Mammographic Density as a Surrogate Marker for the Effects of Hormone Therapy on Risk of Breast Cancer

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Abstract

Background: **Some types of hormone therapy increase both risk of breast cancer and mammographic density, a risk factor for the disease, suggesting that mammographic density may be a surrogate marker for the effects of hormones on risk of breast cancer. This research was undertaken to determine whether the effect of hormone therapy on breast cancer risk is mediated by its effect on mammographic density.**

Methods: **Individually matched cases and controls from three nested case-control studies in breast screening populations were studied. Cases had developed invasive breast cancer at least 12 months after the initial screen. Information was collected on hormone use and other risk factors at the time of the baseline mammogram, and percent density was measured by a computer-assisted method.**

Results: **There were 1,748 postmenopausal women, of whom 426 (24.4%) were using hormones at the time of their initial screening mammogram. Current use of hormone therapy was associated with an increased risk of breast cancer (odds ratio, 1.26; 95% confidence interval, 1.0-1.6) that was little changed by adjustment for percent density in the baseline mammogram (odds ratio, 1.19; 95% confidence interval, 0.9-1.5). Percent density in the baseline mammogram was among cases greater in current users of hormones that in never-users (difference = 5.0%, $P < 0.001$), but the difference was smaller and nonsignificant in controls (difference = 1.6%, $P = 0.3$).**

Conclusion: **Although the effects of hormone therapy on mammographic density were greater in cases than controls, we did not find evidence that these effects were causally related to risk of breast cancer.** (Cancer Epidemiol Biomarkers Prev 2006;15(5):961–6)

Introduction

Mammographic density refers to the white radiodense appearance of breast tissue on a mammogram that reflects the amount of stroma and epithelium in the breast (1). Women with density in ≥75% of the breast have a risk of breast cancer four to five times that of women with little or no density (2, 3). Radiologically dense breast tissue decreases with increasing age, body weight, parity, and menopause (4-6), suggesting that density reflects exposure of the breast to hormones.

Evidence from observational studies (7, 8), and a randomized controlled trial (9), shows that combined hormone therapy with estrogen and progesterone increases risk of breast cancer. Although observational studies have suggested that therapy with estrogen alone may increase risk (10), the results of a randomized controlled trial suggest that it may reduce risk (11). Further, evidence from a randomized trial has shown that combined hormone therapy increases mammographic density, whereas estrogen alone does not (12).

These observations suggest that mammographic density might be used as a surrogate for breast cancer in clinical trials of the effects of hormone therapy on risk of breast cancer. If trials could use density, rather than cancer, as an end-point, they could be smaller, of shorter duration, and be less expensive (13). However, for density to be used as a valid surrogate for the effects of hormones on breast cancer, the effects of hormone therapy on mammographic density should be related causally to, and mediate, risk of breast cancer.

The purpose of this article is to determine whether the effect of hormone therapy on breast cancer risk is mediated by its effect on density. If it is, then the risk of breast cancer associated with hormones should be reduced or eliminated by controlling for density in analysis. However, adjustment for density will have little effect if hormone therapy has separate effects on cancer risk and density (13).

Materials and Methods

General Method. We used data from three nested case-control studies carried out in screening populations to examine in postmenopausal women the association of hormone therapy at the time of entry to the screening program, with mammographic density in the baseline screening mammogram and with subsequent risk of breast cancer.

Ethical approval of the study was obtained from the University of Toronto, The University Health Network (Toronto), The Ontario Breast Screening Program, and the University of British Columbia.

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 (14, 15). 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 Ontario Breast Screening Program (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

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applications using the data collected, and all 354 subjects diagnosed with invasive breast cancer between 1984 and 1990, and their matched controls, were included (16).

For the OBSP and SMPBC, lists were prepared of subjects with histologically verified invasive breast cancer diagnosed during the years 1992 to 1998 for the OBSP, and 1988 to 1999 for the SMPBC. 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). For each case in the OBSP and SMPBC who provided consent, we selected up to 10 control subjects, individually matched according to year of entry to the screening program (within 1 year), screening center, age at entry to the program (within 1 year), and a duration of follow-up that was at least as long as the time the corresponding case subject had been in the program before cancer had been diagnosed. Fifty percent of cases and 54% of 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 the other two programs, information was collected by self-administered questionnaire at the time of recruitment into the present study. Questions included demographic information, use of hormone therapy, including the date started and duration of use, as well as menstrual and reproductive risk factors. All information was collected with reference to the time of the first screening mammogram.

