Examining the Associations among Fibrocystic Breast Change, Total Lean Mass, and Percent Body Fat

Yuan-Yuei Chen1,2, Wen-Hui Fang2, Chung-Ching Wang2, Tung-Wei Kao2,3,4, Yaw-Wen Chang2,3, Hui-Fang Yang2,3, Chen-Jung Wu2,3,5, Yu-Shan Sun2,3 & Wei-Liang Chen2,3

Fibrocystic breast change (FBC) is extremely common and occurs in 90% of women during their lives. The association between body composition and risk of breast cancer is well established. We hypothesized that the effect might exist during the development of FBC. Our aim was to examine the relationships of total lean mass (TLM) and percent body fat (PBF) with FBC in a general female population. In total, 8477 female subjects aged 20 years or older were enrolled in the study at the Tri-Service General Hospital in Taiwan from 2011 to 2016. Comprehensive examinations including biochemical data, measurements of body composition and breast ultrasound were performed. PBF was positively associated with the presence of FBC (OR = 1.039, 95%CI: 1.018–1.060), and TLM showed the opposite result (OR = 0.893, 95%CI: 0.861–0.926). Condition of metabolic syndrome (MetS), diabetes (DM) and fatty liver modified the association between PBF and FBC (P < 0.001, P = 0.032 and P = 0.007, respectively). Female subjects diagnosed with MetS, DM, and fatty liver had higher risk of developing FBC than control subjects (OR = 1.110, 95%CI: 1.052–1.171; OR = 1.144, 95%CI: 1.024–1.278; OR = 1.049, 95%CI: 1.019–1.080). Those with higher PBF (for highest quartile versus lowest, OR = 2.451, 95%CI: 1.523–3.944) or lower TLM (for highest quartile versus lowest, OR = 0.279, 95%CI: 0.171–0.455) had increased risk of developing FBC. In conclusion, increased PBF and reduced TLM were likely to predict the risk of the presence of FBC in a general female population.

Fibrocystic breast change (FBC), also termed “fibrocystic breast disease”, is the general, all-inclusive term, for a whole range of common and benign breast disorders1. FBC is most common among premenopausal women aged 20–50 years old2. Such changes comprise all types of benign conditions such as cysts, papilloma, apocrine metaplasia, epithelial hyperplasia, and adenosis3. Several studies indicated that the lifetime prevalence of FBC in women might be as high as 70% to 90%4,5.

These fibrocystic changes might be discovered incidentally by radiologists in women who began screening. Generally, FBC is not related to breast cancer. However, accumulating evidence has proposed that the breast cancer risk is involved with FBC. Women with nonproliferative lesions did not have a risk for breast cancer, whereas those with proliferative lesions without atypia had an approximately 2-fold increase in risk and those with atypical ductal or lobular hyperplasia had an approximately 5-fold increase in risk6,7. In a study composed of women diagnosed with benign breast disease, females with atypical epithelial proliferation had higher risk than women over 55 years with the same diagnosis8.

The associations between body composition and breast cancer have been examined and well established for decades9,10. Adipose tissue might increase the risk of breast cancer by influencing sex hormone balance, endocrine function and adipokine expression11. Recently, lean body mass was found to represent a powerful endocrine,
immune and hormonal influence within the body. However, few studies have addressed the effect of obesity on FBC and the association was largely unknown.

Due to the potential risk of FBC in the development of breast cancer, we were inspired to examine whether the alteration in body composition would increase the risk of FBC. The aim of our study was to investigate the associations between FBC with percent body fat (PBF) and total lean mass (TLM) with FBC in a large-scale general female population who had undergone health examinations in a medical center in Taiwan.

Results
Characteristics of the study sample with or without fibrocystic breast change.

