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ORIGINAL REPORT

Electrical Impedance Scanning for the Early Detection of Breast Cancer in Young Women: Preliminary Results of a Multicenter Prospective Clinical Trial

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Authors' disclosures of potential conflicts of interest are found at the end of this article.

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ABSTRACT

Purpose
To evaluate the feasibility and patient satisfaction with electrical impedance scanning (EIS) for early detection of breast cancer in young women.

Methods
Women undergoing screening clinical breast examination, imaging, or biopsy were eligible for EIS examination with T-Scan 2000ED (Mirabel Medical Systems, Austin, TX). Multiple logistic regression analysis evaluated the association between clinical variables and EIS performance. Patients completed a screening EIS satisfaction questionnaire (1 = least satisfied to 5 = most satisfied).

Results
Twenty-nine cancers were identified among 1,103 women. Sixty-six percent (19 of 29) of cancers were nonpalpable and 55% (16 of 29) were in women age ≤ 50 years. EIS sensitivity and specificity in women younger than 40 years was 50% and 90%, respectively. Exogenous estrogen use ($P < .001$) and menopausal status ($P = .007$) correlated significantly with EIS performance. False-positive rates were increased in postmenopausal women and those taking exogenous hormones. No correlation was evident between EIS performance and family history, prior breast cancer, breast density, or palpability. EIS-positive women younger than age 40 were 4.5 times more likely to have breast carcinoma than were women randomly selected from the general population. Patients were highly satisfied with the comfort, speed, and reporting of EIS screening (mean score, 4.8).

Conclusion
EIS seems promising for early detection of breast cancer, and identification of young women at increased risk for having the disease at time of screening. Positive EIS-associated breast cancer risk compares favorably with relative risks of conditions commonly used to justify early breast cancer screening. Patients are satisfied with a screening paradigm involving breast EIS.

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INTRODUCTION

Despite recent controversy,[1,2] mammographic screening currently is considered the best method available for mass screening for the early detection of breast cancer.[3] However, in the United States, mammography (MMG) is not recommended routinely for asymptomatic women younger than age 40 at average risk of developing breast cancer. This, in part, is based on concerns about radiation exposure[4,5] and the reduced sensitivity and specificity of MMG in the setting of dense breast tissue commonly encountered in young women.[6-8] For women younger than age 40, screening is performed

mainly using breast self-examination (BSE) and clinical breast examination (CBE).

By the time a cancer can be detected by CBE, it is by definition at a more advanced stage (requiring more aggressive and expensive treatments), and is associated with decreased survival and quality of life. One in 249 women between the ages of 30 and 40 will be diagnosed with breast cancer.[9] Among young women (ages 15 to 40), breast cancer is the leading cause of cancer-related mortality.[10] Breast carcinomas tend to be more aggressive in young than in older women.[10-13] Consequently, there is a need for a screening modality that can be used along with CBE for early detection of breast cancer in young women.

It was recognized more than 70 years ago that malignant tissue differs from benign/normal tissue in electrical impedance properties because of differences in cellular water and electrolyte content, changes in cell membrane permeability, and orientation and packing density of cells.[14,15] The potential for these electrical differences to be used in cancer detection was subsequently investigated in vitro and in vivo.[16-22] The electrical impedance scanner (EIS) model TS2000 (Mirabel Medical Systems, Austin, TX) demonstrated clinical effectiveness and received US Food and Drug Administration approval for use as an adjunct to MMG. EIS maps electrical impedance (capacitance and conductivity) of breast tissue and produces a real-time gray-scale "image" of differences in impedance measured over a broad range of frequencies. In an electrical impedance image, the nipple is a bright, white area because of its high concentration of ductal tissue that has lower electrical impedance than the surrounding more fatty tissue of the breast. The surrounding normal breast tissue is displayed in varying shades of gray (for more technical detail about EIS, see Scholz and Anderson,[15] Piperno et al,[23] Glickman et al,[24] and the Appendix).

There is evidence that EIS does not simply detect distortions of electrical fields due to a localized cancer, but also reflects more widespread electrical changes in the breast.[25] Studies measuring electrical impedance of the breast suggest that what is being measured is primarily related to generalized, premalignant, tissue-proliferative changes.[25] In this regard, measurements on the nipple are a particularly sensitive indicator of ductal epithelial changes in the breast as a whole.[26] These findings suggest that EIS has the potential to identify women at a high risk of having breast cancer, in the absence of a specific lesion that can be localized. Thus, EIS could be used in conjunction with CBE as a screening tool in young women for whom routine use of MMG is considered impractical. The T-Scan 2000ED (Mirabel Medical, Austin, TX) was developed to provide a tool that would be useful for screening young women. The T-Scan 2000ED (algorithm P) is based on the same technologic principles but uses a different scoring algorithm than the earlier TS2000. The purpose of this study is to evaluate a preliminary algorithm (P) for the T-Scan 2000ED for the early detection of breast cancers in young women.

METHODS

Development of EIS As a Screening Modality

The scoring was accomplished by use of an algorithm (details of the algorithm P and its development are presented in the Appendix) that processes information recorded over a broad frequency range (not only the frequency at which the image or impedance map is displayed). The algorithm uses data obtained from the entire breast, without specific reference to a localized lesion, given the ability of EIS to identify generalized mammary ductal changes associated with carcinoma. In defining new operating thresholds for screening young women, it was considered important to maximize specificity (given the low relative prevalence of carcinoma in young, premenopausal women), and to minimize the number of false-positive results that may require additional diagnostic procedures. A reduced sensitivity of EIS was deemed acceptable; this examination is intended for young women who do not have clinically apparent, palpable lesions. Hence, any cancer discovered by EIS would not be otherwise discovered until it had grown sufficiently large to be palpable during CBE.

The algorithm used for this study was developed on a learning data set comprising 43 cancer and 335 noncancer patients in women age ≤ 50. Operating parameters and EIS algorithm thresholds were determined that discriminated between normal breasts and breasts with cancers. Sensitivity and specificity for this learning group were 37% and 91%, respectively. However, data are needed to test and validate this algorithm independently as well as to provide more accurate estimates of sensitivity. The purpose of this study was to gather such data.

Data Collection

This was a prospective, multicenter clinical trial. All women who came for screening MMG, ultrasound (US), or CBE, as well as selected women who were referred for breast biopsy, were eligible for enrollment onto the study. One thousand one hundred three women underwent EIS examinations as part of this study. Written informed consent was obtained before trial participation. Data for this study were collected at six medical centers: Walter Reed Army Medical Center (Washington, DC; n = 220), Elizabeth Wende Breast Clinic (Rochester, NY; n = 280), University of Pittsburgh Medical Center (Pittsburgh, PA; n = 79), Daniely Clinic (Givataiim, Israel; n = 304), Rambam Hospital (Haifa, Israel; n = 53), and Hadassah Hospital Mount Scopus (Jerusalem, Israel; n = 167).

Women were excluded from this study if they had breast surgery, thoracotomy, or breast core biopsy within the preceding 3 months or breast fine needle aspiration within the preceding 1 month. Patients were also excluded if they were pregnant, had an electrically powered implanted device (eg, pacemaker), or were undergoing aggressive cancer treatment (such as chemotherapy or radiation therapy). Because EIS is intended as a screening modality, a concerted effort was made to recruit young (age ≤ 45 years) women; as such, all analyses were stratified according to age. Demographic and clinical characteristics of the study participants are listed in Table 1.

