REVIEW

Clinical Utility of Proton Magnetic Resonance Spectroscopy in Characterizing Breast Lesions

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Proton magnetic resonance spectroscopy (^{1}H MRS) of the breast has been proposed as an adjunct to the magnetic resonance imaging (MRI) examination to improve the specificity of distinguishing malignant breast tumors from benign breast tumors. In this review, we carry out a pooled analysis of the clinical breast ^{1}H MRS studies undertaken to date to determine the factors that influence the diagnostic performance of this method. In total, five studies of breast ^{1}H MRS from four independent centers around the world have been published to date. Altogether, 153 tumors were examined, 100 of which were confirmed histologically to be malignant and 53 of which were benign. The lesions presenting a detectable composite choline signal in their corresponding ^{1}H MR spectra were diagnosed as malignant, whereas the lesions with no choline signal were diagnosed as benign. The sensitivity and specificity of breast ^{1}H MRS for detecting breast cancer were 83% (95% confidence interval [CI] = 73% to 89%) and 85% (95% CI = 71% to 93%), respectively, and both values could be as high as 92% after technical exclusions. In a subgroup of 20 young women, the sensitivity and the specificity of the method approached 100%. The factors limiting the sensitivity of the examination were mainly technical. The use of the composite choline signal as a marker for malignancy in breast ^{1}H MRS is a robust method with highly reliable interpretation, because it is based on the appearance of a single peak. The method is likely to provide even better results with technologic advances in breast MRS that lead to the improved detection of the composite choline signal. [J Natl Cancer Inst 2002;94: 1197–203]

Breast cancer is a disease of high prevalence among women in western and industrialized countries, with an incidence of about 180 000 new diagnoses each year in the United States alone *(1).* Since the late 1980s, the incidence of breast cancer has been relatively stable *(2).* The mortality rate from breast cancer, currently estimated at about 26 per 100 000 annually *(3),* has been stable since 1950, although mortality rates of various subgroups have changed *(4).* A successful treatment for this disease depends, in part, on early diagnosis. Thus, robust screening methods have been used, such as palpation, ultrasonography, and mammography. Magnetic resonance imaging (MRI) has been increasingly used as a secondary characterizing tool *(5).*

However, after establishing the existence of a lesion, it is critical to determine whether this lesion is benign or malignant. About 75% of the breast tumors detected by mammography and about 50% (a range of 37%–97% has been reported) of the enhancing lesions detected by contrast-enhanced MRI turn out to be benign upon histopathologic characterization *(5).* Sonographic classification of benign and malignant tumors is of a low specificity as well—about 30% *(6).* The high number of biopsy examinations that end up with a benign diagnosis indicates that the specificity of these methods in differentiating breast cancer from benign tumors, as they are commonly used, has been low. Recent advances in contrast-enhanced MRI methodology and interpretation have greatly improved the ability to differentiate malignant from benign breast tumors *(7),* suggesting the potential of MRI to become both highly sensitive and highly specific in breast cancer diagnosis *(5,8,9).* Recent advances in the methodology for reading mammograms and in Doppler sonography are expected to improve the sensitivity and specificity of these techniques as well *(10,11).*

The differentiation of malignant from benign breast lesions in contrast-enhanced MRI is determined by tumor morphology and the permeability of the tumor vasculature to the contrast agent. The addition of magnetic resonance spectroscopy (MRS) to the MRI examination permits noninvasive detection of tissue metabolism. Distinct alterations in metabolite content have been observed in breast cancers but not in benign lesions of the breast. These alterations include increased content of phosphomonoesters (predominantly phosphocholine and phosphoethanolamine) and phosphodiesters (predominantly glycerophosphocholine and glycerophosphoethanolamine) detected by ^{31}P MRS [*(12–15)* and references cited therein] and increased content of composite choline (the combined content of water-soluble choline metabolites such as choline, phosphocholine, glycerophosphocholine, betaine, and analogous compounds containing the ethanolamine head group and taurine) detected by ^{1}H MRS *(16–21).* The biochemical profile of normal breast tissue appears similar to that of benign tumors, with lower levels of phosphomonoesters and phosphodiesters and nondetectable levels of the composite choline signal *(20,22,23).* These findings *in vivo* have been confirmed by a multitude of studies in excised human breast tumors *(24–28)* and in cell culture *(29–31).* Despite the promising findings in ^{31}P MRS of tumors, the use of these methods for characterizing tumors *in vivo* has been hampered by the lower MR sensitivity for detecting ^{31}P signals. To achieve the same signal-to-noise ratio for metabolites detected by ^{1}H MRS, a ^{31}P MRS study requires a tumor that is about 10 times larger. The use of ^{31}P MRS requires special hardware that may not be available in all clinical 1.5-T scanners. In contrast to the ^{31}P MRS examination, the ^{1}H MRS examination can be easily integrated into a

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routine MRI examination with the addition of as little as 10 minutes to the overall scan time.

