RESEARCH ARTICLE

Validation of Electrical Impedance Tomography Qualitative and Quantitative Values and Comparison of the Numeric Pain Distress Score against Mammography

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Abstract

Electrical impedance tomography (EIT) is a potential supplement for mammogram screening. This study aimed to evaluate and feasibility of EIT as opposed to mammography and to determine pain perception with both imaging methods. Women undergoing screening mammography at the Radiology Department of National University of Malaysia Medical Centre were randomly selected for EIT imaging. All women were requested to give a pain score after each imaging session. Two independent raters were chosen to define the image findings of EIT. A total of 164 women in the age range from 40 to 65-year-old participated and were divided into two groups; normal and abnormal. EIT sensitivity and specificity for rater 1 were 69.4% and 63.3, whereas for rater 2 they were 55.3% and 57.0% respectively. The reliability for each rater ranged between good to very good (p<0.05). Quantitative values of EIT showed there were significant differences in all values between groups (ANCOVA, p<0.05). Interestingly, EIT scored a median pain score of 1.51 ± 0.75 whereas mammography scored 4.15 ± 0.87 (Mann Whitney U test, p<0.05). From these quantitative values, EIT has the potential as a health discriminating index. Its ability to replace image findings from mammography needs further investigation.

Keywords: Breast screening - EIT - validation - pain score - mammography - comparison

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Introduction

Breast cancer is the most common malignancy suffered by women worldwide with the prevalence of 1 in 8 women will develop breast cancer (Green, 2013). In our continent, the age-adjusted mortality rate for breast cancer is 9.5 deaths per 100 000. Among Asia countries, leading numbers of breast cancer incidence come from countries such as China, Mongolia and Vietnam. Malaysia in the other hand is still at the contrast scale of those countries (Binns et al., 2013). However, with 1 in 20 women in the country develops breast cancer in their lifetime, urgent measures should be taken to reduce the morbidity and mortality caused by the disease (Hisham and Yip, 2004). The malignancy results in significant economic burden to our country due to costly medical treatment and productivity losses (Sasser et al., 2005). National Cancer Control Program had joined hand with multidisciplinary professionals in order to reduce the incidence and mortality due to breast cancer. The program includes prevention, early diagnosis, relief of pain and palliation of the terminally ill (Lim, 2002).

Until to date the best prevention program in Malaysia to fight breast cancer is still depending on breast selfexamination and annual mammography screening after the age of 40 years old (Hisham and Yip, 2003). The fact that mammography procedure involves exposure to X-ray radiation limits the age group of screening and painful compression had made this procedure less popular in our population (Dahlui et al., 2013). Furthermore, mammography seems very challenging to be implemented as screening method for younger women, despite the radiation, younger women have denser breast and the sensitivity of mammography is low in denser breast. Therefore, for younger women below the age of 40, screening is mainly based on breast self-examination (BSE) and clinical breast examination (CBE) (Kriege et al., 2004).

Future role of imaging in cancer prevention is huge as it is expected to detect abnormalities at pre-symptomatic, minimally invasive and targeted therapy. Early diagnosis has been the major factor in the reduction of mortality and breast cancer management costs (Elmore et al., 2005; Ki-Bong Yoo et al., 2013). BSE and CBE are both

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non-standard and not the ideal breast cancer screening as by the time a cancer is able to be detected via CBE, it is already well defined. The advanced stage may require aggressive and expensive treatment as well as associated with reduced quality of life. All the limitations led us towards subsequent need for a screening modality that can be used together with CBE to screen larger groups of women without age limitation (Smith, 2000; Secginli and Nahcivan, 2011).

Ever since seven decades ago studies had led us to the findings that different tissues have distinct electrical impedance properties. Subsequently, the potential for these electrical differences were seriously being studied for cancer detection purposes (Malich et al., 2001). 3D-EIT MEIK had received its certification E-30-00146-06 in accordance to Directive 93/45/EEC (medical device). The EIT is capable to map electrical impedance (capacitance and conductivity) of breast tissues in 2D and 3D images. Besides that, EIT screening does not involve radiation, sensitive in denser breast, a portable device and does not involve painful compression (Campbell and Dimache, 2007). Thus, this instrument may be a promising screening modality to be used in symphony with BSE and CBE. However, its validility and reliability is yet to be determined.

