American Journal of Epidemiology
Copyright © 2005 by the Johns Hopkins Bloomberg School of Public Health
All rights reserved; printed in U.S.A.

Vol. 162, No. 8
DOI: 10.1093/aje/kwi270
Advance Access publication September 9, 2005

Original Contribution

Mammographic Density and Breast Cancer Risk

The Multiethnic Cohort Study

Gertraud Maskarinec, Ian Pagano, Galina Lurie, Lynne R. Wilkens, and Laurence N. Kolonel

From the Cancer Etiology Program, Cancer Research Center of Hawaii, Honolulu, HI.

Received for publication February 16, 2005; accepted for publication May 13, 2005.

In a nested case-control study (2001–2004), the authors investigated the association between mammographic density and breast cancer risk among women of Caucasian, Japanese, and Native Hawaiian ancestry in the Hawaii component of the Multiethnic Cohort Study. The authors retrieved several prediagnostic mammograms for breast cancer cases and for controls frequency-matched to cases by age and ethnicity. A reader who was blinded to case status and year of mammogram performed computer-assisted density assessment. Suitable mammographic readings were obtained for 607 cases and 667 controls. The authors used unconditional logistic regression to estimate odds ratios and 95% confidence intervals while adjusting for confounders. Mean percent density and mean dense area were significantly greater for cases than for controls: 39.6% vs. 29.7% and 37.3 cm^2 vs. 28.4 cm^2, respectively. For the earliest mammogram taken, the overall odds ratio for a 10% increase in breast density was 1.22 (95% confidence interval: 1.14, 1.30), and the overall odds ratio for a 10-cm^2 increase in dense area was 1.17 (95% confidence interval: 1.11, 1.24). The similar sizes of the areas under the receiver operating characteristic curve (0.66) confirmed that percent density and dense area predicted breast cancer equally well. Because the risk estimates appeared higher for Caucasians and Native Hawaiians than for Japanese women, ethnicity-specific models may be necessary to predict risk from breast density in different ethnic groups.

breast neoplasms; ethnic groups; mammography

Abbreviations: CI, confidence interval; HRT, hormone replacement therapy; MEC, Multiethnic Cohort; ROC, receiver operating characteristic.

A large body of evidence suggests that mammographic density is a strong predictor of breast cancer risk (1–4). Initially, breast density was evaluated according to a qualitative classification scheme (5), but later quantitative approaches using visual estimation (6), planimetric (7), and computer-assisted (8, 9) methods were developed. Women in the highest density category out of five or six levels have a four- to sixfold higher risk of breast cancer than subjects in the lowest category (10).

So far, only two case-control studies using quantitative assessment methods (4, 11) have included substantial numbers of non-Caucasian women, primarily Asian Americans and African Americans. Whereas a study from California described a stronger association between mammographic densities and breast cancer among Chinese, Filipino, and Japanese women than among Caucasian women (4), our study in Hawaii suggested a weaker association among Japanese women than among Caucasian women (11). Cross-sectional studies have shown that women of Asian ancestry have higher percent densities than Caucasian women because of their relatively small breast size (12, 13), but densities were found to be higher among Japanese Americans in Hawaii than among women in Japan, reflecting the difference in breast cancer risk (14). Although breast cancer

Correspondence to Dr. Gertraud Maskarinec, Cancer Research Center of Hawaii, 1236 Lauhala Street, Honolulu, HI 96813 (e-mail: gertraud@crch.hawaii.edu).

Downloaded from https://academic.oup.com/aje/article/162/8/743/122341 by guest on 25 April 2024

incidence is still considerably lower in Japan than in Western countries (15), Japanese migrants to California and Hawaii, who have now reached the third and fourth generations, have a risk level similar to that of Caucasians (16, 17).

We hypothesized that despite ethnic differences in breast density, the relations between mammographic densities and breast cancer risk would be similar in Caucasian, Japanese, and Native Hawaiian women. The Hawaii component of the Multiethnic Cohort (MEC) Study (18) offered us an opportunity to explore the relation between mammographic density and breast cancer risk among women in these three groups and to investigate the relative importance of percent densities versus the size of the dense area.

MATERIALS AND METHODS

Study design and population

This case-control study was nested within the Hawaii component of the MEC Study, which was established between 1993 and 1996. As described in detail elsewhere (18), this large prospective study investigates the association between diet and cancer among 96,810 men and 118,441 women in Hawaii and Los Angeles, California. Subjects are predominately of African-American, Caucasian, Latino, Japanese, and Native Hawaiian ancestry. The population-based sampling frames included driver's license, voter registration, and Health Care Financing Administration files. The original cohort study and the nested case-control study were approved by the Committee on Human Studies at the University of Hawaii. For ascertainment of deaths and incident cancer cases, respectively, data from the Hawaii component of the MEC Study are linked annually to the Hawaii Department of Health vital records database and the statewide Hawaii Tumor Registry, part of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program.

