Adiposity, Adult Weight Gain and Mammographic Breast Density in US Chinese Women

Marilyn Tseng[1] and Celia Byrne[2]
[1] Kinesiology Department, California Polytechnic State University, San Luis Obispo, CA
[2] Division of Cancer Genetics and Epidemiology, Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC

The association of adiposity with dense tissue area in the breast is unclear, but suggests a mechanism by which adiposity might increase breast cancer risk. We examined associations of body mass index (BMI), usual BMI from age 20 to 29, waist circumference and adult weight gain with breast density in a sample of premenopausal United States Chinese immigrant women. Analyses included 415 participants in a longitudinal breast density study in Philadelphia. In addition to detailed questionnaire information, data collection included measures of anthropometry, and assessment of mammographic breast density using a computer-assisted method. We used multivariate linear regression to quantify cross-sectional associations with dense and nondense tissue area and percent breast density assessed at baseline. In adjusted models, BMI and waist circumference were significantly positively associated with nondense tissue area and inversely associated with percent density. BMI was also significantly positively associated with dense tissue area. Adult weight gain was associated with dense tissue area after adjusting for weight from age 20 to 29. In stratified analyses, BMI and adult weight gain were significantly associated with dense tissue area among women with BMI < 23 kg/m^2, and BMI was associated with nondense tissue area among women with BMI ≥ 23 kg/m2. In this sample, adiposity and weight gain were associated with dense breast tissue area, although associations differed by level of adiposity. Given the potential implications of these findings for breast cancer prevention in premenopausal women, comparable studies in other population groups and with longitudinal data are needed. Reasons for the noted differences in associations by level of adiposity also warrant further investigation.

Incidence of breast cancer is low in Chinese women, but in immigrants it increases to converge with rates of white women in the United States (US).1 Adiposity is an established risk factor for breast cancer2,3 that often accompanies westernization in Asian immigrants to the US,4,5 possibly as a consequence of acculturation-related changes to a less moderate diet that is higher in fat and sugar.4,6,7 Although adiposity is generally recognized to increase risk for postmenopausal breast cancer, evidence exists to suggest that it increases risk for premenopausal women, particularly Asian women, as well.3,8

Because of its strong association with breast cancer risk,9,10 breast density, or the portion of total breast area with a mammographicall dense appearance, represents a useful marker for breast cancer risk in epidemiologic studies.10–12 The association between body mass index (BMI) and breast density is complex: although higher BMI and higher density each are associated with breast cancer, BMI is inversely correlated with percent density, suggesting that they are mutual confounders operating through separate mechanisms.[13] That lower-risk Asian women have higher percent breast density than white women in the US but smaller areas of dense tissue,[14–17] however, supports the hypothesis that dense tissue area (absolute area of the breast that appears mammographically dense, measured, for example, in cm^2) rather than percent density (measured as the proportion of the total area of the breast that appears dense) is the more relevant marker of breast cancer risk.[18] Studies in western populations have found either no association or an inverse association between measures of adiposity or weight change and dense tissue area.[19–21] However, in studies that examined the associations of percent and area of breast density with BMI in Chinese women, BMI was negatively associated with percent density as expected but positively associated with dense area.[22,23] This suggests that dense tissue in the breast may yet serve as a useful etiologic marker linking adiposity to breast cancer risk, at least in some populations. We examined associations of BMI, waist circumference and adult weight change with breast density within a sample of US Chinese immigrant women.

Material and Methods

Study sample

Between October 1, 2005, and April 30, 2008, we recruited a convenience sample of 436 women into a study of mammographic breast density through local community organizations working with the recently immigrated Chinese community and contacts in social networks within this same population. Eligibility criteria included Chinese heritage, migration from Asia ≤20 years ago, and being of mammography screening age. Exclusion criteria were: postmenopausal status (no menstruation in the past year); history of breast augmentation/reduction, prophylactic mastectomy, or any cancer except nonmelanoma skin cancer; current pregnancy; current breastfeeding or breastfeeding within last 9 months; or symptoms of new breast problem, such as palpable lump, skin changes, or nipple discharge. Participants received $20 as reimbursement for their time. The study was approved by the Fox Chase Cancer Center Institutional Review Board.

Data collection

Interviewers conducted detailed, language-appropriate health interviews that elicited information on sociodemographic characteristics; reproductive history, including age at menarche, pregnancy history, and oral contraceptive or other hormone use; family history of breast cancer; weight history; and smoking. Women were classified as premenopausal if they reported menses in the last 3 months with no decrease in predictability, early perimenopausal if they reported menses in the last 3 months but with decreased predictability, or late perimenopausal if they reported 3–11 months of amenorrhea. [24,25] Physical activity was assessed using the short, 9-item form of the International Physical Activity Questionnaire, [26] which elicits information on length of time spent sitting, walking and participating in moderate and vigorous activities over the previous 7 days. A weighted estimate of energy expenditure from physical activity in MET-hours per week is calculated as

$$\text{METhourperweek} = \sum t_i \cdot f_i \cdot MET_i$$

where t_i is the amount of time spent on activity category I (walking, moderate activity, vigorous activity), f is number of days per week spent on that activity category, and MET is the MET energy expenditure estimate assigned to that activity level based on the 2000 compendium of physical activities.[27] Each participant also completed 4 days of dietary recall interviews, and responses were entered into the Nutrition Data System for Research (NDS-R, Nutrition Coordinating Center, University of Minnesota). With respect to weight history, participants were asked to estimate their usual weight for each decade of their adult life from their 20s to their current age. Weight change in adulthood was calculated as the difference between their current, measured weight and their estimated weight in their 20s.

