Supplementary Screening Sonography in Mammographically Dense Breast: Pros and Cons

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Sonography is an attractive supplement to mammography in breast cancer screening because it is relatively inexpensive, requires no contrast-medium injection, is well tolerated by patients, and is widely available for equipment as compared with MRI. Sonography has been especially valuable for women with mammographically dense breast because it has consistently been able to detect a substantial number of cancers at an early stage. Despite these findings, breast sonography has known limitations as a screening tool; operator-dependence, the shortage of skilled operators, the inability to detect microcalcifications, and substantially higher false-positive rates than mammography. Further study of screening sonography is still ongoing and is expected to help establish the role of screening sonography.

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Screening is the periodic examination of a population to detect previously unrecognized disease. The concept that early detection of disease will reduce mortality is the mainstay of screening. As for breast cancer screening, mammography has been used as a primary imaging test. The benefit of the early detection of breast cancer has been shown in randomized controlled trials of mammography conducted during the past 40 years with a 22% reduction in breast cancer mortality for women aged 50–69 years who undergo screening (95% confidence interval, 13–30%) (1). Evaluations of population screening programs in practice have similarly demonstrated a benefit in women of this age group (2, 3).

Despite the proven benefits of mammography, results have been less promising for women with dense breast tissue (4). A dense breast parenchyma may mask some noncalcified, nondistorted tumors having X-ray attenuation similar to fibroglandular tissue (5), which increases the difficulty of detecting breast cancer. Mammographic sensitivity was reported to be as low as 30% to 48% in extremely dense parenchyma and dense breast itself was found to be a major determinant of interval cancer (6–8). In addition, dense breast tissue may mimic breast cancer on mammography, which increases recall rates, reduces specificity, and compromises the benefit of screening in women with dense breasts (9). In order to improve sensitivity and efficacy of screening mammography, supplemental screening with sonography has been proposed in women with mammographically dense breasts and has been evaluated in several studies since the 1980s (10, 11).

This article will discuss the pros and cons of screening sonography for breast cancer in mammographically dense breast.

Studies for Screening Sonography

The potential use of sonography for breast cancer screening was first evaluated in the 1980s. Until the early 1990's, however, the studies found that sonography was not useful for screening because of inadequate detection of smaller cancers and excessive false-positive biopsy rates (11). With advances in imaging equipment and techniques of sonography, in 1995, Gordon and Goldenberg (12) first reported the ability of sonography to depict nonpalpable, mammographically occult solid masses, with 3% of these masses being cancers (prevalence, 0.3%). Since that time, investigators have reanalyzed the use of screening sonography in populations of women with dense breasts, which are summarized in Table 1 (10).

The studies consistently showed that in women with mammographically dense breast, sonography was able to detect a substantial number of cancers, with supplemental cancer detection of 0.3–0.5% by sonography alone. In one study including women with fatty breasts (13), 11 of 16 cancers diagnosed at sonography were detected in Breast Imaging Reporting and Data System (BI-RADS) density three and four breast tissue and the remaining five in BI-RADS density one and two breast tissue. Moreover, the data indicated that most breast cancer detected at screening sonography and previously not detected was at an early stage (Table 1). In the study by Kaplan (14), all six cancers were stage 0 or 1 and four of them were smaller than 1 cm in size. Corsetti et al. (15) reported that the proportion of early-stage cancer was significantly higher in the sonography-only detected (65%) than the mammography detected cancers (36%, $p = 0.001$). It is well established from randomized controlled trials of mammographic screening that earlier detection of cancer results in a decrease in mortality which parallels the reduction in size distribution of cancers depicted and closely parallels the reduction in rates of node-positive breast cancer (1).

Pros

As mentioned before, breast density is one of the factors that points out false-negative findings in mammography. Furthermore, mammographically dense breast tissue has been identified as an independent marker strongly associated with breast cancer risk and in particular with a higher risk of interval cancer (16). Supplemental screening imaging such as sonography and MRI can be used to detect those mammographically occult cancers in dense breast. Compared with MRI, sonography is relatively inexpensive, requires no contrast, is well tolerated by patients, and is widely available for equipment, which is attractive as a supplement to mammography. Even more, sonographically guided biopsy of lesions is fast and easy to readily perform (4).

