Research Article

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Association of Body Size Measurements and Mammographic Density in Korean Women: The Healthy Twin Study

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Abstract

Background: Both greater body size and higher mammographic density seem to be associated with a risk of breast cancer. To understand a mechanism through which body size confers a higher risk of breast cancer, associations between mammographic measures and various measures of body size were examined.

Method: Study subjects were 730 Korean women selected from the Healthy Twin study. Body size measurements were completed according to standard protocol. Mammographic density was measured from digital mammograms using a computer-assisted method from which the total area and the dense area of the breast were calculated, and nondense area and percent of dense area were straightforwardly derived. Linear mixed models considering familial correlations were used for analyses.

Results: Total and nondense areas were positively associated with current body mass index (BMI), BMI at 35 years, total fat percent, waist circumference, and waist-hip ratio, whereas percent dense area was inversely associated with these characteristics in both premenopausal and postmenopausal women. Height was not associated with any mammographic measure. Total and nondense areas had strong positive genetic correlations with current BMI, total fat percent, waist circumference, and waist-hip ratio, whereas percent dense area had strong inverse genetic correlations with these body size measurements.

Conclusion: Mammographic density and obesity are inversely associated with each other possibly from common genetic influences that have opposite effects on mammographic density and obesity in Korean women.

Impact: The association between obesity and breast cancer does not seem to be mediated through mammographic density. *Cancer Epidemiol Biomarkers Prev; 19(6); 1523–31. ©2010 AACR.*

Introduction

Mammographic density reflects the relative amount of connective and epithelial tissue (dense area) and fat tissue (nondense area) in a breast (1, 2), which varies among women. Higher mammographic density has been found to confer a greater risk of breast cancer than does lower mammographic density (1, 3-11). Even in nonwhite women with a lower incidence rate of breast cancer compared with Caucasians, higher mammographic density is associated with an increased risk of breast cancer (12, 13).

Body size indices such as body mass index, waist circumference, waist-hip ratio, and height have been found to be associated with breast cancer risk (14-17). Taller (16) and more obese postmenopausal women (14, 15, 17, 18) tend to have a higher risk of breast cancer. The underlying mechanism for the relationship between body size indices and breast cancer risk is still uncertain, and greater height and obesity may increase the risk of breast cancer through their effects on the components of breast tissue. However, the associations of body size indices and mammographic density have not been in accordance with the associations between the body size indices and breast cancer in studies of Western populations (19, 20) as well as of Singaporean Chinese women (21, 22). Replication of these findings in other Asian populations would provide strong evidence that body size increases the risk of breast cancer through another mechanism than their influence on breast tissue components.

In this regard, we conducted a twin and family study in a general Korean population to evaluate the relationship between mammographic measures and various measures of body size considering menopausal status. The association between mammographic measures and body size characteristics considering menopausal status

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is worth examining, given that more obese women have an evidently increased risk of breast cancer only in their postmenopausal years. Investigating families from the general population not selected by their health status and using the various family relationships enabled us not only to examine the association, but also to explore the possible shared genetic factors influencing between body size measurements and measures of mammographic density.

Materials and Methods

Study participants were female members from the Healthy Twin study who had received a mammogram and had body size measurements taken during a routine health examination. Participants were not ascertained by their health status or breast diseases. Details on overall methodology of this multicenter cross-sectional survey have been previously published (23). From April 2005 to December 2007, a total of 2,278 Korean adult (≥30 years of age) twins and their first-degree adult family members were recruited. Among the 734 women who received a mammogram, four were excluded because they were shown to be genetically unrelated with their family by genetic tests. Thus, 730 women from 341 families were finally included in the analysis, with 122 pairs of monozygotic twins, 28 pairs of dizygotic twins, and 430 female family members among them.