At mammographic screenings, trained research staff assessed overall and central adiposity by an anthropometric examination consisting of weight, standing height and waist circumference for each participant, all taken in duplicate by the same interviewer following an established protocol, with the mean used in analyses. BMI (kg/m^2) at these screenings (referred to in this article as ''current'' BMI) was calculated as a measure of overall adiposity, and waist circumference, shown to be highly correlated with abdominal visceral fat as measured by computed tomography,[28] was used as an indicator of central adiposity.

Breast density assessment

Mammograms were conducted at Fox Chase Cancer Center or on its mobile mammography unit or van. Because breast density varies over the course of the menstrual cycle, information on date of onset of last menstruation before the mammogram was obtained to estimate menstrual cycle phase, and participants were also contacted 1–2 weeks after the mammogram in order to determine the first day of onset of their next cycle.

For most participants, cranio-caudal mammographic views were digitized using a Kodak LS-85 laser film scanner at a resolution of 100 pixels/cm. Beginning in April, 2007, Fox Chase Cancer Center began a transition to digital mammography equipment; therefore, for 46 participants recruited after that time, digital images were directly available, eliminating the need to scan and digitize images. Breast density was assessed using a highly reproducible computer-assisted method,[29–31] and average density for both breasts was calculated. [30] In 10% reproducibility samples, intrabatch and interbatch intraclass correlation coefficients were all >0.94, indicating excellent reproducibility.

Statistical analyses

Of 436 women enrolled in the study, 3 women subsequently did not complete the questionnaire, we were unable to obtain mammographic images for 16, and 2 women were missing data on at least one of the main anthropometric variables of interest, leaving a sample of 415 women for this analysis.

We used linear regression to quantify associations between anthropometric measures and 3 outcomes of interest—dense and nondense tissue areas and percent density. Anthropometric measures examined in preliminary analyses were current BMI, current weight, height, and waist circumference, estimated BMI from their 20s, 30s and 40s, and adult weight change (change between 20s and study enrollment). Findings for BMI in their 30s and 40s was not materially different from those for current BMI and are therefore not presented. Because of high correlations of BMI with waist circumference ($r = 0.78$) and adult weight change ($r = 0.67$) and current weight with waist circumference ($r = 0.76$), we followed an approach used by Han et al.[32] in analyses including these variables, modeled after a commonly used method of adjusting for energy intake in dietary studies when energy intake and a nutrient of interest are strongly correlated.[33] We adjusted for waist circumference by including residuals of the regression of waist circumference on BMI or weight, with the idea of mutual adjustment while also reducing extraneous variation in waist circumference due to variation in BMI/ weight. We used a similar strategy to adjust for current BMI in models examining adult weight change.

Because results were not materially different when we conducted analyses for digitized film and digital images separately, we present results for all images combined, with adjustment for image modality. All linear regression models were adjusted at a minimum, therefore, for age (years) and original mammographic image modality (digitized film or digital). Variables were included in multivariate models as potential confounders if they were associated with at least 1 of the 3 density outcomes (dense and nondense tissue areas or percent density); these were perimenopausal stage (premenopausal, early perimenopausal or late perimenopausal), a combined variable representing number of live births (0–1, 2, ≥3) and age at first live birth (<25 or ≥25), and number of months of breastfeeding (none, ≤1 year, >1–2 years, >2 years). Other variables evaluated as potential confounders but found not to be significantly associated with any of the breast density measures were age at menarche, level of education, having a first or second degree relative with breast cancer, having ever used oral contraceptives or hormones, week of menstrual cycle, and level of physical activity. We examined the possibility of a difference in association by BMI in models including all women, with a cross-product term representing the predictor of interest X BMI < 23.0 or ≥23.0.

Results

Most women in the sample were born in China (97%), spoke no English at home (70%), and had never attended college (83%) (Table 1). Mean length of US residence among participants was 7.2 years. With respect to dietary intake, women consumed more pork than beef and had relatively high intake of fruits and vegetables. Most women (68%) were premenopausal, while 22% were categorized as early perimenopausal, and 9% were in the late perimenopause. Thirteen percent reported having ever used oral contraceptives, and only 1% of women reported a family history of breast cancer. Mean percent density was 46.5%. Dense tissue was significantly correlated with both nondense tissue area (Pearson r = 0.38, p < 0.0001) and percent density (r = 0.37, p = < 0.0001), while nondense tissue was inversely associated with percent density (r = -0.64, p < 0.0001).