The ^{1}H MRS of the breast has been proposed as an adjunct to MRI examination to improve the specificity of distinguishing malignant from benign breast tumors. The purpose of this review was to perform a pooled analysis of the existing breast ^{1}H MRS studies and to determine the factors that influence the diagnostic performance of this method. To date, five studies of breast ^{1}H MRS examining the use of ^{1}H MRS to distinguish malignant and benign tumors have been performed by four different groups in four independent centers around the world. Presently, breast MRS studies are not routinely performed as part of a breast MRI examination, in part because, historically, MRS studies have been technically challenging.

The combined data set presented in this review permits an evaluation of the clinical diagnostic performance of this method. In spite of the different patient populations studied and the variation of acquisition parameters used in MRS, the statistical results of the pooled analysis are very encouraging. Automation of MRS studies has removed some of the technical challenges associated with this method.

Statistical Methods

An unordered exact contingency table test was used to test for the ability to pool sensitivity, specificity, and concordance data across studies. In addition, a logistic regression model was used to predict the probability of detecting the composite choline signal as a function of the largest dimension of the tumor for patients with malignant tumors. An ordered exact contingency table test was used to test for size effect of tumors grouped as less than 2.5 cm, 2.5–4.9 cm, and 5.0 cm or more. Ninety-five percent confidence intervals (95% CIs) were computed for overall sensitivity, specificity, and concordance with an exact binomial distribution calculation. Positive and negative predictive values were also computed by standard definitions. All statistical tests were two-sided.

Results

To date, six studies of *in vivo* breast ^{1}H MRS using the composite choline signal to detect breast cancer have been published. Five of these studies *(16–19,21)* (conducted by four different groups) tested the diagnostic performance of ^{1}H MRS for distinguishing benign from malignant lesions of the breast. The number of cancerous and benign tumors included in each study and the diagnostic results of these studies are summarized in Table 1. The sixth study *(22)* tested the capability of ^{1}H MRS to differentiate cancerous breast tissue from unaffected breast tissue. Data from the five studies that examined the use of ^{1}H MRS to distinguish benign and malignant lesions (Table 1) were confirmed separately for sensitivity ($P = .62$), specificity ($P = 1.00$), and concordance ($P = .79$); the results indicated that the data could be pooled into one dataset. In total, the five studies examined 153 lesions, of which 100 were malignant tumors and 53 were benign tumors (Table 1). The combined data set demonstrated a sensitivity of 83% (95% CI = 73% to 89%) and a specificity of 85% (95% CI = 71% to 93%) for the breast ^{1}H MRS examination (Table 1). Overall concordance (percent true-positive results plus percent true-negative results) was 84%. The positive predictive value of composite choline detection was 91%, and the negative predictive value was 73%.

To better understand the factors that influence the diagnostic performance of breast ^{1}H MRS, the data from different studies were compared by several criteria, including lesion size, lesion subtype, and patient age. Taking advantage of the relatively large number of patients in the pooled data, we were able to test whether tumor size and patient age influence the diagnostic performance of breast ^{1}H MRS.

Sensitivity of Breast ^{1}H MRS and Lesion Size

The sensitivity of breast ^{1}H MRS is defined as the percentage of malignant lesions diagnosed correctly; these are the true-positive cases—malignant lesions showing the composite choline signal. The studies of Cecil et al. *(16),* Yeung et al. *(19),* and Roebuck et al. *(18)* provided detailed information on the individual lesions examined, including the tumor's largest dimension. In these three studies, the largest dimension (average ± standard deviation) of the malignant lesions that showed a detectable choline signal (true-positive) was 2.7 ± 1.0, 5.1 ± 2.6, and 2.2 ± 1.0 cm, respectively, whereas that of the malignant lesions that did not show a choline signal (false-negative) was smaller (1.9 ± 0.3, 3.1 ± 0.9, and 1.6 ± 1.3 cm, respectively). The logistic regression model for the probability of choline detection in malignant tumors identified a statistically significant tumor size effect ($P = .046$), indicating that choline was more likely to be detected in larger malignant tumors than in smaller malignant tumors. This size dependence could be explained by detection thresholds related to the ability of the scanner and spectral acquisition method to detect smaller quantities of composite choline. In the studies of Kvistad et al. *(17)* and Jagannathan et al. *(21),* the individual size of the lesions that did or did not show

Table 1. Breast proton magnetic resonance spectroscopy (^{1}H MRS) studies and results*

Study	No. of malignant tumors	No. of benign tumors	Largest dimension, cm†	Sensitivity, %	Specificity, %	No. of true positives	No. of true negatives	No. of false negatives	No. of false positives
Cecil et al. *(16)*	23	15	2.6	83	87	19	13	4	2
Yeung et al. *(19)*	24	6	4.9	92	83	22	5	2	1
Roebuck et al. *(18)*	10	7	2.0	70	86	7	6	3	1
Kvistad et al. *(17)*	11	11	3.2	82	82	9	9	2	2
Jagannathan et al. *(21)*	32	14	—	81	86	26	12	6	2
Total	100‡	53		83	85	83	45	17	8

*— = data not given in detail.

