) and standard errors (SEs) from conditional or unconditional logistic regression models conducted specifically for this meta-analysis. Because menopausal status is associated with both mammographic density and breast cancer risk, all analyses were conducted separately for premenopausal and postmenopausal status at the time of mammography. Menopausal status was self-reported in 10 studies and based on age (≤50 years premenopausal, >50 years postmenopausal) at the time of mammography in three studies. Each mammographic density phenotype was divided into quartiles based on its distribution among the control subjects. Quartiles were modeled as categorical variables using the lowest quartile as the reference. Because the distributions of the mammographic density phenotypes differed across studies (Table 1), each study transformed the mammographic density phenotypes so that they were approximately normally distributed and then provided the βs and their standard errors associated with one standard deviation (SD) increments in each mammographic density phenotype. We were thus able to compare the magnitude of the associations between the different mammographic density phenotypes and breast cancer risk.

The following covariables, measured at the time of mammography, were included in the analyses: age (available for all studies; self-reported in all studies), body mass index (BMI; kg/m^2; available for 12 studies; self-reported in 7 studies and technician-measured in 5 studies), parity (available for 12 studies; self-reported in all studies), and, among postmenopausal women only, use of hormonal replacement therapy (HRT; ever use available for 11 studies and current use for 9 studies; self-reported in all studies). The covariables age and BMI were modeled as continuous variables, whereas parity (nulliparous, 1–2 children, ≥3 children) and both ever and current HRT use (yes, no) were modeled as categorical variables.

For each density phenotype, as detailed in Tables 2 and 3, statistical models were run adjusting 1) for age at mammography, and 2) additionally for BMI and parity (ie, the fully adjusted model for percentage dense area). For dense and nondense area, models were also fitted adjusting 3) for age and the other absolute phenotype (dense or nondense area, as appropriate) and 4) additionally for BMI and parity (ie, the fully adjusted model for absolute dense and nondense area).

Table 1. Characteristics at or around the time of mammography among case patients and control subjects for each study included in the meta-analysis*

Study name	AGE		CAHRES		CBDS		EPIC-NL		MCCS		MCMAM	
Study type	Nested case–control study		Nested case–control study		Nested case–control study		Nested case–control study		Nested case–control study		Nested case–control study	
Country	UK		Sweden		Canada		Netherlands		Australia		US	
Ethnicity†	White		White		White		White		White		White	
Mammogram view‡	MLO		MLO		CC		MLO		CC		CC (MLO)	
Threshold technique	Cumulus		Cumulus		Cumulus		Cumulus		Cumulus		Cumulus	
Study period	1991–2005		1993–1995		1980–1999		1990–2007		1990–2007		1990–2001	
Year of screening program initiation in the country of study	1988		1986		1984		1989		1991		1991	
Screening or interval detected breast cancer	Both		Both		Both		Both		Both		Both	
BMI ascertainment	Self-reported		Self-reported		Self-reported		Measured		Measured		Measured	
Menopausal status ascertainment	Self-reported		Based on age		Self-reported		Self-reported		Based on age		Self-reported	
Reference	17		9		10		5		16		11	
Include carcinoma in situ cases	No		No		No		Yes		Yes		Yes	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
Premenopausal												
Number	317	457	–	–	292	276	95	276	44	60	58	119
Age, y, mean	41.1	41.2	–	–	47.3	47.3	52.8	52.2	46.0	46.0	46.5	47.3
Absolute dense area, cm^2, mean	54.9	43.4	–	–	47.1	38.9	36.9	30.0	36.4	26.4	43.7 (49.4)	39.8 (43.4)
Absolute nondense area, cm^2, mean	77.3	89.1	–	–	68.8	82.3	90.4	101.6	85.2	103.9	67.3 (81.2)	79.0 (93.0)
Percentage dense area, %, mean	44.8	36.1	–	–	44.2	36.2	30.5	25.8	31.9	24.0	41.1 (39.0)	35.2 (33.3)
BMI, kg/m^2, mean	24.9	25.4	–	–	24.2	24.7	25.5	25.4	25.6	26.4	26.1	27.2
Parity, No., mean§	2.1	2.1	–	–	2.5	2.7	2.0	2.1	2.0	2.0	2.5	2.8
Postmenopausal												
Number	–	–	1,511	1,674	872	879	358	859	380	964	313	558
Age, y, mean	–	–	62.5	63.9	59.7	59.7	60.1	59.1	61.0	61.0	63.6	63.7
Absolute dense area, cm^2, mean	–	–	28.5	22.3	36.0	29.1	22.5	20.3	20.5	13.8	35.0 (36.0)	28.5 (30.6)
Absolute nondense area, cm^2, mean	–	–	143.1	152.5	103.1	108.1	127.3	119.6	121.0	122.4	96.7 (114.0)	99.9 (115.9)
Percentage dense area, %, mean	–	–	18.0	14.0	28.7	23.9	16.9	16.6	16.4	11.6	28.8 (25.8)	24.7 (22.6)
BMI, kg/m^2, mean	–	–	25.7	25.7	25.2	25.0	26.6	26.0	27.7	26.5	27.9	27.0
Parity, No., mean‖	–	–	2.2	2.4	3.0	3.2	2.3	2.5	3.0	3.0	3.2	3.3
Ever HRT use, %, mean	–	–	41.8	51.0	45.5	40.7	27.7	25.3	38.4	33.1	26.3	31.2
Current HRT use, %, mean	–	–	36.5	14.0	25.6	23.1	–	–	27.6	21.8	–	–