Means and standard deviations of the anthropometric measures examined in these analyses are shown in Table 2. Mean BMI in the sample was 23.4 kg/m$_2$ (mean weight 58.3 kg/m$_2$, mean height 157.7 cm), mean BMI in the 20s was 20.5 kg/m$_2$ (mean weight 51.1 kg), mean waist circumference was 79.5 cm, and women gained an average of 7.3 kg between their 20s and the study screening. Current BMI was strongly correlated with BMI in the 20s (r = 0.35, p < 0.0001), waist circumference (r = 0.74, p < 0.0001) and adult weight change (r = 0.67, p < 0.0001) (correlations not shown in table). Adult weight change was itself correlated with waist circumference (r = 0.58, p < 0.0001), and inversely correlated with BMI at age 20 (r = -0.46, p < 0.0001).

In minimally adjusted linear models, BMI, weight, BMI in 20s, waist circumference and weight change in adulthood were associated with nondense area and inversely with percent density (Table 2). Current BMI, weight and BMI in 20s also predicted dense tissue area. Adjustment for other nonanthropometric covariates in multivariate models did not materially change these findings, but it did attenuate the estimate for BMI in 20s with percent density. In models that adjusted for other anthropometric variables, current BMI, weight and waist circumference remained significant predictors of nondense tissue area and percent density; current BMI andweight also remained significantly associated with dense tissue area. Height was inversely associated with nondense tissue area and positively associated with percent density only after adjustment for other anthropometric variables. Adult weight change became a significant predictor of dense tissue area only after additional adjustment for weight in 20s, while estimates for nondense tissue area and percent density were attenuated.

Because previous studies among women with generally higher BMI distributions[19–21] showed little or an inverse association between BMI and dense tissue area, we explored whether current BMI and weight change were associated with greater dense tissue area only among women with lower BMI. As a cutpoint for stratified analyses, we selected 23.0 kg/m^2, suggested by the World Health Organization to define overweight in Asian women.[34] In stratified analyses, current BMI and adult weight change were significantly associated with dense tissue area only among women with lower BMI, although interaction p-values were not significant (Table 3). Current BMI was significantly associated with nondense tissue area and significantly inversely associated with percent density only among women with higher BMI, but again, p-values for interaction were not significant.

Discussion

Notable findings from our sample of US Chinese women were that current BMI and adult weight change were significantly associated with dense tissue area, and that these associations appeared to differ between women with lower and higher BMI. Current BMI and weight change were significantly associated with dense tissue area only among women with lower BMI. Among higher BMI women, in contrast, BMI was associated with nondense tissue area and inversely associated with percent density.

Previous studies consistently show associations of anthropometric measures of adiposity with nondense tissue area and inverse associations with percent density,[13,35] as we did for BMI, weight and waist circumference. These associations likely reflect correlations between body fat and fatty tissue in the breast, which then drives an inverse association with percent density. However, with some exceptions,[22,23,36] most observed an inverse association or no association between BMI and area of dense tissue.[19–21] This has led to the conclusion that BMI and percent breast density are independent predictors of breast cancer, and negative confounders for each other.[13] With respect to weight change, although one intervention trial found that women who gained weight had an increase in dense tissue area,[36] other studies show no association of dense tissue area with weight gain.[19,20] Reeves et al.[19] observed an association between BMI and dense tissue area in cross-sectional comparisons but no association between annual changes in BMI and dense tissue area.

Our finding of an association between BMI and dense tissue area in this premenopausal sample suggests that in certain populations, adiposity may in fact increase risk by increasing dense tissue area. Of potential relevance is the observation that the studies that showed a positive association between BMI and dense tissue area,[22,23] including the present study, were conducted in Asian women, with generally lower BMI distributions than those observed in non-Asian samples. Indeed, in stratified analyses we found that BMI was associated with dense tissue area only among women with lower BMI. Among women with higher BMI, BMI was associated with fatty tissue, not dense tissue, in the breast, and hence inversely associated with percent density.

BMI is an established risk factor for postmenopausal breast cancer in western populations, likely because adipose tissue is the major source of estrogens after the menopause. Although many previous studies have reported an inverse association between BMI and premenopausal breast cancer,[2] recent evidence suggests that an increase in risk with greater BMI among premenopausal women is evident when models adjust for the negative confounding of mammographic density. [13] Mechanisms by which BMI might increase proliferation and dense tissue area and/or breast cancer risk include effects on levels of androgens,[37,38] insulin[39–41] and inflammatory factors.[42–49] Previous studies that examined sex steroid hormones[50–52] and insulin-related measures[53–57] in relation to breast density have not consistently confirmed these mechanisms. However, most focused only on percent density rather than also examining associations with dense tissue area, and all were conducted in women with higher BMI distributions than our sample.

A question that warrants further investigation is why any of these mechanisms might be limited to women of lower BMI, as suggested by our study. Two previous studies found that an inverse association of parity with percent breast density[58,59] and positive associations of age at menarche and age at first birth[58] with percent breast density were apparent primarily among women with lower BMI. Investigators of those studies suggested that effects of these reproductive factors are most visible in the absence of effects of excess adiposity on circulating sex hormone levels. Our results may reflect a similar phenomenon, in which effects of BMI and weight gain on sex steroid hormones or insulin and subsequently dense breast tissue are most visible only among women below some threshold for adiposity, resulting in an apparent ceiling effect.