The benefit of detection with supplemental sonography in mammographically occult cancers can increase with increasing grades of breast density (10, 13, 17). For the sonography of dense breast, most breast cancers are relatively hypoechoic within a background of hyperechoic

Table 1. Results with Screening Breast Sonography

Study	Breast Density[a]	No. of Exams	No. of Bx (%)	No. of Cancers (% of Bx, % of All Participants)	Cancer Histology		N0 Stage (%)	Mean Tumor Size (mm)
					Invasive (%)	Noninvasive (%)		
Buchberger et al., 2000 (31)	2–4	8103[b]	362 (5)	32 (9, 0.4)	ND[g]	ND[g]	ND	ND[g]
Kaplan, 2001 (14)	3–4	1862	51 (3)	6 (12, 0.3)	5 (83)	1 (17)	6 (100)	9.0
Kolb et al., 2002 (8)	2–4	12,193[c]	320 (3)	33 (10, 0.3)	ND[h]	ND[h]	ND	ND[h]
Crystal et al., 2003 (32)	2–4	1517[d]	38 (3)	7 (18, 0.5)	7 (100)	0 (0)	6 (86)	9.6
Leconte et al., 2003 (13)	1–4	4236[e]	ND	16 (ND, 0.4)	14 (88)	2 (13)	ND	10.9
Corsetti et al., 2008 (15)	3–4	9157	449 (5)	37 (8, 0.4)	36 (97)	1 (3)	32 (86)	ND
Berg et al., 2008 (19)	2–4	2637[e, f]	ND	12 (ND, 0.5)	11 (92)	1 (8)	8 (89[i])	12.6

Note.— a = Density of breast parenchyma on mammogram according to gradation of American College of Radiology BI-RADS protocol on scale of 1–4: type 1, breast is almost entirely fat; type 2, there are scattered fibroglandular densities; type 3, breast tissue is heterogeneously dense; and type 4, breast tissue is extremely dense breast. b = Not included are another 867 examinations performed in women with abnormal mammographic or physical finding. c = Not included are another 1354 examinations performed in women with abnormal mammographic or physical finding. d = 318 women at high risk of breast cancer were included, e = Women with abnormal mammographic findings were included. f = All women were at high risk of breast cancer. g = In published series (31), 35 invasive and 5 noninvasive cancers with mean size of 9.1 mm were detected with sonography in women including symptomatic group. h = In published series (8), 36 invasive and 1 noninvasive cancers with mean size of 9.9 mm were detected with sonography in women including group with abnormal mammographic or physical findings. i = 8 of 9 participants with staging
Bx: biopsy, ND: not determined

fibroglandular tissue, which would make lesions more conspicuous and detectable. In contrast, about one-third of breast cancers are only mildly hypoechoic with respect to fat, and these very subtle, mildly hypoechoic or isoechoic lesions are more likely to be indistinguishable from surrounding fat in fatty breast (18).

In the studies of screening sonography in women with mammographically dense breasts, three to four breast cancers per 1000 women were detected by sonography only, and generally at an early stage (Table 1). This suggests that sonography as an adjunct screening test may provide further benefit in screening women with dense breast tissue. However, most studies were performed at single center and sonographic interpretations might be biased because readings were not truly blinded to mammographic findings and in many cases, performed sonography only when the mammogram was negative (17). To address those limitations, a prospective multicenter trial of screening sonography for women with intermediate and high breast cancer risk (American College of Radiology Imaging Network [ACRIN] protocol 6666) (19) was performed. The sequence of performing mammography and sonography was randomized to help control the biases of recruiting women with vague mammographic abnormalities, and examinations were performed by radiologists who were masked to results of the other examination. As a result, sonography was associated with a 55% increase in diagnosing breast cancer compared with mammography alone. Adding a single screening sonography to mammography yielded an additional 4.2 cancers per 1000 high-risk women. The study provided evidence for the importance of supplemental breast sonography screening. Furthermore, these results were consistent and generalizable across 21 international centers, so that standardized scanning and interpretive criteria in this trial proved to be practicable for independent performance and interpretation (16).

