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ARTICLE

Investigation of Mammographic Breast Density as a Risk Factor for Ovarian Cancer

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Background Endogenous hormones and growth factors that increase mammographic breast density could increase ovarian cancer risk. We examined whether high breast density is associated with ovarian cancer risk.

Methods We conducted a cohort study of 724 603 women aged 40 to 79 years with 2 506 732 mammograms participating in the Breast Cancer Surveillance Consortium from 1995 to 2009. Incident epithelial ovarian cancer was diagnosed in 1373 women. We used partly conditional Cox regression to estimate the association between breast density and 5-year risk of incident epithelial ovarian cancer overall and stratified by 10-year age group. All statistical tests were two-sided.

Results Compared with women with scattered fibroglandular densities, women with heterogeneously dense and extremely dense breast tissue had 20% and 18% increased 5-year risk of incident epithelial ovarian cancer (hazard ratio [HR] = 1.20, 95% confidence interval [CI] = 1.06 to 1.36; HR = 1.18, 95% CI = 0.93 to 1.50, respectively; P_{trend} = .01). Among women aged 50 to 59 years, we observed a trend in elevated risk associated with increased breast density (P_{trend} = .02); women with heterogeneously and extremely dense breast tissue had 30% (HR = 1.30; 95% CI = 1.03 to 1.64) and 65% (HR = 1.65; 95% CI = 1.12 to 2.44) increased risk, respectively, compared with women with scattered fibroglandular densities. The pattern was similar but not statistically significant at age 40 to 49 years. There were no consistent patterns of breast density and ovarian cancer risk at age 60 to 79 years.

Conclusions Dense breast tissue was associated with a modest increase in 5-year ovarian cancer risk in women aged 50 to 59 years but was not associated with ovarian cancer at ages 40 to 49 or 60 to 79 years.

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Most risk factors identified for ovarian cancer are related to menstrual and reproductive factors, lifestyle, and medical history (1–3). However, these factors explain little of the etiology of ovarian cancer, likely because of the heterogeneity of ovarian tumors (4). One unexplored potential risk factor is mammographic breast density, which is one of the strongest risk factors for breast cancer (5,6). Breast and ovarian cancers are both associated with endogenous and exogenous sex hormones and share similar risk and protective factors in their etiology (7,8).

It is plausible that circulating and tissue sex hormones that increase ovarian cancer risk are also associated with dense breast tissue. The underlying biologic mechanism resulting in high breast density and elevated breast cancer risk remains unclear. Martin and Boyd suggest that breast density reflects cumulative exposure to factors that influence endogenous estrogen exposure; high exposure possibly affects cell division and predisposes breast tissue to genetic damage (9). As a marker of cumulative estrogen effect, breast density might also be a marker of ovarian cancer risk. Ovarian cancer has hormonal etiology through androgens, estrogens, and gonadotropins (10). The prevailing hypothesis for the development of non-*BRCA1/2* ovarian cancer focuses on increased number of ovulatory cycles and the hormones that influence menstrual cycles (10,11).

Breast density is assessed on mammography by the amount of radiodense (or light) areas in epithelial tissue and stroma on a mammogram, often using the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) categories (12). Given the widespread assessment of breast density on routine screening mammography, breast density has the potential to be an easily identified risk factor for ovarian cancer. Nearly 75% of US women aged 40 years or older report having had at least one mammogram (13), and women can know their breast density several years before the median age of ovarian cancer incidence at age 63 (14).

We evaluated the association between breast density and 5-year ovarian cancer risk among more than 700 000 women who received a mammogram in the Breast Cancer Surveillance Consortium (BCSC) (15), a national consortium of breast imaging registries. We also assessed whether the association was modified by known ovarian cancer risk factors.

Methods

Study Cohort

The BCSC, a collaborative network of breast imaging registries (15), began in 1994 with the goal of assessing the delivery and quality of breast imaging and related patient outcomes in the United States. Data were obtained from the National Cancer Institute–funded BCSC Research Resource (http://breastscreening.cancer.gov/). Five BCSC registries were included in this analysis: Group Health (Washington state), New Hampshire Mammography Network, New Mexico Mammography Project, San Francisco Mammography Registry, and Vermont Breast Cancer Surveillance System. Mammography registries and the Statistical Coordinating Center each received 1) institutional review board approval for active or passive consenting processes or a waiver of consent to enroll participants, link data, and perform analyses and 2) a Federal Certificate of Confidentiality and other protections for the identities of women, physicians, and facilities. All procedures were Health Insurance Portability and Accountability Act compliant.