Thus, this study aimed to validate the sensitivity and specificity of the EIT against screening mammography and also to determine its reliability. This study also aimed to determine the difference of pain perception among women exposed to both modalities. Furthermore, this is a preliminary study in determining the potential used of EIT quantitative values in breast imaging.

Materials and Methods

Data collection

This is a cross-sectional study done at Radiology Department National University of Malaysia Medical Centre. All women aged 40-65 year-old who came for screening mammography and met the inclusion and exclusion criteria were invited to participate. Women who were pregnant, lactating and had an electrically powered implanted device (eg: pacemaker) were excluded from this study. Those who were previously undergone aggressive cancer treatment (chemotherapy/radiotherapy), breast surgery including cosmetic surgery, breast biopsy, breast fine needle aspiration were also excluded.

This study was conducted from February 2012 until February 2013. 164 women underwent screening mammogram took part in this study. Written informed consent was obtained before participation. This study was approved by the National University of Malaysia Research and Ethical Committee, ethical approval number was NN-136-2011.

Patient survey

Upon agreeing to participate, subjects were required to complete a standard questionnaire which contains sociodemography, family and medical history and other risk of breast cancer as listed in Gail Model.

Mammography and EIT examination

All subjects underwent mammography before they went for EIT screening. Mammography were done by designated radiographer with supervision of a radiologist during the session. The mammogram used in this study was Selenia Dimensions with AWS 5000 configuration. All mammography data were exclusively from National University of Malaysia Medical Center and being reported by designated radiologist.

In this study, subjects were divided into two particular groups (Group 1= women without any significant findings during screening mammography; Group 2=women with significant findings during screening mammography regardless benign or suspicious of malignancy). The classification is based on recommendations whereby any suspicious abnormalities captured during screening mammography requires further imaging diagnostically or histologic analysis whenever surgeons find necessary (Hisham and Yip, 2004; Sasser et al., 2005).

EIT examination was done in supine position. Wet cloth was dabbed at the examined breast to moisture the surface area of contact with the electrodes. Then the device was placed on the breast with intention of maximizing electrode contact to the surface. Indicator for justifying sufficient contact is provided together in the software. More than 80% contact was considered as good contact.

The examination was performed by a single qualified operator to avoid operator bias. The EIT MEIK 404 was used for this study. The scoring and data was accomplished using a post-processing algorithm provided together with the software which supported the device. The instrument has 256 electrodes which injected sequentially 0.5 MA current at 50 kHz into the breast and the potential difference was measured by the rest of the 255 electrodes to a depth of 5.4 cm from the top of the breast resulting in 65280 measurements. The software application then computes the electrical conductivity profiles of the different breast tissues and compares them with 3000 histograms in the data bank. Breast tissues images were then displayed on a grey scale in 2D and 3D. Two independent raters were selected for interpretation of EIT images. The raters include were two oncologists with special interest in breast cancer that interpret based on the image outcome of the EIT. A technical specialist was involved to interpret based on the device self-capability of pointing out suspicious area of abnormality. They were all blinded from the mammogram results and each other's results. Images were than recorded as normal and abnormal based on their interpretation.

Numeric pain distress scale

The numeric pain distress scale used was a standard scale which consists of a horizontal line 100mm in length with 11-point scale consisting of integers from 0 through 10.0 represents 'No pain' and 10 represents 'Worst imaginable pain' (Ferreira-Valente et al., 2011). Subjects were then required to select the single number that best represents their pain intensity after each session of mammography and EIT. Separate scale sheet were provided after each session.