(Table continues)

Table 1 (Continued).

Study name	MEC		MMHS		NHS1		NHS2		SBSP		UK NHS		USC	
Study type	Nested case–control study		Nested case–control study		Nested case–control study		Nested case–control study		Nested case–control study		Nested case–control study		Case–control study	
Country	US-Hawaii		US		US		US		Singapore		UK		US	
Ethnicity†	Mixed		White		White		White		Asian		White		Mixed	
Mammogram view‡	CC		CC		CC		CC		CC		MLO		CC	
Threshold technique	Cumulus		Cumulus		Cumulus		Cumulus		Cumulus		Cumulus		Madena	
Study period	1993–2000		2003–2011		1989—2004		1995–2003		1994–1997		1995–2004		1989–1998	
Year of screening program initiation in the country of study	1991		1991		1991		1991		2002		1988		1991	
Screening or interval detected breast cancer	Both		Both		Both		Both		Both		Both		Both	
BMI ascertainment	Self-reported		Measured		Self-reported		Self-reported		Measured		-		Self-reported	
Menopausal status ascertainment	Self-reported		Self-reported		Self-reported		Self-reported		Self-reported		Based on age		Self-reported	
Reference	8		12		6		6		13		14		15	
Include carcinoma in situ cases	Yes		Yes		Yes		Yes		Yes		No		No	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
Premenopausal														
Number	59	100	99	272	284	591	172	386	69	113	–	–	287	184
Age, y, mean	49.1	48.7	46.3	46.4	48.9	49.0	44.4	44.8	53.1	52.7	–	–	42.0	42.3
Absolute dense area, cm^2, mean	46.7	39.1	29.8	26.0	65.2	52.1	107.1	94.9	74.1	68.6	–	–	51.9	46.9
Absolute nondense area, cm^2, mean	67.4	89.0	106.2	117.8	94.1	110.6	131.3	152.0	78.2	108.9	–	–	91.4	91.8
Percentage dense area, %, mean	46.8	37.5	24.4	21.5	44.9	36.9	48.2	42.0	51.6	44.0	–	–	42.6	39.6
BMI, kg/m^2, mean	24.6	26.8	27.1	27.9	25.0	25.1	24.9	25.3	24.8	24.4	–	–	24.7	25.1
Parity, No., mean§	1.5	2.5	2.4	2.4	2.6	2.6	1.7	1.9	2.3	2.4	–	–	1.6	1.9
Postmenopausal														
Number	548	567	349	1,054	903	1,568	37	75	400	843	634	1,880	338	266
Age, y, mean	62.8	61.8	64.3	63.7	61.3	61.9	49.5	49.7	58.0	57.9	57.3	57.4	54.7	53.9
Absolute dense area, cm^2, mean	34.7	27.1	22.8	19.2	48.2	40.6	103.2	73.1	58.2	51.0	46.2	36.5	44.7	35.7
Absolute nondense area, cm^2, mean	83.9	91.2	136.0	137.7	139.8	156.3	188.0	197.2	111.8	141.9	123.9	131.7	107.6	129.7
Percent dense area, %, mean	33.8	27.7	15.8	13.9	28.8	22.9	38.4	30.5	39.4	31.1	29.3	23.8	33.1	23.9
BMI, kg/m^2, mean	24.9	25.3	29.0	28.0	26.1	26.0	27.1	27.7	25.2	24.5	–	–	25.4	26.5
Parity, No., mean[4]	2.5	2.6	3.0	3.0	3.0	3.2	1.6	1.5	2.8	3.3	–	–	2.3	2.5
Ever HRT use, %, mean	79.9	73.5	64.8	65.8	71.5	62.4	89.2	96.0	18.5	13.3	–	–	27.8	21.8
Current HRT use, %, mean	59.7	60.1	29.2	28.9	51.6	39.5	78.4	80.0	10.5	5.9	–	–	0.0	0.0

* Results are presented separately for women who were premenopausal and postmenopausal at the time of mammography. Em dashes (–) indicate lack of data availability. AGE = UK AGE Trial nested case–control study; BMI = body mass index; CAHRES = Cancer and Hormones Replacement in Sweden study; CBDS = Canadian Breast Density Study; CC = craniocaudal; EPIC–NL = Dutch contribution to the European Prospective Investigation into Cancer and Nutrition study; HRT = hormone replacement therapy; MCCS = Melbourne Collaborative Cohort Study; MCMAM = Mayo Clinic Mammography Study; MEC = Hawaii component of the Multiethnic Cohort Study; ML = mediolateral oblique; MMHS = Mayo Mammography Health Study; NHS1 = Nurses' Health Study 1; NHS2 = Nurses' Health Study 2; SBSP = Singapore Breast Cancer Screening Project; UK NHS = Norwich & Cambridge UK NHS Breast Cancer Screening Program; USC = University of Southern California mammographic density study.