All women who enrolled onto the study received a CBE. To estimate sensitivity, we used data only from women with

Table 1. Demographic and Clinical Characteristics of Women at the Time of Entry Onto the Study (N = 1,103)

Category	Age (years)					
	< 40		40-49		≥ 50	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Total	580	52.6	450	40.8	73	6.6
Menopausal status						
Premenopausal	556	95.7	390	86.7	18	24.7
Postmenopausal	16	2.8	50	11.1	52	71.2
Not recorded	8	1.4	10	2.2	3	4.1
Hormone use (premenopausal)						
Using oral contraceptives or hormones associated with IUD	222	38.3	61	13.6	7	9.6
Using other hormones (fertility drugs, tamoxifen)	3	0.5	7	1.6	0	0
Not using hormones	310	53.4	305	67.8	9	12.3
Not recorded	21	3.6	17	3.8	2	2.7
Hormone use (postmenopausal)						
Using HRT	6	1.0	13	2.9	15	20.5
Other hormones (tamoxifen)	1	0.2	3	0.7	0	0
Not using hormones	8	1.4	27	6.0	28	38.4
Not recorded	1	0.2	7	1.6	9	12.3
Family history						
No first-degree relatives with breast cancer	454	78.3	301	66.9	19	26.0
One first-degree relative with breast cancer	72	12.4	66	14.7	9	12.3
Two or more first-degree relatives with breast cancer	5	0.9	11	2.4	1	1.4
Not recorded	49	8.4	72	16.0	44	60.3
History of breast cancer						
Previous history of breast cancer	5	0.9	15	3.3	3	4.1
No previous history of breast cancer	516	89.0	409	90.9	67	91.8
Not recorded	59	10.2	26	5.8	3	4.1
CBE result						
Palpable lesion	132	22.8	76	16.9	6	8.2
No palpable lesion	438	75.5	360	80.0	56	76.7
Not recorded	10	1.7	14	3.1	11	15.1

Abbreviations: IUD, intrauterine device; HRT, hormone replacement therapy; CBE, clinical breast examination.

histologically proven malignancy. To estimate specificity, we assumed that all women who were negative for breast cancer on other screening examinations, or who had lesions that were not deemed sufficiently suspicious to warrant biopsy, in addition to those with biopsy-proven benign lesions, did not have breast cancer. All EIS examinations were performed before biopsy. Hence, the examiner was blinded to the pathologic diagnosis. In addition to collecting data on results of the EIS examination and other breast examinations, menopausal status and exogenous hormone use were also recorded.

The EIS Examination

The EIS examination was performed using the T-Scan 2000ED; the scoring was accomplished using a postprocessing algorithm (algorithm P). The instrument consists of a flat screen monitor with a computer mounted on the back. A metal cylinder held in the woman's hand contralateral to the breast being examined was connected to the computer that provided a low-level, electric signal (1.0 to 2.5 V) transmitted via the metal cylinder to the patient's body. The electrical current was measured on the skin overlying the breast with a probe.

An EIS examination requires the placement of a conducting gel (Gamma Massage and Ultrasound Gel; Pharmaceutical Innovations Inc, Newark, NJ) on the breast surface probe as well as on the metal cylinder used to transmit electrical voltage. Measurements were made with a noninvasive, hand-held probe (detector) of several locations (sectors) on the breast, including the nipple, according to a predetermined computer-guided sequence. The examination was performed with the woman recumbent, similar to the position generally used during US examination, with the arm ipsilateral to the examined breast, raised above the head. The purpose of this position was to flatten the breast as much as possible, allowing optimal contact of the flat surface of the scan probe with the breast tissue.

To make a recording, the flat sensor surface of the probe was pressed firmly on the breast, and capacitance and conductance images (maps) were displayed in real-time at 1 kHz on the computer monitor. The probe was moved in such a way as to remove air bubbles and to ensure good contact with the breast. Air bubbles were identified as black holes in the image. Areas of poor contact were identified as black or white lines along the edges or in the corners of the image. When an adequate image free of artifact was obtained, the image was recorded. During recording, capacitance and conductivity were measured over seven frequencies (ranging, 100 Hz to 2,000 kHz).

When recording for the entire breast was completed (nine measurements), the postprocessing algorithm in the software was

activated. If the measurements for the breast were within the normal range as determined by the algorithm, a green line appeared next to the image of the breast; if the measurements were above the normal range, a red line appeared next to the image of the breast. It should be noted that the final output of the examination (suspicious [red]/not suspicious [green]) was based on a number computed automatically by the algorithm without any operator intervention. The real-time image was only used in this examination to ensure that adequate contact was achieved between the probe and the skin surface during the measurements.

Thus, the final output or result of a study is a binary (green [negative] or red [positive]) indicator bar. Unlike the earlier US Food and Drug Administration–approved device (TS2000), this investigational device (T-Scan 2000ED) does not identify a spot corresponding to an underlying breast lesion. Thus, even if the instrument succeeds in detecting the presence of nonpalpable lesions smaller than 1 centimeter, the problem remains in localizing the abnormality. In our experience, limitations of MMG in young premenopausal breasts can be overcome with increased sensitivity associated with breast ultrasound and magnetic resonance imaging (MRI) in appropriately selected patients. Combined sensitivity of 95% may be achieved with CBE plus MMG plus US plus MRI. Thus, the issue of follow-up targeted diagnostic imaging in the relatively few EIS-positive patients (50 of 1,000; specificity, 95%) is not considered problematic.

Patient Survey

A consecutive series of 320 participants from a single center (Walter Reed Army Medical Center) were asked to complete a nonstandardized six-part survey on their own after completion of the CBE and the EIS examination. The questionnaire was implemented to learn more about the patients and how important they consider breast cancer screening in young women, and to determine level of satisfaction with the breast EIS examination (Fig 1).

Data Analysis

The successful identification of breast cancer along with the sensitivity, specificity, and positive and negative predictive values of EIS were determined: % sensitivity = [true positives/(true positives + false negatives)] × 100; % specificity = [true negatives/(true negatives + false positives)] × 100; % positive predictive value = [true positives/(true positive + false positives)] × 100; % negative predictive value (NPV) = [true negatives/(true negatives + false negatives)] × 100.

True-positive examinations in all patients were based on biopsy-proven cancer (ductal carcinoma-in-situ and invasive cancer). False-negative findings on EIS were identified by other

Subject No.: _____ Age: _____ Date: _____ Study Site: _____

1. What is your race/ethnic background (check the selection that applies to you)?
   ☐ Asian ☐ White/Caucasian ☐ Black/African American ☐ Native American
   ☐ Other _____
2. How did you learn about the T-Scan/EIS exam (check the selection that applies to you)?
   ☐ Physician referral ☐ Friend or relative ☐ Internet ☐ Newspaper
   ☐ Other _____
3. How important do you think it is to screen young women age 20 to 40 years for breast cancer (check the selection that applies to you)?
   ☐ Extremely important ☐ Somewhat important ☐ Important ☐ Not important
4. Do you personally know anyone under the age of 40 that has or has had breast cancer (check the selection that applies to you)?
   ☐ Yes; if so, age: _____ years ☐ No
5. How satisfied are you with the following aspects of T-Scan? (Circle selection that applies to you)

	Very Dissatisfied	Dissatisfied	Neither Satisfied nor Dissatisfied	Satisfied	Very Satisfied
Comfort of T-Scan exam	1	2	3	4	5
Speed of T-Scan exam	1	2	3	4	5
Reporting of T-Scan exam result	1	2	3	4	5
Patient education about T-Scan	1	2	3	4	5
Staff professionalism	1	2	3	4	5

6. Would you recommend this examination to a family member or friend (check the selection that applies to you)?
   ☐ Yes ☐ No
   Comments: _____

Fig 1. Patient questionnaire.

imaging modalities (US, MMG, or MRI) and confirmed histologically. Breast US, MMG, and MRI were interpreted by board-certified radiologists specializing in women's breast imaging.

