Original Investigation

The Addition of Automated Breast Ultrasound to Mammography in Breast Cancer Screening Decreases Stage at Diagnosis

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Rationale and Objectives: This study aimed to determine the best screening strategy using automated whole-breast ultrasound and mammography in women with increased breast density or an elevated risk of breast cancer.

Materials and Methods: After an institutional review board waiver was obtained, a retrospective review of 122 cancer cases diagnosed in 3435 women with increased breast density or an elevated risk of breast cancer, screened with mammography and supplemental automated whole-breast ultrasound, was performed. The imaging modality on which each cancer was seen was noted. Screening strategies were postulated.

For each screening strategy, rates of advanced cancer diagnosis, with 95% confidence limits, are calculated using the Clopper-Pearson method. Differences in outcomes were calculated using Cochrane Q test and McNemar test for paired observations. Results were expressed for all stages of cancer and for invasive cancers only.

Results: When all cancer stages are considered, mammographic screening reduces advanced cancers by 31% over no screening. Ultrasound-only screening results in a 32% reduction. The combination of mammographic and ultrasound screening reduces advanced cancers by 40% ($P < .05$).

Compared to mammographic screening, mammographic plus ultrasound screening reduces advanced-stage cancers by 5.7% ($P = 0.03$) for all stages and 10.8% ($P = 0.02$) for invasive cancers.

Conclusions: For women with increased breast density or who are at high risk of developing breast cancer, a combination of screening mammography and whole-breast automated ultrasound is superior to mammographic screening. Screening ultrasound alone is also an effective screening strategy.

Key Words: Human; female; ultrasonography; mammary; breast density; breast neoplasms.

INTRODUCTION

Mammographic screening has been shown to improve subsequent breast cancer treatment outcomes. Several randomized studies have shown a mortality benefit when cancers are diagnosed through mammographic screening (1). Cancers diagnosed through screening are also less expensive to treat, even when modern treatment is used (2). Early-stage cancers can be treated with less invasive surgery and often minimal chemotherapy, resulting in decreased morbidity (3).

All the benefits of screening occur through a reduction of stage at diagnosis. Breast cancers detected by screening asymptomatic women are lower in stage when compared to cancers that are diagnosed only after they become symptomatic (3). Breast cancers can be missed on mammogram, resulting in the development of interval, symptomatic cancers. This often occurs in women with increased breast density or in women who are at high risk of developing breast cancer (4–6).

Automated whole-breast ultrasound (ABUS) can be used to image the breast and axilla. ABUS detects breast cancers that are not seen on mammogram in women who have dense breasts or at elevated risk (7–10). This improves breast cancer detection sensitivity (11).

The detection of breast cancers not seen on mammogram should lead to an overall decreased stage at diagnosis, because these cancers will not progress to form advanced cancers at diagnosis. To test this hypothesis, we reviewed the experience of a community-based, single-center, breast cancer clinic that uses ABUS as an adjunct to mammographic screening for women at increased risk, based on the 2009 Society of Breast Imaging recommendations (12).

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MATERIALS AND METHODS

An institutional review board waiver was obtained through Ethical and Independent Review Services Inc. (Independence, MO).

Screening and Supplemental Imaging

Beginning on April 21, 2011, women at a community-based breast cancer clinic were screened according to the 2009 Society of Breast Imaging recommendations for Screening with Breast Imaging (12). All women were stratified based on breast density and Tyrer-Cuzick–modeled risk (13). Women of average risk had a Tyrer-Cuzick risk of less than 15% and Breast Imaging Reporting and Data System (14) category A or B breast density. Moderate-risk clients had a Tyrer-Cuzick risk of between 15% and 20% or Breast Imaging Reporting and Data System C or D breast density. High-risk women included everyone with a Tyrer-Cuzick risk of 20% or greater.

Average-risk women received a recommendation for annual imaging with mammography alone and are not included in this analysis. Women of moderate risk were advised to undergo an annual screening mammogram and ABUS study. High-risk women were offered annual screening mammography and magnetic resonance imaging (MRI). Those who refused MRI were offered an annual ABUS study.

Screening mammogram studies were performed using a GE Senographe full-field digital imaging system (GE Healthcare Inc., Wauwatosa, WI). For each study, bilateral craniocaudad, mediolateral oblique, and exaggerated craniocaudad views were performed at the discretion of the technologist.

ABUS studies were performed using a Somo-V scanner (U-Systems, Inc., San Jose, CA) before June 2015 and with an Invenia (GE Healthcare Inc.) scanner thereafter. Each study included bilateral anteroposterior, medial, and upper-outer quadrant imaging volumes, with additional volumes as necessary to obtain complete coverage of the bilateral breasts and axillae.

Cancer Case Review

All cancer cases diagnosed in moderate- to high-risk women, between April 21, 2011 and August 31, 2016, were retrospectively reviewed. For each cancer case, data were extracted including stage at diagnosis, method of diagnosis, and age at diagnosis.

Symptomatic patients were defined as patients who presented initially for screening, but were found, during screening, to have a symptom that led to the diagnosis of their cancer. Each imaging modality on which the cancer could be seen before diagnosis was noted.

Classification of Cancer Diagnoses and Postulated Screening Strategies

The individual cancers were grouped by stage. For this project, early-stage cancers were defined as cancers with an American Joint Committee on Cancer, Seventh Edition stage (15) of 0 or 1, because mortality for these lesions is relatively low. Cancers of stage 2 or greater were considered advanced cancers.

From these data, screening strategies are postulated as shown in Table 1. The no screening strategy was developed using symptomatic cancers. For each strategy, rates of advanced cancers, as a proportion of the total diagnosed, were calculated. The rates of advanced cancers were expressed both as a proportion of all cancers and as a proportion of all invasive cancers. MRI-detected cancers were not included in this analysis.

TABLE 1. Postulated Screening Strategies

Strategy	Based On
No Screening	Symptomatic cancers
Mammogram (alone)	Mammogram-detected and symptomatic cancers
Ultrasound (alone)	Ultrasound-detected and symptomatic cancers
Mammogram and ultrasound	Mammogram or ultrasound detected, and symptomatic cancers

Statistical Considerations

Each strategy's rate of advanced-cancer diagnosis underwent 95% confidence interval determination by the Clopper-Pearson method for binomial, independent proportions (16).

Differences in advanced cancer rates were evaluated for all strategies in aggregate using Cochran Q-test. Then, the differences in rates of advanced-cancer diagnoses between the individual screening strategies are calculated using McNemar test for paired observations. Confidence intervals are then adjusted using Bonferroni correction for multiple comparisons. A two-tailed P value of less than .05 was considered significant for all statistical tests.

Screening yields for mammogram- and ultrasound-detected cancers are calculated as cancers diagnosed per 1000 asymptomatic women screened. Recall rates are calculated as the percent of screening studies that resulted in additional imaging, even if performed on the same day.

RESULTS

A total of 3435 unique women were screened with an average number of screening cycles of 2.3 per client. Most screening events included a mammogram, but 347 events consisted of ABUS imaging only because of refusal of mammographic imaging.

Cancers were diagnosed in 129 women, with a stage distribution as shown in Table 2. An example of cancer detected on ultrasound only is shown in Figures 1 and 2. Of the 129 cancers, seven were found on MRI without being seen on mammogram, and were excluded in their entirety from this analysis.