That we observed an association between BMI and dense tissue area while others did not[19–21] might be due to other features, besides lower mean BMI, which distinguish our sample from others[19,20,60,61]—for example, low prevalence of oral contraceptive use and older age at menarche. However, analyses stratifying on history of hormone use and age at menarche did not reveal any meaningful differences by stratum (results not shown), suggesting that these factors are unlikely to explain the difference in findings between our sample and others. Preliminary analyses also suggest some distinguishing features of food consumption in our study population (Table 1), but dietary intake in this sample has yet to be explored more fully. It is also possible that associations of BMI and weight gain with dense breast tissue area are evident only in women at low risk for breast cancer. The age-standardized breast cancer mortality rate was 17.4 per 100,000 in the US in 2000; in China it was 7.0 per 100,000 in urban areas, 4.3 per 100,000 in rural areas.[62] Clarifying the reasons for the apparent difference in findings has implications for our understanding of breast cancer etiology. With respect to prevention, it might also help identify the subset of women for which dense tissue area can serve as a marker of the effect of change in adiposity on breast cancer risk in intervention trials.

Our observation that height was inversely associated with nondense tissue area and positively associated with percent density is consistent with previous work.[63,64] In the study by Dite et al.,[64] height was also positively associated with dense tissue area although it was not in the current study. Potential mechanisms linking height to greater percent density have focused on factors promoting preadolescent growth. That participants were recruited as a convenience sample leaves open the possibility of bias. For example, the observed results might have resulted from an over-representation of participants who were both thinner (lower BMI) and at lower risk for breast cancer (manifested by lower breast density).

Another limitation is that analyses on adult weight gain were based on participants' recalled weight, which, while reasonably accurate, may be influenced by other characteristics such as current weight.[65–67] The accuracy of recalled weight in a lean sample of Chinese immigrant women is not known, and its potential for bias is difficult to speculate on. Nevertheless, unlike many studies in western populations, results for current BMI and weight were based on measured rather than self-reported measures. As such, the findings offer compelling evidence for a role of adiposity in increasing breast cancer risk in a unique sample of women undergoing social, cultural and health transitions upon migration to the US. These findings, particularly with respect to weight gain, merit confirmation in longitudinal analyses.

Our study is the first to provide evidence that associations of BMI and weight gain with dense tissue area in the breast may differ by level of adiposity. Our findings support the possibility that adiposity, which is modifiable in adulthood, can have visible effects on breast density and possibly breast cancer risk. If confirmed, our findings point to weight gain as a modifiable risk factor for premenopausal women. These results require confirmation in other population samples, and in longitudinal data. Determining the reasons for different effects by level of adiposity also warrants investigation.

Acknowledgements

The authors are indebted to Ms. Wanzi Yang, Ms. Qi He, Ms. Rong Cheng, Ms. Bingqin Zheng, Ms. Zemin Liu and Ms. Yun Song for their crucial work in the collection and management of data for this study. The authors also thank Mr. Andrew Balshem and the Fox Chase Cancer Center Population Studies Facility for their data management support, and Dr. Babette Zemel of the Children's Hospital of Philadelphia for her early guidance in anthropometry training. Finally, for their generous assistance in participant recruitment and provision of care, the authors are deeply grateful to Dr. Philip Siu and Dr. Thomas Yuen of Chinatown Medical Services, and Dr. Ari Brooks and Ms. Sriya Krishnamoorthy of the Drexel University College of Medicine.

