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13. ABSTRACT (Maximum 200 Words) In a cross-sectional design, healthy women from different ethnic backgrounds, recruited at mammography screening clinics in Hawaii, completed self-administered questions related to medical, reproductive, and diet history. After scanning the cranio-caudal mammogram films into a PC, computerized mammographic density assessment was performed. Student's t-tests, analysis of variance, and multiple linear regression were applied. The mean area of the breast was 50% larger for women with Caucasian and Native Hawaiian ancestry than for women with Chinese and Japanese ancestry. The mean dense area was 15% smaller in Chinese and Japanese women than in the Caucasian/Hawaiian group. In comparison to Caucasian/Hawaiian women, the percent densities were 20% higher in Chinese and Japanese women. Body mass index, age, menopausal status, age at menarche, parity, and hormone replacement therapy were associated with mammographic density patterns. The results of this study suggest that the area of dense tissue in the breast may be smaller in Chinese and Japanese than in Caucasian women. However, because of their relatively smaller breast size, the percent of the breast occupied by dense tissue in Chinese and Japanese women appears to be greater than in Caucasian women because of the smaller breast size.				
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FOREWORD

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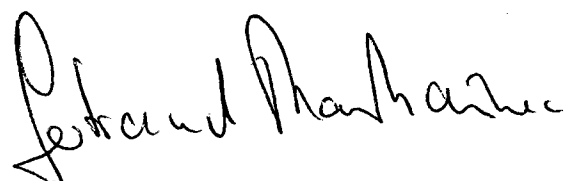
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(5) Introduction

Breast cancer risk differs greatly by ethnicity. In 1988-1992¹, the U.S. breast cancer incidence rates (invasive cases only, age-adjusted to 1970 U.S. population) were 112/10⁵ for Caucasian women, 106/10⁵ for Native Hawaiian women, 82/10⁵ for Japanese women, 73/10⁵ for Filipina, and 55/10⁵ for Chinese women. In Japan², incidence rates between 23/10⁵ and 31/10⁵ (age-adjusted to the World Standard population) have been reported for the same period.

Mammographic density patterns which refer to the distribution of fat, connective, and epithelial tissue in the female breast have been shown to be related to breast cancer risk³. They are not abnormalities but variations of healthy breast tissue. Fat appears dark on mammograms, whereas the radiographically light areas representing epithelial and connective tissue are relevant to breast cancer risk. A high percentage of dense parenchyma on mammographic images appears to confer a fourfold risk to develop breast cancer^{4,5}. Therefore, the hypothesis was proposed that women from ethnic groups with high breast cancer risk are more likely to have a dense parenchymal pattern than women from ethnic groups at low risk for breast cancer. The purpose of this report is to investigate ethnic differences in and determinants of mammographic density patterns among a population of women with Caucasian, Chinese, Filipino, Japanese, and Native Hawaiian ancestry living in Hawaii.

(6) Body

Recruitment and Data Collection. In a cross-sectional study design, women were recruited at 5 mammography facilities on the island of Oahu. A flyer describing the study was either mailed with the appointment reminder or handed to the women at the time of their appointment. Interested women returned their address to the mammography clinic or to the Cancer Research Center. In the second year, we added a rural clinic serving primarily Native Hawaiians in an effort to increase the number of Native Hawaiian women enrolled in this study. In addition, we mailed invitation letters to women who had received a mammogram through the Breast and Cervical Cancer Screening Program funded by the Centers for Disease Control and Prevention and administered by the Hawaii Department of Health. The study protocol was approved by the Committee on Human Subjects at the University of Hawaii and by the research boards of all participating institutions. All study participants signed informed consent and completed a validated questionnaire⁶ asking for a detailed dietary and reproductive history. Both cranio-caudal views of the mammogram were obtained from the mammography clinics after the radiologic evaluation had been completed and ruled out any malignancy. Women who did not speak English and women who reported a history of breast cancer or augmentation surgery were excluded from the study.

We received responses from 773 women who had received a letter or a study flyer in a mammography clinic. Of these, 526 (68%) agreed to participate in the study and returned the study questionnaires. The return rates differed by clinic with a high of 78% and a low of 29%. Seven of the 521 women had to be excluded from the analysis: for 5 women their mammograms

could not be located and 2 mammograms showed a previous breast augmentation. The final study population for analysis was 514.

Mammogram Density Assessment. Mammograms were requested from the clinics after the radiologists had completed their evaluation. The two cranio-caudal mammogram films were scanned into a PC using an X-ray digitizer (Cobrascan CX-612-T). Computerized mammographic density assessment was performed using a method that was first developed in Toronto⁷ and later modified at the University of Southern California in Los Angeles⁸. The reader first draws the outline of the breast (using an outlining tool) and then searches for the best threshold gray level value X where all pixels with values above X are considered to represent mammographic densities. The pixel count corresponding to the area colored within the outline of the breast is determined by the computer, as is the total area within the outline of the breast. The proportion of the breast with densities is calculated as the ratio of the colored area to the total area of the breast. Two readers (G.M. and L.M.) read all mammograms and a third reader (G.U.) checked a sample of mammograms. The correlation between the two readers was 0.92.