†Mean largest dimension of malignant tumors. The data were reproduced from the above publications or calculated from data presented therein.

‡Malignant tumors (total = 100): 88 infiltrating and *in situ* ductal carcinoma, one *in situ* ductal carcinoma, three infiltrating and *in situ* lobular carcinoma, two poorly differentiated adenocarcinomas, one medullary carcinoma, one invasive mammary carcinoma, one adenoid cystic carcinoma, one mucinous carcinoma, one undifferentiated carcinoma, and one *in situ* intracystic papillary carcinoma.

the composite choline signal was not given in detail. In the study of Gribbestad et al. *(22),* all of the carcinomas that showed a choline signal (100% sensitivity) were 2 cm in diameter or larger.

To further characterize the dependence of breast ^{1}H MRS sensitivity on the lesion size, the data [in the studies of Cecil et al. *(16),* Yeung et al. *(19),* and Roebuck et al. *(18)*] were divided into three size groups (<2.5, 2.5–4.9, and ⩾5 cm). The sensitivity of the examination in these size-dependent subgroups had increased from 72% to 90% to 100%, respectively, in a statistically significant manner ($P = .025$, two-sided exact Kruskal–Wallis test).

Thus, the sensitivity of breast ^{1}H MRS is dependent on tumor size. This dependency appears to be based on the technical issues related to the detection of smaller quantities of composite choline.

Diagnostic Performance of Breast ^{1}H MRS in Younger Women

The differentiation between malignant and benign breast tumors in younger women (40 years of age and younger) is of special interest for two main reasons. First, the sensitivity of the mammographic examination in these patients is lower *(32–34),* which makes MRI/MRS a good candidate for imaging these women. Second, the ratio of the number of benign breast lesions compared with the number of breast carcinomas in this population may be slightly higher than in the entire population. Recently, a comparative study between MRI and mammography *(35)* demonstrated the higher sensitivity of MRI in younger women with a hereditary risk of breast cancer. However, as in the general population, the specificity of both the MRI and the mammography was low *(35).* These results indicate that there is a need for a diagnostic method that is both highly sensitive and highly specific in this population of young women.

Each study discussed in this review included a small number of patients who were 40 years of age or younger. Combining the results of these studies in retrospect provides valuable information about this particularly important patient population. The studies of Cecil et al. *(16),* Yeung et al. *(19),* and Roebuck et al. *(18)* included a total of 20 patients (11 patients with breast carcinoma and nine patients with benign lesions of the breast [excluding two patients with tubular adenomas, for reasons discussed below]). All of the malignant tumors in this population were diagnosed correctly with ^{1}H MRS (100% sensitivity, 95% CI = 73% to 100%), and eight of the nine benign lesions were diagnosed correctly as well (89% specificity, 95% CI = 57% to 100%). The ninth patient with a benign lesion was 20 years old, and the lesion was classified as a fibroadenoma by fine-needle aspiration (but the lesion was not excised). Choline was detected in this lesion when the size of the lesion increased, as documented on consecutive ultrasonographic scans. Her repeat MRS examination, performed a year later, was negative for choline, and the lesion was shown to be static in size *(19).* In this combined population of patients who were 40 years of age and younger, ^{1}H MRS of the breast had a sensitivity of 100% and a specificity of 89%–100% (depending on whether the ninth benign lesion described above is included or not, respectively). Thus, these results show a very promising role for breast ^{1}H MRS examination in differentiating malignant lesions from benign ones in younger women.

Factors That Limit the Sensitivity of Breast ^{1}H MRS

The sensitivity of breast ^{1}H MRS is determined by the percentage of true-positive cases (malignant lesions showing the composite choline signal) detected. The factors that limit the sensitivity of breast ^{1}H MRS may be determined by reviewing the false-negative cases (malignant lesions not showing the composite choline signal). False-negative cases have been reported in the studies of Cecil et al. *(16)* (four cases), Yeung et al. *(19)* (two cases), Kvistad et al. *(17)* (two cases), Jagannathan et al. *(21)* (six cases), and Roebuck et al. *(18)* (three cases) (Table 1).