The study population was made up of women aged 40 to 79 years who received at least one mammogram from which density was measured at a BCSC mammography facility during the period from 1995 to 2009. Women who self-reported at the time of the mammogram prior bilateral oophorectomy (n = 55 774) or who had a previous diagnosis of ovarian cancer (n = 1435) were excluded.

Measurement of Breast Density

Mammographic breast density was assessed by the interpreting radiologist as part of routine clinical care and reported on the American College of Radiology BI-RADS scale as: 1, almost entirely fatty; 2, scattered fibroglandular densities; 3, heterogeneously dense; or 4, extremely dense (16). The primary analysis included both screening and diagnostic mammograms. The analysis included all eligible mammograms for each woman.

Patient Characteristics

Self-administered patient questionnaires given at each mammogram were used to ascertain age, race, ethnicity, parity status, current use of oral contraceptives and postmenopausal hormone therapy at the time of the mammogram, and family history of breast and ovarian cancer. Body mass index (BMI; kg/m^2) was calculated from self-reported height and weight. Menopausal status was ascertained based on the questionnaire, and women were defined as postmenopausal if they reported natural menopause or were aged 55 years or older.

Ascertainment of Cancer and Mortality Outcomes

Ovarian cancer diagnoses including stage and morphology were obtained by linkage to Surveillance, Epidemiology, and End Results (SEER) programs (for Group Health, New Mexico, and San Francisco) or to state cancer registries (for New Hampshire and Vermont) (17). The primary outcome for analysis was incident epithelial ovarian cancer or histology not otherwise specified (NOS) (International Classification of Diseases 9th and 10th editions; ICD-9 = 183 and ICD-10 = C56) (18) diagnosed within 5 years after mammography (n = 1373 cases). Diagnosis of breast cancer before the mammogram was based on self-report on the patient questionnaire or identification through linkage with cancer registries and pathology databases. Vital status was obtained through linkage to cancer registries and state vital statistics departments.

Statistical Analysis

We describe the distribution of risk factors at each woman's first mammogram in BCSC by breast density category and ovarian cancer status within 5 years. We modeled 5-year risk of incident epithelial ovarian cancer using partly conditional Cox regression to account for potential correlation among repeated mammograms during the study period (19). Models included each mammogram with a breast density measurement (mean = 3.2 mammograms per woman). Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated. Standard errors are based on a robust sandwich estimator for repeated measures survival data (20). Follow-up began at the date of the mammogram and ended at the first of the following: ovarian cancer diagnosis, report of bilateral oophorectomy, death, or 5 years after the mammogram. Models included indicator variables for BI-RADS breast density categories relative to the most common category, scattered fibroglandular densities (21). We evaluated linear trends in hazard ratios by examining the Wald test *P* value for linear density categories. Models were stratified on BCSC registry and adjusted for age (continuous in years), parity status, current oral contraceptive use, current hormone therapy use, prior breast cancer diagnosis, and first-degree family history of breast or ovarian cancer. Models in women age 40 to 49 years, 50 to 59 years, and all ages were also adjusted for menopausal status. We selected factors for adjustment based on a priori assessment, existing literature, and the impact on the hazard ratios associated with breast density. To evaluate effect modification, we examined interaction terms between breast density and each risk factor using the Wald test. Again using a partly conditional Cox regression accounting for correlation within women, a priori covariates evaluated for effect modification were age, current oral contraceptive use, parity status, menopausal status, current hormone therapy use, and family history of breast or ovarian cancer. Oral contraceptive use was modeled as yes, no, or missing/unknown, given the large proportion of missing data for this variable. The proportional hazards assumption was assessed by examining log–log plots. All statistical tests were two-sided, and a *P* value of less than .05 was considered statistically significant. Analyses were performed using Stata version 12 (StataCorp, College Station, TX).

In sensitivity analyses, we 1) restricted the outcome to hormonally responsive epithelial ovarian cancer [based on morphology codes for surface epithelial stromal tumors, including 802 carcinoma undifferentiated NOS, 805 papillary carcinoma, 814 adenocarcinoma NOS, 826 papillary adenocarcinoma, 831 clear cell adenocarcinoma, 838 endometroid adenocarcinoma, 844 cystadenocarcinoma NOS, 845 papillary cystadenocarcinoma NOS, 846 papillary serous cystadenocarcinoma, 847 mucinous cystadenocarcinoma NOS, 848 mucinous adenocarcinoma, 857 adenocarcinoma with metaplasia, and 900 Brenner tumor malignant (22)]; 2) randomly selected one mammogram for each woman; 3) adjusted for BMI ; 4) extended follow-up from 5 to 10 years to evaluate ovarian cancer risk; and 5) excluded exams from women with a prior breast cancer diagnosis.