Statistical Analysis. We inspected the data for missing values and errors and performed the appropriate corrections or replacements. Several variables showed non-normal distributions and were transformed using their natural logarithms. If necessary, we created categorical variables. Ethnicity was classified as follows. Women who reported more than one ethnicity were classified as Native Hawaiian if they reported any Native Hawaiian ancestry. Otherwise, they were assigned the non-Caucasian ethnicity or the first listed ethnicity if they reported several other ethnicities. We calculated the body mass index (BMI) using the formula weight in kg divided by the height in meter squared. Student's t-tests and analysis of variance⁹ were applied to assess differences between groups. Multiple linear regression models⁹ were used to explore relations between variables. All analyses were performed using PC-SAS®, release 6.12 (SAS Institute, Cary, NC).

Results. The mean age of the 514 study participants was 53.9 years (range: 35 to 85 years) (Table 1). Caucasians and Japanese women represented the largest groups. We observed considerable differences in mean BMI with Native Hawaiian women reporting the highest body weight and Chinese and Japanese the lowest body weight. Smoking was reported at a much lower rate in all ethnic groups than the 18% among women in the state's population¹⁰. More than 10% of participants reported a family history of breast cancer. Reproductive behavior differed slightly among ethnic groups. Women with Chinese and Japanese ancestry had children at an older age, while Native Hawaiian women gave birth earliest in life and to the greatest number of children. Current hormone replacement therapy among postmenopausal varied between a high of 57% among women with Japanese ancestry and a low of 35.7% among women with Filipino ancestry. Oral contraceptive use was relatively low.

Among this group of women, the mean area of the breast was approximately 50% larger for Caucasian and for Native Hawaiian than for Japanese and Chinese women (Table 2). The size of the dense area in the breast was similar in Caucasian and Native Hawaiian women and also in

Chinese and Japanese women. While the mean dense area was 15% smaller in Japanese and Chinese women, the percent densities were 20% higher in Japanese and Chinese women than in Caucasian and Native Hawaiian women. The non-dense areas, i.e., the area of the breast with fatty tissue, was considerably larger in the Caucasian and Native Hawaiian population. The differences between groups were significant for all parameters except the dense areas, probably the result of the large standard deviations.

We observed a strong relation between BMI and mammographic patterns (Table 3). As expected, women with higher BMI had larger breasts than women with BMIs below 25. As a result, percent densities were nearly twice as high in light women as in heavy women. At the same time, the effect of BMI on the dense areas was limited to Caucasian and Native Hawaiian women. The size of the dense areas was significantly higher among women with BMI below 25. Mammographic patterns differed by menopausal status (Table 4). The dense areas and the percent densities were larger in pre- than in postmenopausal women, while breast size and non-dense areas were smaller after menopause. In all ethnic groups, premenopausal women had larger dense areas and greater percent densities than postmenopausal women. Whereas, the differences in percent densities were statistically significant for all ethnic groups, the size of the dense areas showed a significant difference only for Caucasian and Native Hawaiian women. As a group, women who reported current hormone replacement therapy (Table 5) differed only slightly from women who did not report hormone replacement use. However, among Caucasian and Native Hawaiian women the dense areas and the percent densities were significantly greater among users of hormone replacement than among non-users. For Chinese and Japanese women, mammographic density patterns did not differ significantly either by menopausal status or between users and non-users of hormone replacement therapy.

We regressed BMI and reproductive factors on mammographic patterns (Table 6). Because mammographic patterns for Chinese and Japanese women showed more similarities with each other than with any other group, we combined these 2 groups and contrasted them to all the others. The best model for dense area explained 11% of the variance. BMI, Japanese and Chinese ethnicity, age, and postmenopausal status were inversely related to the size of the dense areas, whereas hormone replacement therapy showed a positive relation. Nearly half of the variance in the size of the non-dense areas could be explained by 5 variables. BMI, age, and parity predicted higher non-dense areas; Chinese or Japanese ethnicity and menarche at 13 years or above were related to smaller non-dense areas. Percent densities were negatively associated with BMI, age, parity of three children or more, and postmenopausal status, resulting in a model with 40% explained variance. The following variables were not selected in any model: age at menopause, parity of 1 or 2 children, family history of breast cancer, years of education, and age at first live birth. Comparing the full models to simple models containing only ethnicity indicates that the importance of ethnicity was eliminated after including the other variables in the model for percent densities. In the non-dense area model, the partial correlation coefficient for ethnicity was greatly reduced after introducing the other variables. However, for the dense area model ethnicity slightly increased its relation with dense area after introducing the other variables, but the contribution remained extremely low.