All mammograms were taken using the same full-field digital mammography system (Senographe 2000D/DMR/DS, General Electric Company) in female participants if they were age ≥40 years at the time of participation in the study, or were willing to undergo a mammogram. A single observer measured one cranio-caudal view of the right breast of each woman using a computer-assisted thresholding technique called Cumulus, in which the total area of the breast and the area of dense tissue are measured. Nondense area and percent dense area were straightforwardly derived. This measure has been shown to be highly reproducible and reliable (24).

Mammograms were randomized first by family into reading sets of approximately 100, ensuring that all twins and/or relatives of the same family were measured in the same set. The reader was blinded to all identifying information, and a 10% random sample of repeats was included in each set and between every third set to test the reliability of the measurement.

Body size measurement

All measurements of body size for each participant were completed twice by trained research assistants, and the average value of two measurements was used for the analysis. Body weight (kg) was measured to the nearest 0.1 kg using a digital scale with the participant in light clothing and wearing no shoes. Height (cm) was measured to the nearest 0.1 cm using a stadiometer while the participant stood with heels together, arms to the side, legs straight, shoulders relaxed, and the head positioned so the gaze was straight ahead. Body mass index (BMI) was calculated as the weight divided by the height squared (kg/m^2). Waist circumference (WC) was measured (cm) at the narrowest area between the lower margin of the rib cage and iliac crest as viewed from the front while the participant stood erect with arms at the side. Hip circumference (cm) was measured at the point of greatest circumference around the buttock with the participant standing. Waist-hip ratio (WHR) was calculated by dividing the waist circumference by the hip circumference. Total percent fat was measured using a Lunar Prodigy version 8.50 dual-energy X-ray absorptiometer (Lunar Radiation/Delphi W, Hologic). Total fat percentage was calculated as fat mass divided by the sum of fat mass, lean mass, and bone mineral content.

A self-administered questionnaire collected information pertaining to weight at 20 years of age and at 35 years of age (if applicable), health behaviors (smoking, alcohol consumption, and physical activity), reproductive history (age at menarche, age at first childbirth, live birth, duration of breast feeding, menopause, use of oral contraceptives, and use of hormone replacement therapy), and medical and demographic characteristics (age, education level). An additional face-to-face interview was carried out by a trained interviewer to clarify incomplete or ambiguous responses.

Zygosity of twin pairs was identified by 16 short tandem repeat markers (15 autosomal short tandem repeat markers and one sex-determining marker) in 67% of twin pairs. For the remaining 33% of twin pairs, zygosity was determined by a self-administered zygosity questionnaire that was validated as being 94.3% accurate through a short tandem repeat marker study (25).

All participants provided written informed consent when they visited one of the study centers. The study protocol was approved by the Korea Center for Disease Control and the institutional review board of the three participating centers (Samsung Medical Center, Pusan Paik Hospital, and Dankook University Hospital).

Statistical analysis

Intraclass correlation coefficients were estimated to assess reliability of repeated measurements of mammographic density within reading sets. Age-adjusted residuals of each of the mammographic measures were inspected for normality, and log transformations were applied to all of the mammographic measures.

As mammographic density is strongly associated with age, age-adjusted measures according to body size level were calculated using analysis of covariance. Linear trends of the mammographic measures with the body size measures were examined using age-adjusted linear regression analysis.

Associations of body size characteristics with the mammographic measures were evaluated using mixed linear models in which household and twin effects were adjusted as random effects and other covariates (age, smoking, alcohol consumption, physical exercise, educational level, number of live children, age at birth of first child, duration of breast feeding, and use of oral contraceptives) were adjusted as fixed effects. Correlation structures from family relationships were adjusted by using a mixed linear model, in which both family (as family number) and twin (as twin number) effects were considered as random effects (26). For postmenopausal women, hormone replacement treatment was added in the model as a fixed effect.