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 and 12 bits precision, and measured by one observer (N.F.B.) using a previously described interactive thresholding technique (17). Average reliability for measuring percent density was assessed by rereading a 10% random sample of images, within and between each session, and was 0.94 both within and between reads.

Statistical Methods. Only subjects who were postmenopausal at the time of the baseline mammogram were included. Eighty-eight subjects were excluded because of missing data. The data analyzed contained 1,741 subjects, among whom were 724 matched case-control pairs in which both members of the pair were postmenopausal.

Case and control subjects 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. All *P* values were calculated from two-tailed tests of statistical significance. The association of hormone therapy with risk of breast cancer was examined using logistic regression for unmatched data, and conditional logistic regression for matched data. Percent density was square root transformed for analysis and is shown after back-transformation in the tables.

Results

Characteristics of Subjects. Table 1 shows selected characteristics of the subjects in each of the three screening populations, separately and combined. In the combined data, earlier age at menarche, nulliparity, a smaller number of live births, later age at menopause, and a history of breast cancer in first-degree relatives, were all more frequent among cases of breast cancer than in controls.

In the combined data, cases had more frequently used hormone therapy than controls, and had a longer average

Table 1. Selected characteristics for all postmenopausal subjects

	NBSS (*n* = 416)		OBSP (*n* = 708)		SMPBC (*n* = 617)		Combined (*n* = 1,741)		
	Case* (*n* = 204)	Control (*n* = 212)	Case (*n* = 350)	Control (*n* = 358)	Case (*n* = 311)	Control (*n* = 306)	Case (*n* = 865)	Control (*n* = 876)	*P*†
Age (y)	52.55 (4.8)	52.45 (4.9)	61.91 (6.7)	61.97 (6.8)	61.63 (8.3)	61.97 (8.1)	59.61 (8.0)	59.67 (8.0)	
BMI	25.76 (4.4)	25.67 (4.3)	25.39 (4.6)	25.08 (4.0)	24.70 (4.0)	24.48 (4.1)	25.23 (4.4)	25.01 (4.1)	0.58
Age at menarche (y)	12.66 (1.4) *n* = 203	12.85 (1.4) *n* = 209	12.90 (1.5) *n* = 333	13.10 (1.6) *n* = 342	12.91 (1.5) *n* = 301	13.12 (1.5) *n* = 302	12.85 (1.5) *n* = 837	13.04 (1.5) *n* = 853	0.01
Age at first birth (y)	24.89 (4.3) *n* = 163	24.68 (4.3) *n* = 186	24.02 (4.4) *n* = 292	24.16 (4.2) *n* = 318	24.93 (4.8) *n* = 277	23.90 (4.5) *n* = 276	24.56 (4.5) *n* = 732	24.19 (4.3) *n* = 780	0.1
Parity (% parous)	79.4	87.7	84.9	89.9	89.4	90.2	85.2	89.5	0.01
No. live births	2.49 (2.1)	2.93 (2.1)	2.78 (2.0) *n* = 349	2.87 (1.9)	2.46 (1.5)	2.79 (1.6)	2.59 (1.8) *n* = 864	2.86 (1.8)	0.001
Breast cancer in first-degree relatives (%)									
0	80.88	86.32	78	85.47	77.81	79.41	78.61	83.56	0.003
1	17.65	13.68	19.71	13.13	17.68	18.3	18.5	15.07	
2+	1.47	0	2.29	1.4	4.51	2.29	2.89	1.37	
Age at menopause (y)	46.23 (6.9) *n* = 196	45.26 (6.6) *n* = 201	46.38 (6.7) *n* = 298	46.12 (6.7) *n* = 310	46.32 (7.3) *n* = 285	45.29 (7.3) *n* = 268	46.32 (7.0) *n* = 779	45.61 (6.9) *n* = 779	0.02
Type of menopause (%)									
Natural	NA	NA	49.4	54.2	49.5	53.9	49.5	54.1	0.06
Surgical			38.9	39.6	43.4	40.9	41	40.2	
Other			1.7	0.6	1.3	1	1.5	0.8	
Unknown			10	5.6	5.8	4.2	8 *n* = 661	5 *n* = 664	
HRT (% ever use)	47.5	47.2	45.7	39.9	45	37.6	45.9	40.9	0.03
HRT (% current use)	22.1	19.3	29.4	27.7	24.1	20.6	25.8	23.2	0.21
Years of HRT use	1.74 (3.4)	1.71 (3.7)	3.61 (6.6) *n* = 341	3.20 (6.4) *n* = 350	3.45 (7.0) *n* = 302	3.17 (6.9) *n* = 295	3.10 (6.2) *n* = 847	2.82 (6.1) *n* = 857	0.04
Percent density	29.3 (19.4)	23.0 (18.8)	27.8 (18.1)	23.5 (17.5)	29.8 (17.1)	25.0 (16.5)	28.9 (18.1)	23.9 (17.5)	<0.001