Recruitment

All female members of the MEC Study who resided in Hawaii and were diagnosed with a primary breast cancer between cohort entry and December 2000 were identified as potential cases (n = 1,587). From Hawaii MEC Study participants who were not known to have breast cancer, a similar number of randomly selected controls was identified within the ethnic and 5-year age groups of the cases (n = 1,584). For this nested case-control study, subjects had to be alive at the time of recruitment and sign an informed consent form and a mammogram release form. Exclusion criteria for cases and controls included diagnosis of breast cancer before entry into the cohort study, either by record linkage or by self-report at baseline; no mammogram; and a history of breast augmentation or reduction, but not breast biopsy, as stated in the breast health questionnaire. We learned about deaths that had occurred by the time of recruitment and about additional prevalent cases from the subjects and their mammography records; we excluded these women after obtaining the additional information. Subjects were recruited by mail during 2001–2002 with a maximum of three reminders; we avoided more aggressive recruitment in order not to jeopardize future participation of subjects in cohort studies. The recruitment package included a study description, a consent form, a mammogram release form, a breast health questionnaire, and a questionnaire assessing the consumption of soy foods. Among the 1,584 potential controls selected from the MEC Study database, 19 had been diagnosed with breast cancer by the time of recruitment and reclassified as cases, but only nine of these women participated in the study.

Of the 3,171 subjects originally identified (table 1), 8.7 percent were ineligible, primarily because of death or preexistent breast cancer. Although 54 percent of eligible women responded to the mailings, only 50.6 percent returned both signed forms. The response rate was slightly higher among cases than among controls. For 127 cases and 64 controls, we had no suitable mammogram to scan, leaving us with 43.5 percent ($n = 607$) and 44.5 percent ($n = 667$) of eligible cases and controls, respectively. These proportions were highest for Caucasians (50 percent and 48 percent), followed by Japanese (44 percent for both), and were lowest for Native Hawaiians (34 percent and 47 percent) and others (41 percent and 25 percent). More cases than controls were ineligible, primarily because of death. Japanese cases had an 11 percent ineligibility rate, whereas the rate was 15–16 percent for all other groups; for controls, the rates were 3–5 percent.

When we compared the 1,274 women in the analysis with the 1,622 women who were eligible but not included, we observed only small differences. The included women were 1.4 years younger ($p < 0.001$) and more likely to be postmenopausal. After age adjustment, the included women had a later age at first livebirth (0.7 years; $p < 0.001$) and a higher prevalence of use of hormone replacement therapy (HRT) (72.9 percent vs. 60.4 percent; $p < 0.001$) and were more likely to have been born in the United States (92 percent vs. 89 percent; $p = 0.03$). However, included and excluded women did not differ with regard to body mass index (weight (kg)/height (m)^2), family history of breast cancer, parity, or age at menarche.

Data collection

At entry into the cohort, all subjects completed a survey, including an extensive food frequency questionnaire especially designed for the MEC Study, that also inquired about demographic background, anthropometric measures, reproductive behavior, and family history of breast cancer (19). The survey information underwent extensive cleaning and editing procedures. As part of the recruitment for the nested case-control study, the women completed a one-page breast health questionnaire that asked about previous breast surgery (especially breast augmentation or reduction), menopausal status, mammography history, and HRT use. The women using HRT were asked to write in the name of their HRT medication, and HRT was classified into estrogen-only or combined estrogen/progesterone therapy.

Mammographic density assessment

Mammograms were requested from all 33 clinics listed on the release forms. These facilities were accredited according to the Mammography Quality Standards Act

Downloaded from https://academic.oup.com/aje/article/162/8/743/122341 by guest on 25 April 2024

TABLE 1. Numbers of women recruited for and participating in a case-control study nested in the Hawaii component of the Multiethnic Cohort Study, 2001–2004

Category and reason for exclusion	Cases		Controls		Total	
	No.	%*	No.	%	No.	%
Identified from Multiethnic Cohort Study	1,587		1,584		3,171	
Ineligible	210	13.2	65	4.1	275	8.7
Deceased	114		8		122	
Prevalent case	85		40		125	
Unable to contact	9		5		14	
Breast surgery	2		5		7	
No mammogram	0		7		7	
Adjustment in case status†	+19		−19		0	
Eligible to participate in case-control study	1,396		1,500		2,896	
Responders	783	56.1	777	51.8	1,560	53.9
Refused	47	3.4	42	2.8	89	3.1
Signed consent form	736		735		1,471	
Signed release form	755		742		1,497	
Provided full consent	734	52.6	731	48.7	1,465	50.6
No mammogram for analysis	127	17.3	64	8.8	191	13.0
Clinic not known	13		25		38	
Mammogram not found	17		26		43	
Mammogram not requested	45		13		58	
Mammogram done out of state	5		0		5	
No mammogram before diagnosis	47		0		47	
Final sample	607	43.5	667	44.5	1,274	44.0

* The number of women eligible to participate was used as the denominator, except for percent ineligible, where the population identified from the cohort served as the denominator.

† Women who were selected as controls but had been diagnosed with breast cancer at the time of recruitment.

(20, 21). Of the 6,478 mammograms in the final data set, 1,615 (25 percent) came from one organization. The other clinics contributed 8–571 images each. We did not have suitable mammograms for 191 women, for several reasons (table 1). From the many mammograms available for each woman, we selected films to cover as wide a time frame as possible, using the following criteria. For cases, the goal was to include only films taken before diagnosis; but for five cases, only the contralateral mammogram of the healthy breast taken at the time of diagnosis before initiation of treatment was available. Whenever possible, we scanned at least one mammogram taken before 1995 and one taken after 1995 and at least one mammogram taken during 1990–2000. However, for five controls and one case, we could only locate a mammogram taken before 1990; and for seven controls, we could only locate an image from 2001–2003. In the final data set, 86 percent of all mammograms were performed between 1990 and 2000.