To ascertain evidence of common genetic regulation between percent dense area and body size indices, we conducted bivariate variance-component-based genetic analysis to partition the phenotypic correlations into genetic (ρ_G) and environmental correlations (ρ_E) using SOLAR (Sequential Oligogenic Linkage Analysis Routines) version 2.0 (27). The bivariate variance-component analysis allows examining whether the correlation between two or more phenotypes of an individual and among family members is concurrently determined by shared genes and environments. If a significant genetic correlation existed, it was considered evidence of pleiotropy, genetic effect of a single gene on multiple phenotypic traits, or common genetic factors influencing both phenotypes through shared pathways. To estimate independent genetic correlations, age was adjusted at first and then other covariates were adjusted additionally.

Results

When we estimated the reliability of mammographic density measurement in 65 randomly chosen women, intraclass correlation coefficients between the repeated measurements for total area, dense area, nondense area, and percent dense area were 0.99, 0.98, 0.97, and 0.98, respectively.

Tables 1 and 2 show the characteristics of participating women and the distribution of the mammographic measures according to quartiles of body size characteristics. Women with higher current BMI, higher BMI at 20 and at 35 years of age, higher total fat percent, higher WC, and higher WHR had greater total and nondense areas, and less percent dense area (all $P < 0.001$). Dense area was inversely associated with current BMI ($P < 0.05$), WC ($P < 0.01$), and WHR ($P < 0.01$). There was no relation between height and any of mammographic measures (all $P > 0.05$).

Table 3 shows the associations between the body size characteristics and the mammographic measures by menopausal status. Consistent with Table 2, in both premenopausal and postmenopausal women, total and nondense area were positively associated with current BMI, total fat percent, WC, and WHR, whereas percent dense area was inversely associated with those characteristics. The inverse associations found between dense area and current BMI, WC, and WHR existed in premenopausal women only (all $P < 0.01$). Height was not associated with any of mammographic measures in both premenopausal and postmenopausal women.

Table 1. Characteristics of study participants

Characteristics	Mean (SD)
Number of participants	730
Age at mammogram, y	47.2 (11.9)
Total mammographic area, cm^2	110.6 (40.2)
Percent dense area, %	34.4 (23.2)
Current BMI, kg/m^2	23.6 (3.3)
BMI at 35 y old (*n* = 598), kg/m^2	22.1 (2.80)
BMI at 20 y old (*n* = 582), kg/m^2	20.6 (2.31)
Total body fat percent, %	32.5 (6.34)
Waist circumference, cm	78.9 (8.86)
Waist-hip ratio	0.84 (0.07)
Height, cm	156.0 (5.7)
Ever smoked, %	9.8
Ever drank alcohol, %	54.1
Regular physical exercise, %	34.5
Years of education, %	
<12	31.5
12-15	46.7
≥16	21.8
Age at menarche, %	
<12 y	3.3
12-15 y	67.8
>15 y	28.9
Nulliparous, %	9.6
Age at first childbirth, %	
<25 y	30.5
25-29 y	55.8
≥30 y	13.8
No. of living children, mean (SD)	2.5 (1.7)
Duration of breast feeding	
Never	9.8
<6 mo	22.3
6-11 mo	16.5
12-23 mo	24.3
≥24 mo	27.2
Ever use of oral contraceptives, %	16.3
Ever use of estrogen replacement, %	9.6
Postmenopausal status, %	36.7
Breast cancer of family member, %	3.2

Table 4 shows the analysis of additive cross-trait correlations between the mammographic measures and body size characteristics. Total and nondense area showed strong positive genetic correlation with current BMI, total fat percent, WC, and WHR, whereas percent dense area showed strong inverse genetic correlation with these body size measurements (all $P < 0.01$). There were significant but weak inverse genetic correlations between dense area and current BMI, WC, and WHR (all $P < 0.05$). The estimates of genetic correlation did not change materially when covariates were fully adjusted (Table 4).

