Ultrasonography alone for diagnosis of breast cancer in women under 40

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ABSTRACT

INTRODUCTION Recent guidelines suggest that ultrasonography should be used as the primary imaging modality in women under 40 years of age with mammography being offered if further imaging is required. The aim of this study was to assess the adequacy of ultrasonography and the utility of mammography in this patient group by reviewing the role these imaging techniques had in the diagnosis of breast cancer in our unit.

METHODS All breast cancers diagnosed in patients 39 years or younger from June 2009 to June 2011 were reviewed. This was a retrospective review of presentation, clinical findings, imaging modality (ultrasonography, mammography, magnetic resonance imaging [MRI]) and histology. Mammography was the primary imaging modality until May 2011 in women between 35 and 39 years of age. Both invasive and intraductal carcinoma were included in the study but lobular carcinoma in situ was excluded.

RESULTS A total of 2,495 patients were referred to the symptomatic breast clinic in this age group during the study period. Thirty women were identified with either invasive cancer ($n=27$) or ductal carcinoma in situ ($n=3$). Twenty-eight patients underwent mammography, graded as uncertain, suspicious or malignant in the majority. Malignancy was missed in one patient. All 30 patients underwent ultrasonography, reported as uncertain, suspicious or malignant, an indication for diagnostic core biopsy. Ultrasonography alone did not miss any cancers but did fail to detect multifocal disease in one patient.

CONCLUSIONS In this study group, ultrasonography was reliable as the primary imaging modality for women under 40, identifying all cancers in this cohort. Mammography and/or MRI remain essential adjuncts to accurately determine multifocality and/or the extent of disease.

KEYWORDS

Primary imaging – Ultrasonography – Mammography – Women under 40 years

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Guidelines published in 2010 suggest that ultrasonography should be adopted as the primary imaging modality in patients below the age of 40 years presenting with clinically benign or uncertain breast lesions, mammography being offered if further imaging is required.¹ Caveats in the guidelines that support the use of mammography include clinically suspicious lesions, patients aged 35–39 years with normal ultrasonography and a clinically indeterminate lesion, and the provision of additional diagnostic information for indeterminate (U3) lesions. However, inferior performance of mammography compared with ultrasonography in this generally symptomatic group of patients has been reported.^{2–5}

Ultrasonography has greater sensitivity and specificity than mammography in women under 35 years of age, and is the imaging investigation of choice in this patient group.⁶ Nevertheless, numerous studies have confirmed this to also be the case in women up to 40–45 years of age.^{2,4,5} Improved

technology including high frequency ultrasonography probes has resulted in sensitivities of up to 100% when used in this age group⁴ and has demonstrated that ultrasonography is able to detect occult malignancy in the dense breast tissue inherent in younger women.^{7–9} In contrast, high recall rates, high rates of additional imaging and low cancer detection rates are associated with mammography in this group of women.¹⁰ This study aimed to assess the adequacy of ultrasonography and the role of mammography in patients under 40 years of age by reviewing the diagnostic accuracy of these imaging modalities in this age group in our unit.

Methods

The hospital Somerset Cancer Register was used to retrieve details on eligible patients and information required for this retrospective study. A total of 2,495 patients under 40 years

of age were referred to our breast department at University Hospital of North Staffordshire between 1 June 2009 and 30 June 2011, and 1,592 mammography and 2,854 ultrasonography scans were performed on these patients.

All diagnoses were confirmed by reviewing the histopathology reports, and medical records were reviewed to verify eligibility and confirm demographic/presentation details. Cancer cases included all types of invasive carcinoma and ductal carcinoma in situ; lobular carcinoma in situ cases were excluded. All patients with imaging features that were indeterminate (R3) or suspicious of malignancy (R4) but with subsequent benign pathology on core biopsy or surgery were excluded from the study group.

All imaging was performed as part of the triple assessment process. Clinical breast examination, performed by a breast surgeon, was undertaken in the majority of patients before imaging. However, in 2010 the 'one-stop' symptomatic clinic was reconfigured and became radiology-led. The imaging report is available to the clinician when the patient consults the breast surgeon later that day. All patients with indeterminate or suspicious findings have immediate ultrasonography guided biopsy of the breast lesion(s) and needle core biopsy of morphologically abnormal axillary lymph nodes.

Standard practice in the department was that all patients aged 35 and over underwent mammography, together with 'targeted' ultrasonography of the area of clinical concern. All patients under 35 had ultrasonography as the primary imaging modality.