† All studies with ethnicity listed as white include >90% whites. The MEC study includes 30% whites, 46% Asians, and 24% of other ethnicity. The USC study includes 47% whites, 20% Asians, and 33% blacks. The SBSP study includes 100% Asians.

‡ Data provided for the MCMAM cohort are based on data from the craniocaudal mammogram view; data from the mediolateral oblique mammogram view are given in parentheses. For the mediolateral oblique view, data on mammographic density were only available for 309 case patients and 556 control subjects.

§ Among parous women.

Table 2. Summary odds ratios (ORs) and 95% confidence intervals (CIs) for mammographic density phenotypes and risk of breast cancer among women who were premenopausal at the time of mammography

Main exposure	Covariables in model*	Summary OR† (95% CI)	*P* for heterogeneity by				
			Study	Age	BMI	Mammogram view	Ethnicity
Absolute dense area	Age	1.38 (1.30 to 1.48)	.61	.44	.99	.07	.73
Absolute dense area	Age, absolute nondense area	1.38 (1.29 to 1.48)	.89	.84	.86	.15	.39
Absolute dense area	Age, BMI, parity	1.37 (1.29 to 1.47)	.50	.38	.94	.05	.68
Absolute dense area	Age, BMI, parity, absolute nondense area	1.39 (1.30 to 1.49)	.73	.76	.92	.13	.38
Absolute nondense area	Age	0.81 (0.76 to 0.86)	.79	.26	.84	.99	.07
Absolute nondense area	Age, absolute dense area	0.84 (0.78 to 0.91)	.28	.06	.79	.22	.03
Absolute nondense area	Age, BMI, parity	0.78 (0.71 to 0.86)	.20	.08	.32	.78	.01
Absolute nondense area	Age, BMI, parity, absolute dense area	0.82 (0.71 to 0.94)	.02	.03	.38	.42	.01
Percentage dense area	Age	1.45 (1.35 to 1.55)	.54	.40	.75	.34	.04
Percentage dense area	Age, BMI, parity	1.52 (1.39 to 1.66)	.27	.31	.46	.38	.01

* Covariables are measured at (within a few years) the time of mammography. Absolute dense area (per standard deviation), absolute nondense area (per standard deviation), percentage dense area (per standard deviation), age (per year), and body mass index (BMI; per kg/m^2) are modeled as continuous variables, and parity is modeled as a categorical variable (nulliparous, 1–2, ≥3 children). Random effects models. All statistical tests were two-sided.

† Odds ratios represent one standard deviation increases in the mammographic density phenotypes.

Table 3. Summary odds ratios (ORs) and 95% confidence intervals (CIs) for different mammographic density phenotypes and risk of breast cancer among women who were postmenopausal at the time of mammography

Main exposure	Covariables in model*	Summary OR† (95% CI)	*P* for heterogeneity by						
			Study	Age	BMI	Mammogram view	Ethnicity	Current HRT use	Ever HRT use
Absolute dense area	Age	1.37 (1.33 to 1.40)	.58	.41	.59	.97	.29	.43	.87
Absolute dense area	Age, absolute nondense area	1.37 (1.33 to 1.41)	.49	.60	.83	.78	.69	.32	.74
Absolute dense area	Age, BMI, parity	1.38 (1.31 to 1.44)	.15	.80	.19	.43	.37	.30	.76
Absolute dense area	Age, BMI, parity, absolute nondense area	1.38 (1.32 to 1.45)	.14	.46	.43	.37	.80	.18	1.00
Absolute nondense area	Age	0.89 (0.84 to 0.94)	<.01	.25	.15	.34	.90	.26	.61
Absolute nondense area	Age, absolute dense area	0.96 (0.88 to 1.03)	<.01	.64	.21	.20	.52	.10	.33
Absolute nondense area	Age, BMI, parity	0.79 (0.73 to 0.85)	<.01	.95	.81	.02	.41	.21	.41
Absolute nondense area	Age, BMI, parity, absolute dense area	0.85 (0.75 to 0.96)	<.01	.76	.74	.04	.29	.12	.27
Percentage dense area	Age	1.37 (1.32 to 1.42)	.07	.24	.36	.14	.54	.32	.30
Percentage dense area	Age, BMI, parity	1.53 (1.44 to 1.64)	.01	.45	.69	.03	.26	.46	.27

* Covariables are measured at (within a few years) the time of mammography. Absolute dense area (per standard deviation), absolute nondense area (per standard deviation), percentage dense area (per standard deviation), age (per year), and body mass index (BMI; per kg/m^2) are modeled as continuous variables, and parity is modeled as a categorical variable (nulliparous, 1–2, ≥3 children). Random effects models. All statistical tests were two-sided.

