Electrical Impedance Scanning as a New Breast Cancer Risk Stratification Tool for Young Women

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Background: Electrical impedance scanning (EIS) measures changes in breast tissue associated with breast cancer (BrCa) development. The T-Scan(tm)2000 (ED is designed to use EIS to identify women ages 30–39 with elevated risk of breast cancer (i.e., T-Scan+ women). Aim: To estimate the relative probability of breast cancer in a T-Scan+ woman compared to a randomly selected young woman. Methods: A prospective, two-cohort trial was conducted in pre-menopausal women. The Specificity (S)2-Cohort evaluated T-Scan specificity in 1,751 asymptomatic women ages 30–39. The Sensitivity(S)-Cohort evaluated T-Scan sensitivity in 390 women ages 45–30 scheduled for biopsy. Specificity, sensitivity, and conservative estimate of disease prevalence were used to calculate relative probability.

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RESULTS: In the S-C Cohort, 93 of 1,751 women were T-Scan+ (S_0 = 94.7%; 95% CI: 93.7–95.7%). In the S-C Cohort, 23 of 87 biopsy-proven cancers were T-Scan+ (S_0 = 26.4%; 95% CI: 17.4–35.4%). Given S_0 = 94.7%, S_1 = 26.4% and prevalence of 1.5 cancers/1,000 women (ages 30–39), the relative probability of a T-Scan+ woman having Br-Ca is 4.95: (95% CI: 3.16–7.14).

Conclusion: EIS can identify a subset of young women with a relative probability of breast cancer almost five times greater than in the population of young women at-large. T-Scan+ women have a sufficiently high risk of Br-Ca to warrant further surveillance or imaging.


KEY WORDS: screening; breast cancer; electrical impedance

INTRODUCTION

There are approximately 20 million American women between the ages of 30 and 39 [1]. While the prevalence of breast cancer is lower in this population than in older women, breast cancer in younger women remains a significant clinical problem and diagnostic challenge [2–5]. In absolute terms, approximately 12,000 new breast cancer cases are detected annually in women aged 30–39 in the United States (U.S.) each year [6]. This incidence parallels the roughly 13,000 cervical cancers that are identified in women of all ages in the U.S. each year. Effective screening methods exist to detect cervical cancer and many young women are screened for it routinely each year [7]. However, in women under 40, there are no effective screening tests recommended for early breast cancer detection.

While annual screening mammography has been shown to improve early detection and reduce breast cancer mortality in women over 40, it is not recommended for average-risk women between the ages of 30 and 39. The lower incidence of breast cancer, the increased breast density, and the consequently lower sensitivity of mammography in these young, pre-menopausal women are amongst the reasons given for not supporting routine mammographic screening of this population. Mammography screening is offered to women under age 40 only if they have known familial, genetic, or personal risk factors for breast cancer. Yet the vast majority (~90%) of women in this age group who develop breast cancer do not have any established risk factors [8–10].

In addition, both MRI and ultrasound have been studied as possible screening modalities for young women; however, the expense, invasiveness and reduced specificity of MRI, and the time-consuming, operator-dependent nature of ultrasound render both unsuitable for initial population-based screening of average risk women [11,12]. Furthermore, the role of these modalities in screening and detecting breast cancer in women who are at increased risk or who exhibit certain symptoms has grown substantially, and is expected to continue to evolve.

Under the current standard of care, women ages 30–39 are generally screened with clinical and/or breast self-examination (CBE/ BSE) [13–15]. However, CBE is of limited effectiveness because it is not sensitive for small lesions, is highly dependent on examiner experience and technique, and is difficult to compare from year to year. Consequently, studies show that most cancers in women under 40 are not detected until they have grown sufficiently large that the woman herself detects a palpable mass [13,14]. Predictably, these self-detected cancers are often at a relatively advanced stage. Delayed breast cancer diagnosis subsequently leads to more aggressive and costly treatment regimens, greater morbidity and lower survival when compared to disease diagnosed at an earlier stage in these young patients [15,16].

Reliance upon CBE and known risk factors fails to identify most young women that develop breast cancer as at-risk. As a result, recent attention has focused on technologies and practices that could identify a select cohort of young women at increased risk for either having or developing the disease. Implementation of risk assessment methods could identify elevated breast cancer risk in young women who would otherwise be overlooked by current standards of care, but who may benefit from additional surveillance or imaging.

Previously, we conducted a multi-center prospective evaluation of a new approach to breast cancer screening specifically directed toward women under 40. The evaluated technology, electrical impedance scanning (EIS), measures tissue-specific impedance changes across each breast to identify impedance patterns that may be associated with cancer risk [17–20]. This study used the T-Scan™ ED200 (Miribel Medical Systems, Austin, TX) to evaluate the use of EIS for breast cancer risk assessment in 1,103 women. Results from this study suggested that EIS may effectively identify a subset of women with a level of risk that significantly exceeds that of their average-risk age-matched peers. More specifically, this study estimated the absolute breast cancer risk of T-Scan positive women at 1 in 147, as compared to 1 in 1,186 for T-Scan negative women [19].