Cons

Although the addition of a single screening sonography to mammography increased the diagnostic yield, it also substantially increased the number of false positives. The positive predictive value for lesions subjected to biopsy on the basis of screening sonography findings ranged from 8% to 18% (mean, 9%) (Table 1). Compared with the positive predictive value of 25% to 40% recommended for lesions undergoing biopsy on the basis of screening mammographic findings, screening sonography may be expected to result in 2.5 to 4.0 times as many false-positive biopsy findings per cancer detected (11). Although it is one of the advantages of sonography that sonographically guided biopsy is relatively simple and less invasive, minimizing unnecessary patient anxiety and costs is a critical goal of any new screening procedure (17). In the ACRIN protocol 6666 trial, the false-positive rates for mammography plus sonography (10%) and sonography alone (8%) were higher than that of mammography alone (4%), even if the radiologist investigators in this trial were all specialists in breast imaging who met experience requirements and completed qualification tasks in sonography (19, 20).

As for cancer characteristics, the vast majority of cancers seen only on sonography were invasive (94%) because ductal carcinoma in situ (DCIS) is difficult to see on sonography (Table 1). Tabar et al. (21) found that microcalcifications were the predominant mammographic feature in 85% of cases of high-grade DCIS and 69% of cases of intermediate- and low-grade DCIS. The interaction of ultrasound with normal breast tissue produces tiny bright echoes known as speckle, which simulate faint microcalcifications and make detection of true microcalcifications difficult (22). By projecting ultrasound beams from several angles, compound imaging will diminish speckle, but also reduces resolution (11). In contrast, invasive cancers which often present as hypoechoic masses on sonography, would be more conspicuous and detectable within a background of dense fibroglandular tissue (23). However, it is uncertain whether the detection of DCIS is required or whether the detection of node-negative invasive breast cancer is sufficient for a screening test (19).

Breast sonography is limited by operator dependence. The detection of an abnormality at sonography is completely dependent on the perception and skill of the person performing the procedure (24). Unlike most other radiologic examinations, a lesion not detected while performing breast sonography will generally not be documented; and additionally, having representative normal images is not proof that a mass was not present (25). This is a limitation of ultrasound in general (24). Given that sonography is operator-dependent, intra- or interoperator variability is to be expected in screening sonography. Although Berg et al. (25) found substantial reliability for reporting lesion size, location, and key features, as was moderate agreement for lesion management with whole-breast sonography, participating examiners were physicians specialized and highly skilled in breast sonography and they performed sonography using a standardized scanning protocol and interpretive criteria. Conversely, without the implementation of a standardized technique and interpretation, as well as training and qualification for screening sonography, the result in general

practice could vary from the aforementioned study. Difficulty with reproducibility potentially limits the ability to accurately monitor the sonography-only masses that are thought to probably be benign and suitable for surveillance with follow-up examinations (24).

Screening sonography is so time-consuming and would require a much larger number of qualified breast radiologists than currently available. In the ACRIN protocol 6666 trial (19), a breast screening sonography takes an average of 19 minutes of physician time. In comparison, breast radiologists will complete less than three screening sonographic studies per hour. However, a breast radiologist, if involved in batch reading of screening mammograms, will read about 50 studies per hour (26). Moreover, the time of 19 minutes does not include comparison to prior studies, discussion of results with patients, nor the creation of a final report (19). At this time, however, there is insufficient evidence to address the efficacy of technologist-performed screening sonography (27). Furthermore, many incidental lesions will be detected during screening sonography which require a biopsy or follow-up. Whether the additional cost of screening with sonography will be cost-effective should be determined (28).

Further Researches

To overcome the lack of uniformity or reproducibility and the shortage of qualified personnel limiting the wide implementation of screening sonography, automated whole breast sonography may be helpful. In a study of automated whole breast sonography added to mammography in asymptomatic women with dense breasts and/or at an elevated risk of breast cancer (29), adding automated whole breast sonography to mammography yielded an additional 3.6 cancers per 1000. This finding is consistent to supplemental yield findings of earlier studies using handheld sonography (2.7 to 4.6 per 1000), and moreover, 87% of cancer detections added by automated whole breast sonography were found in 68% of studies in women with dense breasts. However, clinical validation by further studies is needed to be implemented in breast cancer screening.

