Body Size, Mammographic Density, and Breast Cancer Risk

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Abstract

Background: **Greater weight and body mass index (BMI) are negatively correlated with mammographic density, a strong risk factor for breast cancer, and are associated with an increased risk of breast cancer in postmenopausal women, but with a reduced risk in premenopausal women. We have examined the associations of body size and mammographic density on breast cancer risk.**

Method: **We examined the associations of body size and the percentage of mammographic density at baseline with subsequent risk of breast cancer among 1,114 matched case-control pairs identified from three screening programs. The effect of each factor on risk of breast cancer was examined before and after adjustment for the other, using logistic regression.**

Results: **In all subjects, before adjustment for mammographic density, breast cancer risk in the highest quintile of BMI, compared with the lowest, was 1.04 [95% confidence interval (CI), 0.8-1.4]. BMI was associated positively with breast cancer risk in postmenopausal women, and negatively in premenopausal women. After adjustment for density, the risk associated with BMI in all subjects increased to 1.60 (95% CI, 1.2-2.2), and was positive in both menopausal groups. Adjustment for BMI increased breast cancer risk in women with 75% or greater density, compared with 0%, increased from 4.25 (95% CI, 1.6-11.1) to 5.86 (95% CI, 2.2-15.6).**

Conclusion: **BMI and mammographic density are independent risk factors for breast cancer, and likely to operate through different pathways. The strong negative correlated between them will lead to underestimation of the effects on risk of either pathway if confounding is not controlled.**
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Introduction

The extent of radiologically dense breast tissue, referred to here as mammographic density, varies among women and reflects differences in breast tissue composition. Stroma and epithelium attenuate X-rays more than fat and appear light in a mammogram, whereas fat appears dark (1). The extent of mammographic density can be measured or estimated, and expressed as a percentage, by determining the proportion of the total projected area in the breast that is occupied by dense tissue. Women with density in 75% or more of the breast have a risk of breast cancer four to six times that of women with little or no density (2-5).

The extent of mammographically dense breast tissue is influenced by several risk factors for breast cancer, and is less extensive in women who are parous or postmenopausal (6, 7), and is increased by hormone therapy (8) and reduced by tamoxifen (9). For each of these factors, the direction of their effect on mammographic density is the same as their effect on risk of breast cancer, although it is not yet known if the influence of these factors on risk is mediated through their effects on density. Body weight, however, seems to be an exception. Obesity is associated with an increase in the risk of breast cancer in postmenopausal women, but is associated with a decrease in risk in premenopausal women (10, 11). In both premenopausal and postmenopausal women, body weight is inversely associated with the percentage of mammographic density (12-14), because greater weight is associated with a larger area of non–dense tissue in the mammogram, reflecting a greater quantity of fat in the breast. The associations of mammographic density with body weight are thus in the same direction as their effects on breast cancer risk in premenopausal women, but opposite in direction in postmenopausal women.

Previous studies, using qualitative methods of classifying mammographic features, have shown that the effects on risk of breast cancer from both weight and mammographic density became stronger after adjustment in analysis for the other factor (12, 15). These studies suggest that body size and mammographic density are negative confounders of each other in their association with risk of breast cancer.

The purpose of this study was to examine the association of indices of body size with mammographic density, assessed quantitatively, and with risk of breast cancer. The computer-assisted quantitative measure of mammographic density used has been shown to be strongly associated with risk of breast cancer (4), and generates separate measures of the total area of the breast and the area of dense tissue on a mammogram, from which the area of non–dense tissue can be derived (16). We have examined the association of each of these measures with measures of body size, and the effects of adjustment for these mammographic features on the risk of breast cancer associated with measures of body size.

Materials and Methods

General Method. We used data from three nested case-control studies carried out in screening populations to examine the association of indices of body size at the time of entry to the screening program, with features in the baseline screening mammogram, and with risk of breast cancer during subsequent follow-up. Ethical approval of the study was obtained from the University of Toronto, The University Health Network (Toronto), The Ontario Breast Screening Program (OBSP), and the University of British Columbia.