† Odds ratios represent one standard deviation increases in mammographic density phenotypes.

Finally, for postmenopausal women, we examined models additionally adjusted for ever HRT use and, separately, for current HRT use.

Meta-analysis. For each of the analyses described above, we pooled the study-specific βs using DerSimonian and Laird random-effects models to obtain a combined estimate, which we then exponentiated to arrive at a pooled odds ratio (OR) and its confidence interval (CI) (20). This method was conducted for the associations for quartiles 2, 3, and 4 (vs 1) and for the continuous effects of one standard deviation increases. For all analyses, we assessed heterogeneity across studies using Cochran's Q test. We further investigated heterogeneity using the I^2 statistic, which describes the percentage of total variation across studies resulting from heterogeneity rather than chance (21,22). We conducted all statistical analyses of categorical exposures using MIX version 2.0 Professional (BIOSTATXL) (23,24) and analyses of continuous exposures using the METAANAL macro (http://www.hsph.harvard.edu/faculty/donna-spiegelman/files/metaanal) for SAS version 9 (SAS Institute, Cary, NC). Forest plots were created using Microsoft Excel 2010 for Windows.

We used meta-regressions to assess effect modification by the following factors, chosen a priori: average age at mammography among control subjects, average BMI at mammography among control subjects, method of BMI ascertainment (self-reported or technician-measured), mammogram view (CC or MLO), ethnicity (white, Asian, or mixed), percentage ever having used HRT among control subjects (among postmenopausal women only), and percentage currently using HRT (among postmenopausal women only) among control subjects. Analyses of effect modification were conducted using STATA/IC 10.0 for Mac (STATACorp, College Station, TX).

All tests were two-sided with P less than .05 considered to be statistically significant.

Results

Of the 13 studies in the meta-analysis (Table 1), 11 contributed data for premenopausal women (n = 1776 breast cancer cases; n = 2834 control subjects), and 12 contributed data for postmenopausal women (n = 6643 breast cancer cases; n = 11 187 control subjects). Ten studies included almost exclusively (>90%) white women from the United States, Canada, Europe, or Australia, two studies included women of various ethnicities from the United States (including 20% and 46% Asians, respectively), and one study (the SBSP cohort) included only Asian women from Singapore. With the exception of the SBSP cohort, and to some extent the studies including women of various ethnicities, all studies were conducted in populations with a generally high risk of breast cancer (http://globocan.iarc.fr). The mean ages at mammography among premenopausal case patients and control subjects were 46 and 47 years, respectively, whereas the mean age among both postmenopausal case patients and control subjects was 61 years. In all studies, at both premenopausal and postmenopausal ages, absolute dense areas were higher among case patients than control subjects by between 2 and 13 cm^2, with one study (NHS2 at postmenopausal ages) finding a greater difference of 30 cm^2. Mean study-specific percentage dense area was also consistently higher in case patients than in control subjects by between 2 to 10 absolute percentage points, with the exception of the EPIC-NL study at postmenopausal ages where no appreciable difference was observed. In contrast, the distributions were largely reversed for absolute nondense area, where study-specific mean nondense areas were between 1 and 30 cm^2 lower in case patients than control subjects, again with the exception of the EPIC-NL study at postmenopausal ages (Table 1). The SBSP cohort, which included only Asian women, had the highest percentage dense area among case patients and control subjects, both among premenopausal and postmenopausal women. The within-study correlation between absolute dense and nondense area varied across studies, ranging from –0.49 to 0.20 among premenopausal women, and from –0.48 to 0.03 among postmenopausal women (Supplementary Table 1, available online).

Premenopausal Women

Results for premenopausal women (n = 1776 breast cancer cases; n = 2834 control subjects) are presented in Table 2 and Figure 1. The age-adjusted summary odds ratio for a one standard deviation increment was 1.38 (95% CI = 1.30 to 1.48) for absolute dense area, 1.45 (95% CI = 1.35 to 1.55) for percentage dense area, and 0.81 (95% CI = 0.76 to 0.86) for absolute nondense area. Additional adjustment for BMI and parity changed the odds ratio for percentage dense area to 1.52 (95% CI = 1.39 to 1.66). Additional adjustment for BMI and parity did not materially change the results for absolute dense area (OR = 1.37; 95% CI = 1.29 to 1.47) or nondense area (OR = 0.78; 95% CI = 0.71 to 0.86). Results for nondense area were similar after further adjustment for absolute dense area (OR = 0.82; 95% CI = 0.71 to 0.94).