References

1. Ziegler RG, Hoover RN, Pike MC, Hildesheim A, Nomura AM, West DW, Wu-Williams AH, Kolonel LN, Horn Ross PL, Rosenthal JF, Hyer MB. Migration patterns and breast cancer risk in Asian- American women. J Natl Cancer Inst 1993; 85:1819–27.
2. Ziegler RG. Anthropometry and breast cancer. J Nutr 1997;127:924S–928S.
3. Ziegler R, Hoover R, Nomura A, West D, Wu A, Pike M, Lake A, Horn-Ross P, Kolonel L, Siiteri P, Fraumeni J, Jr. Relative weight, weight change, height, and breast cancer risk in Asian-American women. J Natl Cancer Inst 1996;88:650–60.
4. Pan Y, Dixon Z, Himburg S, Huffman F. Asian students change their eating patterns after living in the United States. J Am Diet Assoc 1999;99:54–7.
5. Lauderdale DS, Rathouz PJ. Body mass index in a US national sample of Asian Americans: effects of nativity, years since immigration and socioeconomic status. Int J Obes Relat Metab Disord 2000;24: 1188–94.
6. Liu A, Berhane Z, Tseng M. Improved dietary variety and adequacy but lower dietary moderation with acculturation in Chinese women in the United States. J Am Diet Assoc 2010;110:457–62.
7. Lv N, Cason KL. Dietary pattern change and acculturation of Chinese Americans in Pennsylvania. J Am Diet Assoc 2004;104: 771–8.
8. Shu XO, Jin F, Dai Q, Shi JR, Potter JD, Brinton LA, Hebert JR, Ruan Z, Gao YT, Zheng W. Association of body size and fat distribution with risk of breast cancer among Chinese women. Int J Cancer 2001; 94:449–55.
9. Oza AM, Boyd NF. Mammographic parenchymal patterns: a marker of breast cancer risk. Epidemiol Rev 1993;15: 196–208.
10. Boyd NF, Lockwood GA, Byng JW, Tritchler DL, Yaffe MJ. Mammographic densities and breast cancer risk. Cancer Epidemiol Biomarkers Prev 1998;7:1133–44.
11. Byrne C. Studying mammographic density: implications for understanding breast cancer. J Natl Cancer Inst 1997;89:531–3.
12. Cummings SR, Tice JA, Bauer S, Browner WS, Cuzick J, Ziv E, Vogel V, Shepherd J, Vachon C, Smith-Bindman R, Kerlikowske K. Prevention of breast cancer in postmenopausal women: approaches to estimating and reducing risk. J Natl Cancer Inst 2009;101:384–98.
13. Boyd NF, Martin LJ, Sun L, Guo H, Chiarelli A, Hislop G, Yaffe M, Minkin S. Body size, mammographic density, and breast cancer risk. Cancer Epidemiol Biomarkers Prev 2006;15:2086–92.
14. Maskarinec G, Meng L, Ursin G. Ethnic differences in mammographic densities. Int J Epidemiol 2001;30:959–65.
15. Maskarinec G, Meng L. A case-control study of mammographic densities in Hawaii. Breast Cancer Res Treat 2000;63: 153–61.
16. El-Bastawissi AY, White E, Mandelson MT, Taplin S. Variation in mammographic breast density by race. Ann Epidemiol 2001;11:257–63.
17. Maskarinec G, Pagano I, Chen Z, Nagata C, Gram IT. Ethnic and geographic differences in mammographic density and their association with breast cancer incidence. Breast Cancer Res Treat 2007; 104:47–56.
18. Haars G, van Noord PA, van Gils CH, Grobbee DE, Peeters PH. Measurements of breast density: no ratio for a ratio. Cancer Epidemiol Biomarkers Prev 2005;14: 2634–40.
19. Reeves KW, Stone RA, Modugno F, Ness RB, Vogel VG, Weissfeld JL, Habel LA, Sternfeld B, Cauley JA. Longitudinal association of anthropometry with mammographic breast density in the Study of Women's Health Across the Nation. Int J Cancer 2009;124:1169–77.
20. Samimi G, Colditz GA, Baer HJ, Tamimi RM. Measures of energy balance and mammographic density in the Nurses' Health Study. Breast Cancer Res Treat 2008;109:113–22.
21. Irwin ML, Aiello EJ, McTiernan A, Bernstein L, Gilliland FD, Baumgartner RN, Baumgartner KB, Ballard-Barbash R. Physical activity, body mass index, and mammographic density in postmenopausal breast cancer survivors. J Clin Oncol 2007; 25:1061–6.