The explanations for false-negative results varied but were mainly attributed to technical problems. In the study of Cecil et al. *(16),* it appeared that all of the four false-negative results were obtained when technical limitations arose: detection of one case of invasive mammary cancer was technically limited by a hardware failure for both MRI and MRS. The MRS examination for one patient with ductal carcinoma *in situ* occurred after an aspiration procedure. In reviewing the images of this patient in retrospect, a blinded MRI reader indicated that the region of interest demonstrated recent hemorrhage and was uncertain as to the diagnosis. Blood products can degrade the local field homogeneity, which is extremely important for successful MRS studies. Two cases of invasive ductal carcinoma were acquired with a small voxel size (1 cm^3, the volume of tissue from which the data were acquired) after a relatively long time in the scanner, potentially causing the patients to become restless. Movement on the part of a patient could lead to incorrect sampling of the lesion thereby including contributions from surrounding fatty breast tissue. This incorrect sampling may potentially mask the choline signal in these individuals. In the study of Yeung et al. *(19),* one of the two false-negatives was attributed to technical difficulties. Patient motion, indicated by MR image misregistration, appeared to lead to mislocalization of the ^{1}H MRS and, therefore, to a false diagnosis, because unaffected breast tissue does not contain a detectable level of composite choline. The other false-negative result was in the diagnosis of a rare type of carcinoma classified as medullary carcinoma, and no technical limitation was reported for this case. It is unclear whether the absence of choline observed is in any way related to the prognosis of this variant of ductal carcinoma. Medullary carcinoma has been associated with a better prognosis and survival than ductal carcinoma, although the underlying mechanism for these observations remains unclear *(19).* In the studies of Kvistad et al. *(17)* and Jagannathan et al. *(21),* two and six cases, respectively, of invasive carcinomas were falsely diagnosed as benign, but no further details were provided. In the study of Roebuck et al. *(18),* three malignant breast lesions (infiltrating and intraductal carcinoma, *in situ* and infiltrating ductal and lobular carcinoma, and infiltrating and lobular carcinoma) were falsely diagnosed as benign. In this work, technical limitations were not suggested as possible factors limiting the sensitivity of the ^{1}H MRS test. We, however, suggest that these lesions were most susceptible to patient motion, because for all studies listed in Table 1, the average size of the malignant tumors studied was the smallest and the voxel was the smallest. Consequently, it is possible that patient motion in these studies led to mislocalization of the spectra and recording of spectra from unaffected breast tissue that does not contain a detectable level of composite choline. Thus, the failure of breast ^{1}H MRS to detect elevated levels of choline in a limited number of confirmed cases of cancer appears to be predominantly caused by technical and signal-to-noise

limitations. The failure of ^{1}H MRS to detect the composite choline in the smaller malignant tumors in each study (described above) may also be a signal-to-noise limitation.

Limits of Breast ^{1}H MRS Specificity

The specificity of breast ^{1}H MRS is defined as the percentage of benign lesions diagnosed correctly. These are the true-negative cases: the benign lesions not showing the composite choline signal. The factors that limit the specificity of breast ^{1}H MRS may be determined by reviewing the false-positive cases, i.e., benign lesions showing the composite choline signal. False-positive cases have been reported in the studies of Cecil et al. *(16)* (two cases), Yeung et al. *(19)* (one case), Kvistad et al. *(17)* (two cases), Jagannathan et al. *(21)* (eight cases), and Roebuck et al. *(18)* (one case) (Table 1). In the study of Cecil et al. *(16),* two benign processes (one case of fibrocystic disease with extensive stromal changes and one case of tubular adenoma) were falsely diagnosed as malignant. In the study of Yeung et al. *(19),* one case of fibroadenoma was falsely diagnosed as malignant, discussed in detail above concerning the diagnostic performance of ^{1}H MRS in women who are 40 years of age and younger. The study of Kvistad et al. *(17)* included two false-positive diagnoses: one case of fibroadenoma and one case of fibrocystic disease. In the study of Jagannathan et al. *(21),* the subtype of the eight benign lesions in which the composite choline signal was detected was not given in detail. The study of Roebuck et al. *(18)* included one false-positive diagnosis of tubular adenoma. Thus in the studies with detailed subtype information on benign lesions, six of 39 benign tumors were diagnosed as malignant tumors and two of these six false-positives were tubular adenomas. Tubular adenomas are benign processes that are readily identifiable on MR images and on other breast imaging modalities by their distinctive architectural features *(36).* Because tubular adenomas are extremely rare, they can be excluded when evaluating the performance of ^{1}H MRS for diagnosing common benign breast lesions. The other four cases (two of fibroadenoma and two of fibrocystic disease) probably represent the actual limits of the specificity of breast ^{1}H MRS in correctly diagnosing common benign tumors.