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Data analysis

Two independent qualified raters which were trained for interpreting EIT were chosen as independent raters to interpret the image findings. They were both blinded of the subjects' identity and mammography findings. Both raters were also randomly given 50 images to be read twice in order to determine intrarater reliability. Reliability of EIT interpretation was done using Kappa Cohen analysis. Sensitivity, specificity, % positive predictive value (PPV), and % negative predictive value (NPV) of EIT for screening purposes were determined: %sensitivity=[true positives/(true positives+false negatives)]X100; %specificity=[true negatives/(true negatives+false positives)]X100; %PPV=[true positives/ (true positive+false positives)]X100; %NPV= [true negatives/(true negatives+false negatives)]X100. Both true positive and false negative findings were identified based on mammography.

EIT quantitative values used for this study were based on extremum value (conductive value that appear the most in each logarithmic calculation); distribution discrimination percentage (percentage of difference between the examined breast and normal histogram built based on normal women breasts with almost the same characteristics as the examined woman); and tomogram percentage discrimination (percentage of difference between left and right breast of the examined woman). Each breast (left and right) were analysed independently as each breast will have separate values.

Statistical analysis was performed using SPSS version 19.0 (IBM Corp, New York, USA). All statistical tests were two-sided and a p value <0.05 was considered significant.

Results

Study population

164 women with age ranged from 40-year-old to 65-year-old participated in this study. Most subjects were Malay of 63% (n=103), followed by Chinese 31% (n=51) and Indians about 6% (n=10).

Majority of the subjects were married 89.6% (n=147) and 10.4% (n=17) were widowed or never been married. A total of 80 subjects (48.8%) had tertiary education either at colleges or universities, their years of education ranged from 13 to 23 years (mean 17.60 years). The rest of the subjects (51.2%; n=84) never had tertiary education; their years of education ranged from 9 (form 3) to 11 years (form 5) (mean 10.8 years). There were 51. 8% (n=85) of the women were classified as not working and 48.2% (n=79) of them were classified as working. Based on Department of Statistics Malaysia official portal, most of the subjects in this study were classified as middle class socioeconomic status 75% (n=123), followed by high 17.07% (n=28) and low 7.93% (n=13)(Malaysia, 2012).

Classification of subjects based on mammogram findings

Based on mammogram findings gained, 48.2% (n=79) were classified as normal with no significant findings from the imaging protocol, their mammogram image were scored as BI-RADS 1, whereas 51.83% (n=85) of subjects were classified as abnormal with significant findings of benign or suspicious malignancy from their mammogram images. Out of the 85 subjects, 71 subjects were scored as BI-RADS 2 (83.54%) and 10 subjects with BI-RADS 3 (11.76%) and 4 subjects with BI-RADS 4 (4.70%).

Factors associated with risk of breast abnormalities

Factors such as marital status, age at menarche, family history of breast cancer, menopausal status, age at first pregnancy, history of pregnancy and lactation history were taken into account as independent variables that may be related with increased risk of breast cancer (Key et al., 2001; Osborne et al., 2005; Yang and Jacobsen, 2008). Thereby, the risk factors were than calculated simultaneously using logistic regression (Mantel Haenszel method) and expressed as adjusted Odds Ratios (OR) with 95% Confidence Interval (CI). Table 1 showed that there were no significant differences between all independent variables in both group 1 and group 2 subjects (p>0.05).

Other lifestyle factors such as smoking history and alcohol intake were not included in the table as all subjects

Table 1. Factors Associated	with Breast Cancer	among Subjects
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		Normal (n=79)		Abnormal (n=85)		Crude OR	
		Ν	(%)	Ν	(%)	(95%CI)	p value
Marital status	Married	72	91.1	75	88.2	0.75 (0.265-2.140)	0.54
	Not Married	7	8.9	10	11.8		
Age of menarche	ŀ	<i>i</i> =12.56		µ=12.3		0.96 (0.796-1.162)	0.51
		s.d=1.4		s.d=1.3			
Family history	Yes	29	36.7	26	30.6	1.33 (0.684-2.573)	0.41
	No	50	63.3	59	69.4		
Menopausal status	Premenopause	22	27.9	25	29.4	0.93 (0.470-1.826)	0.83
	Menopause with HRT	25	31.7	20	23.5		
	Menopause without HRT	32	40.5	40	47.1		
Age of first pregnancy	No child	11	13.9	22	25.9	1.10 (0.453-2.238)	0.79
	<30 year old	63	79.8	53	62.4		
	≥30year old	5	6.3	10	11.8		
History of pregnancy	Yes	64	81.0	68	80.0	1.21 (0.418-3.477)	0.87
	No	15	19.0	17	20.0		
Lactation history	Yes	50	63.3	56	65.9	1.33 (0.684-2.573)	0.73
·	No	29	36.7	29	34.1		