NOTE: Data are not matched in pairs.

Abbreviations: BMI, body mass index; HRT, hormone therapy; NA, not available.

*Mean (SD).

†*P* values for symmetrically distributed variables are based on *t* tests, for nonsymmetrically distributed variables are based on Wilcoxon rank sum test, and for categorical variables are based on Mantel-Haenszel χ^2 test. All tests are two sided.

Table 2. Percent mammographic density and hormone use in cases and controls

Program	Status	HRT use	Percent density			
			n	Least-square mean (95% CI)*,†	Difference % (*P*)‡	*P*§
NBSS (*n* = 416)	Case	Never	107	31.1 (23.0-40.4)		
		Past	52	31.5 (22.7-41.9)	0.4 (0.90)	
		Current	45	36.6 (27.0-47.6)	5.5 (0.14)	0.17
	Control	Never	112	24.2 (18.7-30.4)		
		Past	59	18.9 (13.5-25.4)	−5.3 (0.09)	
		Current	41	21.9 (15.5-29.5)	−2.3 (0.52)	0.33
OBSP (*n* = 708)	Case	Never	190	20.5 (16.5-25.0)		
		Past	57	25.9 (20.3-32.3)	5.4 (0.02)	
		Current	103	26.4 (21.2-32.2)	5.9 (0.002)	0.001
	Control	Never	215	22.9 (17.6-28.8)		
		Past	44	16.4 (11.1-22.9)	−6.5 (0.01)	
		Current	99	25.3 (19.5-31.8)	2.4 (0.23)	0.51
SMPBC (*n* = 617)	Case	Never	171	25.7 (21.7-30.0)		
		Past	65	29.1 (23.8-34.9)	3.4 (0.14)	
		Current	75	30.0 (24.8-35.8)	4.3 (0.05)	0.04
	Control	Never	191	21.6 (16.9-26.9)		
		Past	52	23.0 (17.0-29.9)	1.4 (0.57)	
		Current	63	23.5 (17.5-30.4)	1.9 (0.40)	0.36
Combined (*n* = 1,741)	Case	Never	468	25.1 (22.3-28.0)		
		Past	174	28.1 (24.6-31.8)	3.0 (0.04)	
		Current	223	30.7 (27.2-34.5)	5.6 (<0.001)	<0.001
	Control	Never	518	23.5 (19.8-27.5)		
		Past	155	19.7 (15.8-24.0)	−3.8 (0.01)	
		Current	203	25.1 (20.8-29.7)	1.6 (0.26)	0.6

*Least-square means and 95% CI are back transformed for illustration, differences are calculated from the back-transformed least square means, and *P* values are from transformed analysis.
†Adjusted for age, BMI, age at menarche, parity, number of live births, age at first birth, age at menopause, and breast cancer in first-degree relatives (0, 1, 2+).
‡*P* values for difference between never and past and current users of hormone therapy.
§*P* values for linear trend.

duration of use. However, a similar proportion of cases and controls were current users at the time of the baseline mammogram. Average percent density in the baseline mammogram was in the combined data 5.0% greater in cases than in controls.