Effects of Technical Difficulties and Inclusion of Tubular Adenomas in the Studies on the Sensitivity and Specificity of Breast ^{1}H MRS

The inclusion of the results of examinations in which there were technical problems will alter the calculation of the sensitivity and specificity for ^{1}H MRS. As mentioned above, technical limitations were the main cause for false-negative diagnoses. However, a fraction of false-positive cases was largely composed of tubular adenomas (two of six cases), which is extremely rare in general practice.

To assess the effects of technical difficulties and inclusion of tubular adenomas on the diagnostic performance of breast ^{1}H MRS, we analyzed the effects of removing these examinations from the pooled data set. We first omitted false-negative cases caused by technical failure (hardware failure, patient motion, and one examination performed in the presence of hemorrhage caused by fine-needle aspiration) and then omitted false-positive cases that were tubular adenomas. This analysis was performed on the retrospective data set of three studies [Cecil et al. *(16),* Yeung et al. *(19),* and Roebuck et al. *(18),* in which the false-positive and the false-negative diagnoses were reported in detail] and is summarized in Table 2. As expected because of these modifications, the sensitivity of breast ^{1}H MRS increased (92%) and the specificity increased (92%) (Tables 1 and 2). Thus, the sensitivity and specificity of breast ^{1}H MRS could be increased by optimizing the detection of the choline signal and identifying the lesion subtypes for which this diagnostic method is most beneficial.

Discussion

In this review, we have demonstrated the clinical utility of breast ^{1}H MRS to distinguish between malignant and benign breast lesions by use of the composite choline signal. Elevated levels of choline metabolites have been reported in many studies of excised human breast tumors *(24–28),* cultured human breast cancer cells *(29–31,37),* and animal models [*(38–40)* and references cited therein].

An investigation of the relationship between the malignant lesion size and the sensitivity of breast ^{1}H MRS showed that smaller tumors tended to be diagnosed as benign (false-negative) because of the lack of a detectable composite choline signal. The sensitivity of ^{1}H MRS of the breast, thus, may be limited more by technical factors than by intrinsic properties of the tumors, such as carcinomas that do not contain a high concentration of composite choline. Therefore, any improvement in the signal-to-noise ratio that will effectively enhance the detection of composite choline may increase the sensitivity and improve the diagnostic performance of breast ^{1}H MRS. Detection of composite choline in breast tumors could be improved by approaches that increase the signal-to-noise ratio of choline detection by increasing the choline signal, decreasing the noise level, or both. One approach to increase the choline signal is to use MR scanners operating at a magnetic field higher than 1.5 T. All studies discussed in this review were performed at a field strength of 1.5 T. Clinical MR scanners that operate at field strengths of 3–4 T are becoming available. For human studies, the signal-to-noise ratio increases linearly with field strength. The choline signal can also be increased by use of MR pulse sequences that are specifically optimized to detect signals at 3.2 parts per million (the chemical shift of the composite choline resonance). An

Table 2. Breast proton magnetic resonance spectroscopy (^{1}H MRS) studies and results*

Study	No. of malignant tumors	No. of benign tumors	Sensitivity, %	Specificity, %	No. of true positives	No. of true negatives	No. of false negatives	No. of false positives
Cecil et al. *(16)*	19	14	100	93	19	13	0	1
Yeung et al. *(19)*	23	6	96	83	22	5	1	1
Roebuck et al. *(18)*	10	6	70	100	7	6	3	0
Total	52	26	92	92	48	24	4	2

*Cases in which hardware failed, the patient moved during examination, MRS was done after fine-needle aspiration procedure, and cases of tubular adenoma (in studies where these cases were reported in detail) were excluded. Data were reproduced from studies cited or calculated from data presented therein.

additional method for improving the detection of composite choline in breast tumors may involve advances in the design of MR coils that are more suitable for spectroscopic examination of the breast.

In addition, it should be noted that the technical demands of ^{1}H MRS are not prohibitive. With the advent of automated brain ^{1}H MRS software packages, spectroscopy sequences have been routinely added to neuroradiologic MRI examinations in the United States, and these sequences are currently used in the classification of brain tumors *(41)*. Similar automation for examination of breast tumors should be straightforward.

All of the breast ^{1}H MRS studies described here have addressed the issue of short and long echo times (31–450 ms) in the pulse sequence used. Use of short and long echo times involves a tradeoff between signal intensity (high with short echo time) and signal contrast (the ability to resolve the composite choline signal from the lipid signal, which is higher with long echo time). Despite the loss of signal intensity, the use of long echo times ($\geq$135 ms) typically led to an improved visibility of the composite choline signal because of a decreased overlap with the lipid signal *(18,19)*. The magnitude of the lipid signal has been shown to be of no diagnostic value in breast tumors *(18)*. In contrast, as shown in the studies discussed above, the composite choline signal appears to have an important diagnostic value for breast tumors. Therefore, it appears that the breast ^{1}H MRS examination should be performed with a long echo time (135–270 ms) to increase the visibility of the composite choline signal.