In general, the rate of cancers detected in patients screened for the first time (prevalent cancers) should be much higher than in a population that has been screened previously (incidental cancers). Thus, knowledge of the proportion of initial screening examinations to follow-up screening examinations can be extremely useful in interpreting the results (30). Although Kolb et al. (8) performed multiple rounds of screening sonography, they did not distinguish results from each round. The other series to date reported on a single prevalence screen; an estimate of the yield from annual screening sonography is not available. Compared with mammographic screening, the cancer detection rate of sonographic screening (2.7–4.6/1000 exams) was lower than would be expected from a mammographic prevalence screen (6–10/1000 first-time exams), but was comparable to a mammographic incidence screen (2–4/1000 follow-up exams). The reason for similar results of screening sonography to mammographic incidence screening could be attributed to the fact that many women in these studies probably had several previous mammographic screenings but no previous sonographic screening. Moreover, factors favoring sonographic detection are different from those favoring mammography detection (11). The data on incident screens from subsequent rounds in the ACRIN protocol 6666 trial will be forthcoming and will be important for determining stage distribution of breast cancers in subsequent rounds of screening with mammography plus sonography in this study (1, 27).

In conclusion, although mammography remains the mainstay of breast cancer screening, screening sonography in women with mammographically dense breast has been reported consistently to detect a substantial number of sonography-only cancers at an early stage. However, further study is needed to validate and implement the screening sonography in clinical practice, which is ongoing. Radiologists need to be familiar with the pros and cons of screening sonography and also be able to frame a proper concept of sonography for breast cancer screening.

References

1. Berg WA. Beyond standard mammographic screening: mammography at age extremes, ultrasound, and MR imaging. *Radiol Clin North Am* 2007;45:895-906
2. Smith RA, Saslow D, Sawyer KA, Burke W, Costanza ME, Evans WP 3rd, et al. American Cancer Society guidelines for breast cancer screening: update 2003. *CA Cancer J Clin* 2003;53:141-169
3. Houssami N, Lord SJ, Ciatto S. Breast cancer screening: emerging role of new imaging techniques as adjuncts to mammography. *Med J Aust* 2009;190:493-497
4. Berg WA. Rationale for a trial of screening breast ultrasound: American College of Radiology Imaging Network (ACRIN) 6666. *AJR Am J Roentgenol* 2003;180:1225-1228
5. Kolb TM, Lichy J, Newhouse JH. Occult cancer in women with dense breasts: detection with screening US--diagnostic yield and tumor characteristics. *Radiology* 1998;207:191-199
6. Ciatto S, Visioli C, Paci E, Zappa M. Breast density as a determinant of interval cancer at mammographic screening. *Br J Cancer* 2004;90:393-396
7. Mandelson MT, Oestreicher N, Porter PL, White D, Finder CA, Taplin SH, et al. Breast density as a predictor of mammographic detection: comparison of interval- and screen-detected cancers. *J*