We observed dietary differences between the different ethnic groups (Table 7), in particular for soy protein, tofu, and fat intake. The most commonly consumed soy food was tofu which has a much higher weight than soy protein because of its water content. Fruit and vegetable intake was relatively high in all groups, but did not differ significantly. Women with Chinese, Filipino, Japanese, and Native Hawaiian ancestry consumed significantly more soy protein and tofu than women of Caucasian ancestry. Whereas we did not observe a relation between soy intake and the size of the dense areas, we found a weak association between soy protein intake (5+ g/day vs. <5 g/day) and percent mammographic densities after adjusting for ethnicity, BMI, age, menopausal status, percent fat in diet, and parity. However, the size of the non-dense areas, i.e. the fatty part of the breast, was inversely related to soy intake after adjustment for ethnicity, BMI, age, caloric intake, percent fat in diet, age at menarche, and parity.

Discussion. The results of this study show that the area of dense tissue in the breast appears to be smaller in Japanese and Chinese than in Caucasian and Native Hawaiian women. However, because of their relatively smaller breast size due to the considerable smaller size of the non-dense areas, the percent of the breast occupied by dense tissue in Chinese and Japanese women was 20% higher than in Caucasian and Native Hawaiian women. The effects of BMI, menopausal status, hormone replacement therapy on mammographic density patterns were significant only among Caucasian and Native Hawaiian women. Ethnicity had the greatest effect on the size of the non-dense areas. The regression results suggest that ethnicity may not be an independent determinant of mammographic patterns, but a result of other risk factors, including BMI, reproductive behavior, and other yet undetermined factors. Because of their small sample size, it is inappropriate to make any conclusions about mammographic densities in Filipino and other women. The dietary results suggest that dietary soy consumption may be associated with the growth of the female breast and the risk to develop breast cancer. However, further dietary analyses need to be performed.

This is the first study comparing mammographic density patterns of women with Chinese and Japanese ancestry to patterns in Caucasian women using the quantitative assessment method. So far, the majority of the small number of publications describing mammographic density patterns among non-Caucasian populations used Wolfe's classification scheme¹¹. High Wolfe grades are equivalent to high percent densities in the quantitative assessment method. Our findings disagree with reports^{12,13} suggesting that the proportion of the breast covered by dense tissue is lower among Japanese women. The current report suggests that percent densities are higher in Chinese and Japanese women, but that the size of the area differs between low and high risk ethnic groups. Results from a mammography screening study in Tokushima, Japan¹³ suggested a very low prevalence of the DY (mammary dysplasia) patterns. Normal premenopausal Japanese women were found to have significantly more favorable mammographic patterns when Wolfe grades were assigned than British women¹². A case-control study¹⁴ showed that breast cancer patients were nearly 7 times as likely to be classified as one of the two high risk Wolfe categories than controls. When mammograms from 34 breast cancer cases belonging to different ethnic groups in Hawaii¹⁵ were classified according to the Wolfe categories, ethnicity was not related to breast structure type. However, all subjects had been diagnosed with breast cancer and no healthy

controls were included in the study. The proportion of high risk patterns (P2 and DY) was high in both groups, 73% in the Caucasian cases and 87% in the other women suggesting a higher percentage of densities among the non-Caucasian group. In a regression analysis from another study from Hawaii¹⁶, ethnicity was not significant in predicting the proportion of high-risk mammograms classified by Wolfe's categories. A small cross-sectional study in Japan¹⁷ described a relation between age at menarche and mammographic densities in premenopausal women and significant associations for age, family history of breast cancer, and age of menopause with mammographic densities in postmenopausal women.

Our report agrees with other studies that have shown lower density patterns after menopause^{5,18}, an inverse relation between body weight and mammographic densities¹⁹⁻²² and a positive relation between hormone replacement therapy and mammographic densities²³⁻²⁵. In contrast to previous reports, a family history of breast cancer²⁶⁻²⁸ and age at first live birth²⁹ were not associated with mammographic patterns in this study.

This study had several limitations. In particular, the selection of study participants does not represent the general population in Hawaii very well. The women in this study were very well educated and reported a very low smoking rate. Recruitment through mammography clinics did not exclude women with lower socio-economic status because health insurance coverage in Hawaii³⁰ is greater than 90% and mammography participation¹⁰ is above 80%. We made a particular effort to include women with different socioeconomic backgrounds by inviting women from a community health center and from the Breast and Cervical Cancer Screening program. As in many epidemiologic studies, the response rates for Native Hawaiian and Filipino women was relatively low. The high BMI of the small number of Filipino women in the study suggests that these women were not representative of this population who has a small breast cancer risk. Language problems and a large refusal rate when asked to participate limited the recruitment process among Filipino women. However, the selection bias should not seriously affect the ethnic comparison of mammographic pattern since the same selection process was used for all groups.