Mammography was undertaken in all patients regardless of age if there were ultrasonic and/or clinically suspicious or malignant findings. It was also performed in patients with clinically indeterminate (P3) lesions if ultrasonography was normal. Following the publication of the national guidelines,¹ ultrasonography became the primary imaging modality in patients below the age of 40 from May 2011. Magnetic resonance imaging (MRI) was performed in patients with lobular cancer, multifocal disease or if there was a discrepancy between either imaging modalities or imaging and clinical findings.

During the study period, all breast ultrasonography was performed on either an HDI® 5000 imaging platform (Philips, Amsterdam, Netherlands) using a 5–12MHz linear array transducer or an Aplio™ MX (Toshiba, Crawley, UK) with a 7–18MHz probe. For any breast mass classified as suspicious (U4) or malignant (U5), local protocol dictated that whole breast and axillary ultrasonography was performed together with conventional two-view (craniocaudal and mediolateral oblique) mammography. Mammography was performed on a Mammomat® 3000 Nova (Siemens, Frimley, UK) prior to the transition to digital imaging. Thereafter, a full field digital Mammomat® Inspiration system (Siemens) was used.

Images were reported prior to histological diagnosis by two consultant radiologists and two consultant radiographers specialising in breast disease. All breast symptomatic imaging was single read/autonomously reported. Reports were summarised as an index of suspicion score, in line with the American College of Radiology's Breast Imaging Reporting and Data System (BI-RADS)/Royal College of Radiologists

Breast Group classification.¹¹ Sonography was interpreted according to the guidelines reported by Stavros *et al.*¹² Representative images of a benign (U2) ultrasonography lesion, an indeterminate (U3) lesion, a suspicious (U4) lesion and a malignant (U5) lesion are illustrated in Figures 1–4.

All biopsies were performed under ultrasonography guidance using a 14G tru-cut needle, mounted on a Pro-Mag™ Ultra (Angiotech, Vancouver, Canada) automated gun, with a standard 25mm throw, after infiltration with 3–5ml of 1% lignocaine, by a consultant radiologist or consultant radiographer specifically trained in breast intervention. One to three core samples were obtained, at the discretion of the operator. Ten patients also had preoperative ultrasonography guided needle core biopsy of morphologically abnormal axillary nodes.

All needle core biopsy results were reviewed at the multidisciplinary team meeting. The pathological analysis of core biopsies and excised lymph nodes followed the National Health Service Breast Screening Programme and the Royal College of Pathologists tissue pathways guidelines for non-operative diagnostic procedures and reporting.^{13,14} The diagnosis of multicentric disease was based on positive histology from core biopsies performed in different quadrants of the breast. The postoperative surgical specimen was regarded as the 'gold standard' for tumour size, grade, type and lymph node status.

The ethics committee was approached prior to the study and advised that as there was no change to practice, in that mammography would still be undertaken in addition to ultrasonography, formal ethics approval was not required.

Results

A total of 2,495 women under 40 years of age attended the symptomatic breast clinic between June 2009 and June 2011. Of these, 2,331 were referred for ultrasonography assessment, generating 2,854 ultrasonography examinations. In addition, 829 patients also underwent mammography, generating 1,592 mammograms. Of these patients, 328 (14.1%) were referred for diagnostic biopsy, resulting in 372 biopsies.

Following histological analysis, 30 patients were identified with either invasive ($n=27$) or in situ ($n=3$) disease. The rate of malignancy was therefore 9.1% in those patients undergoing diagnostic biopsy and 1.3% in those referred for imaging. The mean age was 36 years (range: 27.5–39.8 years) (Table 1). Among the 27 patients with invasive disease, 35 tumours were identified. The majority of these (91.4%) were ductal carcinomas of no special type. The median tumour size on histopathological assessment was 32.5mm (range: 10–120mm).

The majority of these 30 patients ($n=25$, 83.3%) presented with a breast lump. A further two patients (6.7%) presented with nipple distortion, and one patient (3.3%) each with axillary lump, axillary pain and breast lump, and advanced disease. Patient demographics, presentation and disease status are outlined in Table 1.

Ultrasonography identified all patients with malignant disease. In these 30 patients, ultrasonography identified 34 abnormalities on imaging: 5 (14.7%) graded as BI-RADS 3,

Figure 1 Local characterisation of a benign (U2) lesion. A well defined, solid, homogenous lesion (arrow) with posterior acoustic enhancement.