All mammographic films from both breasts were scanned with a Kodak LS85 Film Digitizer (absorbance range, 0.001–4.1; Eastman Kodak Company, Rochester, New York) at a resolution of 98 pixels per inch (pixel size equal to 260 μm). The 8-bit images are displayed in 256 shades of gray. One of the authors performed computer-assisted density assessment (8, 22) for batches of 100 mammograms. All images for one woman were assessed during the same session, but the reader was blinded as to group status and year of mammogram. After the reader determined a threshold for the edge of the breast and the edge of the dense tissue (8), the computer calculated the total number of pixels in the digitized image that constituted the total area and the dense area and computed the ratio between the two values. We converted pixels into square centimeters using a factor of 0.000676.

Since the readings for the two sides were very similar ($r =$ 0.92–0.97), we averaged the values for the right and the left breast to obtain one mammographic measure when both films were available, but 689 (19.3 percent) measures were based on one side only. This proportion was higher for cases (33.2 percent) than for controls (2.5 percent), because some cases did not have screening mammograms taken before their diagnosis. On average, 3.2 and 2.4 density measures on different dates were available for cases and controls, respectively. Therefore, subjects with at least two mammograms had three different variables: earliest, latest, and mean mammographic reading. The 226 women with only one mammogram taken at one point in time were included in all of these analyses, using the single value each time.

Downloaded from https://academic.oup.com/aje/article/162/8/743/122341 by guest on 25 April 2024

The unadjusted mean ages for the earliest, latest, and all mammograms among cases versus controls were 57.0 versus 57.5 years, 62.1 versus 61.7 years, and 59.6 versus 59.7 years, respectively, indicating excellent matching. The mean time between the earliest mammogram and the breast cancer diagnosis was 6.3 years, while the earliest and the latest mammogram were, on average, 4.2 years apart for controls and 5.1 years apart for cases. A random sample of 410 mammograms was read in duplicate to assess the reliability of the mammographic readings. The intraclass correlation coefficients (23) were 0.96 (95 percent confidence interval (CI): 0.95, 0.97) for the size of the dense area and 0.996 (95 percent CI: 0.995, 0.997) for the total breast area, resulting in an intraclass correlation coefficient of 0.974 for percent density (95 percent CI: 0.968, 0.978).

Statistical analysis

Because of our inclusion criteria, there were no missing values for ethnicity or mammographic parameters. On the basis of all ethnic backgrounds reported for both parents, persons with several ethnic backgrounds were classified into one category, giving first priority to Native Hawaiian ancestry and then to Japanese, Caucasian, and other ancestry (18). Because cancer cases and controls were matched on ethnicity and age, these variables were entered only to adjust for incomplete matching, and results were not interpreted. Information on body mass index and reproductive variables was collected at entry into the cohort, and additional information on HRT use was obtained when the women enrolled in the mammographic density study. A comparison of the HRT information obtained from the two questionnaires found good agreement for overlapping years when both questionnaires reported on HRT use. On the basis of the breast health questionnaire, we created an HRT use variable (use or no use) for each year from 1990 to 2000. To classify the type of medication, we first utilized the information from the breast health questionnaire. If a woman indicated that she had used HRT at any time but the write-in field was empty, we assigned the type of HRT from the cohort questionnaire completed at baseline. For the 69 women with missing information on HRT type, we imputed the type based on hysterectomy status (24): estrogen only for women with a hysterectomy and combined therapy otherwise. As a result, each woman had a binary HRT use variable for each year but only one HRT type variable, because the questionnaire did not allow the entry of more than one type of HRT.

Breast cancer cases and controls were compared overall and within each ethnic group with regard to each of the risk factors. Either the t test or the χ^2 test was used to assess differences by case status. We used the SAS Logistic procedure (25) to perform unconditional logistic regression analysis (26), and we estimated odds ratios and 95 percent confidence intervals for incident breast cancer while adjusting for demographic, anthropometric, and reproductive confounding variables. The mammographic density predictors were modeled as continuous measures and as categorical variables. Analyses were repeated for the earliest mammogram, the latest mammogram, and the mean value of readings from all mammograms, because we wanted to explore whether age at the time of mammogram influences the strength of the association between density and breast cancer risk. Separate analyses were performed for percent density and dense area (cm^2). Percent density was classified as less than 10 percent, 10–24.9 percent, 25–49.9 percent, and 50 percent or more, while for dense area, 15 cm^2, 30 cm^2, and 45 cm^2 were used as the limits of the categories. We chose four categories rather than six, as were used in other reports (2, 4), in order to apply the same grouping to all ethnic groups despite the differences in breast density. To compare the ability of percent and the size of the dense area of the earliest mammogram to predict breast cancer, we computed the area under the receiver operating characteristic (ROC) curve (25), a method used in sensitivity-specificity analyses that assesses the effectiveness of a test for determining the presence of a disease. A plot of the ROC curve is the graph of sensitivity versus 1 minus specificity. If the test is perfect, the area under the ROC curve is equal to 1.0; if it performs no better than chance, the area will be equal to 0.5. Because logistic regression predicts membership in one of two groups (e.g., disease vs. no disease), the ROC curve assesses the goodness of fit of these models.

The following covariates were included in all models because of their known relation to breast cancer risk (17) and breast density (10, 27, 28): ethnicity, age at mammogram as a continuous variable, body mass index at baseline (<22.5, 22.5–25.0, 25.1–30.0, or >30), age at first livebirth (<21, 21–30, or >30 years, or no children), number of children (0–1, 2–3, or ≥4), age at menarche (<13, 13–14, or ≥15 years), age at menopause (<45, 45–49, or ≥50 years, or premenopausal), HRT use in the year of the mammogram (never, estrogen only, or estrogen with progesterone), and family history of breast cancer (breast cancer in a first-degree relative, or no history). To maximize the number of observations for the case-control analysis, we replaced missing values with the most likely values among subjects in the mammographic density study: age at first livebirth (32 missing), 21–30 years; number of children (12 missing), 2–3; and breast cancer family history (36 missing), no history. For the nine women with missing data on body mass index and 16 women with missing data on age at menarche, we assigned the median values of their respective ethnic groups. All analyses were repeated after stratifying by ethnicity, stratifying by weight status (body mass index <25 vs. ≥25), including only women without any missing values (n = 1,109), and excluding in situ cases (n = 125).