Differences in the quality of films between clinics and subjects may have introduced some bias. Recently, mammography has moved toward dark films to increase the ability to detect abnormalities. This makes it harder to detect the skinline of the breast. The films from one institution were considerably darker than from all others. We had to apply a special feature in the scanning software to make the skin line visible and to measure the size of the breast. Because we applied the same techniques to all mammograms, the size of the breast may have been slightly overestimated resulting in lower percent densities. Therefore, it is possible that our density categories may be systematically lower than those in the Canadian study⁵ which utilizes different hard- and software. To minimize the subjective component of the assessment method, we spent much effort in training the readers and compared the results between the readers frequently. The high correlation coefficient indicates a high level of standardization in mammographic assessment.

Although breast cancer incidence rates still differ among ethnic groups in Hawaii, the differences have become smaller as the majority of women with Chinese and Japanese descent are at least third generation migrants. For example, the breast incidence for Japanese women in Hawaii has increased from 41/10⁵ in 1973-77³¹ to 88/10⁵ in 1988-92¹. Assuming that Chinese and Japanese women with a higher breast cancer risk are more likely to participate in mammography screening and in a research study, the Japanese and Chinese women in this study may have a breast cancer risk that is fairly close the risk experienced by Caucasian women. We plan to explore this issues by using published breast cancer risk estimation models³². Because only a small number of recent immigrants whose breast cancer risk is still close to that of their country of origin have participated in this study, the observed differences in mammographic densities may be relatively small in Hawaii.

(7) Key Research Accomplishments

- The area of dense tissue in the breast appears to be smaller in Chinese and Japanese than in Caucasian women, but the percent of the breast occupied by dense tissue in Chinese and Japanese women appears to be greater than in Caucasian women because of the smaller breast size in Asian women.
- Urinary isoflavone excretion and self-reported soy intake are strongly correlated and are now used in a study exploring dietary risk factors for breast cancer.
- A large proportion of the ethnic variation in mammographic densities is due to anthropometric and reproductive risk factors, but dietary and other risk factors may also contribute to ethnic differences.

(8) Reportable Outcomes

Manuscripts

- Maskarinec G, Singh S, Meng L, Franke AA. Dietary Soy Intake and Urinary Isoflavone Excretion Among Women from a Multi-Ethnic Population. *Cancer Epidemiology, Biomarkers & Prevention* 1998; 7:613-619.
- Franke AA, Hankin JH, Yu MC, Maskarinec G, Low S-H, Custer LJ. Isoflavone levels in soy foods consumed by multiethnic populations in Singapore and Hawaii. *Journal of Agricultural and Food Chemistry* 1999; 47:977-986.
- Maskarinec G, Lyu L-C, Meng L, Theriault A, Ursin G. A Pilot Study Investigating Diet, Ethnicity, and Mammographic Densities. *Ethnicity & Disease* (Submitted).
- Maskarinec G, Meng L, Ursin G. Ethnic Differences in Mammographic Density Patterns. *Journal of the National Institute*. (Submitted in September 1999).

Abstracts

- Maskarinec G, Lyu L-C, Meng L, Ursin G. Preliminary results on ethnicity, soy, and mammographic densities. The Department of Defense - Breast Cancer Research Program Meeting. *Proceedings* 1997; 1: 5-6.
- Maskarinec G, Meng L, Ursin G. Ethnic Differences in Mammographic Density Patterns. *Supplement to the Journal of Epidemiology* 1998; 8: S67.
- Maskarinec G, Singh S, Meng L, Lyu L-C, Franke A. Dietary soy intake and urinary isoflavone excretion among women from a multi-ethnic population. *Proceedings of the American Association for Cancer Research* 1998; 39:388.
- Maskarinec G, Meng L, Shumay D, Ursin G. Ethnicity, Diet, and Mammographic Density Patterns. The 1st European Breast Cancer Conference. *European Journal of Cancer* 1998; 34:S23.
- Maskarinec G, Meng L. Determinants of Mammographic Density patterns among women in Hawaii. *Proceedings of the American Association for Cancer Research* 1999; 40:148.
- Franke AA, Yu MC, Fanti P, Zheng W, Tanaka Y, Maskarinec G, Cooney RV and Custer LJ. Cancer Protection by Dietary Flavonoid Agents. 1999 *Proceedings of the Korean Association of Cancer Prevention*, p. 8-10

Presentations

- Ethnicity, Diet, and Mammographic Density Patterns. The 1st European Breast Cancer Conference. Firenze, Italy, 9/98.
- Soy Intake and Mammographic Densities among Multi-ethnic Women, International Conference on Diet and Cancer Prevention. Tampere, Finland, 6/99.
- An Investigation of Soy Intake and Mammographic Densities Among Women with Different Ancestries in Hawaii. Third International Symposium on the Role of Soy in Preventing and Treating Chronic Disease. Washington, DC, 10/99.