Results

We identified 781 812 women eligible for inclusion into the study. With exclusions for report of prior bilateral oophorectomy and previous diagnosis of ovarian cancer, the final study sample included 724 603 women with 2 506 732 mammograms.

Characteristics of women differed by BI-RADS breast density category (Table 1). The majority of women with extremely dense breasts were aged 40 to 49 years at their first mammogram in BCSC. Women with dense vs fatty breasts were more likely to use oral contraceptives and be Asian and less likely to be Black or

Table 1. Characteristics obtained at the first breast density measurement for each woman by Breast Imaging Reporting and Data System (BI-RADS; mammographic breast density category) in the Breast Cancer Surveillance Consortium, 1995 to 2009

	Breast density				
	Total	BI-RADS 1, almost entirely fatty	BI-RADS 2, scattered fibroglandular densities	BI-RADS 3, heterogenously dense	BI-RADS 4, extremely dense
Characteristic	(n = 724 603) %	(n = 69 150) %	(n = 306 089) %	(n = 276 710) %	(n = 72 654) %
Age, y					
40–49	46.8	26.7	38.0	55.5	69.1
50–59	27.7	28.2	30.1	26.7	21.5
60–69	15.8	26.0	19.5	11.6	6.4
70–79	9.7	19.1	12.4	6.1	3.1
Race/ethnicity					
White, non-Hispanic	73.4	70.7	74.3	73.3	72.4
Black, non-Hispanic	2.3	3.4	2.4	2.1	1.6
Asian	7.6	4.0	5.3	9.2	14.1
Hispanic	13.6	17.2	14.6	12.8	9.5
Other/mixed	3.1	4.7	3.4	2.7	2.3
Missing*	(6.7)	(9.1)	(7.0)	(6.1)	(5.6)
Body mass index, kg/m^2					
<18.5	1.8	0.6	1.0	2.0	5.8
18.5 to <25	46.5	20.8	37.3	55.7	72.6
25 to <30	28.9	30.4	32.8	27.5	16.3
≥30	22.8	48.2	28.9	14.8	5.2
Missing*	(16.4)	(17.7)	(17.4)	(15.7)	(13.9)
Parity status					
Parous	82.6	86.6	86.1	80.4	72.4
Nulliparous	17.4	13.4	13.9	19.6	27.6
Missing*	(13.1)	(14.6)	(13.7)	(12.1)	(12.7)
Menopausal status					
Premenopausal	45.8	23.1	36.4	55.7	70.2
Postmenopausal	54.2	76.9	63.6	44.3	29.8
Missing*	(14.6)	(12.9)	(14.2)	(15.6)	(14.6)
Oral contraceptive use†					
Yes	2.9	1.3	2.1	3.8	4.7
No	51.4	52.4	48.3	53.7	54.6
Missing‡	45.7	46.3	49.6	42.5	40.7
Hormone therapy use†					
Yes	18.6	17.4	19.8	18.5	14.5
No	81.4	82.6	80.2	81.5	85.5
Missing*	(9.3)	(8.4)	(9.4)	(9.6)	(8.7)
Prior diagnosis of breast cancer					
Yes	3.4	3.7	3.9	3.1	2.5
No	96.6	96.3	96.1	96.9	97.5
Missing*	(6.7)	(6.8)	(7.4)	(5.9)	(6.7)
First-degree family history of breast or ovarian cancer					
Yes	13.6	13.0	13.4	13.8	13.9
No	86.4	87.0	86.6	86.2	86.1
Missing*	(4.5)	(4.9)	(4.1)	(4.8)	(4.6)

* Percentage of total.
† At time of mammogram.
‡ Retained in analysis.

Hispanic. Women with fatty vs dense breasts were more likely to be postmenopausal, parous, and overweight or obese (BMI ≥25 kg/m^2).

