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EPIDEMIOLOGY

Ethnic and geographic differences in mammographic density and their association with breast cancer incidence

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Abstract The objective of this pooled analysis was to compare differences in dense areas and percent mammographic densities to breast cancer incidence in populations at different breast cancer risk. The data set included 1,327 women aged 40–80: Caucasians from Norway, Arizona, and Hawaii, Japanese from Hawaii and Japan, Latina from Arizona, and Native Hawaiians from Hawaii. One reader performed computer-assisted quantitative density assessment for all mammographic films. Multiple linear regression models evaluated the influence of the covariates on breast density. Spearman correlation coefficients (r_s) estimated the association between breast density and breast cancer incidence for the seven populations. After adjustment for covariates, ethnicity, but not location, was significantly associated with breast density. In the full model, 19% of the variation in the dense areas and 46% in the variation of percent densities were explained by measured risk factors. Native Hawaiians had the largest dense areas and women in Japan the smallest, whereas percent densities were highest among Native Hawaiians and Japanese in Hawaii and lowest among Norwegian women. The mean age-adjusted dense area had the strongest association with breast cancer incidence ($r_s = 0.93$, $P = 0.003$); the relation with percent density was considerably weaker ($r_s = 0.32$, $P = 0.48$). The correlation between age-adjusted dense area and breast cancer incidence remained strong after selectively removing individual data points. This comparison of mammographic densities suggests that, on a group level, age-adjusted dense areas may reflect breast cancer incidence better than percent densities.

Keywords Breast density · Breast cancer incidence · Ethnicity · Risk factors

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Introduction

The burden of breast cancer is unevenly distributed by geographic location and by ethnicity. Breast cancer incidence rates vary approximately 3-fold between Japanese women in Japan and Caucasian women in the United States (Table 1), whereas women in Norway and Latina women in the United States experience an intermediate risk to develop the disease [1]. Breast cancer incidence for Japanese-Americans in Hawaii is close to three times higher than for Japanese in Japan and has reached the risk for Caucasians in recent years [2, 3]. The observation that breast cancer risk in Asian women who migrated to the United States approaches the risk among U.S. Whites after two or three generations [4] suggests that environmental factors [5] may be important determinants of breast cancer risk in addition to the well established reproductive factors and body weight [6]. Mammographic density refers to

Table 1 Breast cancer incidence rates by location and ethnicity age-adjusted to the world standard population

Location	Ethnicity	Incidence rate*	Years	Source
Arizona	Caucasian	99.8	2001	Arizona cancer registry
Arizona	Latina	50.3	2001	
Hawaii	Caucasian	106.5	1995–2000	Hawaii tumor registry
Hawaii	Japanese	99.5	1995–2000	
Hawaii	Native Hawaiian	123.1	1995–2000	
Japan, Osaka	Japanese	32.5	2001	Osaka cancer registry
Norway, Tromsø	Caucasian	68.4	1998–2002	Norwegian cancer registry

* Per 100,000 women

the distribution of fat, connective, and epithelial tissue in the female breast. A high percentage of dense parenchyma on mammographic images appears to confer a 4- to 6-fold higher risk to develop breast cancer [7–10]. Women of Chinese and Japanese ancestry tend to have considerably smaller breast sizes than Caucasian and Native Hawaiians resulting in a higher percent of the breast occupied by dense tissue [11]. However, the dense areas and percent densities appear to be smaller among women living in Japan than in Hawaii despite similar breast sizes [12]. Among three ethnic groups in California [13], the dense areas rather than percent mammographic density reflected the lower breast cancer risk of Asian Americans as compared to African Americans and Caucasians. Based on the hypothesis that mammographic densities represent the cumulative exposure to factors that stimulate growth of breast cells since puberty and influence breast cancer incidence [14, 15], we compared differences in the dense areas and percent mammographic densities to breast cancer incidence in populations at different risk. We also examined how much of the variation in mammographic density is explained by known and suspected breast cancer risk factors, such as body mass index (BMI) and reproductive variables [6, 16].

Methods

Study design

The participants of this study were recruited as part of previous epidemiologic studies in four locations: Hawaii and Arizona in the United States, Gifu in Japan, and Tromsø in Norway. Despite differences in study design, combining data from these diverse populations provided an epidemiologic opportunity to examine women with a wide range of ethnic backgrounds and lifestyles. The women in all locations were recruited through mammography clinics. Eligibility criteria common to the four study locations were: screening mammogram that was found to be without suspicious lesions by a radiologist [17] and no history of cancer (except non-melanoma skin cancer) and breast surgery, such as breast reduction and enlargement. Women taking hormone replacement therapy (HRT) were included in all locations except Arizona. The Committee on Human Studies at the University of Hawaii approved the overall project and the respective Institutional Review Boards at all four institutions had approved the original projects. All study participants gave written informed consent.