A prospective, two-cohort trial was designed to further assess the utility of EIS in detecting the risk of breast cancer in women ages 30–39. An interim analysis of the results from the current multicenter prospective trial demonstrated that T-Scan positive women had a significantly increased estimated absolute risk of breast cancer (1 in 108) compared to a T-Scan negative women (1 in 918) [20]. Herein, we report the final results of this follow-on pivotal trial, including estimates of the sensitivity and specificity of T-Scan-based EIS. These values, together with a conservative estimate of disease prevalence, enable a calculation of the relative probability of having breast cancer associated with a positive T-Scan result. The results of this study will help determine if a screening paradigm using this technology could offer a clinically useful approach to widespread screening and risk assessment in women under 40.

MATERIALS AND METHODS

EIS Algorithm Development

The T-Scan 2000ED is a modified version of the original FDA-approved T-Scan 2000 (Miribel Medical Systems). This version has been designed to address the unmet clinical need of assessing breast cancer risk in otherwise healthy young women. Compared to the predecessor, it uses a distinct frequency range and incorporates a novel software algorithm that utilizes different thresholds and a different operating point on the receiver operating characteristics curve. These operating characteristics were optimized to maximize specificity (minimize false negatives) while maintaining a reasonable sensitivity at a ratio consistent with the requirements of a screening tool for a low risk population. This design ensures that the yield, in terms of absolute risk for breast cancer in young pre-menopausal women, would be consistent with or higher than the average absolute risk in women age 40–49 who are recommended for routine annual screening.

The T-Scan Breast Screening Examination

The details of the T-Scan examination have been provided previously [19,20]. Briefly, T-Scan examination of the breast is performed after verifying normal CBE. The surface probe is placed in contact (facilitated by commercially available ultrasound conducting gel) with the patient's breast, and is directed over each of nine sectors
in a device-guided, pre-determined sequence. The device measures tissue electrical impedance in each sector over multiple frequencies by applying an electrical signal via a cylindrical signal transmitter held in the patient's hand contra-lateral to the examined breast. The examination is painless and takes 5–10 min to complete. The device detects impedance differences that are associated with malignancy based on the principle that malignant tissue has lower relative electrical impedance. The device algorithm analyzes the differences and displays a solid green horizontal line if the result is negative and a red-hatched line if the result is positive. The device does not produce any image or data that can be used for diagnosis.

**Examiner Training**

All exams were performed by examiners trained by an Applications Expert. Training sessions were conducted over the course of a single day and reviewed the technical operation of the device and the essential elements of conducting an appropriate study. These elements include assuring good contact between the skin and the probe, eliminating air bubbles from the conducting gel, positioning the probe correctly on the breast, and maintaining the stability of the probe during recording.

**Overview**

Based on current standards of care, a relative risk for breast cancer of 2.0 or more (e.g., having a first-degree relative with breast cancer) was determined to represent a threshold at which younger women are frequently considered "at-risk" and offered breast imaging, more frequent surveillance and/or enrollment in specific management protocols [8–10]. A successful study outcome was thus determined to be a relative risk or probability of 2.0 or more associated with a positive T-Scan result.

This was a two-cohort, prospective, multi-center controlled trial conducted over a 23-month period (August 2003 to July 2005) at 25 institutions in the United States and Israel with minimal overlap (five sites) between sites contributing to each study cohort. One study cohort was used to estimate T-Scan specificity (and false positive rate) and the other estimated T-Scan sensitivity. In the Specificity Cohort, data were obtained from a consecutive series of examinations of average-risk, asymptomatic women ages 30–39 undergoing a one-time T-Scan procedure after a confirmed negative CBE. There was no mandated follow-up of women with positive EIS findings. All women included in this study cohort continued with their standard course of clinical care. Negative T-Scan results were not taken into consideration in the clinical management of women in either study cohort.

The Sensitivity Cohort consisted of an enriched population of women scheduled to undergo breast biopsy for a suspicious finding during prior diagnostic work-up. The age range was expanded from 30–39 to 30–45 years old and also included women with palpable breast masses. Expansion of the age range to include women ages 39–45 was required due to the low frequency of breast cancer in women under 40. If the inclusion criterion had been restricted to women under 40, a prohibitively large sample size would have been required. This decision was supported by the fact that breast tissue impedance is not age-dependent; EIS measurements of the breast are affected principally by menopausal alterations in the systemic hormonal milieu [20–22]. Excluding patients over 45 and postmenopausal patients ensured the device was tested in women who had breast tissue consistent with women in the intended use population. Inclusion of women age 40–45 undergoing annual mammographic screening enabled the evaluation of device performance in clinically occult, radiologically apparent lesions. Physicians performing screening exams were blinded to the T-Scan result and pathology findings at the time of the exam.

The primary endpoint of the two-arm trial was relative probability, which was defined as the probability that a T-Scan positive woman has cancer relative to the probability that a randomly selected woman has cancer.

**Participating Sites**

All study sites (listed in Appendix 1) had a high-volume gynecological or breast screening practice, an expressed interest in new diagnostic modalities, and previous participation in clinical research. In general, gynecological centers participated in the Specificity Cohort, whereas private surgery and radiological centers participated in the Sensitivity Cohort. The Specificity Cohort of the study was conducted at 17 sites (15 in the U.S. and two in Israel) and included civilian, military, academic and high-volume private clinical practices. The Sensitivity Cohort of the study was conducted at 18 sites (12 in the U.S. and 6 in Israel). Both cohorts were studied under an IRB or Helsinki Committee approved protocol at all study sites. Informed consent was obtained from all women prior to enrollment.