Summary statistics were obtained using established methods. Associations between categoric variables were evaluated using the χ^2 test and logistic regression. We analyzed the following clinical factors: age, divided into three categories (younger than 40 years, 40 to 49 years, and $\geq$ 50 years); menopausal status, premenopausal versus postmenopausal (a woman was considered postmenopausal if she had gone 6 months without menstruating); exogenous hormone use (oral contraceptives, contraceptive implants, or intrauterine devices with hormones if premenopausal, hormone replacement therapy if postmenopausal); previous history of breast cancer, yes or no; family history of breast cancer (categories were no first-degree relatives with breast cancer, one first degree [sister/mother] relative with breast cancer, or two or more first-degree relatives with breast cancer); palpability of lesion (palpable mass present or not present); and breast tissue density. Methods for scoring breast tissue density varied among centers. The methods included the Breast Imaging Reporting and Data System (BIRADS) numerical system, a verbal four-level system (which corresponded to the BIRADS system), and a verbal three-level system. For the purposes of this analysis, women were classified into one of three categories: primarily fatty breasts, heterogeneously dense breasts, and primarily dense breasts.

Statistical analysis was performed using STATA software (STAT Corp, Santa Monica, CA). All statistical tests were two-sided and a P value $\leq .05$ was considered significant.

RESULTS

General Description of the Study Population

The study involved 1,103 female participants. Twenty-nine biopsy-confirmed cancers (23 invasive, six intraductal) were diagnosed. Sixty-six percent (19 of 29) of cancers were nonpalpable and 21% (six of 29) were in women younger than 40 years. Two of the six cancers in the age group younger than 40 years were nonpalpable. Table 2 compares EIS-positive to EIS-negative cancers, and Table 3 lists the results of MMG according to EIS and biopsy results. EIS-positive patients were significantly younger than their EIS-negative counterparts (mean age, 41.2 years; standard deviation [SD] 11.8 years *v* mean age 53.0 years; SD, 11.6 years; Student's t test $P < .05$). The smallest carcinoma detected by EIS in this study was 7 mm. One of the EIS-positive cancers was a clinically occult ductal carcinoma in situ evident as microcalcifications on MMG. All women

Table 2. Mean and Standard Deviation of Breast Cancer in EIS-Positive and -Negative Patients

Characteristic	EIS Positive (n = 5) No.	EIS Positive (n = 5) %	EIS Negative (n = 24) No.	EIS Negative (n = 24) %	*P*
Age, years					< .05
Mean	41.2		53.0		
SD	11.8		11.4		
Palpable	3 of 5	60	7 of 24	29	NS
Tumor size, cm					NS
Mean	1.7		1.7		
SD	1.0		1.4		
BIRADS					NS
Mean	4.0		3.8		
SD	1.4		1.4		
Histology					
IDC	4 of 5	80	12 of 24	50	NS
ILC	0 of 5	0	3 of 24	13	
DCIS	1 of 5	20	5 of 24	20	
IDC + DCIS	0 of 5	0	4 of 24	17	

	EIS Positive (n = 3)	EIS Negative (n = 3)
Cancer 1	IDC; size, 20 mm; detected on MMG (BIRADS 5 spiculated lesion) and US BIRADS 4 solid lesion; palpable; ER positive, PR negative, HER2 positive	DCIS, noncomedo; size, 20 mm; detected on US as BIRADS 4 solid lesion; MMG negative; nonpalpable; intermediate grade
Cancer 2	IDC; size, 5 mm; detected on US as BIRADS 4 solid lesion; MMG not done; palpable; grade 2	IDC; size, 12 mm; detected as solid lesion on US and on MMG as BIRADS 0; nonpalpable; ER positive, PR positive, HER2 positive
Cancer 3	IDC/ILC; size, 15 mm; detected on MMG as BIRADS 5 calcified mass; US not done; palpable; grade 2	DCIS; size unknown; detected as BIRADS 5 microcalcifications on MMG; US negative, palpable; high grade

Abbreviations: EIS, electrical impedance scanning; SD, standard deviation; NS, not significant; BIRADS, Breast Imaging Reporting and Data System; IDC, infiltrating ductal carcinoma; ILC, infiltrating lobular carcinoma; DCIS, ductal carcinoma in situ; MMG, mammography; ER, estrogen receptor; PR, progesterone receptor; US, ultrasound.

Table 3. CBE, US, and MMG Findings in Women With Positive and Negative EIS Examinations

Examination	EIS Negative			EIS Positive		
	No. of Patients	No. of Biopsies	No. of Cancers	No. of Patients	No. of Biopsies	No. of Cancers
CBE						
Normal	790	98	17	99	9	2
Abnormal	198	66	7	16	6	3
MMG						
0 (needs additional imaging)	9	8	1	1	0	0
1 (negative)	235	17	2	22	4	0
2 (benign)	127	12	1	16	1	1
3 (probably benign)	35	16	0	3	1	0
4 (suspicious)	76	72	12	5	3	1
5 (highly suggestive)	10	10	7	2	2	2
US						
No finding	102	18	4	16	5	0
Simple cyst	59	9	0	10	0	0
Solid lesion	120	91	15	14	6	3
Mixed solid/cystic	7	5	0	1	1	0

NOTE. The tabulated numbers do not total 1,103 because not all women had all listed examinations.
Abbreviations: EIS, electrical impedance scanning; CBE, clinical breast examination; MMG, mammography; US, ultrasound.

with cancer were those who had been referred for breast biopsy; none were from the screening population. There were no adverse events and no patient reported discomfort during the screening examination.

Sensitivity and Specificity

EIS measurements are strongly affected by hormonal factors. In general, breast electrical impedance tends to decrease with age. Therefore, any algorithm that uses measured capacitance and conductance has to have decision thresholds that are tailored to the age group on which it is to be used. For the algorithm used in this study that is intended for use on a young population, the thresholds for identification of women at higher risk of having cancer are set at a fairly high level because the baseline impedance measurement tends to be high. Thus, older women who on average have a much lower impedance measurement will tend to fall below this threshold, even if they have cancer. Hence, the sensitivity is expected to be lower in the older age group.

Women without cancer were classified in one of three categories. Screening patient cases were either asymptomatic women screened only by CBE and found to be negative, or women who were screened by MMG or US in addition to CBE but without an identifiable lesion. Women who had a palpable finding on CBE were included in this category if that finding was deemed by the examining physician to be within normal limits (it did not warrant additional workup). Benign patient cases without biopsy were patients who had an identifiable benign finding on an imaging modality but did not undergo biopsy. Benign patient cases with biopsy were those who had a histologically established benign diagnosis. Sensitivity and specificity for various clinical and age categories are listed in Table 4.