Abbreviations: OR, Odds Ratio; CI, confidence interval; *p<0.05 using respective analysis described

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were non-smokers and only a small number of subjects took alcohol occasionally (less than 5 glasses per year).

EIT qualitative values

As discussed in the methodology, validation of EIT images (qualitative values) against images from mammogram was done in three independent occasions. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of EIT images read by independent raters were moderate. Rater 1 scored sensitivity of 69.4%, specificity of 63.3%, PPV was 67.1%, and NPV was 65.8%. Second rater scored sensitivity of 55.3%, specificity of 57.0%, PPV was 58.0%, and NPV was 54.2%. Sensitivity scored by solely depending on the device capabilities of pointing out affected area was even worse with only 5.9% sensitive. However, the device specificity was high (81.1%) indicates that if there was any area of the breast was highlighted by the device's marker, there was high chances for the particular area will also appear abnormal in the mammogram image. The device also shown moderate PPV (51.8%) and NPV (44.4%) scored.

Reliability analysis using Kappa statistic was performed to determine consistency among both independent raters. The intrarater reliability for rater 1 was very good with Kappa=0.88 (p<0.001) and reliability for rater 2 first and second readings was also good with Kappa=0.79 (p<0.001). However interrater reliability for the raters was found to be poor with Kappa=0.22 (p<0.001).

EIT quantitative values

Subjects mean extremum Cu for right breast is 0.41+0.11 and left breast was 0.31+0.18. Mean subjects' distribution discrimination percentage was 25.21+11.63% for right breast and 28.71+10.65% for left breast.

Mean extremum value for subjects with normal findings (group 1) was higher (0.34+0.12 cu) than mean extremum value for subjects with abnormal findings (group 2) (0.15+0.2). The difference was statistically

significant (p< 0.05, partial eta-squared of 0.384 and power of test=95.5%). Mean of distribution discrimination percentage between both groups and mean of tomogram comparison percentage also showed there was a significant difference between both groups with p value of <0.05. Percentage of distribution discrimination was higher in group 2 (36.71+17.68%) compared to group 1 (29.76+15.83%). Tomogram percentage comparison also showed the same result with higher percentage difference was found in group 2 (15.44+11.51%) compared to group 1 (9.68+4.17%). Table 2 described the comparison of EIT quantitative values between group 1 and group 2. The covariates and factors that taken into account in this study were based on Gail Model (Gao et al., 2012).

Family history, ethnicity and menopausal status were the independent factors analysed together with subjects' mammogram result. Analysis of multiple factor covariance (2-way-ANCOVA) was done for all three parameters and the results were similar with the initial result. Thereby there were still significant difference in mean of all three quantitative values (p<0.05) when controlled for age, age at first menarche and age at first child bearing (Table 2). The aim of adding co-factors was to determine the interaction and confounding between these factors independently with mammogram result that may affect EIT quantitative values (Table 3). There were interaction effects between menopausal status and mammogram findings that may impact the EIT quantitative values of extremum values and tomogram values (p<0.05).