In the fully adjusted model, we observed statistically significant heterogeneity between studies (P = .02) for absolute nondense area (Table 2). After exclusion of the USC study, the heterogeneity was reduced (summary OR = 0.78; 95% CI = 0.69 to 0.89; $P_{heterogeneity}$ = .09). In the fully adjusted models, there was also statistically significant heterogeneity by ethnicity for both absolute nondense and percentage dense area (both P = .01). In analyses restricted to studies including almost exclusively white women, the summary odds ratio for absolute nondense area was 0.78 (95% CI = 0.71 to 0.87; $P_{heterogeneity}$ = .36), and for percentage dense area it was 1.60 (95% CI = 1.47 to 1.75; $P_{heterogeneity}$ = .99) (Supplementary Table 3, available online). The corresponding odds ratios for the three studies including non-white women were 0.92 (95% CI = 0.53 to 1.57; $P_{heterogeneity}$ = .01) and 1.31 (95% CI = 0.97 to 1.78; $P_{heterogeneity}$ = .11). There was also statistically significant heterogeneity by age at the time of mammography for absolute nondense area in the fully adjusted model (P = .03); in general, the inverse association between the absolute nondense area and breast cancer risk increased with higher average age of each study's participants at the time of mammography (Supplementary Figure 1, available online). In analyses of the fully adjusted models restricted to studies including almost exclusively white women, the P for heterogeneity by age at the time of mammography was .09.

Postmenopausal Women

In postmenopausal women (n = 6643 breast cancer cases; n = 11 187 control subjects) (Table 3; Figure 2), the age-adjusted summary odds ratio for a one standard deviation increment in absolute dense area was 1.37 (95% CI = 1.33 to 1.40). Much like among premenopausal women, additional adjustment for BMI and parity did not materially change the results (OR = 1.38; 95% CI = 1.31 to 1.44), nor did additional adjustment for absolute nondense area