Table 1. Characteristics of study sample with or without fibrocystic breast change.

| Variables                  | Fibrocystic change (−) (N = 7478) | Fibrocystic change (+) (N = 999) | P Value |
|----------------------------|-----------------------------------|----------------------------------|---------|
| Continuous Variables, mean (SD) |                                  |                                  |         |
| Total lean mass (kg)       | 20.74 (3.08)                      | 20.79 (2.68)                     | 0.690   |
| PBF (%)                   | 31.91 (6.66)                      | 32.17 (6.67)                     | 0.370   |
| Age (years)               | 42.96 (16.19)                     | 45.77 (11.81)                    | <0.001  |
| BMI (kg/m²)               | 22.94 (4.11)                      | 22.76 (3.66)                     | 0.211   |
| Total cholesterol (mg/dL) | 185.50 (35.53)                    | 190.19 (34.50)                   | <0.001  |
| Uric acid (mg/dL)         | 4.74 (1.10)                       | 4.70 (1.03)                      | 0.293   |
| Creatinine (mg/dL)        | 0.68 (0.21)                       | 0.67 (0.11)                      | 0.154   |
| AST (U/L)                 | 18.97 (13.54)                     | 19.57 (14.75)                    | 0.208   |
| Albumin (g/dL)            | 4.43 (0.29)                       | 4.43 (0.27)                      | 0.395   |
| hsCRP (mg/dL)             | 0.21 (0.43)                       | 0.19 (0.27)                      | 0.234   |
| TSH (IU/mL)               | 2.38 (1.85)                       | 2.45 (2.07)                      | 0.366   |
| Category Variables, (%)   |                                  |                                  |         |
| Proteinuria               | 6996 (29.0)                       | 209 (26.7)                       | 0.147   |
| Smoking                   | 650 (9.1)                         | 62 (7.7)                         | 0.178   |
| Drinking                  | 1659 (28.3)                       | 202 (28.9)                       | 0.752   |

Table 2. Association between different anthropometric parameters and the presence of fibrocystic breast change. *Adjusted covariates: Model 1 = unadjusted. Model 2 = Model 1 + age, proteinuria, serum total cholesterol, uric acid, creatinine, AST, albumin, hsCRP. Model 3 = Model 2 + history of smoking, drinking.

| Models | Model* 1 OR (95% CI) | P Value | Model* 2 OR (95% CI) | P Value | Model* 3 OR (95% CI) | P Value |
|--------|----------------------|---------|----------------------|---------|----------------------|---------|
| Variables | Fibrocystic breast change |         | Fibrocystic breast change |         | Fibrocystic breast change |         |
| Total lean mass | 0.811 (0.789, 0.833) | <0.001  | 0.884 (0.853, 0.916) | <0.001  | 0.893 (0.861, 0.926) | <0.001  |
| PBF     | 1.082 (1.066, 1.099)  | <0.001  | 1.045 (1.025, 1.066) | <0.001  | 1.039 (1.018, 1.060) | <0.001  |

Assessments between the presence of FBC with TLM and PBF. As shown in Table 2, the relationships between different anthropometric indices and the presence of FBC were analyzed by logistic regression. TLM showed an inverse tendency for prediction of the risk of FBC with ORs of 0.811, 0.884 and 0.893 (95%CI = 0.789–0.833, 0.853–0.916, 0.861–0.926) in Model 1, 2 and 3, respectively. On the other hand, PBF was positively associated with the presence of FBC with ORs of 1.082, 1.045 and 1.039 (95%CI = 1.066–1.099, 1.025–1.066, 1.018–1.060) in Model 1, 2 and 3, respectively.