RESULTS

Japanese Americans constituted almost half of the study population, which consisted of 607 breast cancer cases and 667 controls (table 2). Despite matching, we did not achieve a good balance in cases and controls for Native Hawaiians. Cases were, on average, 2 years older at the time of recruitment into the MEC Study than controls. The majority of breast cancer cases were detected at an early stage: 21 percent were classified as in situ, 62 percent as localized, 16 percent as regional, and less than 1 percent as distant and

Downloaded from https://academic.oup.com/aje/article/162/8/743/122341 by guest on 25 April 2024

TABLE 2. **Characteristics of cases and controls by ethnic group, adjusted for age at recruitment, in the Hawaii component of the Multiethnic Cohort Study, 2001–2004***

Variable	Ethnic group												All women		
	Hawaiian			Japanese			Caucasian			Other					
	Cases	Controls	*p* value	Cases	Controls	*p* value	Cases	Controls	*p* value	Cases	Controls	*p* value	Cases	Controls	*p* value
Sample size (no.)	79	162		292	292		195	187		41	26		607	667	
Age (years) at recruitment	58.1	54.9	0.004	60.5	59.5	0.16	60.6	57.4	<0.001	56.2	56.8	0.78	59.9	57.7	<0.001
Born in the United States (%)	98.8	99.4	0.66	94.5	93.2	0.52	89.0	91.7	0.38	68.5	49.7	0.13	91.5	92.6	0.44
Body mass index†	27.8	28.1	0.75	23.9	23.4	0.13	24.6	25.4	0.15	23.9	25.4	0.17	24.7	25.1	0.13
Age (years) at earliest mammogram	52.7	55.6	<0.001	57.0	60.2	<0.001	56.5	58.5	<0.001	53.1	55.8	0.005	55.9	58.6	<0.001
Time (years) from first mammogram to diagnosis‡	6.3			6.7			6.7			6.4			6.3		
No. of mammograms	3.2	2.4	<0.001	3.3	2.4	<0.001	3.1	2.5	<0.001	3.2	2.6	0.16	3.2	2.4	<0.001
Family history of breast cancer (%)§	25.4	16.6	0.11	16.0	12.8	0.28	14.7	8.7	0.08	19.6	−0.1	0.02	17.0	12.1	0.02
Age (years) at menarche	12.9	13.1	0.50	12.9	13.1	0.15	13.0	13.1	0.77	13.8	13.5	0.44	13.0	13.1	0.32
Parous (%)	86.3	93.7	0.06	84.9	89.4	0.11	81.4	84.4	0.44	82.6	88.3	0.54	83.8	89.0	0.007
Age (years) at first birth	22.6	23.2	0.29	25.6	25.4	0.70	24.7	25.2	0.38	26.5	23.6	0.02	24.9	24.8	0.51
No. of children	3.0	3.2	0.61	2.2	2.4	0.11	2.1	2.5	0.03	2.4	2.7	0.38	2.3	2.6	<0.001
Postmenopausal (%)	58.9	60.2	0.82	69.9	78.0	0.003	71.2	67.4	0.30	57.0	67.8	0.24	67.4	70.9	0.08
Any HRT¶ use (%)#	52.4	64.0	0.16	78.4	73.6	0.24	66.2	69.3	0.59	82.2	39.4	0.004	71.2	69.2	0.50
ERT¶ use only (%)#	25.4	37.9	0.12	45.9	47.5	0.74	36.2	45.8	0.12	9.0	27.4	0.13	38.0	44.4	0.05
EPRT¶ use (%)#	27.0	26.0	0.90	32.4	26.1	0.15	30.0	23.5	0.23	73.3	11.9	<0.001	33.2	24.7	0.005

* Unless otherwise indicated, mean values are given.
† Weight (kg)/height (m)^2.
‡ Number of years from the earliest scanned mammogram to the diagnosis of breast cancer.
§ Diagnosis of breast cancer in any first-degree relative.
¶ HRT, hormone replacement therapy; ERT, estrogen replacement therapy; EPRT, estrogen/progesterone replacement therapy.
# Percentage of postmenopausal women.

Downloaded from https://academic.oup.com/aje/article/162/8/743/122341 by guest on 25 April 2024

TABLE 3. Mammographic parameters for the study population, by case status and ethnic group, in the Hawaii component of the Multiethnic Cohort Study, 2001–2004*

Mammogram and ethnic group	Percent density			Dense area (cm^2)			Total area (cm^2)		
	Cases	Controls	*p* value†	Cases	Controls	*p* value†	Cases	Controls	*p* value†
Earliest mammogram									
Hawaiian	35.0	26.9	0.008	40.6	31.4	0.01	132.3	140.1	0.38
Japanese	39.4	33.0	0.0002	31.8	26.7	0.001	87.7	90.2	0.40
Caucasian	39.8	26.7	<0.0001	43.0	28.0	<0.0001	128.4	136.5	0.25
Other	47.7	33.6	0.005	42.1	32.9	0.06	93.4	111.0	0.04
All women	39.6	29.7	<0.0001	37.3	28.4	<0.0001	107.4	115.7	0.01
Latest mammogram (all women)	36.0	28.4	<0.0001	36.5	28.0	<0.0001	117.6	121.3	0.28
Mean of all mammograms (all women)	37.8	28.7	<0.0001	37.2	28.0	<0.0001	112.7	119.1	0.05