Natl Cancer Inst 2000;92:1081-1087
8. Kolb TM, Lichy J, Newhouse JH. Comparison of the performance of screening mammography, physical examination, and breast US and evaluation of factors that influence them: an analysis of 27,825 patient evaluations. *Radiology* 2002;225:165-175
9. Carney PA, Miglioretti DL, Yankaskas BC, Kerlikowske K, Rosenberg R, Rutter CM, et al. Individual and combined effects of age, breast density, and hormone replacement therapy use on the accuracy of screening mammography. *Ann Intern Med* 2003;138:168-175
10. Kolb TM. *Breast US for screening diagnosing, and staging breast cancer: issues and controversies*. In: Karellas A, ed. *RSNA Categorical course in diagnostic radiology physics: advances in breast imaging-physics, technology, and clinical applications*. Oakbrook, IL: Radiological Society of North America, 2004:247-257
11. Feig SA. *Current status of screening US*. In: Feig SA, ed. *2005 Syllabus: categorical course in diagnostic radiology-breast imaging*. Oak Brook, IL: Radiological Society of North America, 2005:143-154
12. Gordon PB, Goldenberg SL. Malignant breast masses detected only by ultrasound. A retrospective review. *Cancer* 1995;76:626-630
13. Leconte I, Feger C, Galant C, Berlière M, Berg BV, D'Hoore W, et al. Mammography and subsequent whole-breast sonography of nonpalpable breast cancers: the importance of radiologic breast density. *AJR Am J Roentgenol* 2003;180:1675-1679
14. Kaplan SS. Clinical utility of bilateral whole-breast US in the evaluation of women with dense breast tissue. *Radiology* 2001;221:641-649
15. Corsetti V, Houssami N, Ferrari A, Ghirardi M, Bellarosa S, Angelini O, et al. Breast screening with ultrasound in women with mammography-negative dense breasts: evidence on incremental cancer detection and false positives, and associated cost. *Eur J Cancer* 2008;44:539-544
16. Nothacker M, Duda V, Hahn M, Warm M, Degenhardt F, Madjar H, et al. Early detection of breast cancer: benefits and risks of supplemental breast ultrasound in asymptomatic women with mammographically dense breast tissue. A systematic review. *BMC Cancer* 2009;9:335
17. Berg WA. Supplemental screening sonography in dense breasts. *Radiol Clin North Am* 2004;42:845-851
18. Stavros AT. *Breast anatomy: the basis for understanding sonography*. In: McAllister L, Donnellan K, Martin SP, Rothschild R, eds. *Breast ultrasound*. Philadelphia, PA: Lippincott Williams & Wilkins, 2004:56-108
19. Berg WA, Blume JD, Cormack JB, Mendelson EB, Lehrer D, Böhm-Vélez M, et al. Combined screening with ultrasound and mammography vs mammography alone in women at elevated risk of breast cancer. *JAMA* 2008;299:2151-2163
20. Bevers TB. Ultrasound for the screening of breast cancer. *Curr Oncol Rep* 2008;10:527-528
21. Tabar L, Gad A, Parsons WC, Neeland DB. *Mammographic appearances of in situ carcinomas.* In: Silverstein MJ, Recht A, Lagios MD, eds. *Ductal carcinoma in situ of the breast,* 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2002:87-104
22. Merritt CR. Future directions in breast ultrasonography. *Semin Breast Dis* 1999;2:89-96
23. Soo MS, Baker JA, Rosen EL. Sonographic detection and sonographically guided biopsy of breast microcalcifications. *AJR Am J Roentgenol* 2003;180:941-948
24. Gordon PB. Ultrasound for breast cancer screening and staging. *Radiol Clin North Am* 2002;40:431-441
25. Berg WA, Blume JD, Cormack JB, Mendelson EB. Operator dependence of physician-performed whole-breast US: lesion detection and characterization. *Radiology* 2006;241:355-365
26. Kuhl CK. The "coming of age" of nonmammographic screening for breast cancer. *JAMA* 2008;299:2203-2205
27. Berg WA. Tailored supplemental screening for breast cancer: what now and what next? *AJR Am J Roentgenol* 2009;192:390-399
28. Philpotts LE, Smith RA. Screening for breast cancer. *Semin Roentgenol* 2003;38:19-33
29. Kelly KM, Dean J, Comulada WS, Lee SJ. Breast cancer detection using automated whole breast ultrasound and mammography in radiographically dense breasts. *Eur Radiol* 2010;20:734-742
30. Bassett LW, Jackson VP, Fu KL, Fu YS. *The medical audit*. In: Ross A, Pontee E, eds. *Diagnosis of diseases of the breast,* 2nd ed. Philadelphia, PA: Elsevier Saunders, 2005:135-148
31. Buchberger W, Niehoff A, Obrist P, DeKoekkoek-Doll P, Dünser M. Clinically and mammographically occult breast lesions: detection and classification with high-resolution sonography. *Semin Ultrasound CT MR* 2000;21:325-336
32. Crystal P, Strano SD, Shcharynski S, Koretz MJ. Using sonography to screen women with mammographically dense breasts. *AJR Am J Roentgenol* 2003;181:177-182