Funding based on work supported by this award

- Mammographic Densities and Breast Cancer Risk Among Women in Hawaii, Hawaii Community Foundation. \$41,988. Aug 97 to Jul 99 (PI).
- A Pilot Study of Isoflavones and Breast Cancer Risk in Premenopausal Women, Pharmavite Corporation. \$99,621. Nov 1998 to Mar 2000 (PI).
- Effects of Soy on Estrogens and Mammographic Densities, R01, NIH/NCI. \$1,632,503. Sep 1999 to Jun 2003 (PI).
- Planning a Hawaii/Japan Mammographic Density Study, R03, NIH/NCI. \$127,347. Aug 1999 to Jul 2001 (PI).

(9) Conclusions

The current analysis appear to be in support of our hypothesis that women at low risk for breast cancer have fewer mammographic densities. However, the difference appears to be in the size of dense areas rather than in the percent of the breast covered by densities. Whereas several risk factors, especially BMI, contribute to the ethnic differences, a portion of the variation cannot be explained with anthropometric and reproductive risk factors. The intake of soy foods appear to make a small contribution to the ethnic variation in mammographic densities. Future analyses will include other dietary factors and a case-control study to elucidate the relation between dense areas and percent densities as determinants of breast cancer risk. A comparison of mammographic density patterns using the same assessment method between Japanese women in the United States and in Japan where breast cancer risk remains less than half of the risk for Japanese women in the United States will also help to elucidate the relation between ethnicity and mammographic densities.

(10) References

1. Miller BA, Kolonel LN, Bernstein L, et al. Racial/ethnic patterns of cancer in the United States 1988-1992. National Cancer Institute. NIH Pub. No. 96-4104. Bethesda, MD.
2. Parkin DM, Whelan SL, Ferlay J, Raymond L, Young J, eds. CI5VII: Electronic database of cancer incidence in five continents Vol. VII (IARC Scientific Publications No. 143). Lyon, France: International Agency for Research on Cancer, 1997.
3. Boyd NF, Lockwood GA, Byng JW, Trichler DL, Yaffe MJ. Mammographic densities and breast cancer risk. *Cancer Epidemiol, Biomarkers Prev* 1998;7:1133-44.
4. Gail MH, Benichou J. Assessing the risk of breast cancer in individuals. In: DeVita VTJ, Hellman S, Rosenberg SA, eds. *Cancer prevention*. Philadelphia: JB Lippincott, 1992:1-15.
5. 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.
6. Stram DO, Hankin JH, Wilkens LR, Henderson B, Kolonel LN. Calibration of the dietary questionnaire for a multiethnic cohort in Hawaii and Los Angeles. *Am J Epidemiol* 1999;149:in press.
7. Byng JW, Boyd NF, Fishell E, Jong RA, Yaffe MJ. The quantitative analysis of mammographic densities. *Phys Med Biol* 1994;39:1629-38.

8. Ursin G, Astrahan MA, Salane M, et al. The detection of changes in mammographic densities. *Cancer Epidemiol, Biomarkers Prev* 1998;7:43-7.
9. Armitage P. Statistical methods in medical research. Oxford: Blackwell Scientific Publications, 1971.
10. Hawaii Department of Health. Health Promotion and Education Branch. Hawaii's health risk behaviors, 1993. Honolulu, HI: Hawaii Department of Health, 1995.
11. Wolfe JN. Risk for breast cancer development determined by mammographic parenchymal pattern. *Cancer* 1976;37:2486-92.
12. Gravelle IH, Bulbrook RD, Wang DY, et al. A comparison of mammographic parenchymal patterns in premenopausal Japanese and British women. *Breast Cancer Res Treat* 1991;18:S93-5.
13. Morimoto T, Sasa M, Tamaguchi T, et al. Effectiveness of mammographic screening for breast cancer in women aged over 50 years in Japan. *Jpn J Cancer Res* 1997;88:778-84.
14. Kojima O, Majima T, Uehara Y, et al. Radiographic parenchymal patterns in Japanese females as a risk factor for breast carcinoma. *World J Surg* 1984;8:414-8.
15. Grove JS, Goodman MJ, Gilbert F, Clyde D. Factors associated with breast structure in breast cancer patients. *Cancer* 1979;43:1895-9.
16. Grove JS, Goodman MJ, Gilbert FI, Mi MP. Factors associated with mammographic pattern. *Br J Radiol* 1985;58:21-5.
17. Maskarinec G, Meng L, Shimozuma K. A pilot study of mammographic density patterns among Japanese women. *J Epidemiol* 1999;9:73-7.
18. Brisson J, Sadowsky NL, Twaddle JA, Morrison AS, Cole P, Merletti F. The relation of mammographic features of the breast to breast cancer risk factors. *Am J Epidemiol* 1982;115:438-43.
19. 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.
20. Boyd NF, Connelly P, Bung J, et al. Plasma lipids, lipoproteins, and mammographic densities. *Cancer Epidemiol, Biomarkers Prev* 1995;4:727-33.
21. Bartow SA, Pathak DR, Mettler FA, Key CR, Pike MC. Breast mammographic pattern: A concatenation of confounding and breast cancer risk factors. *Am J Epidemiol* 1995;142:813-9.
22. Gram IT, Funkhouser E, Tabar L. Anthropometric indices in relation to mammographic patterns among peri-menopausal women. *Int J Cancer* 1997;73:323-6.
23. Stomper PC, Van Voorhis BJ, Ravnikar VA, Meyer JE. Mammographic changes associated with postmenopausal hormone replacement therapy: a longitudinal study. *Radiology* 1990;174:487-90.
24. Laya MB, Gallagher JC, Schreiman JS, Larson EB, Watson P, Weinstein L. Effect of postmenopausal hormonal replacement therapy on mammographic density and parenchymal pattern. *Radiology* 1995;196:433-7.
25. Greendale GA, Reboussin BA, Sie A, et al. Effects of estrogen and estrogen-progestin on mammographic parenchymal density. Postmenopausal Estrogen/Progestin Interventions (PEPI) Investigators. *Ann Intern Med* 1999;130(Pt 1):262-9.