22. Heng D, Gao F, Jong R, Fishell E, Yaffe M, Martin L, Li T, Stone J, Sun L, Hopper J, Boyd NF. Risk factors for breast cancer associated with mammographic features in Singaporean Chinese women. Cancer Epidemiol Biomarkers Prev 2004;13:1751–8.
23. Habel LA, Capra AM, Oestreicher N, Greendale GA, Cauley JA, Bromberger J, Crandall CJ, Gold EB, Modugno F, Salane M, Quesenberry C, Sternfeld B. Mammographic density in a multiethnic cohort. Menopause 2007;14:891–9.
24. Lasley BL, Santoro N, Randolf JF, Gold EB, Crawford S, Weiss G, McConnell DS, Sowers MF. The relationship of circulating dehydroepiandrosterone, testosterone, and estradiol to stages of the menopausal transition and ethnicity. J Clin Endocrinol Metab 2002;87:3760–7.
25. Dudley EC, Hopper JL, Taffe J, Guthrie JR, Burger HG, Dennerstein L. Using longitudinal data to define the perimenopause by menstrual cycle characteristics. Climacteric 1998;1:18–25.
26. Craig CL, Marshall AL, Sjostrom M, Bauman AE, Booth ML, Ainsworth BE, Pratt M, Ekelund U, Yngve A, Sallis JF, Oja P. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc 2003;35: 1381–95.
27. Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, O'Brien WL, Bassett DR, Jr, Schmitz KH, Emplaincourt PO, Jacobs DR, Jr, Leon AS. Compendium of physical activities: an update of activity codes and MET intensities. Med Sci Sports Exerc 2000;32: S498–S504.
28. Clasey JL, Bouchard C, Teates CD, Riblett JE, Thorner MO, Hartman ML, Weltman A. The use of anthropometric and dualenergy X-ray absorptiometry (DXA) measures to estimate total abdominal and abdominal visceral fat in men and women. Obes Res 1999;7:256–64.
29. Byng JW, Boyd NF, Fishell E. The quantitative analysis of mammographic densities. Phys Med Biol 1994;39: 1629–38.
30. Byng JW, Boyd NF, Little L, Lockwood G, Fishell E, Jong RA, Yaffe MJ. Symmetry of projection in the quantitative analysis of mammographic images. Eur J Cancer Prev 1996;5:319–27.
31. Byrne C. Mammographic density and breast cancer risk: the evolution of assessment techniques and implications for understanding breast cancer. Semin Breast Dis 1999;2:301–14.
32. Han D, Nie J, Bonner MR, McCann SE, Muti P, Trevisan M, Ramirez-Marrero FA, Vito D, Freudenheim JL. Lifetime adult weight gain, central adiposity, and the risk of pre- and postmenopausal breast cancer in the Western New York exposures and breast cancer study. Int J Cancer 2006;119: 2931–7.
33. Willett W, Stampfer M. Total energy intake: implications for epidemiologic analyses. Am J Epidemiol 1986;124:17–27. 34. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 2004;363: 157–63.
34. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 2004;363: 157-63
35. Boyd NF, Lockwood GA, Byng JW, Little LE, Yaffe MJ, Tritchler DL. The relationship of anthropometric measures to radiological features of the breast in premenopausal women. Br J Cancer 1998;78:1233–8.
36. Boyd NF, Greenberg C, Lockwood G, Little L, Martin L, Byng J, Yaffe M, Tritchler D. Effects at two years of a low-fat, highcarbohydrate diet on radiologic features of the breast: results from a randomized trial. J Natl Cancer Inst 1997;89:488–96.
37. Travis RC, Key TJ. Oestrogen exposure and breast cancer risk. Breast Cancer Res 2003;5:239–47.
38. Key T, Appleby P, Barnes I, Reeves G. Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies. J Natl Cancer Inst 2002;94:606–16.
39. Kaaks R. Nutrition, hormones, and breast cancer: is insulin the missing link? Cancer Causes Control 1996;7:605–25.
40. Rosenthal AD, Jin F, Shu XO, Yang G, Elasy TA, Chow WH, Ji BT, Xu HX, Li Q, Gao YT, Zheng W. Body fat distribution and risk of diabetes among Chinese women. Int J Obes Relat Metab Disord 2004;28:594–9.
41. Wat NM, Lam TH, Janus ED, Lam KS. Central obesity predicts the worsening of glycemia in southern Chinese. Int J Obes Relat Metab Disord 2001;25:1789–93.
42. Tilg H, Moschen AR. Adipocytokines: mediators linking adipose tissue, inflammation and immunity. Nat Rev Immunol 2006;6:772–83.
43. Il'yasova D, Colbert LH, Harris TB, Newman AB, Bauer DC, Satterfield S, Kritchevsky SB. Circulating levels of inflammatory markers and cancer risk in the health aging and body composition cohort. Cancer Epidemiol Biomarkers Prev 2005;14:2413–18.
44. Siemes C, Visser LE, Coebergh JW, Splinter TA, Witteman JC, Uitterlinden AG, Hofman A, Pols HA, Stricker BH. Creactive protein levels, variation in the Creactive protein gene, and cancer risk: the Rotterdam Study. J Clin Oncol 2006;24: 5216–22.
45. Trichopoulos D, Psaltopoulou T, Orfanos P, Trichopoulou A, Boffetta P. Plasma Creactive protein and risk of cancer: a prospective study from Greece. Cancer Epidemiol Biomarkers Prev 2006;15: 381–4.
46. Zhang SM, Lin J, Cook NR, Lee IM, Manson JE, Buring JE, Ridker PM. Creactive protein and risk of breast cancer. J Natl Cancer Inst 2007;99:890–4.
47. Heikkila K, Harris R, Lowe G, Rumley A, Yarnell J, Gallacher J, Ben-Shlomo Y, Ebrahim S, Lawlor DA. Associations of circulating C-reactive protein and interleukin-6 with cancer risk: findings from two prospective cohorts and a meta-analysis. Cancer Causes Control 2009;20:15–26.
48. Margolis KL, Rodabough RJ, Thomson CA, Lopez AM, McTiernan A. Prospective study of leukocyte count as a predictor of incident breast, colorectal, endometrial, and lung cancer and mortality in postmenopausal women. Arch Intern Med 2007;167:1837–44.
49. Lithgow D, Nyamathi A, Elashoff D, Martinez-Maza O, Covington C. C-reactive protein in nipple aspirate fluid associated with Gail model factors. Biol Res Nurs 2007;9:108–16.
50. Tamimi RM, Hankinson SE, Colditz GA, Byrne C. Endogenous sex hormone levels and mammographic density among postmenopausal women. Cancer Epidemiol Biomarkers Prev 2005;14:2641–7.
51. Aiello EJ, Tworoger SS, Yasui Y, Stanczyk FZ, Potter J, Ulrich CM, Irwin M, McTiernan A. Associations among circulating sex hormones, insulin-like growth factor, lipids, and mammographic density in postmenopausal women. Cancer Epidemiol Biomarkers Prev 2005;14: 1411–17.
52. Boyd NF, Stone J, Martin LJ, Jong R, Fishell E, Yaffe M, Hammond G, Minkin S. The association of breast mitogens with mammographic densities. Br J Cancer 2002;87:876–82.