Figure 3 Local characterisation of a suspicious (U4) lesion. An irregular solid lesion infiltrating the breast parenchyma (arrow).

Figure 2 Local characterisation of an indeterminate (U3) lesion. A small solid lesion with indistinct borders (arrow).

Figure 4 Local characterisation of a malignant (U5) lesion. Irregular, spiculated solid mass (arrow) with associated posterior acoustic shadowing.

12 (35.3%) as BI-RADS 4 and 17 (50.0%) as BI-RADS 5. Of the five lesions graded as BI-RADS 3, two were proven to be fibroadenomas on definitive histopathology following core biopsy. However, both lesions occurred in the patients who also had malignant lesions.

Twenty-eight of the thirty patients with malignant breast disease also underwent mammography; one patient refused owing to pain and a further patient presented with advanced fungating cancer. A total of 32 lesions were identified: 1 (3.1%) graded as BI-RADS 2, 9 (28.1%) as BI-RADS 3, 8 (25.0%) as BI-RADS 4 and 14 (43.8%) as BI-RADS 5. The patient graded as BI-RADS 2 was proven subsequently

to have invasive breast cancer on histopathological assessment following core biopsy, performed owing to a BI-RADS 3 score on ultrasonography. Of the nine lesions graded as BI-RADS 3, one was proven to be a fibroadenoma on definitive histopathology following core biopsy.

Ultrasonography was more reliable than mammography in identifying likely malignant disease in patients who presented with a breast lump; 22 of the 25 patients (88%) were graded as BI-RADS 4 or 5 on ultrasonography compared with 16 of 24 (66.7%; one patient did not undergo mammography because of pain) on mammography ($p=0.0955$, Fisher's exact test).

Table 1 Patient and tumour characteristics	
Characteristics	n
Mean age (range) in years	36.0 (27.5–39.8)
Presenting symptom	
Breast lump	25 (83.3%)
Nipple distortion	2 (6.7%)
Axillary lump	1 (3.3%)
Axillary pain and breast lump	1 (3.3%)
Advanced disease	1 (3.3%)
Histology	
Invasive ductal carcinoma NST	32 (91.4%)
Medullary carcinoma	1 (2.9%)
Basaloid type	1 (2.9%)
Invasive lobular carcinoma	1 (2.9%)
Axillary lymph node status	
Grade 3 tumours	
Positive	12 (60.0%)
Negative	8 (40.0%)
Grade 2 tumours	
Positive	4 (57.1%)
Negative	3 (42.9%)
Oestrogen receptor status	
Positive	12 (46.2%)
Negative	14 (53.8%)
Mean Nottingham prognostic index	4.896
Breast density	
BI-RADS 1	8 (28.6%)
BI-RADS 2	8 (28.6%)
BI-RADS 3	6 (21.4%)
BI-RADS 4	6 (21.4%)

NST = no special type; BI-RADS = Breast Imaging Reporting and Data System

MRI was performed on 12 patients, mainly owing to a discrepancy in imaging findings, or imaging and clinical findings, or the presence of multifocal disease. In our study population, MRI was more accurate than ultrasonography or mammography in detecting multifocal disease and in measuring the size of the tumour. Although MRI has been reported to confer a high false positive rate,^{15,16} this was not the case in our study.

Three of the 30 patients identified with malignant disease had had investigations in our unit previously but all were at least one year before. One of these patients had had ultrasonography of the same breast one year prior to diagnosis. However, the area of clinical concern was in a different quadrant of the breast to that with which the patient presented subsequently with malignant disease. A further patient had been investigated with mammography, ultrasonography and MRI three years previously, secondary to family history concerns. The third patient had had an ultrasonography of the same breast six years previously for a breast abscess. Consequently, none of the patients had had disease missed by ultrasonography examination before the study period presentation.