**Eligibility Criteria**

The Specificity Cohort enrolled 1,751 women visiting their obstetrician/gynecologist or breast center for an annual physical exam who did not exhibit breast cancer related signs or symptoms (Table I). Prior to enrollment, the following eligibility criteria were met: (1) women ages 30–39 inclusive; (2) not pregnant; (3) no previous cosmetic breast operation, breast biopsy or operation within 90 days of the exam, or fine needle aspiration (FNA) within 30 days of exam; (4) not lactated within the previous 3 months; (5) no exposure to chemotherapeutic agents; (6) no known breast cancer; (7) no implanted electrical device; and, (8) no palpable breast abnormality. Altogether, 171 of the 179 ineligible patients were either outside the intended age range or had a palpable breast mass. Two women declined participation after providing consent, and the T-Scan examination could not be completed in 14 patients due to technical difficulties.

**TABLE I. Specificity and Sensitivity Cohorts Enrollment Summary**

<table>
<thead>
<tr>
<th>Cohort</th>
<th>n</th>
<th>T-Scan exams attempted</th>
<th>Patient declined exam</th>
<th>Technical difficulty</th>
<th>T-Scan exam results</th>
<th>Ineligible</th>
<th>Age &lt;30 or &gt;39 years</th>
<th>Lactating</th>
<th>Prior breast cosmetic surgery</th>
<th>Prior chemotherapy</th>
<th>Positive CBE</th>
<th>Per protocol exams</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specificity Cohort</td>
<td>1,751</td>
<td>1,946</td>
<td>2</td>
<td>14</td>
<td>1,930</td>
<td>179</td>
<td>112</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>59</td>
<td>1,751</td>
</tr>
<tr>
<td>Sensitivity Cohort</td>
<td>390</td>
<td>597</td>
<td>4</td>
<td>4</td>
<td>545</td>
<td>155</td>
<td>54</td>
<td>2</td>
<td>1</td>
<td>8</td>
<td>24</td>
<td>66</td>
</tr>
</tbody>
</table>

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The Sensitivity Cohort enrolled 390 women with a palpable and/or radiologically detected breast finding who were scheduled to undergo a breast biopsy. Biopsies were performed after T-Scan exam (Table I). Eligibility criteria 2 through 7 above applied to this study arm. The age range was expanded to 30–45 years. Postmenopausal (12 or more consecutive months of amenorrhea) women were ineligible. Reasons for ineligibility are specified in Table I. Importantly, biopsy results were not obtained for 44 women that had consented, because a decision was made on the basis of additional imaging procedures that biopsy was not warranted at the time (n = 40), or the patient declined biopsy (n = 4). The T-Scan examinations performed in the Sensitivity and the Specificity Cohorts were identical except that examiners in the Sensitivity Cohort were “blinded” to the results; neither green nor red line was displayed at the end of T-Scan examination. Sensitivity Cohort examiners were blinded to the results so that T-Scan results would not impact patient management. However, because the results were blinded, technical problems could only be detected during periodic quality control and protocol monitoring visits. As a result, one site accounted for the majority of the technically inadequate data (4 technically inadequate cases had no result and 66 had a result that was considered unreliable because of technical problems) that were identified during such visits. Without blinding, such technical difficulties would have been detected during and immediately after the performance of each examination. Ineligibility due to technical failure was most commonly attributable to mechanical failure of the scanning probe.

### Study Interventions

All study participants signed written informed consent. Prior to T-Scan examination in both study arms, all women underwent CBE by a qualified examiner, and the results were entered into the T-Scan system database. In the Specificity Cohort, all T-Scan examinations were conducted after the CBE. Each woman in the Specificity Cohort who had a positive T-Scan result was informed of the findings and, at the discretion of her physician, was recommended to consider further follow-up. The study did not mandate clinical or imaging-based follow-up. In the Sensitivity Cohort, all T-Scan examinations were conducted after the CBE and before the scheduled breast biopsy. Further follow-up data beyond pathological diagnosis of the biopsy were not collected as part of the study. Experienced breast pathologists determined histological diagnosis. For the purposes of this study, pre-malignant diagnoses of atypical hyperplasia and lobular carcinoma in situ (LCIS) were regarded as benign findings.

### Data and Statistical Analysis

All women in the Specificity Cohort of the study were young and asymptomatic, and they were assumed not to have breast cancer. Hence, all T-Scan positive results in this arm were considered false positives. It should be noted that this assumption biases estimates of specificity against the T-Scan device. In fact, if the rate of breast cancer is 0.0015, then on average one might expect 2–3 cases of breast cancer in 1,751 women. Therefore, it is possible that a small number of cases classified as “false positives” in this study were, in fact, true positives. This misclassification, however, would have a negligible effect on the specificity estimate. Importantly, the assumption that all T-Scan negative patients were breast cancer-free did not affect patient care. For the purposes of this study cohort, specificity (true negative) was defined as the proportion of T-Scan negative cases.