Study populations

The Caucasian, Japanese, and Native Hawaiian women in Hawaii were part of four previous investigations with different eligibility criteria. The subjects from a genetic polymorphism study [18] did not need to meet any additional eligibility criteria ($N = 48$). Controls ($N = 80$) from a case-control study [19] nested within the Hawaii part of the Multiethnic Cohort [20] had donated blood samples for an earlier project [21]. For the two intervention studies ($N = 153$ and 16), subjects were required to be under age 47, consume less than seven servings of soy foods per week during the last year, have regular menstrual periods, an intact uterus and ovaries, take no oral contraceptives or other hormones, and have no intention of becoming pregnant [22, 23]. In Japan, healthy women were recruited at a screening clinic in Gihoku General Hospital in Gifu. Half of the participants were part of a cross-sectional study [12] and the other half served as controls in a case-control study [24]. In Arizona, the subjects were part of a cross-sectional investigation, the Women's Breast and Bone Density study. Women with serious medical conditions, pregnancy, and any kind of hormone medication were excluded. The women from Norway were part of the Mammography and Breast Cancer Study, which was conducted in Tromsø in 2002 in collaboration with the Norwegian Breast Cancer Screening Program. As described in detail elsewhere [25], women were eligible if they were attending the national screening

program at the University Hospital of North-Norway, residing in the municipality of Tromsø, were 55 years or older, and were willing to donate a blood sample.

Data collection

The questionnaires in all locations collected demographic, anthropometric, reproductive, and medical history information. In Hawaii, all participants completed the same food frequency questionnaire (FFQ) that asked about medical history, body weight and height, reproductive behavior, and physical activity (PAL) [26]. The ethnicity question allowed the subjects to mark all ethnic backgrounds for themselves and their parents. In Japan, the women completed a validated semi-quantitative FFQ [27] that included questions about reproductive and anthropometric characteristics. In Arizona, height and weight were measured at the time of the clinic visit and ethnic background was self-reported. The semi-quantitative Arizona FFQ with 153-items was a modification of the Block NCI Health Habits and History Questionnaire [28] and had been validated against dietary recalls and serum carotenoid levels [29]. In Norway, the subjects went through a short interview and had their height and weight measured to the nearest centimeter by a research nurse. The 8-page questionnaire was slightly modified from an instrument developed for the Norwegian Women and Cancer Study [30] and elicited detailed information on dietary habits and PAL, as well as on current and previous HRT use.

Mammographic density assessment

Standard mammography techniques were used at all participating mammography facilities. All mammograms were ordered as part of routine health care. Whereas in Hawaii, Arizona, and Norway each screening mammography consisted of craniocaudal and mediolateral views, the usual practice in Japan is to take mediolateral views only. Therefore, for women in the second Gifu study, only mediolateral views were available. According to a comparison of craniocaudal (CC) and mediolateral (ML) images for 30 women, the correlation coefficients between the measurements from the two different projections were 0.96 for the breast area and 0.92–0.96 for percent density [31]. To correct for the slightly lower percent densities in the mediolateral than in the respective craniocaudal images, we computed an estimated value for the CC images based on the formula ML = 2.6 + 0.86CC [31].

To standardize the measures, mammographic density assessment was performed with the identical method in mammograms from all locations. All images in Japan ($N = 376$) and 77 (35%) of the Arizona images had been obtained with digital mammography. For comparability, they were printed on films, mailed to Hawaii and scanned into a computer using a Kodak LS 85 digitizer from the Eastman Kodak Company (formerly Lumisys Company) in the same way as the regular mammograms. This scanner has a high resolution and optical density (0.001 OD density resolution to 4.1 OD). It produces excellent images that show the skin line of the breast clearly even in very dark images. The mammograms were scanned at a resolution of 260μm per pixel, approximately equivalent to 97.7 dots per inch. Names and other personal information on the mammogram were made invisible. Only the left mammograms were used because it has been shown the measurements for the right and the left breast are highly correlated [31]. For density assessment, we used the computer-assisted method developed in Toronto [9, 32]. It classifies the density of breast tissue by counting pixels within the regions identified as representative of radiographically dense tissue. The software uses 256 different gray levels. In the digitized mammographic image displayed on the computer screen, the reader selects a threshold value (gray scale on the computer screen) that best distinguishes the breast from the dark background. An edge detection computer program (algorithm) is used to outline and measure the total area of the breast (effectively in terms of computer screen pixels). Subsequently, the reader identifies a second threshold value, the gray value that best identifies the edges of the mammographically dense areas within the breast parenchyma. The number of pixels in the areas containing such densities is then measured by the computer, and the fraction of pixels in the breast parenchyma that are located in the dense areas (percent mammographic densities) is calculated and saved to a data file. The size of the non-dense areas was computed as the difference between total and dense area of the breast. The density assessment was performed by one of the authors (GM) who was blinded as to the study participant's identity and place of residence. Mammograms were randomly assigned to batch files with 100 mammograms from all four locations that were read in one session. A random sample of 145 mammograms was assessed in duplicate. The repeated readings indicated a high level of reproducibility. The respective correlation coefficients for the breast area, the dense area, and percent density were 0.996, 0.97, and 0.98 ($P < 0.0001$ for all).