* Data for all mammographic parameters are reported as mean values adjusted for age.
† Probability for difference as determined by a *t* test comparing cases and controls within each group.

unknown. After age adjustment, there was no significant difference in terms of place of birth, body mass index, age at menarche, age at first livebirth, proportion of postmenopausal women, or ever use of HRT by case status. However, cases reported a higher use of combined HRT and a lower use of estrogens only. They also had a higher proportion of nulliparous women, fewer children, and a higher percentage with a family history of breast cancer. Within the three major ethnic groups, anthropometric and reproductive variables did not differ very much by case status, but several of these characteristics varied by ethnicity. Body mass index was highest for Native Hawaiians and lowest for Japanese. Native Hawaiians had more children and reported a family history of breast cancer more frequently than women in the other ethnic groups. The proportion of Japanese women born outside of the United States (6 percent) was not very different from that of Caucasians (10 percent). On the basis of parents' places of birth, we knew that more than half of the parents of the Japanese-American women had been born in the United States, making these women at least third-generation migrants.

Total breast area was 50 percent greater among Caucasian and Native Hawaiian women than among Japanese women, and controls had larger breasts than cases (table 3). For the mean value of all mammograms, percent density was approximately 10 percent higher in cases than in controls ($p < 0.0001$), and the dense area was approximately 9 cm^2 larger ($p < 0.0001$). The difference between cases and controls was greater for Caucasians than for Native Hawaiians and Japanese and was greater for the earliest mammogram as compared with the latest.

Using the percent density for the earliest mammogram, the odds ratio for a 10 percent density increase was 1.22 in the total population (table 4). Stratified by ethnicity, the respective odds ratios were 1.24 for Native Hawaiians, 1.15 for Japanese, and 1.31 for Caucasians. The results using the latest mammogram and the mean density readings were not substantially different, but the risk estimates were slightly weaker for the mammogram taken closest to diagnosis. When we categorized percent densities using the means of all readings, women with densities of 50 percent or more had a 3.59 times higher risk of developing breast cancer than women with less than 10 percent densities; however, the estimated risk appeared to differ by ethnicity: 4.18 for Native Hawaiians, 3.18 for Japanese women, and 5.27 for Caucasians. The ROC areas were also slightly larger for Caucasians (0.736) and Native Hawaiians (0.720) than for Japanese women (0.658). However, a model including an interaction effect produced results that were not significantly different from those of the original model ($p = 0.42$).

The dense area was associated with breast cancer risk to a similar degree as percent densities (table 5). The odds ratio for the mean of all mammograms for an increase of 10 cm^2 was 1.19 overall, 1.22 for Native Hawaiians, 1.15 for Japanese, and 1.25 for Caucasians. The odds ratio for the highest quartile of dense area compared with the lowest, based on the mean of all mammograms, was 2.91. For the model with percent density from the earliest mammogram, the ROC area was 0.664, and for the model with the dense area, it was 0.661—indicating that both mammographic measures predicted breast cancer equally well. When we restricted the analysis to the 1,109 women without any missing values, the association between density and breast cancer risk remained unchanged. In addition, after removal of the 125 subjects with in situ cancer, the strength of the association remained similar. The overall odds ratio for a 10 percent change in percent density was 1.22 (95 percent CI 1.14, 1.31), and for a 10-cm^2 change in dense area, it was 1.19 (95 percent CI: 1.12, 1.27). Interestingly, stratification by body mass index showed a stronger association between percent density and breast cancer risk (based on the mean of all mammograms) for overweight subjects (body mass index $\geq$25) than for women with normal weight. The respective odds ratios were 1.29 (95 percent CI 1.13, 1.43) and 1.16 (95 percent CI 1.07, 1.26). This relation held true in all ethnic groups: 1.29 versus 1.14 in Native Hawaiians, 1.28 versus 1.12 in Japanese, and 1.41 versus 1.27 in Caucasians. However, the model with an interaction between weight status and percent densities was not significantly different ($p = 0.53$), and the areas under the ROC curve differed little: 0.683 for normal-weight women and 0.696 for overweight women.

Downloaded from https://academic.oup.com/aje/article/162/8/743/122341 by guest on 25 April 2024

TABLE 4. Risk estimates for the association between breast cancer and percent mammographic density in the Hawaii component of the Multiethnic Cohort Study, 2001–2004*