Association of Mammographic Density with Hormone Use. Table 2 shows the mean values for percent density in cases and controls, adjusted for the risk factors shown in the footnote to the table, according to hormone use. In each population, the mean percent density in cases who were past or current users of hormone therapy was greater than in never users, and among users, was greater in current than in past users. The difference in cases between current and never users was statistically significant in two of the three populations, and in the combined data, where the average difference was 5.6% ($P < 0.001$).

In controls, in two of the three populations, and in the combined data, past users of hormones had less percent density than never users, and the difference was statistically significant in the OBSP and in the combined data. Current hormone use in controls was associated with a slightly greater percent density than in never users in two of the three populations, but these differences were not statistically significant. In the combined data, the average difference was 1.6% ($P = 0.26$).

A test for interaction between current or past use of hormones, and case or control status, with percent mammographic density as the dependent variable, and controlling for other risk factors for breast cancer, was statistically significant ($P = 0.0015$).

Figure 1 shows the distributions of percent mammographic density in cases and controls who were current users of hormone therapy at the time of the baseline mammogram. Although the distribution for cases is shifted to the right of that for controls, there is considerable overlap.

Association of Hormone Use with Risk of Breast Cancer. Table 3 shows the risk of breast cancer according to hormone use in the three populations. All estimates of risk for the unmatched data are shown after adjustment for the other risk factors for breast cancer, and before and after adjustment for percent mammographic density.

Before adjustment for percent density, current use of hormone therapy was associated, within each population, with a point estimate of risk of breast cancer that was greater than unity, and past use with estimates greater than unity in two populations and in the combined data. Only current use in the combined data was significantly associated with risk of breast cancer, although at a borderline level. The estimates of risk of breast cancer associated with hormone therapy were unchanged, or at most only slightly reduced, by adjustment for percent density.

Analysis in 724 matched pairs of cases and controls, in which both members of the pairs were postmenopausal, gave

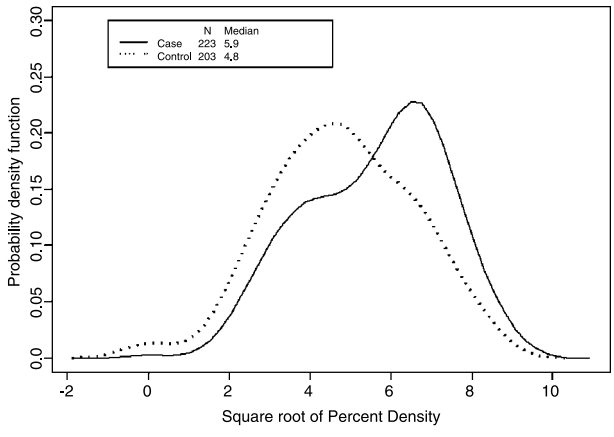

Figure 1. Distribution of mammographic density in current users of hormone therapy according to case or control status, for the three programs combined and square root transformed.

Table 3. Hormone use and risk of breast cancer: with and without adjustment for mammographic density

Program	Hormone use	No. subjects		OR*	OR* adjusted for density
		Case	Control		
NBSS (n = 416)	Never	107	112	1 (Reference)	1 (Reference)
	Past	52	59	0.99 (0.61-1.61)	1.04 (0.64-1.69)
	Current	45	41	1.13 (0.68-1.88)	1.12 (0.66-1.87)
OBSP (n = 708)	Never	190	215	1 (Reference)	1 (Reference)
	Past	57	44	1.48 (0.95-2.32)	1.47 (0.93-2.32)
	Current	103	99	1.20 (0.85-1.71)	1.12 (0.78-1.60)
SMPBC (n = 617)	Never	171	191	1 (Reference)	1 (Reference)
	Past	65	52	1.43 (0.93-2.22)	1.39 (0.90-2.16)
	Current	75	63	1.50 (0.99-2.27)	1.44 (0.95-2.18)
Combined (n = 1,741)	Never	468	518	1 (Reference)	1 (Reference)
	Past	174	155	1.27 (0.98-1.64)	1.27 (0.98-1.65)
	Current	223	203	1.26 (1.00-1.59)	1.19 (0.94-1.51)