Women diagnosed with ovarian cancer were more likely to be older (aged >60 years), white, current users of hormone therapy, postmenopausal, have a prior breast cancer diagnosis, and have a family history of breast or ovarian cancer (Table 2). Women with ovarian cancer were less likely than noncase patients to be parous or current users of oral contraceptives. Ovarian cancer case patients compared with non–case patient did not have a higher proportion of BI-RADS 3 or 4 breast density. Approximately 91.1% of ovarian cancers had invasive morphology, and 8.9% were borderline tumors. The majority of ovarian cancers were diagnosed at regional or distant stage (81.6%; data not shown).

In a fully adjusted model combining all age groups (Table 3), compared with women with scattered fibroglandular tissue, women with heterogeneously dense and extremely dense breast tissue had 20% (HR = 1.20; 95% CI = 1.06 to 1.36) and 18% (HR = 1.18; 95% CI = 0.93 to 1.50) increased 5-year risk of incident epithelial ovarian cancer, respectively. The trend across increasing categories of breast density was statistically significant (P = .01).

Table 2. Characteristics obtained at the first breast density measurement for each woman by incident ovarian cancer status in the Breast Cancer Surveillance Consortium, 1995 to 2009

Characteristic	Ovarian cancer cases (n = 1373) %	Non–cases (n = 723 230) %
Age, y		
40–49	27.4	46.8
50–59	28.8	27.7
60–69	26.1	15.8
70–79	17.8	9.7
Race/ethnicity		
White, non-Hispanic	80.1	73.4
Black, non-Hispanic	1.2	2.3
Asian	4.3	7.6
Hispanic	11.6	13.6
Other/mixed	2.8	3.1
Missing*	(5.6)	(6.7)
Body mass index, kg/m^2		
<18.5	2.4	1.8
18.5 to <25	44.6	46.5
25 to <30	30.0	28.8
≥30	22.9	22.8
Missing*	(16.5)	(16.4)
Parity status		
Parous	77.2	82.6
Nulliparous	22.8	17.4
Missing*	(13.0)	(13.1)
Menopausal status		
Premenopausal	25.4	45.8
Postmenopausal	74.6	54.2
Missing*	(11.2)	(14.6)
Oral contraceptive use†		
Yes	1.0	2.9
No	39.3	51.4
Missing‡	59.7	45.7
Hormone therapy use†		
Yes	24.8	18.5
No	75.2	81.5
Missing*	(10.5)	(9.3)
Prior diagnosis of breast cancer		
Yes	8.0	3.4
No	92.0	96.6
Missing*	(7.7)	(6.7)
First-degree family history of breast or ovarian cancer		
Yes	18.7	13.5
No	81.3	86.5
Missing*	(4.2)	(4.5)
Breast density		
Almost entirely fat	10.9	9.5
Scattered	10.9	9.5
Heterogeneous	45.1	42.2
Extremely dense	34.7	38.2
Missing*	(9.4)	(10.0)

* Percentage of total.
† At time of mammogram.

Table 3. Five-year risk of incident epithelial ovarian cancer: adjusted hazard ratio (HR) and 95% confidence interval (CI) associated with Breast Imaging Reporting and Data System breast density category, overall and stratified by age group

Breast density	No. of ovarian cancer cases*	HR† (95% CI)
All ages‡	1022	
Almost entirely fat	150	0.99 (0.82 to 1.20)
Scattered	565	1.00 (referent)
Heterogeneous	507	1.20 (1.06 to 1.36)
Extremely dense	116	1.18 (0.93 to 1.50)
P_{trend}§		.01
Aged 40–49 y‡	207	
Almost entirely fat	10	1.04 (0.52 to 2.08)
Scattered	73	1.00 (referent)
Heterogeneous	120	1.30 (0.97 to 1.74)
Extremely dense	38	1.22 (0.78 to 1.91)
P_{trend}§		.23
Aged 50–59 y‡	314	
Almost entirely fat	37	1.11 (0.76 to 1.62)
Scattered	146	1.00 (referent)
Heterogeneous	160	1.30 (1.03 to 1.64)
Extremely dense	47	1.65 (1.12 to 2.44)
P_{trend}§		.02
Aged 60–69 y	335	
Almost entirely fat	59	1.03 (0.77 to 1.40)
Scattered	188	1.00 (referent)
Heterogeneous	161	1.33 (1.06 to 1.67)
Extremely dense	19	0.79 (0.47 to 1.33)
P_{trend}§		.19
Aged 70–79 y	290	
Almost entirely fat	55	0.89 (0.65 to 1.21)
Scattered	197	1.00 (referent)
Heterogeneous	114	0.96 (0.76 to 1.20)
Extremely dense	16	0.99 (0.54 to 1.83)
P_{trend}§		.82

* The number of case patients by density and age group sum to more than the total number of case patients because women with multiple mammograms can appear in multiple density and age groups.
† Hazard ratio, stratified by Breast Cancer Surveillance Consortium registry and adjusted for age, oral contraceptive use, hormone therapy use, parity status, prior diagnosis of breast cancer, and family history of breast or ovarian cancer in a first-degree relative.
‡ Additionally adjusted for postmenopausal status.
§ Two-sided Wald test.