Ethnic group and percent density	Earliest mammogram				Latest mammogram				Mean of all mammograms			
	Cases	Controls	OR†	95% CI†	Cases	Controls	OR	95% CI	Cases	Controls	OR	95% CI
Hawaiian												
<10	13	45	1.00‡		17	50	1.00‡		14	47	1.00‡	
10–24.9	17	44	1.42	0.52, 3.91	26	45	1.94	0.80, 4.69	21	43	1.82	0.70, 4.74
25–49.9	28	42	5.19	1.82, 14.80	25	39	2.71	1.03, 7.10	28	47	3.32	1.22, 9.05
≥50	21	31	5.13	1.60, 16.47	11	28	1.95	0.62, 6.10	16	25	4.18	1.30, 13.43
Per 10%	79	162	1.24	1.04, 1.47	79	162	1.10	0.93, 1.31	79	162	1.22	1.02, 1.47
Japanese												
<10	24	43	1.00‡		36	50	1.00‡		23	44	1.00‡	
10–24.9	71	73	1.79	0.93, 3.46	66	72	1.38	0.76, 2.50	68	76	1.94	0.99, 3.80
25–49.9	105	103	1.70	0.88, 3.31	101	103	1.46	0.81, 2.61	110	107	2.23	1.13, 4.39
≥50	92	73	2.27	1.11, 4.65	89	67	2.08	1.09, 3.97	91	65	3.18	1.52, 6.63
Per 10%	292	292	1.15	1.04, 1.27	292	292	1.12	1.02, 1.22	292	292	1.15	1.04, 1.27
Caucasian												
<10	40	58	1.00‡		45	70	1.00‡		41	63	1.00‡	
10–24.9	38	47	1.22	0.62, 2.42	46	48	1.77	0.93, 3.40	42	46	1.63	0.84, 3.17
25–49.9	47	43	2.28	1.15, 4.49	44	38	2.09	1.06, 4.10	47	45	2.17	1.11, 4.25
≥50	70	39	4.28	1.95, 9.39	60	31	4.45	2.06, 9.61	65	33	5.27	2.35, 11.80
Per 10%	195	187	1.31	1.16, 1.47	195	187	1.25	1.11, 1.40	195	187	1.33	1.18, 1.51
All women												
<10	80	151	1.00‡		103	175	1.00‡		82	158	1.00‡	
10–24.9	129	169	1.53	1.03, 2.27	141	169	1.48	1.02, 2.14	133	170	1.61	1.09, 2.39
25–49.9	198	200	2.17	1.46, 3.23	190	194	1.74	1.20, 2.53	207	212	2.16	1.45, 3.20
≥50	200	147	3.14	2.02, 4.88	173	129	2.73	1.80, 4.16	185	127	3.59	2.29, 5.62
Per 10%	607	667	1.22	1.14, 1.30	607	667	1.16	1.09, 1.23	607	667	1.22	1.14, 1.31

* In all models, results were adjusted for ethnicity, age at mammogram, body mass index, age at first livebirth, number of children, age at menarche, age at menopause, use of hormone replacement therapy, and family history of breast cancer.
† OR, odds ratio; CI, confidence interval.
‡ Reference category.

DISCUSSION

This study confirmed the substantial breast cancer risk associated with greater mammographic densities. Women with more than 50 percent densities had a 3.6 times higher risk of breast cancer than women with less than 10 percent densities, but the estimated risk varied by ethnicity. Whereas the odds ratio was 5.3 for Caucasians and 4.2 for Native Hawaiians, it was only 3.2 for women of Japanese ancestry, although this difference was not statistically significant. The ROC areas confirmed that the ability to predict breast cancer was approximately equal for percent density and the size of the dense area. Using the mean readings for all mammograms as opposed to the earliest or the latest mammogram strengthened the association with breast cancer but indicated no material difference in the results.

Our risk estimates for Caucasians were quite similar to those of other studies using quantitative mammographic density assessment methods (2, 3, 29). A previous study in Hawaii based on mammograms performed very close to diagnosis reported substantially lower risk estimates (11), possibly because of use of a different scanner and software and a lack of information on body mass index and other confounders. Our findings disagree with those of the California study (4) that estimated a stronger risk for women with Asian ancestry than for Caucasian women, but the number of Asian women in the California study was relatively low ($n = 210$) and included persons of several ethnicities (Chinese, Filipino, and Japanese).

Although it was not statistically significant, we observed a stronger association between breast cancer risk and mammographic densities among heavier women. The same effect modification was found in all three groups, while Caucasians maintained the highest odds ratios regardless of weight status. Percent density is highly influenced by breast size and body fat (13), and at the same time, body weight is associated with breast cancer risk (30). The lower risk associated with percent density in Japanese could be due to limitations in the two-dimensional density assessment among Japanese women. Capturing the third

Downloaded from https://academic.oup.com/aje/article/162/8/743/122341 by guest on 25 April 2024

TABLE 5. Risk estimates for the association between breast cancer and the size of the dense area in the Hawaii component of the Multiethnic Cohort Study, 2001–2004*