26. Brisson J. Family history of breast cancer, mammographic features of breast tissue, and breast cancer risk. *Epidemiology* 1991;2:440-4.
27. Pankow JS, Vachon CM, Kuni CC, et al. Genetic analysis of mammographic breast density in adult women: evidence of a gene effect. *J Natl Cancer Inst* 1997;89:549-56.
28. Boyd NF, Lockwood GA, Martin LJ, et al. Mammographic densities and risk for breast cancer among subjects with a family history of this disease. *J Natl Cancer Inst* 1999;91:1404-8.
29. de Waard F, Rombach JJ, Collette HJA, Slotboom B. Breast cancer risk associated with reproductive factors and breast parenchymal patterns. *J Natl Cancer Inst* 1984;72:1277-82.
30. Hawaii Medical Service Association Foundation. *Health Trends in Hawaii*. 3rd ed. Honolulu: HMSA, 1997.
31. National Cancer Institute. SEER program: cancer incidence and mortality in the United States 1973-81. Bethesda, MD: U.S. Department of Health and Human Services. NIH Publication no. 85-1837, 1984.
32. Gail MH, Brinton LA, Byar DP, et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. *J Natl Cancer Inst* 1989;81:1879-86.

(11) Appendices

Table 1. Characteristics of the Study Population

Characteristic (Mean)	Caucasian	Chinese	Filipino	Japanese	Native Hawaiian	Other	All
Number	182	73	26	156	63	14	514
Age (years)	54.2	56.7	51.3	53.2	52.7	53.0	53.9
Body mass index	25.3	22.8	26.3	23.2	30.3	24.9	24.9
Years of education	16.1	16.7	13.9	16.1	14.6	14.5	15.8
Currently smoking (%)	4.1	9.3	0.0	4.5	11.1	28.6	7.4
Family history of breast cancer (%)	12.3	10.6	7.7	12.8	11.7	8.3	11.8
Age at menarche	12.5	12.2	13.2	12.2	12.4	12.1	12.4
Parous (%)	81.0	87.0	73.1	86.6	85.0	83.3	83.7
Age at first live birth	24.8	26.8	25.6	27.1	21.6	22.2	25.3
Number of children	1.6	2.1	2.6	2.0	2.8	2.2	2.0
Number premenopausal	73	26	12	70	28	4	213
Currently on oral contraceptives (%)	13.7	7.7	16.7	8.6	14.3	0	11.3
Number postmenopausal	109	47	14	86	35	10	301
Age at menopause	48.1	47.5	45.6	47.0	45.8	45.8	47.2
Currently on hormone replacement (%)	53.2	53.2	35.7	57.0	48.6	40.0	52.5

Table 2. Mammographic Patterns by Ethnicity

Ethnicity	N	Breast Size	Dense Area	Non-Dense Area	Percent Densities
		Mean (<i>s.d.</i>)	Mean (<i>s.d.</i>)	Mean (<i>s.d.</i>)	Mean (<i>s.d.</i>)
Caucasian	182	1,209,692 613,784	293,890 199,848	915,802 597,168	28.8 18.3
Chinese	73	807,967 442,026	249,362 126,929	558,605 418,640	36.2 16.8
Filipino	26	1,110,533 725,462	289,142 181,086	821,391 615,944	28.9 12.3
Japanese	156	789,404 359,745	254,438 131,365	533,966 327,008	34.9 14.4
Native Hawaiian	63	1,352,870 666,477	306,690 207,342	1,046,180 655,533	26.4 17.4
Others	14	1,213,064 803,426	331,982 113,107	881,082 820,248	35.5 18.5
All	514	1,037,401 587,662	277,959 171,017	759,442 557,465	31.6 16.9
F-value*	6 groups	17.3	0.93	15.6	4.92
<i>p</i>		0.0001	0.46	0.0001	0.0002
F-value*	2 groups	81.5	1.53	74.2	20.8
<i>p</i>	Ch,J vs. C,F,H,O	0.0001	0.22	0.0001	0.0001