Table 2. Age-adjusted levels of the mammographic measures by quartiles of body size characteristics

Body size characteristics	Number of participants	Total area, cm^2 Mean (SE)	Nondense area, cm^2 Mean (SE)	Dense area, cm^2 Mean (SE)	Percent dense area, % Mean (SE)
Current BMI, kg/m^2					
<21.2	178	84.7 (2.42)	50.0 (2.29)	34.8 (1.50)	44.8 (1.19)
21.2-23.2	190	103.6 (2.29)	67.5 (2.18)	36.1 (1.43)	36.2 (1.13)
23.3-25.3	180	112.2 (2.35)	79.3 (2.23)	32.9 (1.46)	30.6 (1.16)
≥25.4	182	141.6 (2.41)	110.0 (2.29)	31.5 (1.50)	26.0 (1.19)
P for trend		<0.001	<0.001	0.049	<0.001
BMI at 35 y, kg/m^2					
<20.1	146	90.0 (2.69)	56.0 (2.63)	34.0 (1.65)	42.3 (1.36)
20.1-21.8	147	105.1 (2.67)	69.5 (2.61)	35.6 (1.65)	36.0 (1.35)
21.9-23.4	147	114.5 (2.67)	78.8 (2.62)	35.7 (1.65)	33.3 (1.35)
≥23.5	158	132.4 (2.60)	99.5 (2.54)	32.9 (1.60)	27.5 (1.31)
P for trend		<0.001	<0.001	0.486	<0.001
BMI at 20 y, kg/m^2					
<19.1	144	96.8 (2.77)	61.9 (2.72)	34.9 (1.70)	39.9 (1.44)
19.1-20.4	146	105.5 (2.76)	68.9 (2.71)	36.7 (1.69)	38.2 (1.44)
20.5-21.7	138	105.6 (2.83)	67.9 (2.78)	37.7 (1.74)	37.9 (1.48)
≥21.8	154	121.8 (2.70)	82.9 (2.65)	38.9 (1.66)	35.2 (1.41)
P for trend		<0.001	<0.001	0.128	0.003
Total fat percent, %					
<28.1	180	93.0 (2.59)	55.9 (2.48)	37.2 (1.50)	44.2 (1.21)
28.1-32.1	181	100.7 (2.51)	67.3 (2.41)	33.4 (1.45)	35.1 (1.17)
32.2-36.1	186	114.6 (2.49)	82.1 (2.39)	32.5 (1.44)	30.6 (1.16)
≥36.2	183	133.6 (2.53)	101.1 (2.43)	32.6 (1.47)	27.8 (1.18)
P for trend		<0.001	<0.001	0.057	<0.001
Waist circumference, cm					
<72.5	178	86.2 (2.53)	50.0 (2.39)	36.2 (1.53)	46.0 (1.20)
72.5-77.9	183	104.3 (2.40)	68.7 (2.27)	35.5 (1.45)	35.6 (1.14)
78.0-84.4	185	111.4 (2.38)	78.7 (2.26)	32.6 (1.44)	30.3 (1.13)
≥84.5	184	139.8 (2.50)	108.5 (2.37)	31.3 (1.51)	25.9 (1.19)
P value for trend		<0.001	<0.001	0.005	<0.001
Waist-hip ratio					
<0.80	183	89.2 (2.66)	53.9 (2.54)	35.3 (1.52)	43.9 (1.22)
0.80-0.83	174	105.8 (2.61)	69.1 (2.49)	36.7 (1.49)	36.8 (1.20)
0.84-0.88	185	114.8 (2.52)	81.1 (2.40)	33.7 (1.43)	31.1 (1.16)
≥0.89	188	131.8 (2.68)	101.8 (2.56)	30.0 (1.53)	26.0 (1.23)
P for trend		<0.001	<0.001	0.008	<0.001
Height, cm					
<152.2	182	107.5 (2.78)	74.9 (2.75)	32.5 (1.48)	34.7 (1.27)
152.2-155.8	182	107.7 (2.72)	76.0 (2.69)	31.7 (1.45)	33.6 (1.25)
155.9-159.8	178	116.6 (2.76)	79.5 (2.72)	37.1 (1.47)	34.8 (1.26)
≥159.9	188	110.8 (2.73)	76.5 (2.70)	34.2 (1.45)	34.3 (1.25)
P for trend		0.304	0.700	0.223	0.765