In the Sensitivity Cohort, sensitivity was defined as the number of true positives divided by the sum of true positives and false negatives. A true positive was defined as a pathologically verified cancer case that was T-Scan positive. A false negative was defined as a pathologically verified cancer case that was T-Scan negative. In other words, sensitivity was assessed by determining the percent of pathologically verified cancer cases that were identified as T-Scan positive. For this calculation, it was determined that accrual to the Sensitivity Cohort could end at 87 patients with histologically verified breast cancer, since the primary success criterion (Pr ≥ 2.0) could be met even if no further cancers were identified. Hence, accrual to the Sensitivity Cohort of the trial ended with 87 cancer patients in a study arm population of 390 women.

Several potential covariates, including menopausal status, exposure to exogenous hormones, breast size (brassiere cup size: A–B, C–D, >D), and family history of breast cancer (limited to first-degree relatives), were analyzed to assess their effect on the estimates of specificity and sensitivity. Pearson Chi-square or Fisher Exact Test statistics were used to examine the relationship between specificity or sensitivity and each covariate. Multiple logistic regression analysis was used to examine specificity in relation to combinations of covariates. Statistical analysis was performed using Minitab software (State College, PA). All statistical tests were two-sided and a P-value ≤ 0.05 was considered significant. Table II summarizes the Specificity and Sensitivity Cohort populations.

### TABLE II. Specificity and Sensitivity Study Cohorts*

<table>
<thead>
<tr>
<th>Category</th>
<th>Specificity Cohort (n = 1,751)</th>
<th>Sensitivity Cohort (n = 390)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>Cancer (n = 87), n (%)</td>
</tr>
<tr>
<td>Age 30–39 years (specificity); age 30–45 years (sensitivity)</td>
<td>1,751 (100%)</td>
<td>37 (42.5%)</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>34.7 (SD 2.8)</td>
<td>39.5 (SD 3.9)</td>
</tr>
<tr>
<td>Pre-menopausal</td>
<td>1,718 (98.1%)</td>
<td>57 (65.5%)</td>
</tr>
<tr>
<td>No contraceptive/sterility/hormone replacement drugs</td>
<td>968 (55.3%)</td>
<td>68 (78.2%)</td>
</tr>
<tr>
<td>No first-degree relative with breast cancer</td>
<td>1,558 (89.0%)</td>
<td>13 (14.9%)</td>
</tr>
<tr>
<td>≥ 1 First-degree relative with breast cancer</td>
<td>163 (9.3%)</td>
<td></td>
</tr>
<tr>
<td>Brassiere cup size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A–B</td>
<td>839 (47.9%)</td>
<td>26 (29.9%)</td>
</tr>
<tr>
<td>C–D</td>
<td>794 (45.3%)</td>
<td>34 (39.0%)</td>
</tr>
<tr>
<td>&gt;D</td>
<td>84 (4.8%)</td>
<td>3 (3.4%)</td>
</tr>
<tr>
<td>Positive CBE</td>
<td>0 (0%)</td>
<td>17 (19.5%)</td>
</tr>
<tr>
<td>Size of cancer ≤ 2.0 cm</td>
<td>85 (49.5%)</td>
<td>45 (51.7%)</td>
</tr>
<tr>
<td>Mean cancer size (mm)</td>
<td>22.9 (SD 15.1)</td>
<td>15.8 (SD 9.8)</td>
</tr>
</tbody>
</table>

*Some of the variables (menopausal status, hormone usage, family history, and brassiere cup size) had missing data.

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Data Analyses Combining the Results From the Two Study Cohorts

The primary endpoint of the two-arm trial was relative probability, which was defined as the probability that a T-Scan positive woman has cancer relative to the probability that a randomly selected woman has cancer. We used experimentally ascertained sensitivity and specificity levels, along with published data on prevalence of breast cancer in the intended use population to estimate the relative probability (likelihood ratio) that a woman who is positive on EIS examination actually has breast cancer and assessed that estimate in the context of a woman randomly selected from the population at large. This derivation using Bayes' Theorem simply applies the probability of breast cancer, probability of an EIS result conditional upon the patient having breast cancer, and the probability of EIS conditional upon the patient not having breast cancer. Bayes' theorem is applied to determine the probability of disease given a test result, in this case EIS finding. The derivation arrives at the probability of breast cancer if EIS is positive by dividing the conditional probability that a T-Scan positive woman will have breast cancer by the probability that a randomly selected woman has breast cancer.

The estimates of sensitivity and specificity obtained in this study were used to calculate this relative probability:

\[
RP = \frac{S_p}{S_a + (1 - S_p)} \frac{(1 - S_a)}{(1 - R_a)}
\]

The relative probability is a function of the sensitivity (\(S_p\)), specificity (\(S_a\)), and the prevalence of cancer in the population (\(R_a\)). Prevalence of breast cancer in this population was assumed to be 1.5/1,000 women. Lower assumed prevalence levels would yield similar albeit somewhat higher relative risk estimates. Confidence intervals for this relative risk were calculated by computing the upper and lower limits of the 95% confidence intervals for sensitivity and specificity.

Safety Evaluation

All study subjects enrolled in this trial were evaluated for device-related adverse events. They were also queried about any discomfort or pain experienced during the examination.