Association between PBF and the presence of FBC with or without different outcomes. The associations between PBF and diagnoses of FBC with or without underlying diseases such as metabolic syndrome (MetS), diabetes mellitus (DM) and fatty liver performed by multivariable logistic regression are listed in Table 3. Condition of MetS, DM and fatty liver modified the association between PBF and FBC (P for interaction < 0.001, = 0.032 and = 0.007, respectively). People with or without MetS and DM all had a predictive ability for the presence of FBC with ORs of 1.110, 1.031 (95%CI = 1.052–1.171; 1.005–1.058) and 1.144, 1.037 (95%CI = 1.024–1.278; 1.016–1.059), respectively, in the fully adjusted model. However, no significant difference was noted for relationship between individuals without fatty liver and FBC. PBF in subjects who had fatty liver was positively correlated with the presence of FBC with ORs of 1.049 (95%CI = 1.019–1.080).

Association between anthropometric indices in quartiles with the presence of FBC. As shown in Table 4, quartile analysis was used for TLM and PBF to examine the dose-dependent effect on the association...
between anthropometric parameters and FBC. In line with our expectations, participants with reduced TLM had an increased risk of developing FBC with an OR of 0.279 (95%CI = 0.171–0.455) in the fully adjusted model. Those with elevated PBF had an increased risk of the presence of FBC with an OR of 2.451 (95%CI = 1.523–3.944) in the fully adjusted model.

**Discussion**

In our study, we highlighted the important role of body composition in the process of FBC. Subjects with higher TLM had a lower risk of developing FBC. In contrast, higher PBF was significantly associated with an increased risk of the presence of FBC. It appeared that TLM played a protective role; however, increased PBF was detrimental to the general female population. To the best of our knowledge, the present study was the first to examine the relationship between different anthropometric parameters and FBC in a cross-sectional study composed of a large female general population.

The most significant contributing factor to FBC was the normal hormonal variation of women during the menstrual cycle. Sex hormonal alterations with estrogen dominance over progesterone were considered to contribute to the development of hyperproliferation of breast tissue. Adipose tissue has been suggested as an endocrine organ that secretes numerous hormones such as sex hormones. Excessive body fat could raise levels of estrogen and increase the risk of hormone-receptor-positive breast cancer. Numerous studies have reported that postmenopausal women placed on hormone replacement therapy had symptoms of FBC, indicating that hormones might play a role. Aside from estrogen and progesterone, prolactin also led to FBC by expression outside of the breast and acting on the breast in important ways. Prolactin was responsible for the growth and development of mammary glands. There were specific prolactin receptors in breast tissue that increased during pregnancy and throughout estrogen therapy. In a previous study, obesity and increased body fat were reported to be related to high levels of prolactin. Kok et al. demonstrated that release of prolactin was enhanced in obese premenopausal women and was particularly associated with the amount of visceral fat. The above evidence supported our findings that increased PBF was associated with a high risk of FBC in a general female population.

In a case-control study, a higher fat-muscle ratio was associated with increased risk of breast cancer, whereas muscle fraction was negatively associated. The term "sarcopenic obesity", known as TLM loss with fat tissue accumulation was common in breast cancer survivors. TLM loss appears to be associated with metabolic abnormalities and is a positive predictor of adverse outcomes, such as chronic heart failure, chronic kidney disease and cancer cachexia. Villasenor et al. reported that sarcopenia was associated with an increased risk of breast-cancer-specific mortality. It is important to improve prognosis by maintaining and increasing skeletal muscle mass. The direct mechanism underlying the effect of lean body mass on breast diseases and cancer remains

### Table 3

Association between body fat percentage and fibrocystic breast change in the presence of different outcomes. Adjusted covariates: Model 1 = unadjusted. Model 2 = Model 1 + age + BMI + proteinuria, serum total cholesterol, uric acid, creatinine, AST, albumin, hsCRP, TSH. Model 3 = Model 2 + history of smoking, drinking.