* for ANOVA

Table 3. Mammographic Patterns by Body Mass Index

Ethnicity	BMI	N	Breast Size	Dense Area	Non-Dense Area	Percent Densities
	Student's <i>t</i> -test		Mean	Mean	Mean	Mean
Caucasian	<25	101	936,634	310,589	626,045	37.1
	≥25	81	1,550,173	273,068	1,277,105	18.6
	<i>p</i>		0.0001	0.006	0.0001	0.0001
Chinese	<25	57	661,501	243,244	418,257	40.1
	≥25	16	1,329,752	271,159	1,058,593	22.6
	<i>p</i>		0.0001	0.62	0.0001	0.0001
Filipino	<25	14	973,792	293,193	680,599	33.7
	≥25	12	1,270,065	284,416	985,649	23.3
	<i>p</i>		0.099	0.75	0.04	0.03
Japanese	<25	116	695,570	260,884	434,685	38.6
	≥25	40	1,057,624	235,745	821,879	24.3
	<i>p</i>		0.0001	0.19	0.0001	0.0001
Native Hawaiian	<25	18	931,003	388,437	542,566	41.7
	≥25	45	1,521,616	273,991	1,247,625	20.3
	<i>p</i>		0.0002	0.03	0.0001	0.0001
Others	<25	10	1,066,337	335,601	730,736	39.8
	≥25	4	1,579,881	322,935	1,256,946	24.7
	<i>p</i>		0.15	0.85	0.12	0.18
All	<25	316	803,943	284,651	519,293	38.4
	≥25	198	1,409,990	267,279	1,142,711	20.9
	<i>p</i>		0.0001	0.004	0.0001	0.0001

Table 4. Mammographic Patterns by Menopausal Status

Ethnicity	Status	N	Breast Size	Dense Area	Non-Dense Area	Percent Densities
	Student's <i>t</i> -test		Mean	Mean	Mean	Mean
Caucasian	pre	73	1,117,719	358,982	758,737	37.1
	post	109	1,271,289	250,297	1,020,993	23.3
	<i>p</i>		0.09	0.001	0.001	0.0001
Chinese	pre	26	812,736	273,564	539,173	41.3
	post	47	805,328	235,974	569,354	33.5
	<i>p</i>		0.89	0.1	0.4	0.06
Filipino	pre	12	1,212,843	348,768	864,075	32.7
	post	14	1,022,839	238,033	784,806	25.6
	<i>p</i>		0.45	0.03	0.82	0.14
Japanese	pre	70	760,615	266,229	494,386	37.0
	post	86	811,023	244,841	566,181	33.2
	<i>p</i>		0.59	0.3	0.31	0.1
Native Hawaiian	pre	28	1,216,163	336,805	879,358	31.6
	post	35	1,462,234	282,597	1,179,637	22.4
	<i>p</i>		0.08	0.24	0.04	0.04
Others	pre	4	774,160	403,022	371,138	52.4
	post	10	1,388,625	303,566	1,085,059	28.8
	<i>p</i>		0.05	0.13	0.06	0.03
All	pre	231	974,981	315,409	659,572	36.9
	post	301	1,081,572	251,457	830,115	27.9
	<i>p</i>		0.04	0.0001	0.0003	0.0001

Table 5. Mammographic Patterns by Hormone Replacement Therapy

Ethnicity	HRT	N	Breast Size	Dense Area	Non-Dense Area	Percent Densities
	Student's <i>t</i> -test		Mean	Mean	Mean	Mean
Caucasian	no	51	1,368,046	204,742	1,163,305	20.2
	yes	58	1,186,210	290,353	895,856	26.0
	<i>p</i>		0.20	0.01	0.14	0.055
Chinese	no	22	805,020	252,137	552,883	35.1
	yes	25	805,599	221,750	583,849	32.1
	<i>p</i>		0.91	0.94	0.83	0.52
Filipino	no	9	961,508	168,637	792,871	21.3
	yes	5	1,133,234	362,946	770,288	33.2
	<i>p</i>		0.74	0.05	0.86	0.09
Japanese	no	37	782,596	231,146	551,449	33.2
	yes	49	832,488	255,182	577,306	33.3
	<i>p</i>		0.51	0.23	0.52	0.99
Native Hawaiian	no	18	1,458,649	233,041	1,225,608	20.1
	yes	17	1,466,030	335,068	1,130,962	24.8
	<i>p</i>		0.42	0.04	0.87	0.41
Others	no	6	1,663,523	291,019	1,372,503	24.0
	yes	4	976,279	322,386	653,892	35.8
	<i>p</i>		0.23	0.74	0.23	0.28
All	no	143	1,128,163	223,775	904,387	26.1
	yes	158	1,039,404	276,511	762,894	29.6
	<i>p</i>		0.86	0.48	0.39	0.23