The diagnosis made by breast ^{1}H MRS was of a yes–no type: composite choline was detected (malignant) or not (benign). This observation is consistent with the phosphocholine content in human breast cancer cells, which was previously found to be 10-fold higher than that of normal human mammary epithelial cells *(29–31,37)*.

An interesting finding is that a composite choline signal in ^{1}H spectra was found in normal breast tissue of lactating women *(17)*. This finding had been pointed out as a limitation of the use of the composite choline signal as a marker for breast cancer. In fact, the state of lactation is associated with increased choline metabolism because of the need to nourish the newborn with large amounts of choline [supplied in the milk predominantly as phosphatidylcholine, phosphocholine, glycerophosphocholine,

Table 3. Hardware, methods, and acquisition parameters used in breast proton magnetic resonance spectroscopy (^{1}H MRS) studies*

Study	Model and make of 1.5-T magnet	RF coil	Pulse sequence for single-voxel spectroscopy	Pulse sequence for water suppression	TE, ms	NEX	Selection of spectroscopic voxels	Spectroscopic voxel size, mL
Cecil et al. *(16)*	Signa; GE Medical Systems, Milwaukee, WI	Custom-built single-breast multicoil for receive-only, and body coil for transmit	STEAM	CHESS	31 270	128	Region referred from the surgeon or determined from previous imaging, palpation, and a marker adhered to the breast, and MR imaging (contrast-enhanced and noncontrast)	1–3.4
Yeung et al. *(19)*	Gyroscan ACS-NT; Philips Medical Systems, Best, The Netherlands	Standard double-breast coil for receive-only and body coil for transmit	PRESS	Not specified	38 135 270	64	Contrast-enhanced MRI	1–95
Roebuck et al. *(18)*	Signa; GE Medical Systems, Milwaukee, WI	Custom-built single-breast multicoil for receive-only, and body coil for transmit	STEAM	CHESS	31 270	128	Contrast-enhanced MRI	0.7–9.8
Kvistad et al. *(17)*	Picker Edge EPI II; Picker, Cleveland, OH	Custom-built single-breast receive-only or a circular surface coil	PRESS	Frequency-selective inversion pulse at the water resonance	135 350 450	256	Noncontrast MRI. Contrast-enhanced MRI, when necessary.	1–25.2
Jagannathan et al. *(21)*	Magnetom; Siemens	Standard bilateral surface coil for receive-only and body coil for transmit	STEAM	Not specified	135	32 to 64	Noncontrast MRI	1–27
Gribbestad et al. *(22)*	Gyroscan S15 HQ; Philips Medical Systems, Best, The Netherlands	Double breast coil, works for transmit and receive	PRESS	Frequency-selective inversion pulse at the water resonance	136	256	Noncontrast MRI	8–27

*The repetition time was 2000 ms in all studies except for Jagannathan et al. *(21)*, in which 3000 ms was used. RF = radio frequency; TE = echo time; NEX = number of excitations used in the acquisition of each spectrum; STEAM = stimulated echo acquisition mode; CHESS = chemical shift-selective pulses; PRESS = point-resolved spectroscopy; MRI = magnetic resonance imaging.

and free choline *(42)*]. This increased activity of choline metabolism may be the biochemical basis for the composite choline detected in lactating breast tissue. Thus, despite the different biochemical modifications underlying lactation and malignancy of mammary epithelial cells, the end result observed as a detectable composite choline signal in breast ^{1}H MRS is the same. Breast ^{1}H MRS, therefore, is not suitable for differentiating malignant from benign breast tumors in lactating women. However, the unique state of lactation is rarely associated with breast malignancy.

The methods used in the studies discussed in this review varied in terms of hardware, spectral methods, and acquisition parameters, which are summarized in Table 3. Despite the large variability in methods used, results of these studies were similar (as was shown by the pooling analysis described above), indicating the robust capability of breast ^{1}H MRS as an aid in the differentiation of malignant from benign tumors.

In summary, the combined analysis of breast ^{1}H MRS studies demonstrates a sensitivity and a specificity as high as 92% for distinguishing breast cancer from benign tumors of the breast. In a subgroup of younger women (40 years of age and younger), the sensitivity and specificity of this method approached 100%. The factors limiting the sensitivity of the examination were mainly technical and can be overcome in a manner similar to that used for brain ^{1}H MRS. The breast ^{1}H MRS method is robust, easy to interpret, and likely to provide even better diagnostic performance with the development of high-field MRS technologies that are dedicated to the improved detection of the composite choline signal.