RESULTS

There were no reported cardiac, neurological, dermal, thermal or allergic reactions or serious adverse events in this study. In the Specificity Cohort, 93 of 1,751 women were T-Scan positive. Specificity for the pre-protocol population of 1,751 asymptomatic women age 30–39 years in the Specificity Cohort was 94.7% (1,658/1,751; 95% CI, 93.7–95.7%). One center that contributed 17 Specificity Cohort cases had an atypically low specificity (84%); specificity in the other centers of this study arm ranged from 89% to 97%. There was no significant relationship between T-Scan specificity and menopausal status, use of exogenous hormones, or family history. T-Scan specificity varied significantly with brassier cup size (Table III).

Sensitivity for the per protocol population of 390 pre-menopausal women age 30–45 years undergoing biopsy in the Sensitivity Cohort was 26.4% (238/7; 95% CI, 17.4–35.4%) based on 87 pathology confirmed cancers (DCIS, \(n = 14\); invasive duct carcinoma, \(n = 69\); invasive lobular carcinoma, \(n = 4\)). No statistically significant differences were found among centers in sensitivity. The number of cancer cases at each site was small; therefore, sensitivity varied substantially among sites, ranging from 0% to 53%. There was no statistically significant relationship between T-Scan sensitivity and use of exogenous hormones, family history, palpability of breast abnormality, or cancer size, although sensitivity tended to decrease as cancer size increased (size \(\leq 2\) cm, \(S_a = 35.6\%\); size \(> 2\) cm, \(S_a = 22.2\%\); Table IV). Owing to the small sample size, the Sensitivity Cohort was not powered for an extensive analysis of multiple covariates; therefore, these results should be interpreted with caution.

The results from the two study arms, with measured specificity of 94.7% and sensitivity of 26.4%, were combined to estimate the relative probability that a T-Scan positive woman has breast cancer relative to that of a randomly selected woman from the population at large. Assuming a prevalence of breast cancer in women age 30–39 of 1.5/1,000 women, the relative probability of a woman with a positive T-Scan examination having cancer was 4.95 (95% CI, 3.16–7.14). In other words, a T-Scan positive woman was almost five times as likely as the average woman in the 30–39 years old population to have breast cancer at the time of the examination.

Although the present study does not allow for determination of age-specific cancer prevalence, data from the literature was used to generate such estimates [22–26]. A conservative estimate of prevalence of cancer in the population of average risk, 30- to 39-year-old women is 1.5/1,000, there is on average one cancer case for every 666 women. Among T-Scan positive women, it is expected to be one cancer case for every 136 women. If all T-Scan positive women age 30–39 underwent screening mammography, cancer detection rate would be \(\sim 1\) in 194 based on age-specific mammogram sensitivity of

<table>
<thead>
<tr>
<th>TABLE III. Estimated Specificity Levels Associated With Different Clinical Covariates Among the 1,751 Screened Women Age 30–39</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category</td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>Pre-menopausal</td>
</tr>
<tr>
<td>Postmenopausal</td>
</tr>
<tr>
<td>No exogenous hormone (a)</td>
</tr>
<tr>
<td>Exogenous hormone use</td>
</tr>
<tr>
<td>Negative family history</td>
</tr>
<tr>
<td>Positive family history</td>
</tr>
<tr>
<td>Negative CBE</td>
</tr>
<tr>
<td>Positive CBE</td>
</tr>
<tr>
<td>Brasiiere cup size A/B</td>
</tr>
<tr>
<td>Brasiiere cup size C/D</td>
</tr>
<tr>
<td>Brasiiere cup size D+</td>
</tr>
</tbody>
</table>

\(a\)Some of the variables (menopausal status, hormone usage, family history, and brassiere cup size) had missing data. Exogenous hormone use refers to oral contraception, IUD with hormone, and hormone replacement therapy posthysterectomy.

<table>
<thead>
<tr>
<th>TABLE IV. Estimated Sensitivity Levels Associated With Different Clinical Covariates Among 87 Biopsy-Proven Cancer Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category</td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>No exogenous hormone</td>
</tr>
<tr>
<td>Exogenous hormone use</td>
</tr>
<tr>
<td>Negative family history</td>
</tr>
<tr>
<td>Positive family history</td>
</tr>
<tr>
<td>Negative CBE</td>
</tr>
<tr>
<td>Positive CBE</td>
</tr>
<tr>
<td>Bra size A/B</td>
</tr>
<tr>
<td>Bra size C/D</td>
</tr>
<tr>
<td>Bra size D+</td>
</tr>
<tr>
<td>Cancer size (\leq 2) cm</td>
</tr>
<tr>
<td>Cancer size (&gt; 2) cm</td>
</tr>
<tr>
<td>Missing data (a)</td>
</tr>
</tbody>
</table>

\(a\)Of the remaining 15 cancers, eight were detected as microcalcifications alone on mammography. These eight did not have a reported finding on ultrasound, and specific size was not reported on the pathology report. Size was not reported on either the imaging or pathology reports for the additional seven cancer cases excluded from this analysis. \(P\) represents bivariate results.
TABLE V. Estimated Relative and Absolute Risks of Breast Cancer in Different Groups of Women

<table>
<thead>
<tr>
<th>Female population</th>
<th>Relative risk (95% CI)</th>
<th>Absolute risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average age, 30–39</td>
<td>1:667</td>
<td>0.0015</td>
</tr>
<tr>
<td>Average age, 40–49</td>
<td>1:340^</td>
<td>0.0029</td>
</tr>
<tr>
<td>First-degree relative with breast cancer</td>
<td>1:333</td>
<td>0.0030</td>
</tr>
<tr>
<td>T-Scan screen positive</td>
<td>4.95 (3.16–7.14)</td>
<td>1:136 0.0074</td>
</tr>
</tbody>
</table>

*Absolute risk = (1/cancer/4000 mammograms)/85% for assumed mammographic sensitivity in women age 40–49.