*Odds ratio adjusted for age, body mass index, age at menarche, parity, number of live births, age at first birth, age at menopause, and breast cancer in first-degree relatives (0, 1, 2+).

similar results. Compared with never users of hormone therapy (n = 823 subjects), and before adjustment for density, the odds ratio for risk of breast cancer was 1.33 [95% confidence interval (95% CI), 1.0-1.8] for past use, and 1.18 (95% CI, 0.9-1.5) for current use (n = 344 subjects). After adjustment for density, these odds ratios were 1.33 (95% CI, 1.0-1.8) and 1.12 (95% CI, 0.9-1.5), respectively. Similar results were seen when cancers detected by screening or by other means were analyzed (data not shown).

Mammographic Density, Breast Cancer Risk, and Duration of Use of Hormone Therapy. Table 4 shows the least square mean percent density, adjusted for other risk factors, in cases and controls, according to duration of use of hormone therapy. Average percent density increased significantly with increasing exposure to hormones among cases, but not in controls. Before adjustment for density, risk of breast cancer was greatest in those with ≥5 years of use, and was little changed after adjustment for density.

Discussion

These results show that women who were taking hormone therapy at the time of their baseline mammogram had a slightly greater risk of breast cancer during subsequent follow-up than women who had never used hormones. Point estimates of risk were greater than unity in each of three breast screening programs, and the risk for current use in the combined data was 1.26 (95% CI, 1.00-1.59). This is similar to the relative risk of 1.24 for invasive breast cancer (95% CI, 1.01-1.54) found in the Women's Health Initiative randomized controlled trial for those on combined hormone therapy compared with placebo (18). We also found that mammographic density in the baseline mammogram of subjects was greater in current and past users than in those who had never used hormones, particularly in those who later developed breast cancer. These, and other published data on the effects of hormone therapy on mammographic density, and on risk of breast cancer, suggest that density might be a suitable surrogate for breast cancer in assessing the effects of hormone therapy on risk of the disease.

As Schatzkin and Gail (13), Prentice (19), and Fleming and DeMets (20) have pointed out, the occurrence of cancer is a relatively infrequent event and clinical trials to assess the effects of interventions on cancer risk, need to be large and prolonged, and as a result are expensive. Surrogate markers for cancer would allow trials to be smaller, shorter, and less expensive. For a marker to be considered a surrogate to assess the effects of an exposure or intervention on a disease, it should meet three criteria (13). First, the marker should be associated with the disease; second, the exposure or intervention should be associated with the marker; and third, the potential surrogate marker should mediate the entire relation of the intervention to the disease. The third condition is met when the exposure and disease are statistically unrelated once the surrogate is taken into account (13).

There are abundant epidemiologic data showing that mammographic density is related to risk of breast cancer (see refs. 2, 3 for reviews) and is influenced by hormone therapy (12, 21-23). Mammographic density thus meets the first two of

Table 4. Percent density and breast cancer risk according to duration of hormone use

	Duration of hormone use (y)			
	0	0 < 5	5≤	P*
Percent density†				
Case (n = 847)‡	24.5 (21.8-27.5) n = 468	27.8 (24.3-31.5) n = 202	29.7 (26.0-33.7) n = 177	<0.001
Control (n = 857)‡	23.9 (20.1-28.0) n = 518	20.8 (16.6-25.1) n = 178	26.0 (21.4-31.1) n = 161	0.18
Breast cancer risk				
OR§ not adjusted for density	1	1.26 (0.97-1.60)	1.30 (1.01-1.68)	0.04
OR§ adjusted for density	1	1.25 (0.98-1.60)	1.23 (0.95-1.59)	0.11

*P values for linear trend are from transformed analysis.
†Data shown are least square means (95% CI). Transformation (square root) is used on percent density, adjusted for risk factors (n = 1,741); data are back transformed for illustration. Risk factors adjusted for are age, BMI, age at menarche, parity, number of live births, age at first birth, age at menopause, and breast cancer in first-degree relatives (0, 1, 2+).
‡Data on duration of use missing for 18 cases and 19 controls.
§Odds ratios adjusted for age, BMI, age at menarche, parity, number of live births, age at first birth, age at menopause, and breast cancer in first-degree relatives (0, 1, 2+).

these conditions. However, the present results show that adjustment for mammographic density in regression analysis had little effect on the risk of breast cancer associated with hormone therapy and indicate that mammographic density did not mediate this effect and thus does not meet the third of these conditions.