Statistical analysis

All data management and analysis was performed using the SAS statistical software package, version 9 [33]. We combined data from all four study populations after transforming the variables to a common format. Age, BMI, and the mammographic measures were used as continuous variables. Although the distribution of percent density was not perfectly normal, we did not transform the values because the residuals were normally distributed. Educational achievement was classified into <12, 12–15, and 16+ years. Age at menarche was categorized as <12, 12–13, and 14+ years. Parity had four levels: 0, 1–2, 3–4, and 5+ children. Age at first live birth was classified as none, <25 years, and 25+ years. HRT use, oral contraceptive use, and smoking were classified as never, past, and current user. Because the type of HRT was only known for Norway and Hawaii, this information was not included into the data base. PAL was estimated from daily hours spent for sleeping, sitting, low-, moderate- and strenuous activities in Hawaii and Arizona. For Japan, three levels of PAL were available. For Norway, PAL was based on hours spent for work or leisure-related activity. Quartiles were created for PAL and for alcohol intake. Family history of breast cancer was not included because it was not available for all locations and not associated with breast density in the remaining data set. Age at menopause did also not contribute to the model. We imputed a small number of missing variables using the mean or the most common category for the respective location-ethnicity group. For two women above age 50 with missing information, postmenopausal status was assigned.

We applied multiple linear regression models to explore predictors of mammographic characteristics and estimate means by location and ethnicity [34]. The size of the dense areas, the non-dense areas, and percent density were modeled as dependent variables using PROC GLM [33]. Ethnicity and place of residence were entered as independent variables. Since the data represent an incomplete design, i.e., there were no replicates of ethnic-comparisons by location or replicates of location-comparisons by ethnicity, it was not possible to evaluate the statistical significance of a possible interaction effect between ethnicity and location. However, adding the interaction effect to the models allowed us to obtain adjusted means by ethnicity and location. Means for mammographic characteristics were first estimated for each subgroup after age-adjustment, which is essential due to the large age differences of the four study populations and the strong association of mammographic densities with age [7]. Then, anthropometric, reproductive, and lifestyle (smoking, alcohol intake, and PAL) covariates were added to the models because they were found to be related to breast density in previous reports [7, 35, 36]. We performed pairwise *t*-tests for all main effect means in the MEANS statement and applied the Bonferroni correction to evaluate statistical significance. A *P* value smaller than 0.0024 was considered significant (0.05 divided by 21 because seven groups were compared with each other). Spearman correlation coefficients (r_s) between breast density and breast cancer incidence for

Table 2 Characteristics of the study population

Characteristics	Hawaii			Arizona		Japan	Norway	All
	Caucasian	Japanese	Hawaiian	Caucasian	Latina	Japanese	Caucasian	
Sample size	130	105	62	140	81	376	433	1327
Age	49.0	52.6	51.8	53.1	50.0	49.0	61.2	53.9
Body mass index	25.9	24.1	29.3	27.2	27.9	22.7	27.7	25.8
Education (years)	15.7	14.9	14.0	14.9	13.0	11.9	9.4	12.2
Current smoking (%)	3.1	8.6	9.7	9.3	9.9	6.9	24.0	12.8
Physical activity (PAL)	2.15	1.93	1.97	2.16	2.12	1.37	1.37	1.65
Family history (%)	15.4	11.4	22.6	na	na	3.2	6.9	8.0
Age at menarche (years)	13.1	12.8	12.8	13.1	13.1	13.7	13.7	13.4
Parous (%)	72.3	83.8	88.7	72.7	83.5	96.8	93.3	88.5
Age at first live birth (years)	27.9	28.5	25.1	25.9	24.7	26.0	23.9	25.5
Number of children	1.7	2.0	2.9	1.8	2.4	2.2	2.6	2.3
Premenopausal (%)	73.8	63.5	46.5	48.6	69.1	54.3	0.0	39.6
Oral contraceptives (%)	2.1	1.5	2.9	0	0	3.9	na	2.3
Postmenopausal (%)	26.2	36.5	43.5	51.4	30.9	45.7	100.0	60.4
Age at menopause	48.8	49.2	46.2	49.5	48.5	49.8	48.8	49.0
Current HRT use (%)	44.1	26.3	22.2	0	0	0	34.6	22.8
Past HRT use (%)	23.5	29.0	18.5	59.2	33.3	10.5	15.5	19.8

the seven populations were computed. To assess the influence of digital mammograms and the lack of premenopausal mammograms in the Norwegian data set, the correlation analysis was repeated without the respective observations.