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Table 1. Selected characteristics of subjects

Characteristics (N = 1,114 case-control pairs)	Case*	Control	P †
Age (y)	56.7 (9.1)	56.7 (9.1)	
Height (cm)	162.3 (6.6)	162.3 (6.7)	0.97
Weight (kg)	65.7 (11.5)	65.6 (11.3)	0.81
BMI	25.0 (4.2)	24.9 (4.2)	0.91
Age at menarche (y)	12.9 (1.5)	13.0 (1.5)	0.05
	n = 1,084	n = 1,090	
Age at first birth (y)	24.8 (4.7)	24.3 (4.4)	0.05
	n = 932	n = 981	
Parity (% parous)	84.2	88.4	0.004
Number of live births	2.5 (1.8)	2.7 (1.8)	<0.001
	n = 1,113		
Postmenopausal (%)	74.7	76.0	0.46
Natural menopause	42.6	45.0	
Surgical menopause	32.1	31.1	
Age at menopause (y) ‡	50.99 (50.94-51.04)	50.92 (50.85-50.99)	0.03
	n = 992	n = 998	
Hormone replacement therapy (% ever use)	35.7	32.5	0.11
Years of hormone replacement therapy use	2.4 (5.6)	2.1 (5.4)	0.07
	n = 1,096	n = 1,092	
Breast cancer in first degree relative (%)			<0.001
0	79.4	84.4	
1	18.0	14.4	
2+	2.6	1.3	
Percent density	32.7 (19.7)	26.9 (19.1)	<0.001

*Data shown is mean (SD) for continuous variables (except age at menopause), percentage for categorical variables.
†P values for age at menopause is based on log-rank test, for symmetrically distributed variable is based on paired t test, for nonsymmetrically distributed variable is based on Wilcoxon rank sum test, and for categorical variable is based on Mantel-Haenszel χ^2 test. All statistical tests are two-sided.
‡Median age at menopause and 95% CI from Kaplan-Meier estimates.

Screened Populations. The National Breast Screening Study (NBSS) was a randomized trial of screening with mammography and physical examination, with a 1-year screening interval (17, 18). The Screening Mammography Program of British Columbia (SMPBC) uses mammography as the only screening modality at the screening center, and had, during the period of this study, a 1-year screening interval. The OBSP uses mammography and physical examination as screening modalities and has a 2-year screening interval.

Selection of Subjects. For cases in the NBSS, informed consent had been obtained at entry to the trial for research applications using the data collected, and all 354 subjects diagnosed with invasive breast cancer between 1984 and 1990, and their controls matched according to age, center and date of enrollment in screening, and length of time of observation, were included (4).

For the OBSP and SMPBC, lists of subjects with histologically verified invasive breast cancer diagnosed from 1992 to 1998 (for the OBSP) and from 1988 to 1999 (for the SMPBC) were prepared. Subjects diagnosed with breast cancer within 12 months of their first screening examination were excluded.

Eligible cases in the OBSP and SMPBC were sent a letter, followed by a telephone call, and asked to provide informed consent for the release of their mammogram and to complete a self-administered questionnaire (see below; ref. 4). For each case in the OBSP and SMPBC who provided consent, we selected up to 10 individually matched control subjects, according to year of entry to the screening program (within 1 year), screening center, age at entry to the program (within 1 year), and duration of follow up. Potential controls were approached in random order, and we selected the first matched control that provided consent and had an available mammogram. Each control had been followed for at least as long as the corresponding case subject, before cancer had been diagnosed. Fifty percent of the cases and 54% of the controls selected from the OBSP and SMPBC agreed to take part.

Data Collection. In the NBSS, information on risk factors for breast cancer was obtained by self-administered questionnaire at the time of entry. For subjects in the other two programs, information was also collected by self-administered questionnaire at the time of their recruitment into the present study. All information was collected with reference to the time of the first screening mammogram. Questions included demographic information, height and weight, from which we calculated body mass index (BMI), use of hormone therapy, including duration of use, as well as menstrual and reproductive risk factors.

Mammographic Density Assessment. The craniocaudal view of the unaffected breast in cases, and the corresponding breast in controls, was digitized using a Lumisys 85 digitizer at a pixel size of 260 μm with 12-bit precision, and measured by one observer (N.F. Boyd) using a previously described interactive thresholding technique (16). This method gives measures of the total area of the breast, and the area of dense tissue, in the mammogram. Average reliability for measuring the percentage of density was assessed by re-reading a 10% random sample of images, within and between each session, and was 0.94 both within and between reads.