We assessed effect modification of the breast density–ovarian cancer association. Although the interaction between breast density and age in decades was not statistically significant (P = .21), we noted patterns by age group. Among women aged 40 to 49 years, there was a non-statistically significant trend toward denser breast tissue being associated with elevated risk relative to women with scattered fibroglandular densities (Table 3). Among women aged 50 to 59 years, we observed a trend in elevated risk associated with increased breast density (P = .02); women with heterogeneously and extremely dense breast tissue had 30% (95% CI = 1.03 to 1.64) and 65% (95% CI = 1.12 to 2.44) increased risk, respectively, compared with women with scattered fibroglandular densities. Women aged 60 to 69 years with heterogeneously but not extremely dense breasts were at elevated risk compared with those with scattered fibroglandular densities. At age 70 to 79 years, we found no association between breast density and ovarian cancer risk.

We observed no statistically significant variation in the association between breast density and 5-year risk of epithelial ovarian cancer by oral contraceptive use, hormone therapy use, BMI, parity status, menopausal status, or prior breast cancer. However, we detected statistically significant variation by family history of breast or ovarian cancer ($P_{interaction}$ = .002). Among women with a family history, risk was 1.73-fold higher among women with fatty compared with scattered fibroglandular breast density (Table 4). Among women without a family history, risk was not elevated in women with fatty breasts, whereas women with heterogeneously and very dense breast tissue had a statistically significantly increased risk of ovarian cancer of 25% and a non-statistically significantly increased risk of 14%, respectively, compared with scattered fibroglandular density. The average age of women with a family history of breast or ovarian cancer was 57.6 years, and the average age of women without a family history was 56.0 years.

Of ovarian cancer case patients in the analysis, 90% were considered to have a hormonally responsive morphology. The most common of these morphologies were papillary serous cystadenocarcinoma, cystadenocarcinoma not otherwise specified, endometrioid adenocarcinoma, and adenocarcinoma not otherwise specified. We found no notable differences in results when restricting the outcome to ovarian cancer histology types that are primarily associated with hormonal exposure. We also observed similar results when the models included one randomly selected mammogram per woman. Further, the results did not change appreciably when we adjusted for BMI, extended the length of follow-up to 10-year risk, or excluded exams from women with a prior breast cancer diagnosis.

Discussion

Our findings demonstrate that breast density assessed on mammography is a modest risk factor for being diagnosed with incident epithelial ovarian cancer within 5 years for women aged 50 to 59 years; specifically, women with heterogeneously or extremely dense breast tissue are at increased risk compared with women with scattered fibroglandular densities. The associations between density and ovarian cancer risk in women aged 40 to 49 years and 60 to 79 years were not consistent and largely not statistically significant. To our knowledge, this is the first study to evaluate breast density as an ovarian cancer risk factor. Although the relative risks we observed in women in their 50s are of similar magnitude to known ovarian cancer risk factors (4), the absolute risk differences are likely small given the rarity of ovarian cancer. Prior research has also demonstrated that postmenopausal women with high breast density are at increased risk of breast cancer (23).

Women aged 50 to 59 years are transitioning through menopause with the suppression of ovarian function. This crucial time is associated with increasing ovarian cancer risk (14). Breast density decreases with hormonal changes associated with menopause (24). Kelemen et al. demonstrated that percentage density within the breast declines with increasing age within the transition, primarily among women in their 50s. Our data show that women aged 50 to 59 years with dense breasts vs scattered fibroglandular density have 30% to 65% increased risk of ovarian cancer within 5 years, during the age of greatest change in breast density. This is also the age when women are most likely to use postmenopausal hormone therapy, which can increase breast density and ovarian cancer risk (25). The use of estrogen-alone postmenopausal hormone therapy is more strongly associated with ovarian cancer risk than estrogen-progestin therapy (26) Although we did not observe a statistically significant interaction between the effects of age and breast density on risk of ovarian cancer, we may have had insufficient statistical power to observe the interaction.