Results

The study population included 1,327 women of different ethnicities (Table 2): 703 Caucasian women residing in Norway, Arizona, and Hawaii, 481 Japanese women living in Japan and Hawaii, 81 Latina women from Arizona, and 62 Native Hawaiian women from Hawaii. The populations differed considerably by age and weight status. Whereas the mean age in Hawaii, Arizona, and Japan was approximately 50 years, all women in Norway were postmenopausal with a mean age of 61 years. The mean BMI was greater than 29 kg/m^2 for Native Hawaiians and above 27 kg/m^2 for women in Norway and Arizona. Japanese women in Japan had the lowest BMI of all groups with a mean below 23 kg/m^2, whereas Japanese-Americans in Hawaii were intermediate with a mean BMI of 26 kg/m^2. The populations showed significant differences in education, smoking, family history of breast cancer, and reproductive characteristics. None of the women in Japan reported current HRT use and previous use HRT was also low. Current HRT use was an exclusion criterion in Arizona. In all other locations, close to half of the subjects reported previous or current HRT use.

Women in Norway had by far the largest breasts and non-dense areas; they were followed by Native Hawaiians and Caucasians in Hawaii (Table 3). Both areas were somewhat smaller in the Arizona women and smallest among women with Japanese ancestry. Adjustment for confounders reduced the differences considerably because of the strong association between BMI and the non-dense areas ($r = 0.69$, $P < 0.0001$), but did not eliminate them. Ethnicity and location remained statistically significant ($P < 0.001$). In combination with age, ethnicity and location explained 29.6% of the variation in the non-dense areas. BMI increased the R^2 to 60.5% and education, reproductive, and lifestyle factors added another 2.8%.

With only adjustment for age, women in Japan and in Norway had the smallest dense areas (Table 3), whereas Native Hawaiians and Caucasians in Hawaii had the largest. After adjustment for all covariates, there was a 17.7 cm^2 difference between the lowest and the highest group. Native Hawaiians still had the largest dense areas, but Japanese in Gifu were followed by Japanese in Hawaii and Norwegian women as the lowest. The individual comparisons using the Bonferroni adjustment only indicated statistical significance for the differences between Native Hawaiian women and all other groups and between Hawaii Caucasians and Japanese in Gifu. With only adjustment for age, percent densities were significantly lower among women in Norway than all others except Latinas who also had lower percent densities than all Japanese and Native Hawaiian women (Table 3). Native Hawaiian women had significantly higher percent densities than all other groups. None of the differences was significant after Bonferroni adjustment. In the full models for dense area and percent density, ethnicity remained significant, but location was not significant any more (Table 4).

To estimate the relative contribution of the different predictors of mammographic densities, we compared the R^2 from the regression models (Table 4). The complete models accounted for 19.1% variation in dense areas and for 45.7% variation in percent density. Compared to the age-adjusted models, the additional covariates contributed 4.6% to the dense area model and 16.4% to the percent density model. The most important covariate was BMI; it increased the R^2 by

Table 3 Mean mammographic characteristics by location and ethnicity*

Location	Ethnicity	Breast area (cm^2)		Dense area (cm^2)		Non-dense area (cm^2)		Percent density	
		Age	Full	Age	Full	Age	Full	Age	Full
Arizona	Caucasian	119.6	113.9	31.5	32.1	88.1	82.6	31.9	34.2
	Latina	125.7	114.6	31.0	32.0	94.8	83.2	28.6	32.4
Hawaii	Caucasian	134.4	135.0	36.4	35.0	98.0	100.4	32.3	30.8
	Japanese	85.1	99.3	32.0	29.5	53.3	69.2	40.6	35.7
	Hawaiian	139.8	113.5	42.8	44.9	97.0	68.4	36.2	43.2
Japan	Japanese	95.5	119.5	28.3	27.2	67.2	92.1	34.9	30.5
Norway	Caucasian	154.5	142.4	30.1	29.6	124.3	112.5	25.8	29.1
All women		124.2		31.2		93.0		31.5	

* Least-squares means were obtained through general linear models; adjusted for age only or for age, BMI, parity, menopausal status, and HRT use