There was no significant correlation between specificity, age, and clinical category ($t_{age} = -0.36$, $P = .72$; $t_{clinical\ category} = -1.21$, $P = .23$) by logistic regression analysis. Sensitivity was not significantly related to age category ($t_{age} = -1.86$; $P = .07$). However, operational characteristics (sensitivity and specificity) of the instrument were better for younger (younger than age 40) than for older (age $\geq$ 50) women. Age-related EIS sensitivity may be explained by prior findings of significant reduction in breast tissue conductivity and capacitance with increasing number of years since the onset of menopause.[26] Breast conductivity, particularly when measured at the nipple where the highest concentration of ductal tissue is present, correlates with estrogen levels in postmenopausal women, increases with estrogen replacement, and declines, irrespective of estrogen replacement, with duration of menopause.[26] NPV was higher for younger than older women, possibly due to the higher incidence of cancer in the older age group.

Predictors of Algorithm Performance in Subcategories of Women

Sample size of carcinomas was insufficient to examine the relationship between sensitivity and other clinical variables. Hence the analysis was restricted to factors related to specificity. We used multiple logistic regression to examine the relationship between specificity and the following factors: menopausal status, exogenous hormone use, history of previous breast carcinoma, family history, and palpability of lesion (Table 5). The only variables found to be significantly associated with specificity were menopausal status and exogenous hormone use. The influence of breast lesion

Table 4. Specificity, Sensitivity, and 95% CIs in Patient Cases Recorded at All Six Sites (sample sizes are in parentheses)

Variable	All Patient Cases		95% CI	Age (years)					
				< 40		40-49		≥ 50	
	%	No.		%	No.	%	No.	%	No.
Specificity									
Screening	89	819	87% to 91%	90	467	91	320	81	32
Benign/no biopsy	88	105	82% to 94%	87	52	89	53	No observations	
Benign/biopsy	93	150	89% to 97%	91	55	97	67	89	28
Total noncancer	90	1,074	88% to 92%	89	574	91	440	85	60
Sensitivity									
All cancers	17	29	4% to 30%	50	6	10	10	8	13
Invasive cancers	17	23	2% to 32%	75	4	0	8	9	11
NPV									
Total	98	988	97% to 99%	99	516	98	409	81	63
PPV	4	115	0% to 8%	5	64	2	41	10	10

Abbreviations: NPV, negative predictive value; PPV, positive predictive value.

palpability may be important but was not statistically significant ($P = .07$).

Specificity was higher for premenopausal than for postmenopausal women (91% *v* 82%). Use of exogenous estrogens was significantly related to specificity for both pre- and postmenopausal women. Premenopausal women who used exogenous estrogens had higher rates of false-positive examinations than those who did not (14% *v* 7%). Similarly, postmenopausal women who used hormone replacement therapy had higher rates of false-positive examinations (23% *v* 18%) than those who did not use exogenous hormones.

Breast tissue density was evaluated for 192 women in the screening population. Density was evaluated either by MMG for which the images were rated according to the BIRADS American College of Radiology four-point system, or more subjectively by palpation. For the purposes of this analysis, women were classified into one of three categories: primarily fatty breasts (ACR category 1 or primarily fatty by palpation), heterogeneously dense breasts (ACR categories 2 and 3 or heterogeneously dense by palpation), and primarily dense breasts (ACR category 4 or primarily dense by palpation). Specificity was 96% (22 of 23), 93% (89 of 96), and 92% (67 of 73) for the three categories, respectively. There was a decrease (albeit not statistically significant; $P = .58$) in specificity as density increased. Limited sample size precluded statistical comparisons between density and sensitivity.

Table 5. χ^2 From Logistic Regression for the Relationship Between Specificity and Various Clinical Data

Parameter	χ^2	*P*
Family history	0.51	.97
Menopausal status	7.36	.007
Hormone use	12.28	.001
History of breast carcinoma	0.61	.43
Palpability	3.33	.07

Sensitivity was higher for premenopausal (23%; three of 13) than for postmenopausal women (12%; two of 12) and was higher for small lesions (≤ 10 *v* > 10 mm) in both pre- and postmenopausal women, respectively (one of two *v* one of six, and two of 11 *v* one of six, respectively); however, the limited sample size precludes definitive comparisons.

Probability of Having Carcinoma

It is possible to calculate for the data in this study the relative probability that an EIS-positive woman will have cancer relative to an EIS-negative woman in the intended population. This relative probability is given by positive predictive value/(1 − NPV). When this calculation was used, the overall probability that a woman who was EIS positive in this study would have cancer was higher (relative probability, 2.0) than that of a woman who was EIS negative. This value was even higher (relative probability, 5.0) when data were examined from women younger than age 40. However, this value for relative probability is not representative of a random population sample because the frequency of cancer in this study sample (given the selection of some participants presenting for breast cancer screening or evaluation of a suspicious lesion) is higher than that in the general population.

It is possible to use the estimated sensitivity and specificity to calculate the probability that a woman who is EIS positive will have cancer relative to a randomly selected woman from the general population. In this calculation the relative probability (P_r) is a function of the sensitivity (S_n), specificity (S_p) and the rate of cancer in the population (R_{ca}):

$$P_r = \frac{S_n}{[S_n R_{ca} + (1 - S_p)(1 - R_{ca})]}$$

The estimated increased relative likelihood of cancer in an EIS-positive woman as a function of age is listed in Table 6.

Table 6. Probability of Breast Cancer for an EIS-Positive Woman Relative to That of a Woman Randomly Selected From the Population According to Age

Age (years)	Sensitivity (%)	Specificity (%)	Rate of Carcinoma	Increased Relative Likelihood
All ages	17	89	6 of 1,000	1.53
< 50	25	90	3 of 1,000	2.48
< 40	50	89	1.5 of 1,000	4.52

Abbreviation: EIS, electrical impedance scanning.

Breast EIS examinations of young women (younger than age 40) are intended to serve as a basis for recommending follow-up examinations that may identify whether a suspicious lesion is indeed present, and if so, to identify its location. Therefore, it may be worthwhile to compare the relative probability of an EIS-positive woman with that for a woman who has other conditions that are used as a basis for recommending breast imaging for women younger than age 40 (Table 7).[27-29] It should be emphasized that relative risks in Table 7 are lifetime relative risks, whereas the values in Table 6 represent increased relative likelihood of finding cancer in an EIS-positive breast at the time of the examination. The relative probability for a woman in any of the categories of having breast cancer at time of screening examination in Table 6 would be expected to be considerably lower than the lifetime risk estimates presented in Table 7. Hence, the increased likelihood of finding cancer with a positive EIS in this study compares favorably with the relative increased lifetime risk of breast cancer associated with the various conditions commonly used to justify early breast cancer screening.

Patient Survey

A consecutive series of 320 study participants responded to a questionnaire (Fig 1). The ethnicity of respondents in order of frequency was white (65.6%), African American (23.1%), Hispanic (5.3%), Asian (4.7%), and Native American/other (1.3%). Women surveyed learned about the study from physicians (48.7%), friends and relatives (15.0%), and sources other (21.3%) than the newspaper (10.9%) or Internet (4.1%). The majority of those surveyed regarded breast cancer screening in young women as being extremely important (84.1%) and almost half (44.4%) knew someone who developed breast cancer at a young age (younger than age 40). Study participants reported high levels of satisfaction with the comfort (mean, 4.9; SD, 0.4), speed (mean 4.9; SD 0.4), reporting (mean, 4.8; SD, 0.6), and education (mean, 4.8; SD, 0.5) associated with screening breast EIS. Thus, almost all (99.4%) of those patients that completed the questionnaire indicated that they would recommend the EIS examination to a family member or friend.