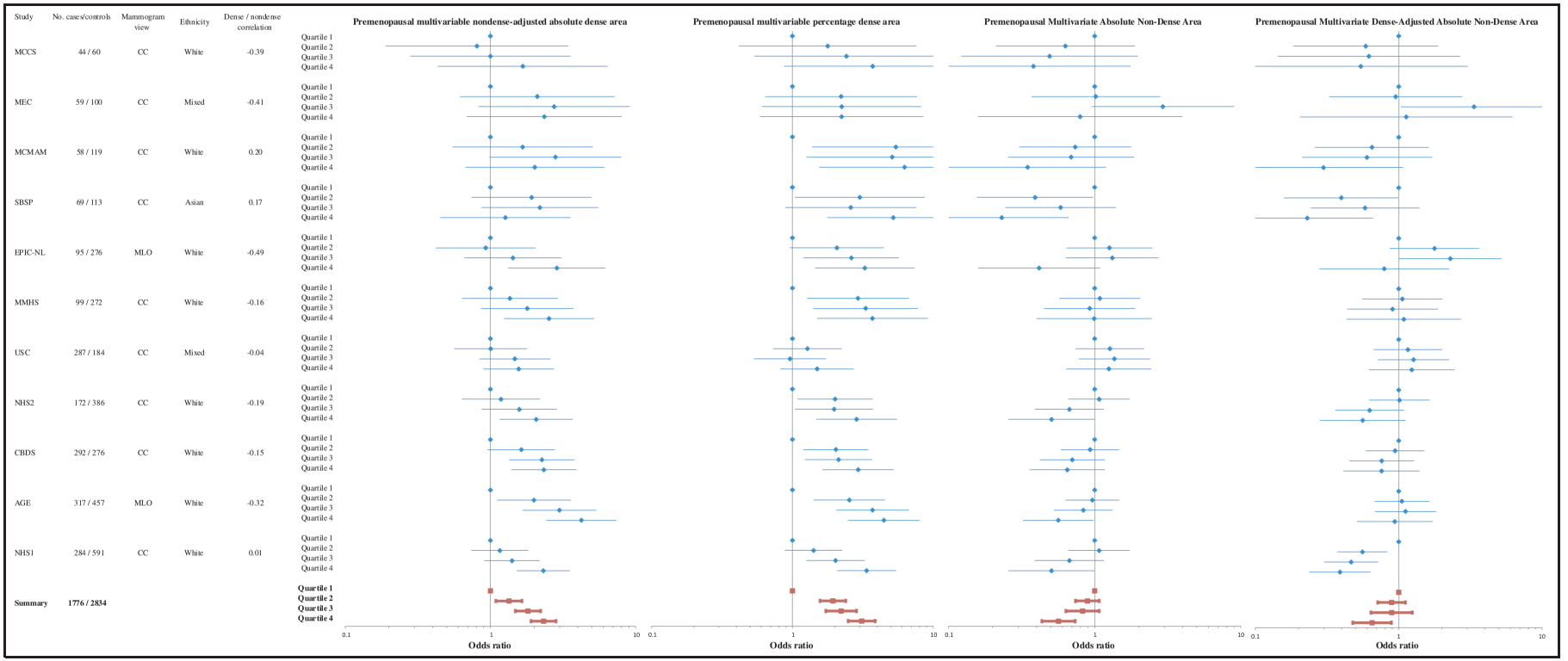

Figure 1. Odds ratios (ORs) and 95% confidence intervals (CIs) for mammographic density phenotypes and risk of breast cancer among women who were premenopausal at the time of mammography. Random effects models. All statistical tests were two-sided. Additional analytical details are in Supplementary Table 2 (available online). AGE = UK AGE Trial nested case–control study; CAHRES = Cancer and Hormones Replacement in Sweden study; CBDS = Canadian Breast Density Study; CC = craniocaudal; EPIC–NL = Dutch contribution to the European Prospective Investigation into Cancer and Nutrition study; HRT = hormone replacement therapy; MCCS = Melbourne Collaborative Cohort Study; MCMAM = Mayo Clinic Mammography Study; MEC = Hawaii component of the Multiethnic Cohort Study; ML = mediolateral oblique; MMHS = Mayo Mammography Health Study; NHS1 = Nurses' Health Study 1; NHS2 = Nurses' Health Study 2; SBSP = Singapore Breast Cancer Screening Project; UK NHS = Norwich & Cambridge UK NHS Breast Cancer Screening Program; USC = University of Southern California mammographic density study.