Table 4 Factors associated with the size of the dense areas and percent density*

Mammographic measure	Covariate #	Model 1: Age		Model 2: +BMI		Model 3: +Reproduction		Model 4: Full	
		F value	*P* > *F*	*F* value	*P* > *F*	*F* value	*P* > *F*	*F* value	*P* > *F*
Dense area	Ethnicity	3.0	0.03	4.5	0.004	5.6	0.0008	5.4	0.001
	Location	3.0	0.03	2.8	0.04	1.5	0.22	0.8	0.49
	Age (yrs)	129.2	<0.0001	127.0	<0.0001	19.6	<0.0001	17.6	<0.0001
	BMI			14.9	0.0001	8.8	0.003	9.4	0.002
	Education					1.0	0.38	1.0	0.36
	Menopause					6.7	0.01	6.4	0.01
	Hormone replacement					8.2	0.0003	8.0	0.0004
	Age at first live birth					0.3	0.58	0.3	0.60
	Parity					11.8	<0.0001	11.2	<0.0001
	Age at menarche					0.01	0.99	0.0	0.99
	Oral contraceptives					0.14	0.87	0.2	0.84
	Smoking							0.6	0.58
	Alcohol use							0.7	0.55
	Physical activity							0.3	0.84
	R-square (%)	14.5		15.5		18.8		19.1	
Percent density	Ethnicity	3.4	0.02	4.3	0.005	6.7	0.0002	6.8	0.0001
	Location	6.5	0.0002	8.5	<0.0001	2.1	0.10	1.6	0.19
	Age (yrs)	245.8	<0.0001	277.8	<0.0001	37.6	<0.0001	37.1	<0.0001
	BMI			297.5	<0.0001	251.4	<0.0001	256.1	<0.0001
	Education					1.1	0.33	1.0	0.37
	Menopause					20.8	<0.0001	19.1	<0.0001
	Hormone replacement					7.3	0.0007	7.4	0.0006
	Age at first live birth					2.0	0.16	1.8	0.18
	Parity					8.8	0.0002	8.6	0.0002
	Age at menarche					0.9	0.42	0.7	0.48
	Oral contraceptives					0.2	0.80	0.2	0.86
	Smoking							2.6	0.08
	Alcohol use							0.7	0.55
	Physical activity							0.4	0.75
	R-square (%)	29.3		42.4		45.3		45.7	

* Based on general linear models # all variables except age and BMI were modeled as categorical variables

1.0% and 13.1%, respectively. BMI was inversely associated with dense areas and percent densities and directly with the non-dense areas. The reproductive variables contributed 3.3% and 2.9% in variance to the dense area and the percent density model, but the respective values for lifestyle factors were only 0.3% and 0.4%. Menopause was positively related to the non-dense areas and inversely associated with the dense areas and with percent densities. Educational achievement was significant in a model with percent densities (data not shown), but reproductive characteristics accounted for its effect. To explore whether the predictors for percent density were similar in all groups, we stratified the multiple linear regression by group. The proportion of explained variance was 62% for Native Hawaiians, 53% for Hawaii Caucasians, 51% for Arizona Caucasians, 46% for Hawaii Japanese, 43% for Japanese in Gifu, and 32% for Norwegian women.

Plots of breast cancer incidence (Table 1) against the adjusted mean dense area and percent density for each subgroup (Fig. 1) indicated that the age-adjusted dense area had the strongest association with breast cancer incidence ($r_s = 0.93$; $P = 0.003$), whereas it was slightly lower after adjustment for other covariates ($r_s = 0.86$, $P = 0.01$). The association of breast cancer incidence with percent density was considerably weaker: $r_s = 0.32$ ($P = 0.48$) for the age-adjusted means and $r_s = 0.61$ ($P = 0.15$) for the fully adjusted means. After restricting the analysis to the six populations with pre- and postmenopausal women, the correlation coefficients for age- and fully adjusted density were 0.94 ($P = 0.005$), whereas the respective relations with percent density were $r_s = 0.20$ ($P = 0.70$) and $r_s = 0.60$ ($P = 0.21$). In a further sensitivity analysis that excluded all digital mammograms, mean age-adjusted density remained highly correlated with breast cancer incidence ($r_s = 0.83$; $P = 0.04$), while the other correlation coefficients were weakened ($r_s = 0.49$ for fully adjusted dense area and $r_s = 0.54$ for both percent density models). Restricting the analysis to Caucasian women resulted in a close to perfect

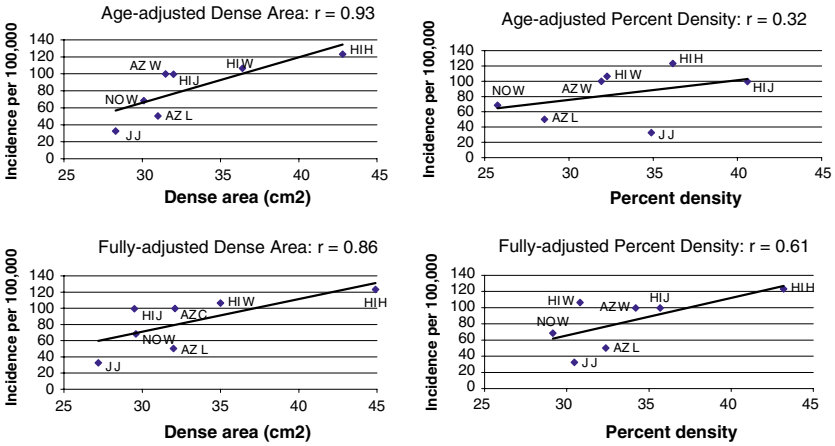


Fig. 1 Association between breast cancer incidence rate and different measures of breast density. AZ, Arizona; HI, Hawaii; J, Japan; NO, Norway; J, Japanese; H, Native Hawaiian; L, Latina; W, Caucasian; *r*, Spearman rank correlation coefficient

correlation for age-adjusted percent density, while the fit for the age-adjusted dense areas was somewhat weaker (data not shown).