Discussion

In this Korean female twin and family study, we found that body size characteristics that describe obesity were associated with mammographic measures, whereas height was not associated with any of the examined mammographic measures. Our study has its unique strength in several aspects. First, we examined the relationship of mammographic density with various measures of obesity, including abdominal obesity and BMI level at various ages. Second, we examined genetic correlation between mammographic density and body size

Table 3. Associations between body size characteristics and the mammographic measures in premenopausal and postmenopausal women

	Premenopausal women (*n* = 462)				Postmenopausal women (*n* = 268)			
	Total area, cm^2	Nondense area, cm^2	Dense area, cm^2	Percent dense area, %	Total area, cm^2	Nondense area, cm^2	Dense area, cm^2	Percent dense area, %
Current BMI, kg/m^2	0.059* (0.049-0.067)	0.121* (0.102-0.140)	−0.031* (−0.050 to −0.013)	−0.082* (−0.009 to −0.067)	0.064* (0.052-0.076)	0.081* (0.064-0.100)	−0.045 (−0.090 to 0.002)	−0.101* (−0.144 to −0.056)
BMI at 35 y, kg/m^2	0.053* (0.042-0.065)	0.106* (0.083-0.131)	−0.016 (−0.038 to 0.007)	−0.065* (−0.085 to −0.045)	0.047 (NA)	0.064 (NA)	−0.058 (NA)	−0.101 (NA)
BMI at 20 y, kg/m^2	0.040* (0.025-0.053)	0.060* (0.031-0.088)	0.012 (−0.013 to 0.038)	−0.026† (−0.048 to −0.002)	0.010 (NA)	0.013 (NA)	−0.017 (NA)	−0.026 NA
Total fat percent, %	0.019* (0.014-0.023)	0.049* (0.040-0.058)	−0.009 (−0.019 to 0.000)	−0.028* (−0.037 to −0.019)	0.019* (0.012-0.027)	0.029* (0.019-0.039)	−0.016 (−0.040 to 0.010)	−0.034† (−0.059 to −0.008)
Waist circumference, cm	0.018* (0.015-0.021)	0.041* (0.035-0.048)	−0.014* (−0.021 to −0.007)	−0.031* (−0.038 to −0.026)	0.023* (0.019-0.028)	0.029* (0.023-0.037)	−0.016 (−0.034 to 0.004)	−0.038* (−0.057 to −0.019)
Waist-hip ratio	5.740* (3.250-9.676)	68.062* (27.531-166.001)	−0.820* (−0.929 to −0.542)	−0.976* (−0.990 to −0.944)	8.272* (3.389-18.590)	16.939* (5.411-49.149)	−0.591 (−0.971 to 4.842)	−0.957† (−0.997 to −0.311)
Height, cm	0.003 (−0.003 to 0.009)	0.003 (−0.009 to 0.015)	0.005 (−0.006 to 0.016)	0.0003 (−0.010 to 0.011)	0.000 (−0.010 to 0.010)	−0.001 (−0.015 to 0.012)	0.005 (−0.027 to 0.038)	0.003 (−0.031 to 0.039)

NOTE: β coefficients (95% confidence intervals, indicated in parenthesis) were assessed by linear mixed model. Then, percent differences were calculated by subtracting 1 from exponentiated β coefficient. For premenopausal women, random effect (household, twin pair) and fixed effect (age, smoking habit, alcohol consumption, physical exercise, educational level, number of live children, age at menarche, age at birth of first child, duration of breast feeding, and use of oral contraceptives) were adjusted. For postmenopausal women, hormone replacement treatment (fixed effect) was additionally adjusted.

*$P < 0.01$.

†$P < 0.05$.

characteristics using various types of family relationships, including monozygotic twins and nontwin family members.

Consistent with results from previous studies involving Western populations (19, 28-30), measures of obesity had strong positive associations with nondense mammographic area, whereas it had a weak inverse association with dense area. Menopausal status did not confer any difference in the associations between the body size characteristics and the other mammographic measures.