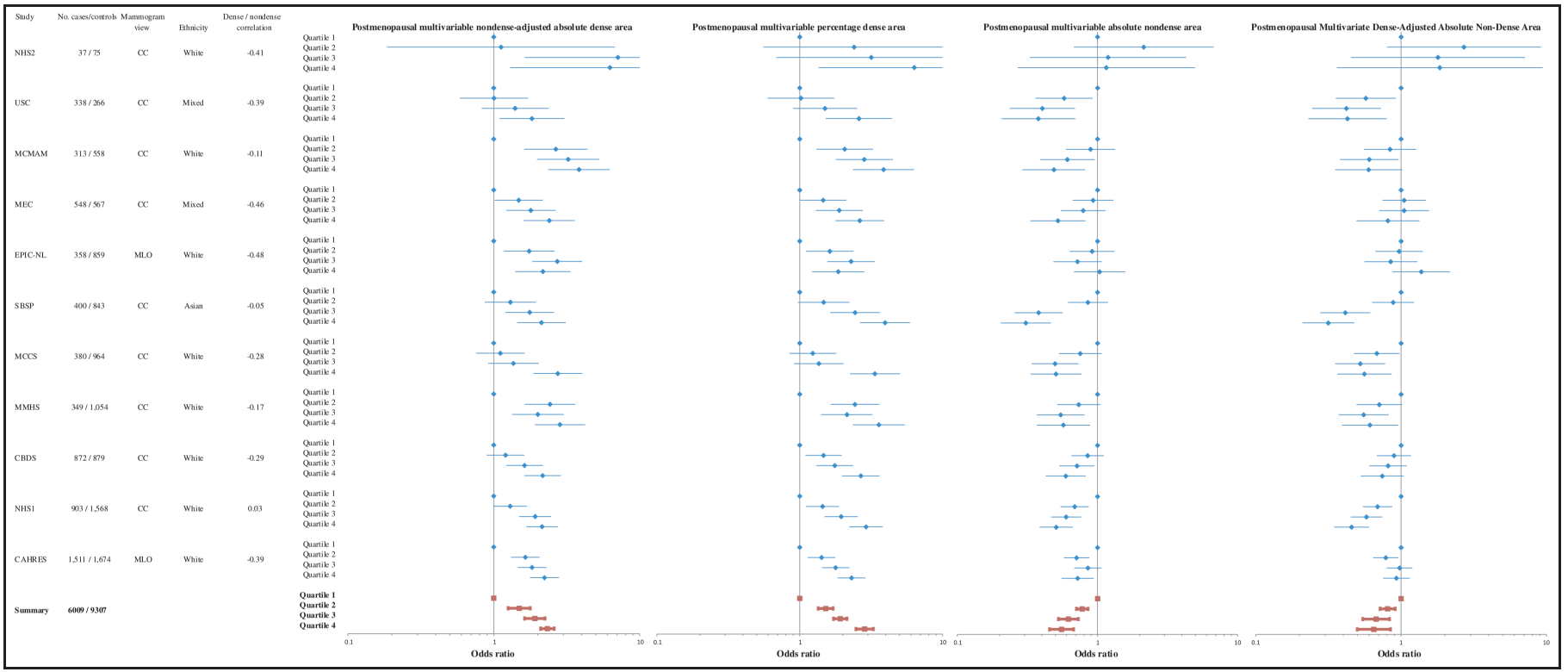

Figure 2. Odds ratios (ORs) and 95% confidence intervals (CIs) for mammographic density phenotypes and risk of breast cancer among women who were postmenopausal at the time of mammography. Random effects models. All statistical tests were two-sided. Additional analytical details are in Supplementary Table 4 (available online). AGE = UK AGE Trial nested case–control study; CAHRES = Cancer and Hormones Replacement in Sweden study; CBDS = Canadian Breast Density Study; CC = craniocaudal; EPIC–NL = Dutch contribution to the European Prospective Investigation into Cancer and Nutrition study; HRT = hormone replacement therapy; MCCS = Melbourne Collaborative Cohort Study; MCMAM = Mayo Clinic Mammography Study; MEC = Hawaii component of the Multiethnic Cohort Study; ML = mediolateral oblique; MMHS = Mayo Mammography Health Study; NHS1 = Nurses' Health Study 1; NHS2 = Nurses' Health Study 2; SBSP = Singapore Breast Cancer Screening Project; UK NHS = Norwich & Cambridge UK NHS Breast Cancer Screening Program; USC = University of Southern California mammographic density study.

(OR = 1.38; 95% CI = 1.32 to 1.45). For percentage dense area, the age-adjusted summary odds ratio was 1.37 (95% CI = 1.32 to 1.42), which increased to 1.53 (95% CI = 1.44 to 1.64) after additional adjustment for BMI and parity. For absolute nondense area, the age-adjusted summary odds ratio for a one standard deviation increment was 0.89 (95% CI = 0.84 to 0.94). Additional adjustment for BMI and parity changed the odds ratio to 0.79 (95% CI = 0.73 to 0.85). In the model further adjusted for absolute dense area, the corresponding summary odds ratio was 0.85 (95% CI = 0.75 to 0.96). Additionally adjusting for ever or current use of HRT did not materially change the results (data not shown).

In the fully adjusted models, there was statistically significant between-study heterogeneity for absolute nondense area ($P < .01$) and for percentage dense area ($P = .01$) with respect to breast cancer risk (Table 3). Between-study heterogeneity remained statistically significant in all analyses excluding the studies one by one (data not shown). In the fully adjusted models, there was also statistically significant heterogeneity by mammogram view for both absolute nondense area ($P = .04$) and percentage dense area ($P = .03$). For both mammographic density phenotypes, the associations were stronger in studies using CC vs MLO view mammograms (Supplementary Table 5, available online). For absolute nondense area, the summary odds ratio among studies using CC views was 0.79 (95% CI = 0.70 to 0.88; $P_{heterogeneity} < .01$), and the summary odds ratio among studies using MLO views (including the MLO view for the MCMAM study) was 1.00 (95% CI = 0.81 to 1.23; $P_{heterogeneity} < .01$). For percentage dense area, the summary odds ratio among studies using CC views was 1.59 (95% CI = 1.49 to 1.69; $P_{heterogeneity} = .12$), and the summary odds ratio among studies using MLO views (including the MLO view for the MCMAM study) was 1.40 (95% CI = 1.28 to 1.54; $P_{heterogeneity} = .20$). For the MCMAM study, results were generally similar using data from either the CC or MLO view (data not shown).

Discussion

In this meta-analysis of 13 case–control studies assessing the association between different mammographic density phenotypes and breast cancer risk, we confirmed that both absolute and percentage dense area are strong risk factors for breast cancer. The risk estimates for breast cancer were higher for percentage than for absolute dense area in the fully adjusted models. Although the confidence intervals for absolute and percentage dense area overlapped, this finding suggests that percentage dense area is the stronger of the two breast cancer risk factors. Results for absolute nondense area were less consistent across studies; most reported a lower risk of breast cancer with increasing absolute nondense area, but in several studies the association disappeared after adjustment for absolute dense area.

Among premenopausal women, the risk estimate for percentage dense area was higher than for absolute dense area in analyses adjusted for age and higher yet after further adjustment for BMI and parity (Table 2). Among postmenopausal women, the risk estimate for percentage dense area was identical to that for absolute dense area in analyses adjusted for age but substantially stronger in analyses additionally adjusted for BMI and parity (Table 3). Higher BMI is associated with a decreased risk of premenopausal breast cancer and an increased risk of postmenopausal breast cancer (25). Higher BMI is also associated with lower percentage dense area. Prior studies suggest that percentage dense area and BMI are independent risk factors for breast cancer that confound each other (26,27). Our results confirm that BMI is an important confounder of the association between percentage dense area (and absolute nondense area) and breast cancer risk, especially among postmenopausal women. Our results also suggest that BMI is not an important confounder for the association between absolute dense area and breast cancer risk. These results underscore the importance of having data available on BMI when assessing the association between percentage dense area (and absolute nondense area) and breast cancer risk, including in risk prediction modeling studies comparing the predictive ability of the different mammographic density phenotypes. If data on BMI are unavailable, the association between absolute dense area and breast cancer risk should still represent an unbiased estimate (ie, unconfounded by BMI) of the association between dense area and breast cancer risk.