Statistical Methods. Of the 1,209 case-control pairs recruited. To allow both matched and unmatched analyses on the same group of subjects, 95 pairs were excluded because of missing data, for one or both members of the pair, on weight (n = 43), parity (n = 4), menopausal status (n = 28), family history (n = 2), and hormone therapy (n = 31). Twenty-four pairs were excluded from the NBSS, 34 from the OBSP, and 37 from the SMPBC because of missing data, leaving a total of 1,114 matched case-control pairs for analysis.

The characteristics of cases and controls were compared using paired t tests for symmetrically distributed continuous variables, Wilcoxon rank sum tests for continuous variables whose distributions were skewed, and McNemar's test for categorical variables. The association of anthropometric measures with risk of breast cancer was examined using conditional logistic regression for matched data and logistic regression for unmatched data. Taking into account the matching analyses provides better control of confounding by the matched variables, but unmatched analysis has the advantage of being easier to display.

Table 2. Correlations of body size and mammographic measures

	Cases			Controls		
	Height	Weight	BMI	Height	Weight	BMI
All subjects (n = 2,228)						
Percent density	0.04	−0.38$^{###}$	−0.41$^{###}$	0.04	−0.38$^{###}$	−0.41$^{###}$
Dense area	0.05	−0.01	−0.04	0.06$^{#}$	−0.06$^{#}$	−0.10$^{##}$
Non–dense area	0.02	0.60$^{###}$	0.61$^{###}$	−0.004	0.57$^{###}$	0.59$^{###}$
Total area	0.05	0.58$^{###}$	0.58$^{###}$	0.02	0.55$^{###}$	0.56$^{###}$
Premenopausal (n = 549)						
Percent density	0.03	−0.41$^{###}$	−0.46$^{###}$	−0.03	−0.49$^{###}$	−0.50$^{###}$
Dense area	0.07	0.08	0.05	0.03	−0.11	−0.13$^{#}$
Non–dense area	0.04	0.62$^{###}$	0.65$^{###}$	0.08	0.69$^{###}$	0.70$^{###}$
Total area	0.06	0.57$^{###}$	0.58$^{###}$	0.09	0.65$^{###}$	0.65$^{###}$
Postmenopausal (n = 1,679)						
Percent density	0.06	−0.35$^{###}$	−0.39$^{###}$	0.06	−0.34$^{###}$	−0.38$^{###}$
Dense area	0.06	−0.02	−0.05	0.08	−0.04	−0.08$^{#}$
Non–dense area	0.01	0.59$^{###}$	0.60$^{###}$	−0.03	0.54$^{###}$	0.56$^{###}$
Total area	0.03	0.58$^{###}$	0.57$^{###}$	−0.003	0.52$^{###}$	0.53$^{###}$

NOTE: P values for correlation coefficients are indicated by superscript symbols: $^{#}$, $P < 0.05$; $^{##}$, $P < 0.01$; and $^{###}$, $P < 0.0001$; the others are nonsignificant.

The associations of height, weight, and BMI with risk of breast cancer were examined, after adjustment for age and other risk factors for breast cancer, and before and after additional adjustment for the percentage of mammographic density. The association of percentage of mammographic density with risk of breast cancer was also examined after adjustment for age and other risk factors, and before and after adjustment for anthropometric variables. The percentage of mammographic density was examined both as a continuous variable, square-root transformed, and as a categorical variable, divided into six categories (0%, <10%, <25%, <50%, <75%, and >75%) for analysis, based on previous work (4). In the tables, the percentage of density is shown after back-transformation. All P values were calculated from two-tailed tests of statistical significance.

Results

Characteristics of Subjects. Table 1 shows selected characteristics of the subjects. The distribution of risk factors in cases and controls, including weight and BMI, was similar in each of the three populations (data not shown). Furthermore, a test for heterogeneity showed no evidence of an interaction between the study population and the risk of breast cancer associated with mammographic density (P = 0.99). Several risk factors for breast cancer differed between cases and controls, including age at menarche, parity, number of live births, age at menopause, and a history of breast cancer in first-degree relatives. Cases used hormone therapy more often than controls. Mean height, weight, and BMI were similar in cases and controls. The average percentage of mammographic density in the baseline mammogram was 5.8% greater in cases than in controls.

Body Size and Mammographic Measures. Table 2 shows the correlation of the mammographic measures of total area, dense area, non–dense area and percentage of density with height, weight, and BMI in cases and controls. Height was weakly, positively, but not significantly, associated with all mammographic measures. Weight and BMI were strongly positively associated with both the total area of the breast in the mammogram, and the area of non–dense tissue, and was negatively associated with the percentage of density. Weight and BMI were weakly, negatively, and significantly associated with the area of dense tissue in controls, but not in cases.