Table 6. Determinants of Mammographic Patterns
Results of Multiple Linear Regression

Variables	Dense Area*		Non-Dense Area*		Percent Densities	
	β	R ²	β	R ²	β	R ²
Body mass index*	-0.477	0.019	2.028	0.436	-44.88	0.323
Japanese or Chinese ethnicity	-0.125	0.008	-0.284	0.028	--	--
Age (years)	-0.013	0.066	0.009	0.019	-0.294	0.069
Menarche at 13 years or older	--	--	-0.140	0.009	--	--
Parity 3 children or more	--	--	0.110	0.005	-2.472	0.004
Hormone replacement therapy	0.199	0.011	--	--	--	--
Postmenopausal status	-0.159	0.007	--	--	-3.266	0.005
Total model	--	0.111	--	0.497	--	0.401
Simple Model:						
Japanese or Chinese ethnicity	-0.07	0.001	-0.52	0.13	6.72	0.04

* Logarithm was used because of non-normal distribution.

Table 7. Dietary Characteristics of Study Population

Characteristic (Mean)	Caucasian	Chinese	Filipino	Japanese	Native Hawaiian	Other
Number	182	73	26	156	63	14
Caloric intake* (Kcal)	2015	1817	3083	2022	2885	2177
Saturated fat* (g/day)	25.1	19.0	41.4	22.7	33.5	25.3
Percent fat calories*	30.3	27.5	32.9	29.7	31.0	29.2
Fruit intake (servings/day)	1.8	1.8	2.4	1.7	2.6	2.0
Vegetable intake (servings/day)	3.7	3.4	4.4	3.4	4.3	3.7
Soy protein* (g/day)	2.3	4.2	8.1	4.8	5.9	3.1
Tofu* (g/day)	9.3	18.7	22.2	24.4	23.8	21.9

* Duncan test was statistically significant among ethnic groups at $p < 0.05$

(12) Final Report

Bibliography of all Project Publications - Manuscripts

- Maskarinec G, Singh S, Meng L, Franke AA. Dietary Soy Intake and Urinary Isoflavone Excretion Among Women from a Multi-Ethnic Population. *Cancer Epidemiology, Biomarkers & Prevention* 1998; 7:613-619.
- Franke AA, Hankin JH, Yu MC, Maskarinec G, Low S-H, Custer LJ. Isoflavone levels in soy foods consumed by multiethnic populations in Singapore and Hawaii. *Journal of Agricultural and Food Chemistry* 1999; 47:977-986.
- Maskarinec G, Lyu L-C, Meng L, Theriault A, Ursin G. A Pilot Study Investigating Diet, Ethnicity, and Mammographic Densities. *Ethnicity & Disease* (Submitted).
- Maskarinec G, Meng L, Ursin G. Ethnic Differences in Mammographic Density Patterns. *Journal of the National Institute*. (Submitted in September 1999).

Abstracts

- Maskarinec G, Lyu L-C, Meng L, Ursin G. Preliminary results on ethnicity, soy, and mammographic densities. The Department of Defense - Breast Cancer Research Program Meeting. *Proceedings* 1997; 1: 5-6.
- Maskarinec G, Meng L, Ursin G. Ethnic Differences in Mammographic Density Patterns. *Supplement to the Journal of Epidemiology* 1998; 8: S67.
- Maskarinec G, Singh S, Meng L, Lyu L-C, Franke A. Dietary soy intake and urinary isoflavone excretion among women from a multi-ethnic population. *Proceedings of the American Association for Cancer Research* 1998; 39:388.
- Maskarinec G, Meng L, Shumay D, Ursin G. Ethnicity, Diet, and Mammographic Density Patterns. The 1st European Breast Cancer Conference. *European Journal of Cancer* 1998; 34:S23.
- Maskarinec G, Meng L. Determinants of Mammographic Density patterns among women in Hawaii. *Proceedings of the American Association for Cancer Research* 1999; 40:148.
- Franke AA, Yu MC, Fanti P, Zheng W, Tanaka Y, Maskarinec G, Cooney RV and Custer LJ. Cancer Protection by Dietary Flavonoid Agents. 1999 *Proceedings of the Korean Association of Cancer Prevention*, p. 8-10

Presentations

- Ethnicity, Diet, and Mammographic Density Patterns. The 1st European Breast Cancer Conference. Firenze, Italy, 9/98.
- Soy Intake and Mammographic Densities among Multi-ethnic Women, International Conference on Diet and Cancer Prevention. Tampere, Finland, 6/99.
- An Investigation of Soy Intake and Mammographic Densities Among Women with Different Ancestries in Hawaii. Third International Symposium on the Role of Soy in Preventing and Treating Chronic Disease. Washington, DC, 10/99.

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DEPARTMENT OF THE ARMY

US ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
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REPLY TO
ATTENTION OF:

MCMR-RMI-S (70-1y)

21 JUN 2001

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