Table 7. Lifetime RR for Cancer in Women With Various Conditions That May Indicate the Need for Breast Cancer Screening Before the Age of 40 Years[27-29]

Class	Condition	RR
Family history	Two first-degree relatives	2.9
	Three or more first-degree relatives	3.9
Genetic factors	*BRCA1*	5.7
	BRCA2	5.7
Histologic results of breast biopsy	Previous breast cancer	2.0-4.0
	Atypical hyperplasia	4.0
	LCIS	5.9-12.0

Abbreviations: RR, relative risk; LCIS, lobular carcinoma in situ.

DISCUSSION

Breast cancer screening is performed to identify disease at an early and potentially curable stage to reduce cancer-related mortality. Randomized trials have demonstrated a significant reduction in breast cancer mortality among screened women older than age 49 years; however, the impact of screening among younger women remains a matter of controversy.[30] At present, BSE and CBE are the only generally recommended screening methods for detecting breast cancer in women younger than age 40 (and in some parts of the Western world, younger than age 50) who are at average risk for the disease. Thus, current screening recommendations for young women do not generally result in the detection of this disease at an early preclinical stage.

Comparatively more breast cancers are identified by MMG than by CBE, and mammographically detected cancers are significantly smaller and more likely node negative than those found by CBE.[31,32] Combined MMG and CBE annual screening has been advocated for women age 40 to 49; it is recognized that up to 25% of cancers in young women will be missed by MMG, and that CBE detects only 10% of all cancers identified as part of a National Breast Cancer Detection Project.[32-34] There is a paucity of data supporting the use of CBE alone for breast cancer screening and randomized trial data showed no reduction in breast cancer mortality with an intensive program of BSE instruction.[30,35]

The currently accepted standard for screening young women (BSE and CBE) has low sensitivity and specificity. Reduced sensitivity and specificity of MMG for young women due to increased breast tissue density, questionable reduction in mortality, and lack of cost effectiveness makes MMG inadequate for screening young women. US and MRI have been considered for screening in young (age 30 to 39 years) women.

MRI demonstrates high sensitivity for detecting breast cancer; however, its high cost, extremely variable specificity (37% to 97%), and inherent problems with MRI-directed

tissue diagnosis limit its feasibility for generalized population-based screening.[36,37] Even so, recently published results recommend MRI use for high-risk groups.[38,39] The requirement for specialized user training and experience along with high false-positive and false-negative rates make widespread screening with breast US reasonably impractical.[40,41] Consequently, there is a need for an effective breast cancer screening modality for young women that avoids some of the drawbacks of other modalities and that can detect nonpalpable, early-stage, potentially curable cancers in younger women.

This study examined the clinical performance of a device intended for breast cancer screening in women younger than age 40 who do not have palpable lesions. To our knowledge, this is the first study of its kind involving adaptation of existing electrical impedance technology for use in a novel investigational clinical application—screening for the early detection of breast cancer in young women. Sensitivity and specificity in the intended use population (younger than age 40) for the modified EIS breast algorithm (T-Scan 2000ED, algorithm P) was 50% and 90%, respectively; however, sample size for detected cancers in this population is limited and continued follow-up and study are necessary.

Although overall sensitivity was relatively low, EIS is intended for women with nonpalpable lesions (ie, zero sensitivity of CBE). Hence, all cancers discovered by this examination would be cancers that might otherwise not be evident until they had grown to a size detectable by palpation. Given the small sample size for cancers in this study, the size of EIS-positive cancers was the same as that for EIS-negative cancers. Additional investigation is warranted to confirm previous findings using an earlier T-Scan (TS2000) algorithm demonstrating significantly higher sensitivity for smaller ($\leq$ 10 mm) than larger ($>$ 10 mm) cancers.[42]

The EIS system evaluated in this study seems better suited to identify women at a high risk of breast cancer, in the absence of a specific lesion that can be localized. The final output or result of a study is a single green (negative), or red (positive) indicator bar. Unlike the earlier TS2000 device, the T-Scan 2000ED does not identify a spot corresponding to an underlying breast lesion. Thus, even if EIS succeeds in detecting the presence of nonpalpable lesions smaller than 1 cm, the problem remains in localizing the abnormality given the inherent limitations of current breast imaging modalities previously mentioned.

Our preliminary findings of a selected patient population containing a small subset of breast cancers indicate that a woman who is EIS positive is 4.5 times more likely to have breast cancer than a randomly selected woman from the general population. Hence, if this finding is confirmed, EIS-positive or high-risk women may benefit from additional localizing breast imaging examinations. However, at present, diagnostic breast imaging is not considered to be cost effective in EIS-negative or average-risk women younger than age 40 principally because of the low age-specific prevalence of breast cancer and low sensitivity of MMG in women with dense breast tissue.[43]

Breast imaging such as MRI is now frequently carried out in high-risk young women who have a strong family history of breast cancer. A woman with two first-degree relatives is approximately three times more likely to develop breast carcinoma during her lifetime than a woman with no affected primary family members. A woman with three affected first-degree relatives has a four-fold increased lifetime risk. Therefore, the more than four-fold current increased risk of having breast cancer associated with a positive EIS examination may be sufficiently high to justify additional diagnostic imaging and clinical follow-up. Given the preliminary findings in this study, however, larger population-based studies centered on average-risk women younger than age 40 are needed to explore this issue further.

Although no present technology satisfies all criteria of the ideal screening tool, EIS seems well suited to overcome some of the challenges associated with MMG screening of young women: it is noninvasive, is free of radiation, and is associated with minimal risk. The device is easy to use and does not require specialized training to interpret. Breast tissue density does not alter algorithm performance, which seems to be increased for lesions smaller than 1 cm.[42]

False-positive results of screening tests are associated with reduced quality of life, increased medical care costs, and loss of individual productivity.[43-45] The high specificity of EIS reduces the need for unnecessary additional testing and potentially invasive diagnostic procedures. If clinical utility is demonstrated through larger population-based clinical trials, EIS may become an integral part of breast cancer screening, a process considered to be deficient when young women are examined with CBE alone.

If proven efficacious, this new screening paradigm (EIS plus CBE) may increase awareness of (and compliance with) screening MMG, which currently is modest at best. Compliance, a marker of patient acceptance and satisfaction, is an important factor in any screening program. Although the patient survey implemented in this study was not standardized or validated, it does indicate that patient satisfaction with the comfort, speed, and reporting of results of EIS is high. The survey was completed by military health care beneficiaries at a tertiary referral center as part of an equal-access breast cancer screening program, and may not reflect the views of patients in private US and Israeli civilian and university practices included in this multicenter trial. Important considerations of such an approach (EIS plus CBE) will include comfort, safety, patient acceptance, affordable cost, and ease of use.

This preliminary feasibility trial has important limitations that warrant careful consideration. The sensitivity and specificity of a diagnostic test vary according to the

population being tested. The patients in this study do not represent the general population; as such, the relative increased prevalence of disease in this analysis likely reflects spectrum or case-mix bias. Given that some of the data were generated by comprehensive breast care clinics in tertiary university-affiliated teaching centers, referral bias may influence impedance scan algorithm performance as well as the prevalence of the disease in the screened population. The principal limitations of this study are the small sample size for cancers and lack of patient follow-up. Hence, estimates for sensitivity have large confidence intervals and should be interpreted with caution. For cancer screening studies, false-negative findings generally refer to cancers detected within 1 year of a negative test in the same population. This study presents data at a single point in time without longitudinal participant follow-up; however, the overall prevalence of breast cancer is low, such that it cannot affect the results in a substantial manner. The relatively small proportion of patients with breast cancer in the population of interest precludes definitive appraisal of EIS instrument's sensitivity. More data will be needed to determine more accurately the actual sensitivity.