Ethnic group and size (cm^2) of dense area	Earliest mammogram				Latest mammogram				Mean of all mammograms			
	Cases	Controls	OR†	95% CI†	Cases	Controls	OR	95% CI	Cases	Controls	OR	95% CI
Hawaiian												
<15	15	48	1.00‡		19	56	1.00‡		16	50	1.00‡	
15–29.9	18	40	1.56	0.59, 4.08	23	32	2.18	0.87, 5.42	20	38	1.86	0.73, 4.74
30–44.9	24	28	2.85	1.09, 7.48	13	33	1.17	0.43, 3.17	21	34	1.99	0.78, 5.08
≥45	22	46	2.43	0.94, 6.30	24	41	3.05	1.21, 7.72	22	40	2.96	1.14, 7.68
Per 10 cm^2	79	162	1.17	1.03, 1.32	79	162	1.18	1.03, 1.35	79	162	1.22	1.07, 1.40
Japanese												
<15	60	87	1.00‡		64	85	1.00‡		59	83	1.00‡	
15–29.9	101	104	1.37	0.85, 2.20	84	103	1.18	0.74, 1.89	96	112	1.20	0.75, 1.92
30–44.9	73	55	1.75	1.02, 3.01	77	58	1.74	1.03, 2.94	73	56	1.82	1.05, 3.13
≥45	58	46	1.82	1.03, 3.22	67	46	2.08	1.20, 3.60	64	41	2.15	1.21, 3.83
Per 10 cm^2	292	292	1.13	1.03, 1.25	292	292	1.16	1.05, 1.27	292	292	1.15	1.04, 1.28
Caucasian												
<15	42	63	1.00‡		47	73	1.00‡		41	68	1.00‡	
15–29.9	39	51	1.11	0.57, 2.15	40	49	1.26	0.67, 2.37	45	46	1.59	0.84, 3.03
30–44.9	45	33	2.53	1.26, 5.09	34	26	2.32	1.13, 4.77	32	34	1.73	0.84, 3.54
≥45	69	40	3.34	1.72, 6.49	74	39	3.38	1.79, 6.38	77	39	4.34	2.25, 8.37
Per 10 cm^2	195	187	1.24	1.12, 1.37	195	187	1.18	1.08, 1.29	195	187	1.25	1.13, 1.38
All women												
<15	121	204	1.00‡		136	221	1.00‡		121	209	1.00‡	
15–29.9	164	202	1.34	0.95, 1.88	155	190	1.30	0.93, 1.81	166	200	1.40	1.00, 1.96
30–44.9	155	124	2.09	1.45, 3.01	138	125	1.77	1.23, 2.55	139	133	1.84	1.27, 2.65
≥45	167	137	2.40	1.66, 3.46	178	131	2.57	1.80, 3.67	181	125	2.91	2.02, 4.21
Per 10 cm^2	607	667	1.17	1.11, 1.24	607	667	1.16	1.10, 1.23	607	667	1.19	1.12, 1.26

* In all models, results were adjusted for ethnicity, age at mammogram, body mass index, age at first livebirth, number of children, age at menarche, age at menopause, use of hormone replacement therapy, and family history of breast cancer.

† OR, odds ratio; CI, confidence interval.

‡ Reference category.

dimension of breast density may be more important for breasts with small areas than for large breasts. Newer volumetric methods may allow more accurate measurement of the dense cell mass in the breast (31).

Our study had a number of unique features, particularly a large number of US-born Japanese-American women, who are at a similarly high risk of developing breast cancer as Caucasian women (16, 17, 32). To our knowledge, this is the first study exploring the breast density-breast cancer relation with a sufficient number of Native Hawaiian women, an ethnic group with an extremely high breast cancer risk (17). The collection of multiple mammograms over many years for a large proportion of subjects made it possible to conduct separate analyses for mammograms taken many years before diagnosis and mammograms taken closer in time to diagnosis. In our analysis, the timing of the mammograms made very little difference; the odds ratios did not change materially.

A serious limitation of our project was the low participation rate (50.6 percent), which cannot be explained by a lack of mammographic screening; almost 90 percent of women in the cohort reported a previous mammogram at baseline. More intense follow-up may have increased the response rate, but we limited our recruitment efforts to mailings in order not to jeopardize subject participation in future investigations within the MEC Study. Although the success of including women in the study differed slightly by age, ethnicity, and reproductive behavior, we could not detect a systematic bias. Except for ineligibility due to death, similar proportions of cases and controls were included in the final analysis. It appears unlikely that these small differences between eligible subjects and recruited subjects biased the robust risk estimates or that response status would confound the association between mammographic density and breast cancer. The comparison between included women and excluded women did not identify major differences. The assessment of HRT use had serious limitations in that we had to rely on self-reported HRT use and assume a constant type of use during all years. A similar problem existed for body mass index; information on weight was self-reported and

Downloaded from https://academic.oup.com/aje/article/162/8/743/122341 by guest on 25 April 2024

was collected only once at entry into the cohort. The use of body mass index categories did not lead to residual confounding; an analysis using body mass index as a continuous variable gave identical results.

This study confirmed the substantial breast cancer risk associated with higher mammographic densities. The magnitudes of risk estimates were similar for percent density and the size of the dense area. Although the finding was not statistically significant, the association between breast density and cancer risk appeared weaker in Japanese women than in Caucasian and Native Hawaiian women. This finding suggests that, if breast density were to be added to risk prediction models (33), it might be necessary to develop different models for ethnic groups whose mammographic features differ substantially from those of Caucasians.

ACKNOWLEDGMENTS

This case-control study was funded by a grant from the National Cancer Institute (R01 CA 85265). The Multiethnic Cohort Study has been supported by US Public Health Service (National Cancer Insitute) grant R37 CA 54281 (Principal Investigator: Dr. L. N. Kolonel).

The authors are very grateful to Jihae Noh for her outstanding work in mammogram retrieval and scanning, to Andrew Williams for the excellent database and its management, and to Maj Earle for providing data from the Multiethnic Cohort Study.