REFERENCES

(1) Greenlee RT, Murray T, Bolden S, Wingo PA. Cancer statistics, 2000. CA Cancer J Clin 2000;50:7–33.

(2) Chu KC, Tarone RE, Kessler LG, Ries LA, Hankey BF, Miller BA, et al. Recent trends in U.S. breast cancer incidence, survival, and mortality rates. J Natl Cancer Inst 1996;88:1571–9.

(3) National Cancer Institute. Surveillance, Epidemiology, and End Results. Incidence: Breast Cancer. [Last accessed: 07/05/02.] Available at: http://seer.cancer.gov/faststats/html/inc_breast.html.

(4) Chevarley F, White E. Recent trends in breast cancer mortality among white and black US women. Am J Public Health 1997;87:775–81.

(5) Orel SG, Schnall MD. MR imaging of the breast for the detection, diagnosis, and staging of breast cancer. Radiology 2001;220:13–30.

(6) Buchberger W, Niehoff A, Obrist P, DeKoekkoek-Doll P, Dunser M. Clinically and mammographically occult breast lesions: detection and classification with high-resolution sonography. Semin Ultrasound CT MR 2000; 21:325–36.

(7) Degani H, Gusis V, Weinstein D, Fields S, Strano S. Mapping pathophysiological features of breast tumors by MRI at high spatial resolution. Nat Med 1997;3:780–2.

(8) Esserman L, Hylton N, Yassa L, Barclay J, Frankel S, Sickles E. Utility of magnetic resonance imaging in the management of breast cancer: evidence for improved preoperative staging. J Clin Oncol 1999;17:110–9.

(9) Warner E, Plewes DB, Shumak RS, Catzavelos GC, Di Prospero LS, Yaffe MJ, et al. Comparison of breast magnetic resonance imaging, mammography, and ultrasound for surveillance of women at high risk for hereditary breast cancer. J Clin Oncol 2001;19:3524–31.

(10) Madan AK, Nguyen MT, Wakabayashi MN, Beech DJ. Magnification views of mammography decrease biopsy rates. Am Surg 2001;67: 687–9.

(11) Milz P, Lienemann A, Kessler M, Reiser M. Evaluation of breast lesions by power Doppler sonography. Eur Radiol 2001;11:547–54.

(12) Ronen SM, Leach MO. Imaging biochemistry: applications to breast cancer. Breast Cancer Res 2001;3:36–40.

(13) Twelves CJ, Porter DA, Lowry M, Dobbs NA, Graves PE, Smith MA, et al. Phosphorus-31 metabolism of post-menopausal breast cancer studied *in vivo* by magnetic resonance spectroscopy. Br J Cancer 1994;69: 1151–6.

(14) Kalra R, Wade KE, Hands L, Styles P, Camplejohn R, Greenall M, et al. Phosphomonoester is associated with proliferation in human breast cancer: a 31P MRS study. Br J Cancer 1993;67:1145–53.

(15) Sijens PE, Wijredeman HK, Moerland MA, Bakker GJ, Vermeulen JW, Luyten RR. Human breast cancer *in vivo:* H-1 and P-31 MR spectroscopy at 1.5 T. Radiology 1988;169:615–20.

(16) Cecil KM, Schnall MD, Siegelman ES, Lenkinski RE. The evaluation of human breast lesions with magnetic resonance imaging and proton magnetic resonance spectroscopy. Breast Cancer Res Treat 2001;68: 45–54.

(17) Kvistad KA, Bakken IJ, Gribbestad IS, Ehrnholm B, Lundgren S, Fjosne HE, et al. Characterization of neoplastic and normal human breast tissues with *in vivo* (1)H MR spectroscopy. J Magn Reson Imaging 1999;10: 159–64.

(18) Roebuck JR, Cecil KM, Schnall MD, Lenkinski RE. Human breast lesions: characterization with proton MR spectroscopy. Radiology 1998;209: 269–75.

(19) Yeung DK, Cheung HS, Tse GM. Human breast lesions: Characterization with contrast-enhanced *in vivo* proton MR spectroscopy—initial results. Radiology 2001;220:40–6.

(20) Lee JK, Tsai SC, Ho YJ, Chanclai SP, Kao CH. Classification of *in vivo* 1H MR spectra from breast tissue using artificial neural networks. Anticancer Res 2001;21:1481–5.

(21) Jagannathan NR, Kumar M, Seenu V, Coshic O, Dwivedi SN, Julka PK, et al. Evaluation of total choline from *in-vivo* volume localized proton MR spectroscopy and its response to neoadjuvant chemotherapy in locally advanced breast cancer. Br J Cancer 2001;84:1016–22.

(22) Gribbestad IS, Singstad TE, Nilsen G, Fjosne HE, Engan T, Haugen OA, et al. *In vivo* 1H MRS of normal breast and breast tumors using a dedicated double breast coil. J Magn Reson Imag 1998;8:1191–7.