Discussion

In this ecologic analysis, the size of the dense areas in populations at different breast cancer risk appears to reflect population-based breast cancer incidence better than percent densities, but limitations our study populations may have biased these findings. After adjustment for known confounders, geographic location was not associated with the dense areas and with percent densities, but ethnicity remained a significant covariate. BMI was the most important predictor of non-dense areas and percent densities, but the association with the dense areas was relatively weak. Reproductive factors accounted for approximately 3% in variance and lifestyle factors for less than 1%. The respective R^2 for the non-dense areas, dense areas, and percent densities in this study were 63.3, 19.1, and 45.7%. The results for the percent density model are comparable to previous investigations that estimated the proportion of variance that could be explained by covariates as 31–33% in Canada [37], 42% in Hawaii [11], and 37% among premenopausal women in Minnesota [35]. The slightly higher values in the present study may be due to the greater variation in risk factors in these diverse populations. Similarly as for breast cancer risk [38], the association of education with mammographic density was explained by reproductive and lifestyle factors.

In agreement with the current results, ethnic differences in breast cancer risk appear to be better represented by the size of the dense areas than by percent densities [11–13], probably due to the large confounding effect of body weight on percent density. BMI is highly correlated with the non-dense areas, but not with the dense areas [39]. Several case-control studies [19, 40, 41], but not all [10], suggest that the association of breast cancer risk with the size of the dense areas and with percent densities are of similar strength. Whereas the two studies in Hawaii found a somewhat weaker association between mammographic density and breast cancer risk among Japanese than in Caucasians [19, 40], a study from California described a somewhat stronger association [41]. An investigation from Japan [24] reported estimated relative risks comparable to those in Caucasian populations [7].

The major strength of this study is the measurement of breast densities in populations at different breast cancer risk using the same methodology. Assessing density with the same method and in combined batches provided a high level of data standardization despite the inclusion of some digital mammograms. Little is known about differences in densities measured in digital versus regular mammograms. In a small comparison among 60 women [42], percent density was smaller in digital than in regular mammograms due to the better recognition of the skin line that resulted in a larger breast size. When the density in 232 digital and regular mammograms as classified according to the BIRADS system was compared, no significant difference in classification was detected [43]. The advantage of investigating subjects from such diverse groups as Norway and Japan lies in the wide range of exposures experienced by the women living in locations with different lifestyles. In this study, the typical body stature ranged from a mean BMI of less than 23 kg/m^2 in Japan to more than 29 kg/m^2 among Native Hawaiians. An additional benefit of the study design was the inclusion of Japanese women who live in different environments, but have similar genetic backgrounds and anthropometric characteristics.

However, the differences in study protocols, eligibility criteria for recruitment, and questionnaires are

serious limitations of this project and may have introduced selection bias. Specifically, women in Hawaii were chosen for low soy intake and women using HRT were excluded in Arizona, but not in other sites. These criteria may have resulted in differences as compared to the general population. The underlying assumption of this secondary analysis is that the differences in breast cancer risk between populations are greater than the bias introduced by the recruitment procedures. The fact that the proportion of pre- to postmenopausal women differed considerably may have also affected our mean breast density measures because age and menopause are important determinants of breast cancer risk. On the other hand, mammographic densities are quite stable over time except for a relative decline experienced by all women with age [44] and removal of the Norwegian data point with only postmenopausal women did not change the overall association between mean densities and breast cancer incidence. The position of the data point for Arizona Caucasians above the regression line may be due to the fact that HRT users were excluded in that population. The unbiased mean density is expected to be higher in the general population where some women use HRT. Selection bias due to differential mammography participation rates in the different populations may also be responsible for the lack of fit for the data points representing Japanese in Gifu and Arizona Latinas. The breast cancer incidence rates for both populations appear very low given the mean sizes of the dense areas (Fig. 1). Both groups of participants may actually be at higher risk for breast cancer than the general population in their respective locations. Despite invitations from the prefecture, screening rates are thought to be lower than in Gifu than in the United States and Norway where mammography screening includes a large proportion of the general population [25, 45]. The Japanese subjects who participated in mammography screening may have chosen to obtain a mammogram because of their perceived higher breast cancer risk. According to information from the Takayama Cohort Study [46], women who undergo mammographic screening were more likely to be young, married, have a higher education and BMI, but did not differ in reproductive characteristics.