Several innovative technologies are currently under investigation as potential tools for breast cancer detection. These include laser-based technologies, thermography, and EIS. Of these new technologies, only EIS has been approved by the US Food and Drug Administration, albeit as an adjunct to MMG. The data in this primarily descriptive study are a preliminary attempt to examine feasibility of using EIS as a screening modality for young women and provide a basis for optimizing the technology for high-specificity performance. The algorithm tested is one of several algorithms developed for EIS measurements. All of the algorithm optimization processes had been done using prior measurements and were completed before the commencement of the clinical study described in this article. During the study the detection algorithm (P) was predetermined and remained fixed. These data are being used to modify further the EIS screening algorithm to increase sensitivity without a significant concomitant loss in specificity. These later modifications will need additional testing in planned prospective trials. However, on the basis of current experience, it is believed that EIS has promise as a breast cancer screening modality for a group of women for whom no effective screening modality currently exists. EIS seems to identify a population at increased risk of having breast cancer for whom further breast imaging examinations may be warranted.

Appendix

Any new technology used strictly as an adjunct to MMG will inevitably have very limited utility. Breast biopsy is relatively easy to perform and is inexpensive. Hence, in the United States, most radiologists (and surgeons) prefer to biopsy suspicious lesions rather than perform yet another adjunctive examination. However, the clinical effectiveness of the EIS device and in particular the high sensitivity of EIS for small, early-stage carcinomas, indicated that developing this technology for use in early cancer detection was feasible. This may be of particular interest if the technology could be developed for use during routine periodic examination of women at the gynecologist's or general practitioner's office, and in particular for women younger than age 40 years, in whom MMG is not routinely performed for a variety of medical and practical reasons. To begin exploring this concept, various postprocessing algorithms were developed and tested in preliminary studies. All of the algorithm optimization processes had been done using prior measurements and were completed prior to the commencement of the clinical study described in this article. During the study the detection algorithm (P) was predetermined and remained fixed.

To be used in screening, the fundamental device remains, but the signals are processed in a manner to optimize specificity. All clinical data (raw signals that are recorded during each examination) ascertained in previous studies were used in the optimization process as a training and testing data pool. Both a Bayesian Belief Net and a rule-based approach were used to optimize the system for high specificity. Cross validation was initially performed using a leave one out method and later with an independent data set. A description of the basic concept follows.

The EIS algorithms were developed using multifrequency data ascertained in a multicenter study. Impedance data from all of the recorded breast sectors was evaluated and the concept of the crossover frequency applied. There are three frequency ranges: low frequencies, where the skin dominates; high frequencies, where the tissue dominates; and crossover range, where both admittances are significant and the skin capacitance relaxes through the tissue resistance. Both the imaginary part and the phase of the admittance can be used for tissue differentiation. The algorithm uses the phase because it is insensitive to the geometrical parameters (eg, the pixel size and the depth of the breast). In practice, the algorithm selects the frequency with the highest imaginary part, which is closest to the crossover frequency. It divides the 6×6 central pixels into two groups, according to their conductivity values at 200 Hz: nipple pads, with values higher then the 110% of the average, and all the rest, with values lower then that threshold. It then computes the mean phase for each of the two groups. This parameter is used as one classifier that differentiates between healthy and abnormal breasts. The following is a more technical description of the approach used in this procedure.

EIS. Living tissue has complex specific electrical impedance, *z*. We use the inverse of *z* (*y*, admittivity) for most of the analyses in the following discussion. *y* is composed in part of two variables: conductance (*g*) and capacitance (*c*).

$$y = g + i\omega c \quad (1)$$

Note that the parameters of equation 1 are tissue-specific entities, given in units of Siemens (*y*, *g*) and Farads (*c*). Different tissues differ in their admittivity (*y*), and thus tissue differentiation can principally be achieved by EIS[22] or electrical impedance tomography.[46] EIS is the equivalent of x-ray filming: two electrodes are mounted on the tissue and voltage (*V*) is applied between them, resulting in the flow of electric current (*I*). The measured admittance (*Y*) is defined as:

$$Y = I/V \quad (2)$$

Y is also complex entity, which can be expressed as sum of real and imaginary parts:

$$Y = G + i\omega C \quad (3)$$

Here the variables are given in units of Siemens/cm (*Y*, *G*) and Farads/cm (*C*), and they are geometry dependent. One naturally tends to relate *G* and *C* of equation 3 to *g* and *c* of equation 1. However, this is true only in the ideal case of uniform tissue, mounted between two parallel electrodes, without any contact impedance. However, in any realistic situation, the electrical field lines do not follow a linear course; thus the current (*I*) is the sum of subcurrents, each with different amplitude and phase, running through the entire measured tissue and collected by the electrode. In addition, both the skin and the tissue-electrode contact add serial impedance, which, for frequencies of up to about 50 kHz, is larger than that of the tissue.[47] Therefore, the resulting EIS image is not a realistic image of the tissue, and EIS can be either comparative, detecting areas of higher admittance, or it can use average values of an entire sector (sector area being larger than the path length), thereby averaging over the nonuniformities of current distribution. The algorithms of the TS2000 and T-Scan 2000ED consist of measured parameters both of the comparative and the average types, as described in the following sections.

Frequency dependence of EIS. Impedance properties of tissues change with differing frequencies.[19,20,48] The frequency behavior of the admittance is divided into frequency regions. The α region (10 Hz to a few kHz) is associated with extracellular fluid and interfaces such as membranes and skin. The β region (10 kHz to approximately 100 MHz) is associated with the polarization of cellular membranes. This β region is characterized by a significant increase of the imaginary admittance. In addition, the γ region (above 1 GHz) is associated with the activation of polar molecules such as water.

Figure 2 shows simulations of breast tissues, with electrical characteristics from the literature[19,20,49] in T-Scan 2000ED geometry. The α and β regions are clearly seen, marked by two maxima of the imaginary curve. One can also appreciate the potential differentiation power of the various frequency ranges.

Parameters used in the T-Scan 2000ED algorithm. The phase angle for the admittance $Y = G + I\omega C$ at frequency ω is defined as:

$$\varphi_\omega = \arctan\left(\frac{2\pi\omega C}{G}\right) \quad (4)$$

To evaluate conductance (*G*) and capacitance (*C*), the TS2000 uses the probe's internal 36 pixels. Their local *G* and *C* values are averaged, and the phase is evaluated as in equation 4. Note that ϕ is an example of a normalized parameter, a function of the ratio *C*/*G*. However, at low frequencies (below approximately 1 kHz), the skin dominates both *C* and *G*, and therefore ϕ is not related to the tissue, as required. Therefore, phase must be used for higher frequencies only, or for nipple measurements, where the skin admittance is much higher. TS2000 uses $f_{2,000}$ for the nipple data, and $f_{5,000}$ for the non-nipple data. The phase angle is typically larger for malignant than for normal/benign tissue. This is also seen in Figure 2: the imaginary component of cancer tissue (red) is higher than the healthy tissue (blue), whereas the real component is the same at this frequency range. Therefore, the angle is also higher.