(23) Ng TC, Grundfest S, Vijayakumar S, Baldwin NJ, Majors AW, Karalis I, et al. Therapeutic response of breast carcinoma monitored by ^{31}P MRS *in situ.* Magn Reson Med 1989;10:125–34.

(24) Degani H, Horowitz A, Itzchak Y. Breast tumors: evaluation with P-31 MR spectroscopy. Radiology 1986;161:53–5.

(25) Gribbestad IS, Petersen SB, Fjosne HE, Kvinnsland S, Krane J. ^{1}H NMR spectroscopic characterization of perchloric acid extracts from breast carcinomas and non-involved breast tissue. NMR Biomed 1994;7: 181–94.

(26) Gribbestad IS, Fjosne HE, Kvinnsland S. *In vitro* proton NMR spectroscopy of extracts from human breast tumours and non-involved breast tissue. Anticancer Res 1993;13:1973–80.

(27) Speckter H, Blumich B, Just M, Tromel U, Mitze M, Thelen M. *In vitro* NMR spectroscopy of healthy, pathologically changed and carcinomatous breast tissue samples correlated with histological findings. Rofo Fortschr Geb Rontgenstr Neuen Bildgeb Verfahr 1994;161:147–53.

(28) Mackinnon WB, Barry PA, Malycha PL, Gillett DJ, Russell P, Lean CL, et al. Fine-needle biopsy specimens of benign breast lesions distinguished from invasive cancer *ex vivo* with proton MR spectroscopy. Radiology 1997;204:661–6.

(29) Aboagye EO, Bhujwalla ZM. Malignant transformation alters membrane choline phospholipid metabolism of human mammary epithelial cells. Cancer Res 1999;59:80–4.

(30) Singer S, Souza K, Thilly WG. Pyruvate utilization, phosphocholine and adenosine triphosphate (ATP) are markers of human breast tumor progression: a ^{31}P and ^{13}C-nuclear magnetic resonance (NMR) spectroscopy study. Cancer Res 1995;55:5140–5.

(31) Ting YT, Sherr D, Degani H. Variations in the energy and phospholipid metabolism in normal and cancer human mammary epithelial cells. Anticancer Res 1996;16:1381–8.

(32) Kerlikowske K, Grady D, Barclay J, Sickles E, Ernster V. Effect of age, breast density, and family history on the sensitivity of first screening mammography. JAMA 1996;276:33–8.

(33) Johnstone PA, Moore EM, Carrillo R, Goepfert CJ. Yield of mammography in selected patients age < or = 30 years. Cancer 2001;91: 1075–8.

(34) Wang J, Shih TT, Hsu JC, Li YW. The evaluation of false negative mammography from malignant and benign breast lesions. Clin Imaging 2000; 24:96–103.

(35) Stoutjesdijk MJ, Boetes C, Jager GJ, Beex L, Bult P, Hendriks JH, et al. Magnetic resonance imaging and mammography in women with a hereditary risk of breast cancer. J Natl Cancer Inst 2001;93:1095–102.

(36) Soo MS, Dash N, Bentley R, Lee LH, Nathan G. Tubular adenomas of the breast: imaging findings with histologic correlation. AJR Am J Roentgenol 2000;174:757–61.

(37) Katz-Brull R, Seger D, Rivenson-Segal D, Rushkin E, Degani H. Metabolic markers of breast cancer: enhanced choline metabolism and reduced choline-ether phospholipid synthesis. Cancer Res 2002;62:1966–70.

(38) Street JC, Szwergold BS, Matei C, Kappler F, Mahmood U, Brown TR, et al. Study of the metabolism of choline and phosphatidylcholine in tumors *in vivo* using phosphonium-choline. Magn Reson Med 1997;38:769–75.

(39) Degani H, Ronen SM, Furman-Haran E. Breast cancer: spectroscopy and imaging of cells and tumors. In: Gillies RJ, editor. NMR in physiology and biomedicine. San Diego (CA): Academic Press; 1994. p. 329–52.

(40) Katz-Brull R, Margalit R, Degani H. Differential routing of choline in implanted breast cancer and normal organs. Magn Reson Med 2001;46: 31–8.

(41) Preul MC, Caramanos Z, Collins DL, Villemure JG, Leblanc R, Olivier A, et al. Accurate, noninvasive diagnosis of human brain tumors by using proton magnetic resonance spectroscopy. Nat Med 1996;2:323–5.

(42) Rohlfs EM, Garner SC, Mar MH, Zeisel SH. Glycerophosphocholine and phosphocholine are the major choline metabolites in rat milk. J Nutr 1993; 123:1762–8.

NOTES

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