Body Size and Breast Cancer Risk: Adjusted for Mammographic Density. Conditional logistic regression was used to examine the association of anthropometric measures with breast cancer risk in the matched case-control pairs. Results are shown in Table 3 according to menopausal status, in which cases and controls were of the same menopausal status, and before and after adjustment for the percentage of mammographic density.

Height showed no association with risk of breast cancer, in all subjects or in either menopausal group, before or after

Table 3. Height, weight, and BMI and risk of breast cancer before and after adjustment for percentage of mammographic density: matched analysis

Variable	All subjects (n = 1,114 pairs)		Premenopausal group (n = 162 pairs)		Postmenopausal group (n = 727 pairs)	
	β (SE)*	P †	β (SE)	P	β (SE)	P
Height‡ (cm), not adjusted for density	0.0007 (0.007)	0.92	0.0003 (0.016)	0.98	0.0082 (0.009)	0.34
Height§ (cm), adjusted for density	0.0006 (0.007)	0.94	0.0066 (0.017)	0.70	0.0072 (0.009)	0.41
Weight‡ (kg), not adjusted for density	0.0032 (0.004)	0.41	−0.0119 (0.010)	0.21	0.0084 (0.005)	0.09
Weight§ (kg), adjusted for density	0.0139 (0.004)	0.001	0.0036 (0.011)	0.73	0.0185 (0.006)	0.001
BMI‡ (not adjusted for density)	0.0080 (0.011)	0.45	−0.0387 (0.028)	0.17	0.0159 (0.014)	0.24
BMI§ (adjusted for density)	0.0392 (0.012)	0.001	0.0053 (0.031)	0.87	0.0446 (0.015)	0.003

*β is the maximum likelihood estimate of the variable.
†P value: test for β = 0.
‡Adjusted for the following risk factors: age at menarche, age at first birth, parity, number of live births, menopausal status, age at menopause, hormone replacement therapy (ever/never), breast cancer in first-degree relatives (0, 1, 2+). Menopausal status was omitted from the analysis for the separate menopausal groups, and age at menopause from the analysis of the premenopausal group.
§Adjusted for the risk factors above and percentage of mammographic density.

Table 4. Risk of breast cancer according to quintile of BMI (based on the distribution of BMI in controls)

	Quintile of BMI						
	≤21.79	(21.79-23.30)	(23.30-25.02)	(25.02-27.64)	>27.64	No.	*P**
All subjects							
Cases	245	218	208	212	231	1,114	
Controls	232	217	220	224	221	1,114	
OR† (95% CI), not adjusted for density	1	0.93 (0.7-1.2)	0.89 (0.7-1.2)	0.91 (0.7-1.2)	1.04 (0.8-1.4)		0.86
OR‡ (95% CI), adjusted for density	1	1.07 (0.8-1.4)	1.12 (0.8-1.5)	1.21 (0.9-1.6)	1.60 (1.2-2.2)		0.002
Premenopausal							
Cases	86	54	49	42	51	282	
Controls	64	59	46	46	52	267	
OR† (95% CI), not adjusted for density	1	0.69 (0.4-1.1)	0.79 (0.5-1.3)	0.68 (0.4-1.2)	0.76 (0.5-1.3)		0.37
OR‡ (95% CI), adjusted for density	1	0.88 (0.5-1.5)	1.13 (0.6-2.0)	1.06 (0.6-1.9)	1.47 (0.8-2.7)		0.18
Postmenopausal							
Cases	159	164	159	170	180	832	
Controls	168	158	174	178	169	847	
OR† (95% CI), not adjusted for density	1	1.05 (0.8-1.4)	0.95 (0.7-1.3)	1.02 (0.8-1.4)	1.17 (0.9-1.6)		0.43
OR‡ (95% CI), adjusted for density	1	1.16 (0.8-1.6)	1.13 (0.8-1.6)	1.28 (0.9-1.8)	1.67 (1.2-2.3)		0.004

NOTE: Unmatched logistic regression, adjusted for age, age at menarche, age at first birth, parity, number of live births, menopausal status, age at menopause, hormone replacement therapy (ever/never), breast cancer in first-degree relatives (0, 1, 2+), study (NBSS, OBSP, and SMPBC), and observation time (≤2, 2-4, and >4 years), not adjusted for percentage of mammographic density. Menopausal status was omitted from the analysis for the separate menopausal groups, and age at menopause from the analysis of the premenopausal group.