As mentioned, skin impedance dominates EIS measurements in the low-frequency range. As the frequency increases to a few kilohertz, the skin becomes more conductive due to its large parallel capacitance, and the admittance of the tissue beneath can be probed. The crossover frequency is defined as the characteristic frequency for

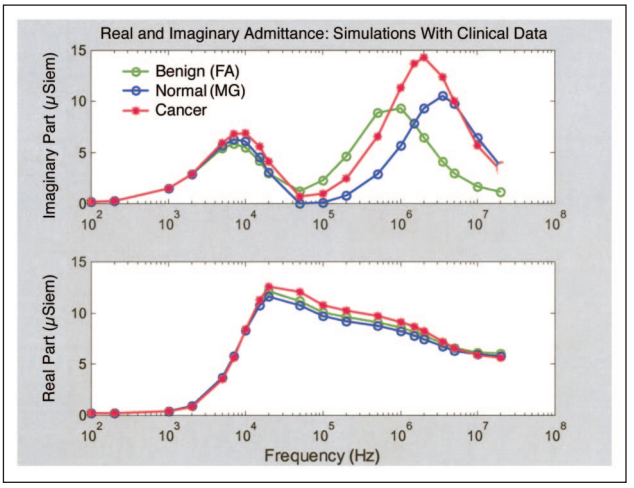

Fig 2. Simulations of T-Scan 2000ED measurements of healthy, benign, and cancerous tissues. Note the differentiation power of the α region (a few kilohertz) and the β region, starting from about 30 kHZ.

the relaxation of the skin capacitance through the resistance of the breast tissue.[22] Typically, this frequency has a value of about 5 kHz, and it is higher for cancerous tissue than for normal/benign tissue. Its importance relies on the fact that it is proportional to the specific conductivity (g) of the tissue:

$$\omega_c = \frac{g_t}{c_s} \quad (5)$$

Where g_t is the specific conductivity of the tissue, and c_s is the specific capacitance of the skin. Therefore, ω_c is a relatively efficient tissue indicator, being related directly to specific tissue conductance, g_t (although somewhat masked by the parameter of the skin).

In the TS2000 algorithm, ω_c is evaluated using the following:

$$\frac{G_i}{C_i} = \omega_s + \frac{\omega_i^2}{\omega_c} \quad (6)$$

where ω_i takes the three values (200, 1,000, and 2,000 Hz); G_i and C_i are the averages of the conductivity and the capacitance data (again over the probe's internal 36 pixels) at the respective ω_i, and ω_s and ω_c are the best-fit parameters of equation 6. ω_c is also the frequency at which the imaginary part takes its local maximum (Fig 2). From the figure it can be appreciated that it is higher for the cancerous (asterisks) than the normal/benign tissue (circles).

Combining parameters. Both of the above descriptors can be used for differentiation between benign and cancer cases. However, to obtain a single level of suspicion, a single unified parameter is evaluated. This is done with receiver operating characteristic curve analysis.[50] This method has two advantages. It is nonparametric in nature (and hence not dependent on the underlying distribution of the data).[51] In addition, it allows estimation of any required threshold by means of maximum-likelihood estimation.[51] For that purpose, each descriptor must be normalized by corresponding values of the learning group.

The threshold for identifying a woman as having cells suggestive of carcinoma was set at a very high level for the T-Scan 2000ED algorithms. It was deemed desirable in this low-prevalence population to minimize false-positive results. A moderate sensitivity was considered acceptable because currently there is no other screening test available for young women with no palpable lesion; hence, screening sensitivity currently is zero for the early detection of breast cancer in young women using CBE alone.

The T-Scan 2000ED algorithms. Essentially, the phase (P) algorithm used in this article is a model-based algorithm, without superfluous free parameters. However, as explained above, adopting the algorithm to a low-risk population requires the resetting of the threshold to ensure the required low false-positive rate. The initial threshold value was suggested by the TS2000 data, with specificity of 91% (Fig 2). This value was then validated on T-Scan 2000ED data, resulting 94% specificity (Fig 3). The P algorithm was developed using a learning group of 128 cancer and 398 benign patient cases, all scanned with the TS2000. ω_c was evaluated for the nipple sector and was normalized by values of the reference group. ϕ_{5000} was evaluated for the upper-outer sector. The upper-outer sector consists of three sectors that are easiest to scan, and therefore are the best to provide EIS data for the whole breast. The contribution of the nipple was averaged with the contribution of the sectors. The results were scaled to give the threshold of specificity $>$ 90%. The algorithm was verified upon test group of T-Scan 2000ED data, with 36 cancer and 476 benign patient cases. The resulting receiver operating characteristic curves of the learning and test groups are shown in Figure 3.

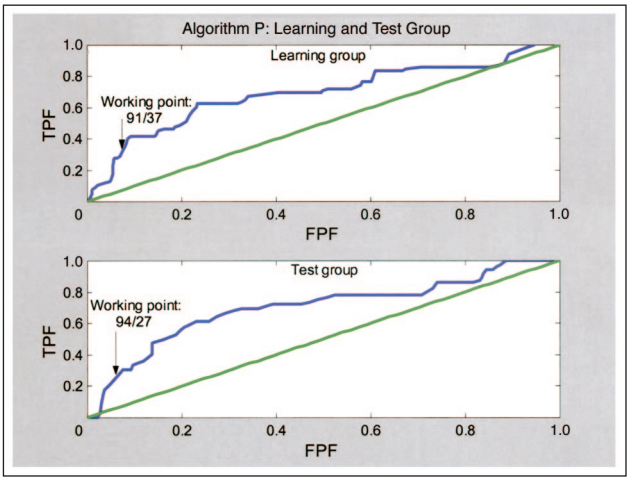

Fig 3. Receiver operating characteristic curve of the results of algorithm P for the learning and test groups. TPF, true-positive fraction; FPF, false-positive fraction.

Authors' Disclosures of Potential Conflicts of Interest

The following authors or their immediate family members have indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. Employment: Sarah Lenington, Mirabel Medical Systems; Ron Ginor, Mirabel Medical Systems. Leadership Position: Ron Ginor, Mirabel Medical Systems. Stock Ownership: Ron Ginor, Mirabel Medical Systems. Expert Testimony: Alexander Stojadinovic, Mirabel Medical Systems; David Gur, Mirabel Medical Systems. For a detailed description of these categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and Disclosures of Potential Conflicts of Interest found in Information for Contributors in the front of each issue.

REFERENCES

1. Olsen O, Gøtzsche PC: Cochrane review on screening for breast cancer with mammography. Lancet 358:1340-1342, 2001

2. Dixon-Woods M, Baum M, Kurinczuk JJ: Screening for breast cancer with mammography. Lancet 358:2166-2167, 2001

3. Committee on the Early Detection of Breast Cancer.Mammography and Beyond: Developing Technologies for the Early Detection of Breast Cancer. Washington, DC, National Academy Press, 2001

4. Jung H: Assessment of usefulness and risk of mammographic screening with exclusive attention to radiation risk. Radiologe 41:385-395, 2001

5. Beemsterboer PM, Warmerdam PG, Boer R, et al: Radiation risk of mammography related to benefit in screening programmes: A favourable balance? J Med Screen 5:81-87, 1998

6. Goergen SK: Characteristics of breast carcinomas missed by screening radiologists. Radiology 204:131-135, 1997

7. Rosenberg RD: The effect of age, breast density and estrogen replacement therapy for sensitivity and cancer stage of screening mammography: A population cased review of 183,233 screening examinations from the Albuquerque Metropolitan Area. Presented at Radiol Soc Am Meetings, Chicago, IL, November 28-December 4, 1997 (abstr)

8. Ma L, Fishell E, Wright B, et al: Case control study of factors associated with failure to detect breast cancer by mammography. J Natl Cancer Inst 84:781-785, 1992