Discussion

This study demonstrates that ultrasonography is highly accurate at identifying suspicious lesions in women under 40 years of age with symptomatic breast disease. Several studies have shown that ultrasonography has greater specificity and sensitivity than mammography in women up to 40–45 years of age.^{2,4,5} Improved technology including high frequency probes has resulted in sensitivities of up to 100% when used in these women⁴ and has demonstrated that ultrasonography is able to detect occult malignancy in the dense breast tissue inherent in this age group.^{7–9} The differentiation between cystic and solid masses has improved, and the characterisation of these solid masses as benign or suggestive of malignancy can be established reliably.¹²

Patients in this age group are either symptomatic or attend clinic owing to a positive family history. Most of the symptomatic patients present with a breast lump or nodularity. In our study, 86.7% presented with a breast lump, which is similar to other reported series.^{10,17} These patients therefore undergo directed sonography. In this setting, ultrasonography has been shown to perform exceptionally well with sensitivities and specificities in excess of those for mammography in younger women. Indeed, in the age group of most contention (36–40 years), ultrasonography has been reported to have a sensitivity of 84.6% and a specificity of 91.9% compared with 69.2% and 83.3% respectively for mammography.² This is largely due to the fact that younger women have predominantly dense breast tissue, favouring the use of ultrasonography. Our study confirms the reliability of ultrasonography in this patient population and corroborates the ability of ultrasonography to detect mammographically occult cancer.

One of the concerns regarding the use of ultrasonography is the ability to discriminate accurately between benign and malignant lesions, and therefore avoid unnecessary biopsies. As mentioned above, improved technology has led to confidence in this categorisation¹² and such concerns appear unfounded. Sonography can accurately determine the likely benign nature of non-palpable breast lesions that are partially or completely obscured at mammography, with an extremely low false negative rate of just 0.2%.¹⁸ The negative predictive value of sonography for palpable non-calcified breast masses with probably benign morphology is high at 99.4% (with a false negative rate therefore of just 0.6%).¹⁹ This has led researchers to suggest that such lesions could be managed in a similar fashion to non-palpable BI-RADS 3 lesions, with short-term imaging follow-up as opposed to immediate biopsy.^{19,20}

The sensitivity of ultrasonography is not age dependent as with mammography. In 2010 researchers from the Breast Cancer Surveillance Consortium in the US presented data on the performance of screening and diagnostic mammography in 117,738 women younger than 40 years of age.¹⁰ The sensitivity of diagnostic mammography was cited as 85.7% although this was slightly lower in those aged 35–39 years at 82.5%. Sensitivity was higher in patients who presented with a lump than in those who presented with other symptoms (87.5% vs 71.5%).

In contrast to sensitivity, however, specificity was lower among women presenting with a lump (86.6% vs 93%).¹⁰ As one might expect, specificity was greatest in women with fatty breasts and decreased with increasing breast density. A positive predictive value of 14.6% was reported for all women under the age of 40 years, with an improved percentage of 18.6% for the subgroup aged 35–39 years. For those presenting with a lump, the positive predictive value was significantly better than for those without.

Accuracy of mammography in a diagnostic setting is likely to improve as technology has advanced over recent years, as has been the case with ultrasonography. Although there appears to be little difference in terms of diagnostic accuracy in older women, in those under 50 years and in women with dense breasts, digital mammography is more accurate than traditional film screen mammography in an asymptomatic population.²¹

Although ultrasonography was extremely reliable in our study at identifying malignancy in this patient population, it was less reliable at identifying multifocal disease. In this respect, MRI outperforms both ultrasonography and mammography. Preoperative MRI has been shown to demonstrate additional suspicious findings in the ipsilateral breast in nearly 50% of women screened, translating to histologically confirmed breast cancer in 40.5% of these patients (ie 20% of additional cancers detected in all women screened).²² This series demonstrated that the correlation between additional MRI findings and proven ipsilateral cancers was greatest in patients aged 39 years or younger. This may reflect the success of MRI in imaging dense breast tissue.^{23,24}

A limitation of our study is that we did not specifically follow those women who had a benign ultrasonography result and who may have been diagnosed later with a breast malignancy after the study period. Nevertheless, any discrepancy between clinical findings and imaging would have resulted in a needle core biopsy. The population of Stoke is relatively stable and as a result, any missed cancer diagnoses would likely have been discovered subsequently. Another weakness is that the study involved a clinically referred population and does not therefore address the accuracy of these techniques as screening modalities.

Conclusions

Accurate diagnosis of breast cancer in younger women is often challenging as a result of inherently dense breast tissue, shorter tumour doubling times and lack of routine screening to provide baseline imaging against which to compare any subsequent imaging. This small study suggests that ultrasonography is a sensitive and safe primary imaging modality in this population. However, mammography and/or MRI remain essential adjuncts, particularly in the identification of multifocal disease.

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