Ovarian cancer risk has been associated with total number of ovulatory cycles and total time exposed to estrogen and other

Table 4. Five-year risk of incident epithelial ovarian cancer: adjusted hazard ratio (HR) and 95% confidence interval (CI) associated with Breast Imaging Reporting and Data System (BI-RADS) breast density category by family history of breast or ovarian cancer*

Family history of breast or ovarian cancer†	Breast density			
	BI-RADS 1	BI-RADS 2	BI-RADS 3	BI-RADS 4
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Yes‡	1.73 (1.21 to 2.48)	1.00 (referent)	1.04 (0.79 to 1.36)	1.32 (0.78 to 2.24)
No§	0.82 (0.66 to 1.02)	1.00 (referent)	1.25 (1.09 to 1.43)	1.14 (0.88 to 1.48)

* Hazard ratio stratified by Breast Cancer Surveillance Consortium registry and adjusted for age, oral contraceptive use, hormone therapy use, parity status, postmenopausal status, and prior diagnosis of breast cancer.
† Test for heterogeneity, two-sided P = .002.
‡ Trend test, two-sided P < .001.
§ Trend test, two-sided P = .40.

hormones (10,11). Although breast density decreases with age and menopause (27), it is unclear how sex hormones contribute to these changes. In premenopausal women, circulating sex hormone binding globulin is associated with increasing percentage breast density (P_{trend} = .02), and there is some suggestion of trend with serum estradiol (P_{trend} = .08) (28). Similarly, in postmenopausal women, increasing breast density is associated with serum progesterone and sex hormone binding globulin but not estradiol or testosterone (29). Thus, circulating levels of sex hormones are inconsistently associated with breast density, suggesting that the extent of breast density may only in part reflect changes in sex hormones over a woman's lifetime and thus is an inadequate surrogate for lifetime exposure to estrogen or other hormones.

We observed variation in the association between breast density and ovarian cancer risk by family history of breast or ovarian cancer. Among women with a family history, we found a 70% increased risk of ovarian cancer associated with fatty vs scattered fibroglandular breast tissue. In contrast, among women without a family history, we observed an elevated ovarian cancer risk only in women with heterogeneously dense breast tissue. Shared genetic factors may exist between family history, fatty breasts, and risk of ovarian cancer. We were unable to assess whether women in our study were *BRCA1/2* carriers.

We conducted a large cohort study to examine the association between breast density and ovarian cancer risk with well-defined exposure variables and outcomes and the ability to adjust for important ovarian cancer risk factors. Few other studies have access to both breast density measures and ovarian cancer outcomes. Despite these strengths, there were limitations to our analysis in terms of assessment of exposure, length of follow-up, and outcome assessment. In general, BI-RADS breast density has good intraobserver agreement, with kappas ranging from 0.72 to 0.90 (30–32), but only modest inter-rater agreement (kappa = 0.58) (30), which would bias our risk estimate toward the null. Continuous measures of breast density may be more reflective of ovarian cancer risk, but continuous measures are not available in usual clinical care. We had limited ability to estimate long-term associations between breast density and ovarian cancer. We limited follow-up for our primary analysis to 5 years after mammogram. Also, because we obtained information about oophorectomy only at the time of mammography, the analysis might have included some women who had a bilateral oophorectomy after a mammogram and before censoring. Our evaluation of ovarian cancer incidence within 5 years of each mammogram minimizes the potential bias. Finally, relatively new research suggests that the precursor lesions to ovarian cancer could begin in the fallopian tube (33). We were unable to include cancers of the fallopian tube or peritoneum in analyses because these data were not collected by the participating breast imaging registries. However, we did restrict our primary outcome for analysis to epithelial ovarian cancer cases, and in a sensitivity analysis, we restricted further to morphologic subtypes most strongly related to hormones with little difference in results.

This study was designed to examine whether mammographic breast density is a risk factor for ovarian cancer. Women in their 50s with dense breasts demonstrated an increased 5-year risk of ovarian cancer that was not present in the older women. Our results could be valuable for research studies of ovarian cancer prevention by replicating the association of breast density and ovarian cancer in women aged 50 to 59 years. Expanding our understanding of ovarian cancer etiology beyond genetic predisposition is critical to better target ovarian cancer prevention.

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