9. American Cancer Society: Breast Cancer Facts and Figures 2001-2002. Department of Epidemiology and Surveillance Research, American Cancer Society, Atlanta, GA, 2003, pp 1-23

10. Peer PG, Verbeek AL, Mravunac M, et al: Prognosis of younger and older patients with early breast cancer. Br J Cancer 73:382-385, 1996

11. Fisher CJ, Egan MK, Smith P, et al: Histopathology of breast cancer in relation to age. Br J Cancer 75:593-596, 1997

12. Yildirim E, Dalgic T, Berberoglu: Prognostic significance of young age in breast cancer. J Surg Oncol 74:267-272, 2000

13. Xiong Q, Valero V, Kau V, et al: Female patients with breast carcinoma age 30 years and younger have a poor prognosis: The M.D. Anderson Cancer Center experience. Cancer 92:2523-2528, 2001

14. Fricke H, Morse S: The electric capacity of tumors of the breast. J Cancer Res 16:310-376, 1926

15. Scholz B, Anderson R: On electrical impedance scanning: Principles and simulations. Electromedica 68:35-44, 2000

16. Singh B, Smith CW Hughes R: In vivo dielectric spectrometer. Med Biol Eng Comput 1745-1760, 1979

17. Surowiec AJ, Stuchly SS, Barr JR, et al: Dielectric properties of breast carcinoma and the surrounding tissues. IEEE Trans Biomed Eng 35:257-263, 1988

18. Morimoto T, Kinouchi Y, Iritani T, et al: Measurement of the electrical bio-impedance of breast tumors. Eur Surg Res 22:86-92, 1990

19. Joissinet J: Variability of impedivity in normal and pathological breast tissue. Med Biol Eng Comput 34:346-350, 1996

20. Joissinet J: The impedivity of freshly excised human breast tissue. Physiol Meas 19:61-75, 1998

21. Chauveau N, Hamzaoui L, Rochaix P, et al: Ex vivo discrimination between normal and pathological tissues in human breast surgical biopsies using bioimpedance spectroscopy. Ann N Y Acad Sci 873:42-50, 1999

22. Assenheimer M, Laver-Moskovitz O, Malonek D, et al: The T-Scan technology: Electrical impedance as a diagnostic tool for breast cancer detection. Physiol Meas 22:1-8, 2001

23. Piperno G, Frei EH, Moshitzky M: Breast cancer screening by impedance measurements. Front Med Biol Eng 2:111-117, 1990

24. Glickman YA, Filo O, Nachaliel U, et al: Novel EIS postprocessing algorithm for breast cancer diagnosis. IEEE Trans Med Imag 21:710-712, 2002

25. Dickhaut M, Schreer I, Frischbier HJ, et al: The value of BBE in the assessment of breast lesions, in Dixon JM (ed): Electropotentials in the Clinical Assessment of Breast Neoplasia. New York, NY, Springer-Verlag, 1996, pp 63-69

26. Piperno G, Lenington S: Breast electrical impedance and estrogen use in postmenopausal women. Maturitas 41:17-22, 2002

27. Gardon J, Boussinesq M, Kamgno J, et al: Effects of standard and high doses of ivermectin on adult worms of Onchocerca volvulus: A randomised controlled trial. Lancet 360:203-210, 2002

28. Schwab M, Claas A, Savelyeva L: BRCA2: A genetic risk factor for breast cancer. Cancer Lett 175:1-8, 2002

29. Feig SA: Mammographic screening of women aged 40-49 years: Benefit, risk, and cost considerations. Cancer 76:2097-2106, 1995

30. Overmoyer B: Breast cancer screening. Med Clin N Am 83:1443-1466, 1999

31. Letton AH, Mason EM, Ramshaw BJ: Twenty-year review of a breast cancer screening project: Ninety-five percent survival of patients with nonpalpable cancers. Cancer 77:104-106, 1996

32. Smart CR, Byrne C, Smith RA, et al: Twenty-year follow-up of the breast cancers diagnosed during the Breast Cancer Detection Demonstration Project. CA Cancer J Clin 47:134-149, 1997

33. Baines CJ: Screening for breast cancer: How useful are clinical breast examinations. J Natl Cancer Inst 92:958-959, 2000

34. Smart CR, Hartmann WH, Beahrs OH, et al: Insights into breast cancer screening of younger women: Evidence from the 14-year follow-up of the Breast Cancer Detection Demonstration Project. Cancer 72:1449-1456, 1993

35. Thomas DB, Gao DL, Ray RM, et al: Randomized trial of breast self-examination in Shanghai: Final results. J Natl Cancer Inst 94: 1445-1457, 2002

36. Orel SG, Schnall MD, LiVolsi VA, et al: Suspicious breast lesions: MR imaging with radiologic-pathologic correlation. Radiology 190: 485-493, 1994

37. Morris EA, Schwartz LH, Dershaw DD, et al: MR imaging of the breast in patients with occult primary breast carcinoma. Radiology 205: 437-440, 1997

38. Warner E, Plewes DB, Hill KA, et al: Surveillance of BRCA1 and BRCA2 mutation carriers with magnetic resonance imaging, ultrasound, mammography, and clinical breast examination. JAMA 292:1317-1325, 2004

39. Kriege M, Brekelmans CT, Boetes C, et al: Magnetic Resonance Imaging Screening Study Group: Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. N Engl J Med 351:427-437, 2004

40. Teh W, Wilson AR: The role of ultrasound in breast cancer screening: A consensus statement by the European group for breast cancer screening. Eur J Cancer 34:449-450, 1998

41. Smith DN: Breast ultrasound. Radiol Clin North Am 39:485-497, 2001

42. Kolb T, Fuchsjager M, Lichy J, et al: The sensitivity and specificity of electrical impedance imaging or carcinoma in women with known breast lesions: The effect of lesion size. Radiological Society of North America, Chicago, IL, November 29-December 5, 2002 (abstr 1237)

43. Elmore JG, Barton MB, Moceri VM, et al: Ten-year risk of false positive screening mammograms and clinical breast examinations. N Engl J Med 338:1089-1096, 1998

44. Lerman C, Trock B, Rimer BK, et al: Psychological side effects of breast cancer screening. Health Psychol 10:259-267, 1991

45. Lowe JB, Balanda KP, Del Mar C, et al: Psychologic distress in women with abnormal findings in mass mammography screening. Cancer 85:1114-1118, 1999

46. Kerner TE, Paulsen KD, Hartov A, et al: Electrical impedance tomography of the breast. IEEE Trans Med Imag 21:638-645, 2002

47. Woo EJ, Hua P, Webster JG, et al: Skin impedance measurements. Med Biol Eng Comput 30:97-102, 1992

48. Osterman KS, Kerner TE, Williams DB, et al: Multifrequency electrical impedance imaging: Preliminary in vivo experience in breast. Physiol Meas 21:99-109, 2000

49. Joissinet J, Schmitt M: Review of parameters for the bioelectrical characterization of breast tissue. Ann N Y Acad Sci 873:30-41, 1999

50. Metz CE: Fundamental ROC analysis, in Beutel J, Van Metter R (eds): Handbook of Medical Imaging, Vol 1: Physics and Psychophysics. Bellingham, WA, SPIE Press, 2000, pp 751-769

51. Metz CE: Statistical analysis of ROC data, in Herbert H, Myers R (eds): Multiple Regression Analysis. New York, NY, AIP Press, 1986