Second to last column is number of cancers/mammogram performed and last column is absolute risk of cancer. Although the present study does not allow for determination of age-specific cancer prevalence, data from the literature was used to generate such conservative estimates.25–26

70% [3,4,23–25]. This rate exceeds the currently accepted rate of approximately 1 in 340 in women age 40–49 who are screened routinely, and women less than age 40 with an affected first-degree relative (~1 in 333; 22,26,27; Table V).

Women in the Specificity Cohort (n = 1,751) were not followed to determine if they had breast pathology, and all positive T-Scan exams were assumed to be false positive. Women with known breast pathology in the sensitivity cohort were divided into two groups according to final pathology results for statistical comparison: women with benign (n = 303) and those with cancer (n = 87). Table VI summarizes rate of T-Scan positive results for these three groups: screening (5.3%), biopsy-benign (19.1%), and biopsy-cancer (26.4%). These three groups differed significantly from one another (P < 0.0001). The odds ratio for cancer detection in this study was 5.0 and for detection of any breast pathology (including benign as well as malignant breast pathology) was 3.9.

DISCUSSION

Attempts have been made to identify groups of younger women for whom earlier imaging based screening would be indicated [6]. Lifetime risk assessment tools are available for women over age 40 to identify those who are at-risk for developing breast cancer. These instruments are not designed to identify increased risk in younger women, however [25]. The principal criterion used to identify high-risk young women is significant family history of breast cancer, which is found in only a small percentage (~5–10%) of younger women with breast cancer [29,30]. Presently, a small fraction of women are known to have genetic risk factors that would herald “early warning” and prompt initiation of early screening. Consequently, breast cancers in young pre-menopausal women unfortunately are most often diagnosed at a more advanced stage, requiring more aggressive and expensive treatments with concomitant reduction in survivorship and quality of life [14–16].

EIS is designed to identify tissue impedance changes associated with malignant or pre-malignant processes [31–33]. The current study evaluated the possible role of breast EIS using a specific device and approach for identifying cancer risk in a target population of younger pre-menopausal women, most of whom would otherwise be screened with CBE alone. Better screening methods are needed to identify young at-risk women who could benefit from earlier image-based screening. EIS holds promise for effectively performing such risk-identification in young pre-menopausal women [19,20]. The current study further suggests that EIS can successfully address the unmet clinical need of risk assessment for young seemingly average-risk women.

The aim of the paradigm suggested here is to identify a subset of women who would otherwise be overlooked by current standards of care utilizing CBE alone, but who are likely to benefit from early surveillance or imaging. This study estimated the probability that a T-Scan positive woman has breast cancer relative to a randomly selected woman from the target population. The pre-specified success criterion, relative probability ≥2.0, corresponding to breast cancer risk in a woman with a first-degree relative with breast cancer [8,9,29,30], was exceeded significantly. The results indicate that the relative probability for breast cancer in a T-Scan positive woman is 4.95 (Table V).

Further analysis shows that this value is meaningful. Relative probability (Pr) was not altered significantly by adjusting estimated disease prevalence in the target population (1.5/1,000 vs. 0.5/1,000; Pr = 4.95 vs. 4.97), indicating that estimates of relative probability are not very sensitive to the actual prevalence of cancer in that population. All specificity levels in the various subgroups of the Specificity Cohort of this study (90.5–97.5%) correlated with a relative probability exceeding the pre-specified success criterion, Pr ≥2.0 (Pr = 2.77–10.41). Similarly, even for the lower bound of the 95% confidence interval of the estimated sensitivity (17.4%), the relative probability significantly exceeded the study success criterion of 2.0 (Pr = 3.27). In fact, T-Scan sensitivity was increased in smaller lesions, consistent with previously published reports [17,18,20]. Importantly, T-Scan specificity and sensitivity were found to be independent of breast lesion palpability on CBE.

The measure of “relative probability” used in this study differs from the more familiar “relative risk”? in two important ways. First, relative risk is dependent on the prevalence of the condition in the population being studied. Relative probability used in this study is based on the published data of prevalence in the population at large and independent of the percentage of cases in this particular study that were malignant. Second, relative risk for breast cancer as measured in other studies typically is a cumulative lifetime relative risk. This study did not include long-term follow-up of T-Scan positive patients. Accordingly, the study does not provide significant insight regarding the extent to which women who are positive on a current T-Scan examination carry a higher future or lifetime risk for breast cancer. Hence, any association between T-Scan positive result and breast cancer risk translates only into current risk of breast cancer relative to the population at large on this basis.