Findings from bivariate analysis suggested that pleiotropy exists between measures of obesity and mammographic density. General and localized adiposity had strong positive genetic correlations with nondense area and weak but significantly inverse correlation with dense area. These findings are compatible with the findings regarding the associations between obesity and mammographic density, and indicate that common genetic factors regulate both general obesity and the nondense area of the breast.

Because percent dense area reflects the relative proportion of parenchyma (dense area) over total breast area (sum of the parenchyma and fat tissue), both dense and nondense areas directly influence the percent dense area. In this study, dense area decreased only slightly with increasing adiposity, but nondense area increased more, which resulted in a strong negative association between obesity and percent dense area.

The biological mechanism explaining the association between obesity and nondense area is still unclear. Given that fat tissue is a major component of mammary nonparenchymal tissue (nondense area), it is plausible that an obese woman could have greater nondense area in mammography regardless of the absolute dense area, and accordingly lower percent dense area, which in theory should lower the risk of breast cancer in obese women. This hypothesis on the adiposity-mammographic density-breast cancer relation is compatible with the commonly observed lower risk of breast cancer in obese premenopausal women (31, 32), and it may be probable that adiposity acts on breast cancer risk through mammographic density in premenopausal women. However, the greater risk of breast cancer in obese postmenopausal women (18, 33) contradicts this hypothesis, and it is less likely that the association between obesity and breast cancer is mediated through breast tissue subcomponents reflected in mammographic density among postmenopausal women.

Evaluations of the relationship among body size, mammographic density, and breast cancer risk have shown that the positive association between obesity and breast cancer becomes stronger with an adjustment for mammographic density, particularly measures that reflect percent dense area, and that the positive association between mammographic density and breast cancer becomes stronger with an adjustment for obesity in both premenopausal and postmenopausal women (6, 28, 34). These findings suggest that obesity and mammographic density independently play a role in the association with breast cancer, rather than a role as a mediating factor (28).

In accordance with this, a randomized controlled trial showed that mammographic density was weakly influenced by level of estrogen (35, 36), whereas obesity renders its main effect on the risk of breast cancer through its effect on estrogen level, especially in postmenopausal women (9, 37, 38). Although some cross-sectional studies reported a positive association between mammographic density and estrogen levels (39, 40), many other studies reported no or inverse association (41-43) when BMI and other risk factors of breast cancer were adjusted. These findings further suggest that adiposity does not act on breast cancer risk through mammographic density at least in postmenopausal women.

Table 4. Additive genetic cross-trait correlation between the mammographic measures and the body size measurements in the same individual

	Age-adjusted estimates*			
	Total area, cm^2	Nondense area, cm^2	Dense area, cm^2	Percent dense area, cm^2
Current BMI, kg/m^2	0.60 (0.04)‡	0.69 (0.04)‡	−0.16 (0.07)§	−0.47 (0.06)‡
BMI at 35 y, kg/m^2	0.57 (0.06)‡	0.57 (0.06)‡	−0.01 (0.08)	−0.34 (0.07)‡
BMI at 20 y, kg/m^2	0.43 (0.08)‡	0.39 (0.08)‡	0.06 (0.08)	−0.18 (0.09)§
Total fat percent, %	0.39 (0.05)‡	0.48 (0.05)‡	−0.10 (0.06)	−0.33 (0.06)‡
Waist circumference, cm	0.57 (0.05)‡	0.69 (0.04)‡	−0.21 (0.07)‡	−0.53 (0.06)‡
Waist-hip ratio	0.46 (0.06)‡	0.59 (0.05)‡	−0.21 (0.07)‡	−0.47 (0.06)‡
Height, cm	0.03 (0.05)	0.01 (0.05)	0.079 (0.05)	0.02 (0.05)

*Estimates (SE) were assessed by bivariate analysis.
†Adjusted for age, age^2, smoking, alcohol consumption, physical exercise, educational level, number of live children, age at menarche, age at birth of first child, duration of breast feeding, use of oral contraceptives, menopausal status, and use of estrogen replacement therapy were considered.
‡$P < 0.01$.
§$P < 0.05$.