Most studies in this meta-analysis reported a lower risk of breast cancer with increasing absolute nondense area, but the associations disappeared after adjustment for absolute dense area in studies with the strongest negative correlation between absolute dense and nondense area. It is unclear why the correlation between absolute dense and nondense area (and thus the association of nondense area and breast cancer risk adjusted for dense area) varies substantially across studies. A possible explanation is measurement error. That is, if dense area is misclassified as nondense area (or vice versa) because of delineation issues with the thresholding technique, this will create a negative correlation between the absolute dense and nondense area. Another possible explanation is that there is a true negative correlation between the absolute dense and nondense area, perhaps because of lobular involution, which varies between populations and studies. Regardless of the underlying mechanism, the between-study variation in the correlation between nondense and dense area in this meta-analysis and the corresponding statistically significant between-study heterogeneity for absolute nondense area in several analyses make it difficult to determine whether absolute nondense area is an independent protective factor for breast cancer. This meta-analysis was limited by the information available to assess between-study heterogeneity. We were able to assess the effect modifiers which we considered to be relevant a priori (eg, BMI, ethnicity, mammogram view). We were unable, however, to determine the extent to which differences across studies in the associations between the mammographic density phenotypes and breast cancer risk were explained by study differences in exposure to other confounding factors, host biology among study participants, underlying breast cancer risk in the study populations, and/or technical differences such as the use of different mammogram machines, digitizers, and readers.

Although the confidence intervals for absolute and percentage dense area overlapped, our results suggest that percentage dense area is the stronger of the two breast cancer risk factors. If correct, this suggests that the ratio of fibroglandular to fatty tissue may be important in breast cancer development. Alternatively, assuming that women with high absolute or percentage mammographic density are at increased risk for breast cancer only because they have large amounts of fibroglandular breast tissue, measurement error may explain the weaker association for absolute dense area, and percentage dense area may be the most accurate estimate of the total amount of fibroglandular breast tissue. The current literature,

however, suggests that percentage dense area on a mammogram has a weak relationship with the total amount of fibroglandular breast tissue. Shepherd and colleagues estimated the fibroglandular volume from digitized film mammograms using single x-ray absorptiometry (28) and reported virtually no association between percentage dense area (measured using a software similar to Cumulus) and fibroglandular volume (r^2 = 0.01). Interestingly, other research has shown a high correlation between standard percentage density and calibrated percentage density measures accounting for acquisition parameters, including breast compression thickness (29). Still, additional studies are needed to determine whether absolute or percentage dense area on a mammogram most accurately reflects the total volume of fibroglandular breast tissue.

There are several biological mechanisms that can explain the association between the different mammographic density phenotypes and breast cancer risk. Absolute and percentage dense area are likely positively associated with breast cancer risk at least partially because they are positively correlated with the number of epithelial cells at risk of malignant transformation. Percentage dense area additionally reflects the amounts of fibroblasts and other stromal cells, connective tissue, and fat cells in the breasts, all which may affect breast cancer risk (30). It has been proposed, for example, that high extracellular matrix content and tissue stiffness or quantitative or structural changes of the stromal collagen such as cross-linking may partly explain the association between percentage dense area and breast cancer risk (31–33). Larger amounts of breast fat, which is the major component of absolute nondense area and inversely associated with percentage dense area, may also decrease breast cancer risk (6,34). The adipocytes that form the breast adipose tissue arise from the differentiation of stromal preadipocytes. Aromatase activity in the breast provides a source of estrogen production that may stimulate tumor growth. Aromatase activity in adipose tissue is primarily in stromal preadipocytes, and activity diminishes with differentiation to mature adipocytes (35,36). The loss of this source of estrogen after the differentiation might contribute to the inverse association between absolute nondense area and breast cancer risk. It should be noted, however, that breast fat has also been suggested to increase breast cancer risk (5,37). Finally, lobular involution is inversely associated with breast cancer risk, positively associated with absolute nondense area, and negatively associated with percentage dense area (38). Thus it is possible that nondense area is inversely associated with breast cancer risk because it reflects the degree of lobular involution.

In conclusion, we confirm that both absolute and percentage dense area on a mammogram are strong predictors of breast cancer risk. Our results also suggest that percentage dense area is a stronger breast cancer risk factor than absolute dense area and that absolute nondense area may be inversely associated with breast cancer risk.

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Notes

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