Another way of interpreting the results of this study is to compare the expected yield of cancers (cancer detection rate) per mammogram in woman age 40–49 that are routinely screened with the cancer detection rate of women 30–39 that are found to be screen positive by T-Scan and, as a result, are referred to the most widely utilized means for breast cancer detection, mammography. Estimates of mammography sensitivity for women age 30–39 vary considerably in mammography screening trials. A review of studies reporting mammography performance in young or pre-menopausal women indicates sensitivity ranging from 67% to 89% [3,4,23–25]. A sensitivity of 70% was selected to compute estimated yield in T-Scan positive women. A positive T-Scan corresponds to a relative cancer risk ~5.0 times greater than the average risk (Table V). Given a prevalence of 1.5 cancers per

<table>
<thead>
<tr>
<th>Screening (n = 1,751)</th>
<th>Biopsy-benign (n = 303)</th>
<th>Biopsy-cancer (n = 87)</th>
<th>Pooled biopsy (n = 390)</th>
<th>Odds ratio cancer screening</th>
<th>Odds ratio pooled screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.3% (4.3–6.3%)</td>
<td>19.1% (14.7–23.5%)</td>
<td>26.4% (17.2–35.6%)</td>
<td>20.8% (16.8–24.8%)</td>
<td>5.0 (2.3–5.5)</td>
<td>3.9 (2.7–5.8)</td>
</tr>
</tbody>
</table>

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1,000 in women ages 30–39, a young, pre-menopausal woman that screens positive by T-Scan has an absolute risk of 1 in 136 (0.0074) of having breast cancer at time of examination. With a diagnostic imaging sensitivity of 70%, 1 cancer per 194 women would be expected to be detected in this cohort. This cancer yield (1 in 194 or 0.0051) is about twice as high as the widely accepted cancer detection rate in women between the ages of 40 and 49 in the United States (~1 cancer per 340 mammograms or 0.0029; Refs. [2,26,27]; Table V).

All per protocol women in the Specificity Cohort of the study were in the intended use population, namely, young (30–39 years), asymptomatic with normal clinical breast examination. Based on this profile and estimated disease prevalence, it was assumed that all study subjects in this study arm were free of breast cancer (i.e., all T-Scan positive exams = false positive screening test). This study design assumption could bias our reported results slightly against the proposed screening approach, as very few cancer cases would have been misclassified as false positives.

T-Scan sensitivity could not be estimated without study population enrichment as over 250,000 screened women in the intended use population would have been required in order to identify the same number (n = 87) of biopsy-proven cancers. Therefore, the inclusion of women age 30–39 and age 40–45 scheduled to undergo biopsy allowed for a cost-effective accrual of patients in the Sensitivity Cohort. This enrichment was considered reasonable, as this study cohort was selected (pre-menopausal) to ensure that breast tissue characteristics were comparable to and consistent with the target population based on data indicating that menopausal physiological changes are the principal determinant of normal breast related impedance characteristics [21,22]. Inclusion of women age 40–45 undergoing annual screening mammography also permitted an assessment of sensitivity in non-palpable lesions since at the age range of 30–39 years women with non-palpable findings are rarely biopsied. In fact, T-Scan sensitivity was increased in smaller lesions, which is consistent with previously published reports [17–20]. Not only are EIS characteristics independent of patient age in the pre-menopausal breast, but also importantly, T-Scan specificity and sensitivity in this study were found to be independent of breast lesion palpability. Actually, slightly higher T-Scan sensitivity in the non-palpable lesions was demonstrated in the Sensitivity Cohort; thus, the inclusion of patients with palpable lesions resulted in a slight bias against the proposed screening paradigm.

The prevalence estimate used in this study was based on the published data for the population at large [2,4,30,34] and was independent of the percentage of cases in this particular study that were cancerous. SEER data were not used to estimate cancer prevalence in the target population for this purpose because SEER data only records the number of new (incident) cancer cases reported. Further, breast cancers in young women under 40 are underestimated in SEER reports, as many cancers in this group generally remain undetected until mammography screening begins at age 40. Finally, SEER incidence rates tend to be lower than those reported in most mammographic screening studies across all age groups largely because compliance rates with mammographic screening remain modest nationwide. Hence, the number of cancers diagnosed per age group across the entire country, as reported by SEER, is expected to be lower than the number of cancers detected in specific screening studies where stricter adherence to protocol-based cohort screening is observed. Unlike the calculation of relative probability in T-Scan positive and negative women age 30–39, which is largely unaffected by prevalence, the comparison of expected cancer detection rate in women age 30–39 as compared to those 40–49 undergoing mammography depends on estimated disease prevalence.

Based on the assumptions above, namely, prevalence of 1.5/1,000 women and mammographic sensitivity of 70%, one cancer is expected to be detected in the cohort pre-menopausal women age 30–39 per 194 women who are T-Scan positive and are followed up with a diagnostic mammogram (assuming T-Scan sensitivity and specificity of 26.4% and 94.7%, respectively, demonstrated in the current study). This cancer yield (1 in 194 or 0.0051) is about twice as high as the widely accepted cancer detection rate in women between the ages of 40 and 49 (~1 cancer per 340 mammograms or 0.0029). We note that all candidates for the screening T-Scan exam are expected to be asymptomatic, under age 40, with no known risk factors or palpable breast abnormality; therefore, these young women would not be identified as at-risk without T-Scan screening, and typically would not be referred to a radiologist until the age of 40 or the detection of a palpable mass.