In this cross-sectional comparison of mammographic densities in four locations with four different ethnic backgrounds, more than 40% of the variation in percent breast density was explained by demographic, anthropometric, reproductive, and lifestyle factors. The observation that ethnicity showed a stronger association with breast density than location agrees with findings from a twin study suggesting that 60% or more of variability in breast density is related to genetic factors [47]. It has been proposed that cumulative exposure to mammographic density reflects inherited and environmental factor that affect breast density and breast cancer risk throughout life [14, 15] in a similar way as Pike and colleagues have demonstrated that the area under the breast-tissue ageing curve corresponds to the age-specific breast cancer incidence curve [48]. Although a larger proportion of the variation in percent densities than the dense areas could be explained by risk factors, we found that on a group level, age-adjusted dense areas reflected breast cancer incidence better than percent densities and may be a better measure of breast cancer risk across ethnically diverse populations than percent densities.

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References

1. Miller BA, Kolonel LN, Bernstein L et al (1996) Racial/ethnic patterns of cancer in the United States 1988–1992. National Cancer Institute, NIH Pub. No. 96-4104, Bethesda, MD
2. American Cancer Society, Cancer Research Center of Hawaii, Hawaii Department of Health (2004) Hawaii cancer facts & figures 2003–2004. American Cancer Society
3. Pike MC, Kolonel LN, Henderson BE et al (2002) 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 11:795–800
4. Ziegler RG, Hoover RN, Pike MC et al (1993) Migration Patterns and breast cancer risk in Asian-American women. J Natl Cancer Inst 85:1819–1827
5. MacMahon B, Cole P, Brown J (1973) Etiology of human breast cancer: a review. J Natl Cancer Inst 50:21–42
6. Henderson BE, Pike MC, Bernstein L, Ross RK (1996) Breast cancer. In: Schottenfeld D (ed) Cancer epidemiology