**P* value for testing the linear trend.

†Adjusted only above factors.

‡Adjusted with above factors and percent mammographic density.

adjustment for percentage of density. Before adjustment for percentage of density, weight and BMI showed no statistically significant associations with risk of breast cancer, in all subjects, or in either menopausal group. After adjustment for percentage of density, both weight and BMI were significantly and positively associated with breast cancer risk in all subjects.

The effect of adjustment for percentage of density in strengthening the association between weight and BMI and risk of breast cancer in all subjects was the result of similar effects in both menopausal groups. In postmenopausal women, the nonsignificant, but positive, association between weight and BMI and risk of breast cancer seen before adjustment, became stronger and statistically significant after adjustment for percentage of density. In premenopausal women, the nonsignificant but negative associations between weight and BMI and risk were reversed after adjustment for the percentage of density, but were still not statistically significant.

Table 4 shows the association of BMI with breast cancer risk in unmatched analysis, according to menopausal status, and before and after adjustment for percentage of mammographic density. In all subjects, before adjustment for percentage of density, no category of BMI was significantly associated with risk of breast cancer, and there was no significant trend of increasing risk across categories of BMI. After adjustment for the percentage of density, the association of BMI with risk of breast cancer became stronger, and was significantly increased in the highest category of BMI. Adjustment for the percentage of density increased the risk in the highest category from 1.01 [95% confidence interval (CI), 0.8-1.3] to 1.55 (95% CI, 1.1-2.1), and changed the *P* value from the test for trend from 0.97 to 0.003.

The effect of adjustment for percentage of density in strengthening the association between weight and BMI and risk of breast cancer in all subjects was the result of similar effects in both menopausal groups. In postmenopausal women, the nonsignificant, but positive, association between weight and BMI and risk of breast cancer seen before adjustment became stronger and statistically significant after adjustment for percentage of density. In premenopausal women, the nonsignificant but negative associations between weight and BMI and risk were reversed after adjustment for percentage of density, but were still not statistically significant. In premenopausal women, adjustment for percentage of density increased the risk in the highest quintile of BMI, compared with the lowest, from 0.76 (95% CI, 0.5-1.3) to 1.47 (95% CI, 0.8-2.7), and in postmenopausal women from 1.17 (95% CI, 0.9-1.6) to 1.67 (95% CI, 1.2-2.3).

Because the effects of body size on risk of breast cancer have been reported to be greater among women not taking hormone therapy (19), we repeated the analysis shown for postmenopausal women including only the 618 cases and 647 controls who were not taking hormones at the time of the baseline mammogram. Before adjustment for density, the risk of breast cancer in the highest quintile of BMI, relative to the lowest, was 1.38 (95% CI, 0.96-1.97), and after adjustment, increased to 1.86 (95% CI, 1.26-2.74). After adjustment for the percentage of density, the *P* value from the trend test changed from 0.15 to 0.004 (data not shown).

The effect of adjustment for the percentage of density on the risk of breast cancer associated with BMI was due mainly to the effect of the non–dense area. Adjustment for the non–dense area gave results similar to those seen for the percentage of density. Adjustment for the dense area did not change the risk associated with BMI (data not shown).

Mammographic Density and Breast Cancer Risk: Adjustment for Body Size. Table 4 shows the association of mammographic density with risk of breast cancer before and after adjustment for BMI. After adjustment for the other risk factors shown in the table legend, and additional adjustment

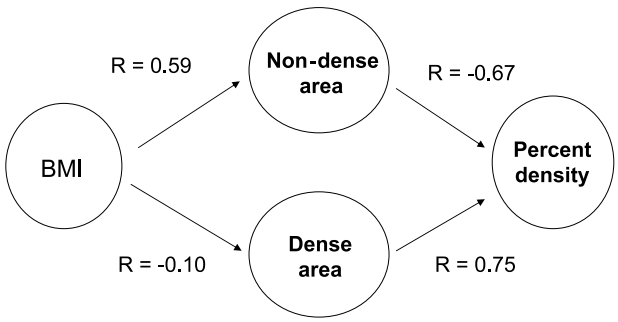

Figure 1. Correlations of BMI with percentage of density and other mammographic measures (control subjects).