The finding that EIS detects general breast pathology (Table VI) is interesting for a couple of reasons. First, breast pathology sufficient to warrant biopsy is, in itself, a risk factor for the ultimate development of breast cancer. It has been reported that women who have a breast biopsy, regardless of their diagnosis, are approximately two to five times as likely as women from the general population to ultimately develop breast cancer (Refs. [35–39]; Table VII). Second, it has been hypothesized that electrical measurements identify pathological changes in breast tissue that precede the development of carcinoma [31,32]. Consistent with this hypothesis, the rate of positive T-Scan exams among women with benign lesions in the Sensitivity Cohort of our prospective case control trial was significantly higher than that among normal, asymptomatic women (Table VI, P < 0.001). This finding supports the hypothesis that EIS identifies women at risk of developing cancer in the future who may therefore benefit from the early initiation of image-based screening. However, as with all case control studies, further research is required to estimate clinical efficacy prospectively in the intended clinical setting.

The targeted use of this non-invasive and low cost low risk stratification tool and the paradigm tested in this study may address an important unmet need in women’s health and provide an opportunity to identify women who otherwise would be excluded from further testing and suffer the consequences of delayed diagnosis of breast cancer. The proposed screening paradigm provides a possible basis for identifying and referring at-risk women who are most likely to benefit from additional surveillance or breast imaging. Importantly, the data assembled to date determines risk at time of examination and suggests risk for developing breast cancer at a later time; however, continued surveillance in T-Scan positive patients is warranted as lifetime risk in this patient cohort is unknown and remains the focus of on-going multi-year trials.

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<table>
<thead>
<tr>
<th>References</th>
<th>Sample size</th>
<th>Length of follow-up (years)</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>35</td>
<td>n = 9,087</td>
<td>25</td>
<td>1.6</td>
</tr>
<tr>
<td>36</td>
<td>n = 11,307</td>
<td>6.7</td>
<td>1.6</td>
</tr>
<tr>
<td>37</td>
<td>n = 2,731</td>
<td>16</td>
<td>1.8</td>
</tr>
<tr>
<td>38</td>
<td>n = 1,441</td>
<td>12.9</td>
<td>2.1</td>
</tr>
<tr>
<td>39</td>
<td>n = 110</td>
<td>16–20</td>
<td>4.8</td>
</tr>
</tbody>
</table>
APPENDIX 1: PARTICIPATING STUDY SITES

The Specificity Arm of the study was conducted at 17 sites (15 in the U.S. and 2 in Israel) including civilian and military, academic and high-volume private clinical practices. The sites that participated in the study are typical of those that would potentially use the T-Scan as a screening modality for young women. All study sites selected for participation in the study had large active gynecological or breast screening practices. Study sites in the United States included: Walter Reed Army Medical Center, Washington, DC; Keller Army Community Hospital, West Point, NY; Cornell University Medical Center, New York, NY; Drexel University, Department of Surgery, Philadelphia, PA; Drexel University Department of OB/GYN, Philadelphia, PA; Austin Area Obstetrics, Gynecology, and Fertility, PA, Austin, TX; Associated Women's Specialists, Tulsa, OK; Private Gynecology Clinic, Sugar Land, TX; Associates in Women's Healthcare, Wayne, NJ; Hendrix Medical Group, Los Angeles, CA; Louisiana Women's Healthcare Associates, Baton Rouge, LA; Private gynecology clinic, New York City, NY; Professional Medical Ultrasounds, Beckley, WV; Robert L. Siebold Clinic, Houston, TX; and, Travis OB/GYN Associates, Austin, TX. Study sites in Israel were Hadassah University Hospital, Mount Scopus, Jerusalem, and Daniely Clinic, Givatayim. The Sensitivity Arm of the study was conducted at 18 sites (12 in the U.S. and 6 in Israel) including university-affiliated academic institutions and private surgery and radiology practices. These study sites had an active breast practice and an expressed interest in new screening modalities. All sites that participated in the Sensitivity Arm had demonstrated previous participation in clinical research and the investigators were familiar with the required procedures and concepts. Study sites in the United States included: Walter Reed Army Medical Center, Washington, DC; Keller Army Community Hospital, West Point, NY; Austin Radiological Association, Austin, TX; Breast Center of Austin, Austin, TX; Drexel University, Department of Surgery, Philadelphia, PA; George Washington University, Washington, DC; Kelsey Siebold Clinic, Houston, TX; Louisiana Women's Healthcare Associates, Baton Rouge, LA; Orange County Surgical Group, Middletown, NY; Rose Featherwood, Center Houston, TX; Rose Joan Gordon Center, Houston, TX; University of Southern California, Los Angeles, CA; Study sites in Israel included Hadassah University Hospital, Mount Scopus, Jerusalem, Assaf Haroof Hospital, Tel Aviv; Bnei Zion Hospital Haifa; Ichilov Hospital, Tel Aviv; Holy Family Hospital, Nazareth; Rambam Hospital, Haifa.

REFERENCES


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