| Variables | Models | Model 1 OR (95% CI) | P Value | Model 2 OR (95% CI) | P Value | Model 3 OR (95% CI) | P Value |
|-----------|--------|---------------------|---------|---------------------|---------|---------------------|---------|
| MetS (−) |        | 1.089 (1.067, 1.111) | < 0.001 | 1.037 (1.011, 1.065) | 0.005   | 1.031 (1.005, 1.058) | 0.019   |
| MetS (+) |        | 1.147 (1.102, 1.193) | < 0.001 | 1.119 (1.063, 1.177) | < 0.001 | 1.110 (1.052, 1.171) | < 0.001 |
| DM (−)   |        | 1.084 (1.067, 1.101) | < 0.001 | 1.043 (1.023, 1.064) | < 0.001 | 1.037 (1.016, 1.059) | < 0.001 |
| DM (+)   |        | 1.146 (1.051, 1.249) | 0.002   | 1.143 (1.029, 1.270) | 0.013   | 1.144 (1.024, 1.278) | 0.017   |
| Fatty liver (−) | | 1.076 (1.051, 1.102) | < 0.001 | 1.033 (1.003, 1.063) | 0.033   | 1.027 (0.997, 1.058) | 0.080   |
| Fatty liver (+) | | 1.110 (1.086, 1.134) | < 0.001 | 1.058 (1.029, 1.088) | < 0.001 | 1.049 (1.019, 1.080) | < 0.001 |

### Table 4

Association between anthropometric parameters in quartile with the presence of fibrocystic breast change. Adjusted covariates: Model 1 = unadjusted. Model 2 = Model 1 + age + BMI + proteinuria, serum total cholesterol, uric acid, creatinine, AST, albumin, hsCRP, TSH. Model 3 = Model 2 + history of smoking, drinking. Range of TLM in quartile. Q1: < 23.80; Q2: 19.20–21.20; Q3: 21.20–23.80; Q4: > 25.90.

| Variable | Quartiles | Models 1 OR (95% CI) | P Value | Models 2 OR (95% CI) | P Value | Models 3 OR (95% CI) | P Value |
|----------|-----------|---------------------|---------|---------------------|---------|---------------------|---------|
| Total lean mass | Q2 vs. Q1 | 0.857 (0.634, 1.158) | 0.315   | 0.840 (0.613, 1.150) | 0.276   | 0.845 (0.617, 1.158) | 0.294   |
|           | Q3 vs. Q1 | 1.002 (0.749, 1.341) | 0.988   | 1.081 (0.782, 1.493) | 0.638   | 1.112 (0.803, 1.539) | 0.322   |
|           | Q4 vs. Q1 | 0.804 (0.658, 1.122) | < 0.001 | 0.235 (0.146, 0.379) | < 0.001 | 0.279 (0.171, 0.455) | < 0.001 |
| PBF      | Q2 vs. Q1 | 2.167 (1.512, 3.104) | < 0.001 | 1.494 (1.021, 2.188) | 0.039   | 1.378 (0.939, 2.023) | 0.101   |
|           | Q3 vs. Q1 | 3.320 (2.336, 4.718) | < 0.001 | 1.864 (1.248, 2.786) | 0.002   | 1.610 (1.071, 2.420) | 0.022   |
|           | Q4 vs. Q1 | 4.794 (3.407, 6.748) | < 0.001 | 2.935 (1.843, 4.673) | < 0.001 | 2.451 (1.523, 3.944) | < 0.001 |
unknown. Concurrent lean mass loss caused by fat tissue accumulation might be a plausible explanation for the induction of elevated levels of estrogen in the development of FBC.

There were still potential limitations in the study. First, a cross-sectional design could not be assessible for casual inference between anthropometric indices and the presence of FBC. A longitudinal survey was suggested to be examined in further studies. Second, only Taiwanese females had enrolled in the study from health examinations at a single medical center. Limited ethnic diversity might not reflect the association in different ethnicities. Last, the measurement of body composition in the health check-up was performed by BIA, but not DEXA, a standard measurement for body composition with higher accuracy.

Conclusion
Our findings highlighted the associations of TLM and PBF with the presence of FBC in a general female population. Decreased fat mass and increased lean mass might reduce the risk of FBC and even retard the progress of cancer. A better understanding of the pathophysiological underlying shared associations of TLM and PBF may provide biological insights into the etiology of FBC.