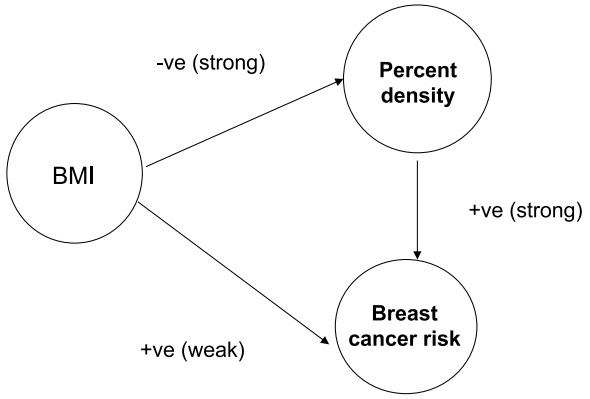

Figure 2. Association of BMI with percentage of density and breast cancer risk. Positive associations (+ve), and negative associations (−ve).

for BMI, the odds ratio for the percentage of density increased in all categories of density. The risk associated with >75% compared with 0% density increased from 4.25 (95% CI, 1.6-11.1) to 5.86 (95% CI, 2.2-15.6).

Discussion

These data show that the percentage of mammographic density and body size, indicated by either weight or BMI, are related to each other, and are independent risk factors for breast cancer. As shown in Fig. 1, the correlation of BMI with the percentage of density is through a strong positive correlation with the non–dense area of the mammogram, which in turn, has a strong negative correlation with the percentage of density. Similar correlations were seen in premenopausal and postmenopausal women.

Because of these relationships, adjustment for the percentage of density increases the strength of the association of body size with risk of breast cancer. Similarly, adjustment for body size increases the strength of the association of percentage of density with risk. Body size and mammographic density are thus each confounders of the association of the other with risk of breast cancer. Failure to take this relationship into account leads to the underestimation of the effects of both of these risk factors. BMI is correlated with the percentage of density, but explains only 16% of the variance in the percentage of density ($r^2 = 0.16$). Potential etiologic models should therefore include both variables. The negative confounder relationship between mammographic density and body size may explain the negative association of body size with risk in premenopausal women that is seen in these data, as well as in previous studies (11, 19, 20), none of which adjusted for mammographic density. After adjustment for the percentage of density, body size in the present data had a positive association with breast cancer risk in both premenopausal and postmenopausal women, although this was statistically significant only in postmenopausal women.

If the variables of body size and mammographic density operated through the same pathway, we would expect adjustment for one of them to weaken or remove the effect of the other variable on risk of breast cancer. Because the effect of adjustment for each variable is to strengthen the effect of the other variable on risk, we conclude that these two risk factors for breast cancer operate through separate pathways, as is illustrated in Fig. 2. This conclusion, suggested by these epidemiologic data, is supported by what is known of their probable mechanisms of action.

Adipose tissue influences exposure to estrogen, primarily in postmenopausal women. It is the site in which androstenedione is converted by aromatization to estrogen, and is the sole source of endogenous estrogen in postmenopausal women. Furthermore, obesity is associated with lower levels of sex hormone–binding globulin, and so with higher levels of free, and biologically active, sex hormones. Key et al. have shown that the increased risk of breast cancer associated with higher BMI in postmenopausal women is mediated through estrogen levels, as adjustment for hormone levels completely removed the effect on risk of BMI (21). Mammographic density was not taken into account in this analysis. The effect of adipose tissue on estrogen production affects mainly postmenopausal women, but the effect of BMI on sex hormone–binding globulin levels affects both premenopausal and postmenopausal women (22).

The biological basis for the association of percentage of density with risk of breast cancer is presently unknown, but the percentage of density is associated with the number of cells, both epithelial and nonepithelial, in the breast (23). A greater number of cells at risk of undergoing a genetic change that gives rise to cancer may be one of the factors that contributes to the increased risk of breast cancer that is associated with extensive density. Extensive mammographic density is associated with an increased risk of atypical hyperplasia and *in situ* breast cancer, a well as invasive cancer (24, 25), which is in keeping with the view that it represents a state of increased susceptibility (26).