and prevention. Oxford University Press, New York, pp 1022–1039
7. Boyd NF, Lockwood GA, Byng JW, Tritchler DL, Yaffe MJ (1998) Mammographic densities and breast cancer risk. Cancer Epidemiol Biomarkers Prev 7:1133–1144
8. Saftlas AF, Hoover RN, Brinton LA et al (1991) Mammographic densities and risk of breast cancer. Cancer 67: 2833–2838
9. Boyd NF, Byng JW, Jong RA et al (1995) Quantitative classification of mammographic densities and breast cancer risk: results from the Canadian National Breast Screening Study. J Natl Cancer Inst 87:670–675
10. Byrne C, Schairer C, Wolfe J et al (1995) Mammographic features and breast cancer risk: effects with time, age, and menopause status. J Natl Cancer Inst 87:1622–1629
11. Maskarinec G, Meng L, Ursin G (2001) Ethnic differences in mammographic densities. Int J Epidemiol 30:959–965
12. Maskarinec G, Nagata C, Shimizu H, Kashiki Y (2002) Comparison of mammographic densities and their determinants in women from Japan and Hawaii. Int J Cancer 102: 29–33
13. Chen Z, Wu AH, Gauderman WJ et al (2004) Does mammographic density reflect ethnic differences in breast cancer incidence rates? Am J Epidemiol 159:140–147
14. Boyd NF, Lockwood GA, Martin LJ, Byng JW, Yaffe MJ, Tritchler DL (2001) Mammographic density as a marker of susceptibility to breast cancer: a hypothesis. IARC Sci Publ 154:163–169
15. Boyd NF, Rommens JM, Vogt K et al (2005) Mammographic breast density as an intermediate phenotype for breast cancer. Lancet Oncol 6:798–808
16. Key TJ, Verkasalo PK, Banks E (2001) Epidemiology of breast cancer. Lancet Oncol 2:133–140
17. American College of Radiology (1993) Breast imaging reporting and data system (BI-RADS). American College of Radiology, Reston, VA
18. Maskarinec G, Lurie G, Williams AE, Le Marchand L (2004) An investigation of mammographic density and gene variants in healthy women. Int J Cancer 112:683
19. Maskarinec G, Pagano I, Lurie G, Wilkens LR, Kolonel LN (2005) Mammographic density and breast cancer risk: the multiethnic cohort. Am J Epidemiol 162:743–752
20. Kolonel LN, Henderson BE, Hankin JH et al (2000) A multiethnic cohort in Hawaii and Los Angeles: baseline characteristics. Am J Epidemiol 151:346–357
21. DeLellis K, Rinaldi S, Kaaks RJ, Kolonel LN, Henderson B, Le Marchand L (2004) Dietary and lifestyle correlates of plasma insulin-like growth factor-I (IGF-I) and IGF binding protein-3 (IGFBP-3): the multiethnic cohort. Cancer Epidemiol Biomarkers Prev 13:1444–1451
22. Maskarinec G, Williams AE, Stanczyk FZ, Franke AA (2002) A randomized isoflavone intervention among premenopausal women. Cancer Epidemiol Biomarkers Prev 11:195–201
23. Maskarinec G, Franke AA, Williams AE et al (2004) Effects of a 2-year randomized soy intervention on sex hormone levels in premenopausal women. Cancer Epidemiol Biomarkers Prev 13:1736–1744
24. Nagata C, Matsubara T, Fujita H et al (2005) Mammographic density and the risk of breast cancer in Japanese women. Br J Cancer 92:2102–2106
25. Gram IT, Bremnes Y, Ursin G, Maskarinec G, Bjurstam N, Lund E (2005) Percentage density, Wolfe's and Tabar's mammographic patterns: agreement and association with risk factors for breast cancer. Breast Cancer Res 7: R854–R861
26. Stram DO, Hankin JH, Wilkens LR, Henderson B, Kolonel LN (2000) Calibration of the dietary questionnaire for a multiethnic cohort in Hawaii and Los Angeles. Am J Epidemiol 151:358–370
27. Shimizu H, Ohwaki A, Kurisu Y et al (1999) Validity and reproducibility of a quantitative food frequency questionnaire for a cohort study in Japan. Jpn J Clin Oncol 29:38–44
28. Block G (1989) Health, habits, and history questionnaire – diet history and other risk factors, personal computer system packet. National Cancer Institute, Bethesda, MD
29. Thomson CA, Giuliano A, Rock CL et al (2003) Measuring dietary change in a diet intervention trial: comparing food frequency questionnaire and dietary recalls. Am J Epidemiol 157:754–762
30. Hjartaker A, Lund E (1998) Relationship between dietary habits, age, lifestyle, and socio-economic status among adult Norwegian women. The Norwegian women and cancer study. Eur J Clin Nutr 52:565–572
31. Byng JW, Boyd NF, Little L et al (1996) Symmetry of projection in the quantitative analysis of mammographic images. Eur J Cancer Prev 5:319–327
32. Byng JW, Boyd NF, Fishell E, Jong RA, Yaffe MJ (1994) The quantitative analysis of mammographic densities. Phys Med Biol 39:1629–1638
33. SAS Institute Inc. (2004) SAS OnlineDoc 9.1.2. SAS Institute Inc., Cary, NC
34. Armitage P (1971) Statistical methods in medical research. Blackwell Scientific Publications, Oxford
35. Vachon CM, Kuni CC, Anderson K, Anderson VE, Sellers TA (2000) Association of mammographically defined percent breast density with epidemiologic risk factors for breast cancer (United States). Cancer Causes Control 11:653–662
36. El Bastawissi AY, White E, Mandelson MT, Taplin SH (2000) Reproductive and hormonal factors associated with mammographic breast density by age (United States). Cancer Causes Control 11:955–963
37. Boyd NF, Lockwood GA, Byng JW, Little LE, Yaffe MJ, Tritchler DL (1998) The relationship of anthropometric measures to radiological features of the breast in premenopausal women. Br J Cancer 78:1233–1238
38. Braaten T, Weiderpass E, Kumle M, Adami HO, Lund E (2004) Education and risk of breast cancer in the Norwegian-Swedish women's lifestyle and health cohort study. Int J Cancer 110:579–583
39. Haars G, Van Noord PA, van Gils CH, Grobbee DE, Peeters PH (2005) Measurements of breast density: no ratio for a ratio. Cancer Epidemiol Biomarkers Prev 14:2634–2640
40. Maskarinec G, Meng L (2000) A case-control study of mammographic densities in Hawaii. Breast Cancer Res Treat 63:153–161
41. Ursin G, Ma H, Wu AH et al (2003) Mammographic density and breast cancer in three ethnic groups. Cancer Epidemiol Biomarkers Prev 12:332–338
42. Harvey JA (2004) Quantitative assessment of percent breast density: analog versus digital acquisition. Technol Cancer Res Treat 3:611–616
43. Skaane P, Balleyguier C, Diekmann F et al (2005) Breast lesion detection and classification: comparison of screen-film mammography and full-field digital mammography with soft-copy reading – observer performance study. Radiology 237:37–44
44. Boyd N, Martin L, Stone J, Little L, Minkin S, Yaffe M (2002) A longitudinal study of the effects of menopause on mammographic features. Cancer Epidemiol Biomarkers Prev 11:1048–1053

45. Hawaii Department of Health (2004) 2003 State of Hawaii Behavioral Risk Factor Surveillance System. Hawaii Department of Health, Honolulu, HI; http://www.hawaii.-gov/health/statistics/brfss/brfss2003/state03.html. Accessed on 1-12-2005
46. Shimizu H (1996) A basic report on Takayama study. Department of Public Health, University School of Medicine, Gifu, Japan
47. Boyd NF, Dite GS, Stone J et al (2002) Heritability of mammographic density, a risk factor for breast cancer. N Engl J Med 347:886–894
48. Pike MC, Krailo MD, Henderson BE, Casagrande JT, Hoel DG (1983) 'Hormonal' risk factors, 'breast tissue age' and the age-incidence of breast cancer. Nature 303:767–770