Methods
Study design. A total of 69226 participants aged 20 years and older were enrolled in health examinations at Tri-Service General Hospital from 2011 to 2016, and all characteristics of the study sample were analyzed in the retrospective cross-sectional study. Study approval was conduct by the Institutional Review Board (IRB) of Tri-Service General Hospital (TSGH), Taiwan. The TSGH IRB waived the need to obtain individual informed consent because these data were analyzed anonymously. Based on our inclusion criteria, males were excluded in the first step. Female participants with missing biochemical data and those lacking comprehensive examinations were excluded. In all, 8477 eligible subjects were included in the final analysis.

Diagnosis of fibrocystic breast change. The study sample in our study was composed of a Taiwanese general female population. Several studies had reported that the morphological view of breast tissue in Asian women is denser than that in Caucasian women. The breast tissue was dense and tightly packed with lobules, ducts and connective tissue in young females. Due to the above supportive evidence, breast ultrasound was better than mammography for evaluating breast condition. Ultrasound imaging used sound waves to produce pictures of the internal structures of the breast. The radiographic features of breast ultrasound for FBC showed prominent fibroglandular tissue in palpable nodules without discernible mass or small cysts in the mammary zone.

Data collection. The baseline data in the present study included age, body composition [body mass index (BMI), TLM, and PBF], laboratory data [serum total cholesterol (TC), uric acid (UA), creatinine (Cr), aspartate aminotransferase (AST), albumin, highly sensitive C-reactive protein (hsCRP), and thyroid-stimulating hormone (TSH)], and personal history (proteinuria, cigarette smoking, alcoholic consumption). A self-reported questionnaire was used to collect age, gender and personal history. TLM and PBF were the indicators used in the study and were measured by BIA (InBody720, Biospace, Inc., Cerritos, CA, USA), an effective and validated method that was widely used for assessing body composition. BMI was measured by trained investigators using a general formula that the weight divided by the square of the height (kg/m²). Biochemistry laboratory data were collected by drawing blood samples from subjects after fasting for at least 8 hours and analyzed by different standard procedures. TC and AST were measured by an enzymatic colorimetric method. The latex-enhanced nephelometry was used to detect hsCRP. UA was measured by the Hitachi 737 automated multichannel chemistry analyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN, USA). Cr was measured by the uncompensated Jaffe method with the alkaline picrate kinetic test. TSH was accessed by an immune-enzymatic assay.

Statistical analysis. First, odd ratios (ORs) for associations between TLM and PBF with the presence of FBC were performed. A univariate logistic model was applied in the first step (Model 1: unadjusted) After adjusting pertinent confounders, multivariate models were investigated (Model 2: Model 1 + age, BMI, proteinuria, TC, UA, Cr, AST, albumin, hsCRP, and TSH. Model 3: Model 2 + history of cigarette smoking and alcoholic consumption). Second, multivariable logistic regression was used for PBF predicting the risk of developing FBC with or without the presence of MetS, DM and fatty liver. The effect of modification by FBC and different health outcomes was tested by including interaction terms in the models for the PBF, and the results were shown in the following table. There were significant interactions between FBC with MetS (p < 0.001), DM (p = 0.032) and fatty liver (p = 0.007). According to the significant findings of the interaction testing, further stratified analyses were performed. Finally, ORs for associations between TLM and PBF with the presence of FBC in quartile analysis were conducted. Multivariable models were adjusted as follows. Statistical estimations used in the study were performed by the Statistical Package for the Social Sciences, version18.0 (SPSS Inc., Chicago, IL, USA) for Windows. The differences between males and females in terms of demographic information and biochemistry data were examined by Student’s t test and Pearson’s chi-square test. A two-sided p-value of ≤0.05 was regarded as the threshold for statistical significance.