Table 4. Additive genetic cross-trait correlation between the mammographic measures and the body size measurements in the same individual (Cont'd)

Multivariate-adjusted estimates†			
Total area, cm^2	Nondense area, cm^2	Dense area, cm^2	Percent dense area, cm^2
0.59 (0.04)§	0.69 (0.04)‡	−0.18 (0.07)‡	−0.49 (0.06)‡
0.57 (0.06)‡	0.57 (0.06)‡	−0.02 (0.08)	−0.37 (0.07)‡
0.45 (0.08)‡	0.41 (0.08)‡	0.11 (0.09)	−0.19 (0.09)§
0.38 (0.05)‡	0.47 (0.05)‡	−0.12 (0.06)	−0.35 (0.06)‡
0.57 (0.05)‡	0.69 (0.04)‡	−0.19 (0.07)‡	−0.53 (0.06)‡
0.47 (0.06)‡	0.59 (0.06)‡	−0.18 (0.07)§	−0.46 (0.07)‡
0.01 (0.05)	−0.01 (0.05)	0.05 (0.05)	0.01 (0.05)

Mammographic density seems to be associated with level of insulin-like growth factor-I (IGF-I; refs. 41, 44-48), especially in premenopausal women (39, 41, 44, 45). Several meta-analyses in which most studies included had controlled for obesity level found that IGF-I level was positively associated with breast cancer, especially in premenopausal women (49-51). Although some exceptional findings exist (40, 52), prolactin level also has been positively associated with mammographic density in both premenopausal (39) and postmenopausal women (41, 53), and a positive association between prolactin level and breast cancer risk independent of BMI level has been reported (54-56). Those findings suggest that IGF-I and prolactin may affect breast cancer risk, at least in part, through their influence on breast tissue morphology as reflected on mammogram.

The inverse association between general adiposity and percent dense area, as well as the inverse additive genetic correlation between them, regardless of menopausal status, suggests a more complex scenario underlying the association of obesity with breast cancer. One possibility is that in the general population local adiposity in breast tissue predominates rather than the hyperplasia of parenchyma from the hyperinsulinemia induced by obesity, whereas in those who are susceptible to breast cancer the parenchymal hyperplasia outgrows or matches increased adiposity. This possibility is supported by the finding of negative associations among weight, BMI, and area of dense tissue in controls but not in those with breast cancer (28).

As our study was done in community-dwelling women and only one breast cancer case was included, we could not examine whether the association between dense area and obesity would differ in the presence of breast cancer. A logical next step would be to explore whether there are genetically susceptible subgroups that are more vulnerable to increased adiposity, or whether there are certain susceptible time windows when both breast parenchymal tissue and adiposity increase and result in an increased risk of breast cancer.

In our study, height was not associated with any of the mammographic measures and, in accordance with this finding, there was no significant genetic correlation between the two. This finding is compatible with findings from previous studies (28, 30) and suggests that height does not operate through relative proportion of breast tissue components manifested in mammographic density on the risk of breast cancer.

To date, the association between breast cancer risk and mammographic density has been established using film-screen mammograms, not digital mammography. However, given that digital mammography has been shown to be similar to or more sensitive than film-screen mammography in overall diagnostic value and in detecting breast cancer (57, 58), it is unlikely that our findings were affected by the use of digital instead of digitized film images. Also, all of the mammograms measured in this study were taken using the same type of digital mammography machine, eliminating any potential bias due to image processing.

In conclusion, mammographic density and measures of obesity were inversely associated with each other, and an inverse additive genetic correlation exists between them in Korean women. The association between obesity and breast cancer, especially in postmenopausal women, does not seem to be mediated through mammographic density.

Disclosure of Potential Conflicts of Interest

The authors have nothing to disclose.

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