We thus find no evidence that the increased risk of breast cancer associated with hormone therapy is a consequence of the effect of this therapy on the risk factor of mammographic density, and conclude that the effects of hormone therapy on mammographic density, and on breast cancer risk, are separate and not related causally.

Some of the limitations of our study may have attenuated the effect of adjustment for mammographic density on the breast cancer risk associated with hormone therapy. These limitations include error in the measurement of mammographic density, reliance on cross-sectional differences in density, rather than measurement of change, and the lack of information about the type of hormones used. However, the measurement used here has been shown to give highly reproductive estimates of risk of breast cancer, and in the present study showed a clear association between increasing duration of use of hormone therapy and greater percent mammographic density in those who subsequently developed breast cancer. Estrogen alone was the most commonly used type of hormone therapy in Canada during the years in which subjects were recruited to the NBSS (24). Combined hormone therapy was more commonly used during the years that subjects entered the OBSP and SMPBC (25), and the effects of hormone use on risk of breast cancer were slightly greater in these populations than in the NBSS. However, the preferred design to examine further the issues raised by our findings would be an intervention study, such as the Women's Health Initiative (18), with mammograms available before and after the start of hormone therapy of known type. Change in density, according to type of hormone therapy, could then be examined in relation to subsequent risk of breast cancer.

The present results suggest that the pathways that are responsible for the increase in mammographic density following exposure to exogenous hormones, and those that increase risk of breast cancer in those taking hormone therapy, are not the same. Although the pathways involved in these processes remain to be determined, hormone therapy seems to have a relatively short-term effect on breast cancer risk, which is greatest in those taking hormones currently or recently, and disappears 5 years after cessation of use (7). The biological basis for the association of mammographic density with risk of breast cancer is unknown, but may be related, at least in part, to the association of density with the number of cells, both epithelial and stromal, that are at risk of undergoing a genetic change that may in time give rise to cancer (1). The increase in density that is associated with use of hormones may be due to an increase in the numbers of these cells, and although this may increase risk over the long term, it is unlikely to have any influence on risk in the short term.

The association of hormone therapy with percent density in the baseline mammogram was greater and showed a linear increase with increasing exposure, only among those who subsequently developed breast cancer during up to 8 years follow-up. These results suggest that the response of breast tissue to exogenous hormones is to some degree predictive of the future development of breast cancer. However, the substantial overlap in the distributions of percent density means that this finding has little clinical application in individuals at present. Measurement of change in density in individuals starting hormone therapy, as well as knowledge of the type of hormone therapy used, might give a clearer separation between those who will develop breast cancer in the future and those who will not.

The observed differences in the association between hormone use and mammographic density in future cases and controls may, however, be important in understanding the etiology of both mammographic density and breast cancer. Twin studies have shown that, at any given age, ~60% of the variation in percent density is explained by inheritance (26). Variations in genes that influence the response of breast tissue to hormones may be important, both in the etiology of this risk factor, and of breast cancer.

Although mammographic density does not meet criteria for a surrogate marker for breast cancer, this finding applies solely to hormone therapy, and it may be a suitable surrogate for other exposures or interventions. Other exposures of potential interest in this context include tamoxifen (27), a gonadotrophin-releasing hormone agonist (28), and a low-fat high-carbohydrate diet (29). Although all of these factors are known to influence mammographic density, for none of them is it yet known whether the effects of these variables on density mediate their effects on risk. Our results emphasize the importance of including cancer as an outcome in studies that examine the role of mammographic density as a surrogate.

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