References
1. Bartow, S. A., Pathak, D. R., Black, W. C., Key, C. R. & Teaf, S. R. Prevalence of benign, atypical, and malignant breast lesions in populations at different risk for breast cancer. A forensic autopsy study. Cancer 60, 2751–2760 (1987).
2. Fitzgibbons, P. L., Henson, D. E. & Hutter, R. V. Benign breast changes and the risk for subsequent breast cancer: an update of the 1985 consensus statement. Cancer Committee of the College of American Pathologists. Archives of pathology & laboratory medicine 122, 1053–1055 (1998).
3. Guray, M. & Sahin, A. A. Benign breast diseases: classification, diagnosis, and management. Oncologist 11, 435–449, https://doi.org/10.1634/theoncologist.11-5-435 (2006).

4. Norwood, S. L. Fibrocystic breast disease. An update and review. Journal of obstetric, gynecologic, and neonatal nursing: JOGNN 19, 116–121 (1990).

5. Love, S. M., Gelman, R. S. & Silen, W. Sounding board. Fibrocystic “disease” of the breast—a nondisease? The New England journal of medicine 307, 1010–1014, https://doi.org/10.1056/NEJMoa982101 (1987).

6. Dupont, W. D. & Page, D. L. Risk factors for breast cancer in women with proliferative breast disease. The New England journal of medicine 312, 146–151, https://doi.org/10.1056/NEJM1985111331201303 (1985).

7. Palli, D., R del Turco, M., Simoncini, R. & Bianchi, S. Benign breast disease and breast cancer: a case-control study in a cohort in Italy. International journal of cancer 47, 703–706 (1991).

8. Hartmann, L. C. et al. Benign breast disease and the risk of breast cancer. The New England journal of medicine 353, 229–237, https://doi.org/10.1056/NEJMoa044383 (2005).

9. Renehan, A. G., Tyson, M., Egger, M., Heller, R. F. & Zwahlen, M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet (London, England) 371, 569–578, https://doi.org/10.1016/s0140-6736(08)60269-x (2008).

10. Connolly, B. S. et al. A meta-analysis of published literature on waist-to-hip ratio and risk of breast cancer. Nutrition and cancer 44, 127–138, https://doi.org/10.1080/01635580902725995 (2002).

11. Roberts, D. L., Dive, C. & Renehan, A. G. Biological mechanisms linking obesity and cancer risk: new perspectives. Annual review of medicine 61, 301–316, https://doi.org/10.1146/annurev.med.080708.082713 (2010).

12. Christensen, J. F. et al. Muscle dysfunction in cancer patients. Annals of Oncology 25, 947–958, https://doi.org/10.1093/annonc/mdt531 (2014).

13. Vorherr, H. Fibrocystic breast disease: pathophysiology, pathomorphology, clinical picture, and management. American journal of obstetrics and gynecology 154, 161–179 (1986).

14. Basdevant, A., Raison, J., De Lignieres, B. & Guy-Grand, B. [Metabolism of sex hormones and adipose tissue], Journal de gynecologie, obstetrique et biologie de la reproduction 15, 147–152 (1986).

15. Campbell, K. L. et al. Reduced-Calorie Dietary Weight Loss, Exercise, and Sex Hormones in Postmenopausal Women: Randomized Controlled Trial, Journal of Clinical Oncology 30, 2314–2326, https://doi.org/10.1200/jco.2011.37.9792 (2012).

16. Pastides, H., Najjar, M. A. & Kelsey, J. L. Estrogen replacement therapy and fibrocystic breast disease. American journal of preventive medicine 3, 282–286 (1987).

17. Peters, F., Schuth, W., Scheurich, B. & Breckwoldt, M. Serum prolactin levels in patients with fibrocystic breast disease. Obstet Gynecol 64, 381–385 (1984).

18. Freeman, M. E., Kanyicska, B., Lerant, A. & Nagy, G. Prolactin: structure, function, and regulation of secretion. Physiological reviews 80, 1523–1631, https://doi.org/10.1152/physrev.2000.80.4.1523 (2000).