REFERENCES

1. Brisson J, Sadowsky NL, Twaddle JA, et al. The relation of mammographic features of the breast to breast cancer risk factors. Am J Epidemiol 1982;115:438–43.
2. Boyd NF, Byng JW, Jong RA, et al. Quantitative classification of mammographic densities and breast cancer risk: results from the Canadian National Breast Screening Study. J Natl Cancer Inst 1995;87:670–5.
3. Byrne C, Schairer C, Wolfe J, et al. Mammographic features and breast cancer risk: effects with time, age, and menopause status. J Natl Cancer Inst 1995;87:1622–9.
4. Ursin G, Ma H, Wu AH, et al. Mammographic density and breast cancer in three ethnic groups. Cancer Epidemiol Biomarkers Prev 2003;12:332–8.
5. Wolfe JN. Risk for breast cancer development determined by mammographic parenchymal pattern. Cancer 1976;37: 2486–92.
6. Brisson J, Morrison AS, Kopans DB, et al. Height and weight, mammographic features of breast tissue, and breast cancer risk. Am J Epidemiol 1984;119:371–81.
7. Wolfe JN, Saftlas AF, Salane M. Mammographic parenchymal patterns and quantitative evaluation of mammographic densities: a case-control study. Am J Roentgenol 1987;148: 1087–92.
8. Byng JW, Boyd NF, Fishell E, et al. The quantitative analysis of mammographic densities. Phys Med Biol 1994;39: 1629–38.
9. Ursin G, Astrahan MA, Salane M, et al. The detection of changes in mammographic densities. Cancer Epidemiol Biomarkers Prev 1998;7:43–7.
10. Boyd NF, Lockwood GA, Byng JW, et al. Mammographic densities and breast cancer risk. Cancer Epidemiol Biomarkers Prev 1998;7:1133–44.
11. Maskarinec G, Meng L. A case-control study of mammographic densities in Hawaii. Breast Cancer Res Treat 2000; 63:153–61.
12. Maskarinec G, Meng L, Ursin G. Ethnic differences in mammographic densities. Int J Epidemiol 2001;30:959–65.
13. Chen Z, Wu AH, Gauderman WJ, et al. Does mammographic density reflect ethnic differences in breast cancer incidence rates? Am J Epidemiol 2004;159:140–7.
14. Maskarinec G, Nagata C, Shimizu H, et al. Comparison of mammographic densities and their determinants in women from Japan and Hawaii. Int J Cancer 2002;102:29–33.
15. Parkin DM, Whelan SL, Ferlay J, et al. Cancer incidence in five continents. Vol 8. Lyon, France: International Agency for Research on Cancer, 2003.
16. American Cancer Society, Cancer Research Center of Hawaii, and Hawaii Department of Health. Hawaii cancer facts & figures 2003–2004. Atlanta, GA: American Cancer Society, 2004.
17. Pike MC, Kolonel LN, Henderson BE, et al. Breast cancer in a multiethnic cohort in Hawaii and Los Angeles: risk factor-adjusted incidence in Japanese equals and in Hawaiians exceeds that in whites. Cancer Epidemiol Biomarkers Prev 2002;11:795–800.
18. Kolonel LN, Henderson BE, Hankin JH, et al. A multiethnic cohort in Hawaii and Los Angeles: baseline characteristics. Am J Epidemiol 2000;151:346–57.
19. Stram DO, Hankin JH, Wilkens LR, et al. Calibration of the dietary questionnaire for a multiethnic cohort in Hawaii and Los Angeles. Am J Epidemiol 2000;151:358–70.
20. Food and Drug Administration, US Department of Health and Human Services. Mammography: information for mammography facility personnel, inspectors, and consumers about the implementation of the Mammography Quality Standards Act of 1992 (MQSA). Rockville, MD: Food and Drug Administration, 2004. (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmqsa/mqsa.cfm). (Accessed December 22, 2004).
21. Linver MN, Osuch JR, Brenner RJ, et al. The mammography audit: a primer for the Mammography Quality Standards Act (MQSA). Am J Roentgenol 1995;165:19–25.
22. Maskarinec G, Williams AE, Carlin L. Mammographic densities in a one-year isoflavone intervention. Eur J Cancer Prev 2003;12:165–9.
23. Shrout P, Fleiss J. Intraclass correlations: uses in assessing rater reliability. Psychol Bull 1979;86:420–8.
24. McKinney KA, Thompson W. A practical guide to prescribing hormone replacement therapy. Drugs 1998;56: 49–57.
25. SAS Institute Inc. SAS OnlineDoc, version 8. Cary, NC: SAS Institute Inc, 2002.
26. Breslow NE, Day NE. Statistical methods in cancer research. Vol 1. The design and analysis of case-control studies. Lyon, France: International Agency for Research on Cancer, 1980. (IARC Scientific Publication no. 32).
27. Greendale GA, Reboussin BA, Slone S, et al. Postmenopausal hormone therapy and change in mammographic density. J Natl Cancer Inst 2003;95:30–7.
28. Vachon CM, Kuni CC, Anderson K, et al. Association of mammographically defined percent breast density with

Downloaded from https://academic.oup.com/aje/article/162/8/743/122341 by guest on 25 April 2024

epidemiologic risk factors for breast cancer (United States). Cancer Causes Control 2000;11:653–62.
29. Brisson J, Merletti F, Sadowsky NL, et al. Mammographic features of the breast and breast cancer risk. Am J Epidemiol 1982;115:428–37.
30. van den Brandt PA, Spiegelman D, Yaun SS, et al. Pooled analysis of prospective cohort studies on height, weight, and breast cancer risk. Am J Epidemiol 2000;152:514–27.
31. Pawluczyk O, Augustine BJ, Yaffe MJ, et al. A volumetric method for estimation of breast density on digitized screen-film mammograms. Med Phys 2003;30:352–64.
32. Hernandez BY. Highlights of recent cancer incidence data in Hawaii. Hawaii Med J 2003;62:17–18.
33. Gail MH, Benichou J. Assessing the risk of breast cancer in individuals. In: DeVita VTJ, ed. Cancer prevention. Philadelphia, PA: J B Lippincott Company, 1992:1–15.

Downloaded from https://academic.oup.com/aje/article/162/8/743/122341 by guest on 25 April 2024