53. Sellers TA, Jensen LE, Vierkant RA, Fredericksen ZS, Brandt KR, Giuliano AR, Pankratz VS, Cerhan JR, Vachon CM. Association of diabetes with mammographic breast density and breast cancer in the Minnesota breast cancer family study. Cancer Causes Control 2007; 18:505–15.
54. Hong CC, Thompson HJ, Jiang C, Hammond GL, Tritchler D, Yaffe M, Boyd NF. Association between the T27C polymorphism in the cytochrome P450 c17a (CYP17) gene and risk factors for breast cancer. Breast Cancer Res Treat 2004;88:217–30.
55. Furberg AS, Jasienska G, Bjurstam N, Torjesen PA, Emaus A, Lipson SF, Ellison PT, Thune I. Metabolic and hormonal profiles: HDL cholesterol as a plausible biomarker of breast cancer risk. The Norwegian EBBA Study. Cancer Epidemiol Biomarkers Prev 2005;14:33–40.
56. Roubidoux MA, Kaur JS, Griffith KA, Sloan J, Wilson C, Novotny P, Lobell M. Correlates of mammogram density in southwestern Native-American women. Cancer Epidemiol Biomarkers Prev 2003;12: 552–8.
57. Diorio C, Pollak M, Byrne C, Masse B, Hebert-Croteau N, Yaffe M, Cote G, Berube S, Brisson J. Levels of C-peptide and mammographic breast density. Cancer Epidemiol Biomarkers Prev 2005;14:2661–4.
58. Titus-Ernstoff L, Longnecker MP, Newcomb PA, Dain B, Greenberg ER, Mittendorf R, Stampfer M, Willett W. Menstrual factors in relation to breast cancer risk. Cancer Epidemiol Biomarkers Prev 1998;7:783–9.
59. Butler LM, Gold EB, Greendale GA, Crandall CJ, Modugno F, Oestreicher N, Quesenberry CP, Jr, Habel LA. Menstrual and reproductive factors in relation to mammographic density: the Study of Women's Health Across the Nation (SWAN). Breast Cancer Res Treat 2008; 112:165–74.
60. Wu A, Ziegler R, Pike M, Nomura A, West D, Kolonel L, Horn-Ross P, Rosenthal J, Hoover R. Menstrual and reproductive factors and risk of breast cancer in Asian-Americans. Br J Cancer 1996;73:680–6.
61. Ursin G, Ma H, Wu AH, Bernstein L, Salane M, Parisky YR, Astrahan M, Siozon CC, Pike MC. Mammographic density and breast cancer in three ethnic groups. Cancer Epidemiol Biomarkers Prev 2003;12: 332–8.
62. International Agency for Research on Cancer and World Health Organization. http://www-dep.iarc.fr, accessed Feb 3, 2010.
63. Vachon CM, Kuni CC, Anderson K, Anderson VE, Sellers TA. Association of mammographically defined percent breast density with epidemiologic risk factors for breast cancer. Cancer Causes Control 2000; 11:653–62.
64. Dite GS, Gurrin LC, Byrnes GB, Stone J, Gunasekara A, McCredie MR, English DR, Giles GG, Cawson J, Hegele RA, Chiarelli AM, Yaffe MJ, et al. Predictors of mammographic density: insights gained from a novel regression analysis of a twin study. Cancer Epidemiol Biomarkers Prev 2008; 17: 3474–81.
65. Casey VA, Dwyer JT, Berkey CS, Coleman KA, Gardner J, Valadian I. Long-term memory of body weight and past weight satisfaction: a longitudinal follow-up study. Am J Clin Nutr 1991; 53: 1493–8.
66. Tamakoshi K, Yatsuya H, Kondo T, Hirano T, Hori Y, Yoshida T, Toyoshima H. The accuracy of long-term recall of past body weight in Japanese adult men. Int J Obes Relat Metab Disord 2003; 27: 247–52.
67. Perry GS, Byers TE, Mokdad AH, Serdula MK, Williamson DF. The validity of selfreports of past body weights by U.S. adults. Epidemiology 1995;6:61–6.

Table 1. Descriptive characteristics of study sample ($N = 415$)

	Mean (SD)
Age (y)	43.9 (4.5)
Length of US residence (y)	7.2 (4.9)
Age at menarche (y)[1]	14.9 (1.7)
Number of livebirths	2.0 (1.0)
Age at first live birth (y)	25.3 (4.6)
MET-hours/week[2]	32.8 (31.2)
Diet[1]	
Mean (SD) amount per day	
Energy (kcal)	1355 (356)
Energy from fat (%)	24.2 (6.0)
Mean (SD)/median servings per week	
Beef	1.7 (3.8)/0
Pork	8.1 (8.3)/6.2
Fruit	11.1 (12.5)/9.4
Vegetables	23.2 (9.7)/21.4
Breast density	
Percent density	46.5 (15.8)
Dense tissue area (cm^2)	36.7 (16.7)
Non-dense tissue area (cm^2)	45.3 (25.9)
	%
Education[1]	
<8 years	48
9–12 years/technical school	35
At least some college	17
Speak English at home[1]	
Not at all	70
A little	21
Somewhat or higher	8
1st or 2nd degree relative with breast cancer	1.2
Perimenopausal stage	
Premenopausal	68
Early perimenopausal	22
Late perimenopausal	9
Total duration of breastfeeding	
None	17
≤1 year	47
>1–2 years	23
>2 years	13
Ever used oral contraceptives	13
Ever used female hormones	1.7

[1] Ns differ due to missing data for length of US residence ($N = 412$); age at menarche ($N = 413$); dietary intake ($N = 387$); education ($N = 414$); speaking English at home ($N = 413$). [2] Based on responses to 9-item International Physical Activity Questionnaire, MET-hours per week was calculated as product of amount of time spent on activity a given category (walking, moderate activity, vigorous activity) × number of days per week spent on that activity category × MET energy expenditure estimate assigned to that activity level,[27] summed over the 4 activity categories.