19. Gill, S., Peston, D., Vonderhaar, B. & Shousha, S. Expression of prolactin receptors in normal, benign, and malignant breast tissue: an immunohistological study. Journal of Clinical Pathology 54, 956–960 (2001).

20. Naliato, E. C. et al. Body fat in men with prolactinoma. Journal of endocrinological investigation 31, 985–990, https://doi.org/10.1007/hb03345636 (2008).

21. Kok, P., Roelfsema, F., Frolich, M., Meinders, A. E. & Pijl, H. Prolactin release is enhanced in proportion to excess visceral fat in obese women. J Clin Endocrinol Metab 89, 4445–4449, https://doi.org/10.1210/jc.2003-032184 (2004).

22. Ronco, A. L. et al. A case-control study on fat-to-muscle ratio and risk of breast cancer. Nutrition and cancer 61, 466–474, https://doi.org/10.1080/01635580902725995 (2009).

23. Rooney, M. & Wald, A. Interventions for the management of weight and body composition changes in women with breast cancer. Clinical journal of oncology nursing 11, 41–52, https://doi.org/10.1188/07.cjono.41-52 (2007).

24. Levine, B., Kalman, J., Mayer, L., Fillit, H. M. & Packer, M. Elevated circulating levels of tumor necrosis factor in severe chronic heart failure. The New England journal of medicine 332, 236–241, https://doi.org/10.1056/nejm199907263230405 (1990).

25. Horwich, T. B. & Fonarow, G. C. Reverse epidemiology beyond dialysis patients: chronic heart failure, geriatrics, rheumatoid arthritis, COPD, and AIDS. Seminars in dialysis 20, 549–553, https://doi.org/10.1111/j.1525-139X.2007.00346.x (2007).

26. Angiles, J. M., Busquets, S., Felipe, A. & Lopez-Soriano, F. I. Molecular mechanisms involved in muscle wasting in cancer and ageing: cachexia versus sarcopenia. The international journal of biochemistry & cell biology 37, 1084–1104, https://doi.org/10.1016/j.biocel.2004.10.003 (2005).

27. Villaseñor, A. et al. Prevalence and prognostic effect of sarcopenia in breast cancer survivors: the HEAL Study. Journal of cancer survivorships research and practice 6, 398–406, https://doi.org/10.1007/s11766-012-0234-x (2012).

28. Hou, M. F. et al. Comparison of breast mammography, sonography and physical examination for screening women at high risk of breast cancer in taiwan. Ultrasound in medicine & biology 28, 415–420 (2002).

29. Lehman, C. D. et al. Accuracy and value of breast ultrasound for primary imaging evaluation of symptomatic women 30–39 years of age. AJR. American journal of roentgenology 199, 1169–1177, https://doi.org/10.2214/ajr.12.8842 (2012).

30. Shetty, M. K. & Shah, Y. P. Sonographic findings in focal fibrocystic changes of the breast. Ultrasound quarterly 18, 35–40 (2002).

Acknowledgements

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Author Contributions

Yuan-Yuei Chen contributed to the design of the study, was responsible for the management and retrieval of data, contributed to initial data analysis and interpretation, drafted the initial manuscript. Yuan-Yuei Chen, Wen-Hui Fang, Chung-Ching Wang, Tung-Wei Kao, Yaw-Wen Chang, Hui-Fang Wu, Yuan-Yuei Chen contributed to the design of the study, was responsible for the management and retrieval of data, contributed to initial data analysis and interpretation, drafted the initial manuscript. Shetty, M. K. & Shah, Y. P. Sonographic findings in focal fibrocystic changes of the breast. Ultrasound quarterly 18, 35–40 (2002).

Additional Information

Competing Interests: The authors declare no competing interests.

Publisher’s note: Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.
Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/.

© The Author(s) 2018