The greater number of cells in the breast associated with extensive mammographic density may reflect the action on the breast of mitogens, particularly those in the growth hormone–insulin-like growth factor I (IGF-I) axis (27). Cross-sectional studies have shown that after adjustment for other risk factors, mammographic density was positively associated with serum IGF-I levels in premenopausal women (see refs. 27-29) as well as with prolactin levels in postmenopausal women (see refs. 27, 30). IGF-I and prolactin have also been found to

Table 5. Risk of breast cancer according to percentage of mammographic density

	Categories of percent density (%)						No.	*P**
	0	<10	10 < 25	25 < 50	50 < 75	≥75		
Case	19	129	296	442	208	20	1,114	
Control	40	217	334	363	150	10	1,114	
OR†, not adjusted for BMI (95% CI)	1	1.21 (0.7-2.2)	1.78 (1.0-3.2)	2.45 (1.4-4.4)	2.86 (1.6-5.2)	4.25 (1.6-11.1)		<0.0001
OR‡, adjusted for BMI (95% CI)	1	1.27 (0.7-2.3)	2.00 (1.1-3.6)	2.98 (1.7-5.4)	3.70 (2.0-6.9)	5.86 (2.2-15.6)		<0.0001

NOTE: Unmatched logistic regression, adjusted for age, age at menarche, age at first birth, parity, number of live births, menopausal status, age at menopause, hormone replacement therapy (ever/never), breast cancer in first-degree relatives (0, 1, 2+), study (NBSS, OBSP, SMPBC), and observation time (≤2, 2-4, and >4 years), not adjusted for BMI.

*P value for testing the linear trend.

†Adjusted only above factors.

‡Adjusted with above factors and BMI.

influence the risk of breast cancer, respectively, in premenopausal and postmenopausal women (31, 32). The blood levels of both growth hormone and IGFBP-3 have been found to be associated with mammographic density in premenopausal women, although these associations became nonsignificant after adjustment for body size (27). The extent of staining on immunohistochemistry for IGF-I in breast tissue has also been found to be associated with mammographic density in the breast from which the tissue was removed (33). Polymorphisms in the pituitary growth hormone gene (34), the *IGFBP-3* gene (35), and the *COMT* gene (36), which are involved in estrogen metabolism, have been found to be associated with mammographic density. The COMT polymorphisms were also associated with variations in blood levels of IGF-I and IGFBP-3 in premenopausal women (36).

In contrast to body size, there is little evidence to indicate that endogenous estrogen is a major influence on mammographic density. Most cross-sectional studies have found either no association, or an inverse association, between blood estradiol levels and percentage of mammographic density in premenopausal and postmenopausal women (27, 30, 37, 38). An exception is the cross-sectional study carried out in the Postmenopausal Estrogen/Progestin Intervention Trial, which found a weak positive association between the percentage of density and estradiol levels (39). However, progesterone levels were also associated with density, suggesting that at least some subjects with density may have been perimenopausal rather than postmenopausal. Bone density, assumed to be a marker of cumulative exposure to estrogen, has also been found to be unrelated to mammographic density in several studies (40-42). One of these was a twin study that found no evidence of a positive association between mammographic density and bone mineral density, and no overlap between the genetic determinants of variation in either measure (41, 42). The Postmenopausal Estrogen/Progestin Intervention Trial is again an exception, in which a weak positive association was found between bone and breast density (43). In randomized clinical trials, the administration of estrogen alone did not influence the extent of mammographic density after 1 year, although combined estrogen and progesterone has been found to increase density (8). Menopause (44), tamoxifen (9), and a gonadotrophin-releasing hormone agonist (45) that reduces exposure to estrogen and progesterone in premenopausal women, all reduce the percentage of density, but the effects are relatively small, and the average reduction in percentage of density is <10%.

These data lead us to conclude that breast cancer risk is influenced by some factors that are related to estrogen, of which body size is an example, and others that are predominately not related to estrogen, one of which is mammographic density (Table 5). The present results show that the estrogen-related factors associated with body size do not influence breast cancer risk through density, and suggest that they may not influence risk through direct effects on breast cell proliferation. Alternative mechanisms, such as the generation of mutagenic intermediate metabolites and reactive oxygen species, may be more important (46). The non–estrogen-related factors that operate through density are still under investigation but, as described above, there are several lines of evidence which suggest that the growth hormone–IGF-I axis is an important influence. Mammographic density has been shown to be highly heritable, and identification of the genes involved is likely to shed further light on the biological processes involved (47).

The present results emphasize the importance of considering both estrogen-related and non–estrogen-related factors when either is examined in relation to risk of breast cancer, as the failure to do so is likely to lead to underestimation of their effects on risk of the disease.

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