Table 2. Associations of anthropometric measures with dense area, nondense area and percent breast density (*N* = 415)

		Beta[1] (*p*-value)		
	Mean (SD)	**Dense area**	**Nondense area**	**Percent density**
BMI (kg/m^2)	23.4 (2.8)			
Minimally adjusted[2]		0.84 (0.004)	3.99 (<0.0001)	−1.6 (<0.0001)
Multivariate[3]		0.90 (0.002)	3.96 (<0.0001)	−1.6 (<0.0001)
+ other anthropometric variables[4]		0.74 (0.02)	3.82 (<0.0001)	−1.5 (<0.0001)
Weight (kg)	58.3 (7.7)			
Minimally adjusted[2]		0.35 (0.0009)	1.18 (<0.0001)	−0.4 (<0.0001)
Multivariate[3]		0.35 (0.001)	1.20 (<0.0001)	−0.4 (<0.0001)
+ other anthropometric variables[5]		0.32 (0.01)	1.47 (<0.0001)	−0.6 (<0.0001)
Height (cm)	157.7 (5.4)			
Minimally adjusted[2]		0.23 (0.13)	−0.28 (0.23)	−0.2 (0.08)
Multivariate[3]		0.16 (0.29)	−0.19 (0.42)	0.15 (0.28)
+ other anthropometric variables[6]		−0.21 (0.24)	−1.07 (<0.0001)	0.42 (0.006)
Waist circumference (cm)	79.5 (7.6)			
Minimally adjusted[2]		0.16 (0.14)	1.38 (<0.0001)	−0.6 (<0.0001)
Multivariate[3]		0.18 (0.11)	1.37 (<0.0001)	−0.6 (<0.0001)
+ other anthropometric variables[7]		−0.11 (0.50)	0.22 (0.002)	−0.4 (0.001)
BMI in 20's (kg/m^2)	20.5 (2.3)			
Minimally adjusted[2]		0.79 (0.02)	2.26 (<0.0001)	−0.9 (0.004)
Multivariate[3]		0.93 (0.01)	1.87 (0.0006)	−0.6 (0.06)
+ other anthropometric variables[8]		0.59 (0.12)	0.49 (0.36)	−0.1 (0.75)
Adult weight change (kg)	7.3 (7.3)			
Minimally adjusted[2]		0.12 (0.29)	0.84 (<0.0001)	−0.3 (0.0006)
Multivariate[3]		0.11 (0.33)	0.94 (<0.0001)	−0.4 (<0.0001)
+ other anthropometric variables[9]		0.39 (0.03)	0.34 (0.17)	0.04 (0.78)

[1] Beta represents cm^2 change in dense or nondense area or absolute 1% change in percent density per unit change in BMI (kg/m^2), waist circumference (cm) or weight change (kg). [2] Adjusted for age and image modality (digitized film *vs.* digital). [3] Adjusted for age, image modality, perimenopausal stage, combined variable representing number of live births and age at first live birth, and months of breastfeeding. [4] Additionally adjusted for BMI in 20s and waist circumference (residual). [5] Additionally adjusted for weight in 20s, waist circumference (residual) and height. [6] Additionally adjusted for current weight, weight in 20s and waist circumference (residual). [7] Additionally adjusted for current BMI and BMI in 20s. [8] Additionally adjusted for current BMI and waist circumference (residual). [9] Additionally adjusted for current BMI (residual), weight in 20s and waist circumference.

Table 3. Associations of current BMI and adult weight change with dense area, nondense area and percent breast density, in analyses stratified on current BMI (17.2–<23 kg/m^2 *vs.* 23.0–33.2 kg/m^2) (*N* = 415)

	Beta[1] (*p*-value)		
	Dense area	**Nondense area**	**Percent density**
Current BMI			
BMI <23.0 (*N* = 198)	1.97 (0.02)	2.42 (0.06)	−0.7 (0.37)
BMI ≥23.0 (*N* = 217)	0.22 (0.74)	4.79 (<0.0001)	−1.8 (0.0004)
Interaction *p*-value[2]	0.10	0.19	0.36
Adult weight change			
BMI <23.0 (*N* = 198)	0.87 (0.01)	−0.22 (0.68)	0.4 (0.20)
BMI ≥23.0 (*N* = 217)	0.23 (0.38)	0.62 (0.07)	−0.1 (0.67)
Interaction *p*-value	0.14	0.21	0.10

[1] Beta represents cm^2 change in dense or nondense area or absolute 1% change in percent density per unit change in BMI (kg/m^2), waist circumference (cm) or weight change (kg). Beta estimates for BMI were adjusted for age, image modality, perimenopausal stage, combined variable representing number of live births and age at first live birth, months of breastfeeding, BMI in 20s and waist circumference (residual). Beta estimates for adult weight change were adjusted for age, image modality, perimenopausal stage, combined variable representing number of live births and age at first live birth, months of breastfeeding, current BMI (residual), weight at age 20 and waist circumference. [2] Interaction *p*-values calculated in models including all participants with an interaction term representing BMI or weight change × BMI <23.0 or ≥23.0.