Subjects were divided into three groups based on their menopausal status (premenopause, menopause with HRT, menopause without HRT). There was a statistically significant difference at the level of p<0.05 in EIT extremum values for the three groups. Despite reaching statistical significance, the actual difference in mean scores between the groups was quite small (premenopause=0.27+0.19 cu, menopause with HRT=0.31+0.12 cu, menopause without HRT=0.24+0.14cu). The effect size calculated using eta-squared was 0.031. Post-hoc comparisons using the Tukey HSD test

Table 2. EIT Quantitative values of Sub	piects in Different Groups	s According to Mammogram	Classification

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EIT parameter	Normal findings [Mean SD)]	Abnormal findings [Mean(SD)]	p value ^a	Power (%) ^a	η2paª	p value ^b	Power (%) ^b	η2pa ^ь
Extremum (cu) n= 328	0.34 (0.12) n= 203	0.15 (0.2) n=125	<0.05*	95.5*	0.384*	<0.05*	98.0*	0.398*
Distribution discrimination (%) n= 328	29.8 (15.8) n= 203	36.7 (17.7) n=125	<0.05*	95.7*	0.04	<0.05*	95.7*	0.057
Tomogram comparison (%) n= 164	9.7 (4.2) n=79	15.4 (11.5) n=85	<0.05*	98.6*	0.198	<0.05*	95.9*	0.138

*Extremum (cu) and distribution discrimination (%) shown n = 328 which represents 164 subjects because each breast (right and left) were analyse separately as each breast has own its own separate value; Tomogram comparison shown n = 164 because the comparison is between individual left and right breast; "Result of EIT quantitative values analysed independently using ANOVA; "Result of EIT quantitative values analysed with covariates of age, age at first menarche and age at first child bearing (ANCOVA)

Table 3. Interaction Effect of Independent factors with Mammogram Findings when Controlled with Respective Covariates

Factors	Extremum			Distribution discrimination (%)			Tomogram comparison (%)		
	p value	Power (%)	η2pa	p value	Power (%)	η2pa	p value	Power (%)	η2pa
Family history	0.559	9.0	0.001	0.124	33.6	0.007	0.204	24.5	0.010
Ethnicity	0.938	6.0	0.011	0.289	27.1	0.008	0.538	15.3	0.080
Menopausal status	<0.05*	98.0*	0.15*	0.3	26.3	0.007	0.007*	98.0*	0.225*

*Indicate significant interaction with mammogram findings that may affect EIT quantitative values; Significant level is set at p<0.05

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indicated that the mean value of the EIT extremum cu of premenopausal group was significantly different from the postmenopausal with HRT group (p<0.05). Previous literature pointed out conflicting results regarding the risk for hormone therapy (Xiao-Jian Ni et al., 2012).

Results of tomogram comparison showed highest difference between left and right breast was found among premenopausal group (18.64+14.28%) followed with postmenopausal women without HRT (10.66+4.32%) and postmenopausal women with HRT (9.90+4.5%). The differences were statistically significant at level of p<0.05, with effect size of 0.17. Post-hoc comparison (Tukey HSD test) showed the mean percentage of EIT tomogram comparison of premenopausal group was significantly different from both postmenopausal with HRT and premenopausal without HRT group (p<0.05).

Numeric pain distress scale of EIT versus mammography

Numeric pain distress scale was used to identify the difference of subjects' perception towards pain after mammography and EIT sessions. Median pain score for compression during EIT session was 1.51+0.75 indicate low pain whereas median pain score for compression during mammography session was 4.15+0.87 indicate moderate pain. All subjects reported pain was involved during compression for the mammography session with 5% of the subjects reported low pain (pain score=1-3), 93% of subjects reported moderate pain (pain score=4-6) and 2% of the subjects reported intense pain involve (pain score=7-6). Interestingly, during compression for the EIT session, there were 20% of subjects reported no pain (pain score=0) and 80% of subjects reported low pain (pain score=1-3). Based on Mann Whitney test the range of pain score difference between both procedures were statistically significant (p<0.05).

Discussion

This study is the first of its kind in Malaysia to obtain the validity of a non-invasive breast cancer screening modality (EIT) among a multi-ethnic Asian women. Screening tools are expected to be very sensitive whereas moderate to low specificity is acceptable (Dahlui et al., 2013). In this study, the sensitivity and specificity is moderate when the image was interpreted by independent raters. The EIT device has a special feature of highlighting the suspicious area in different colour. It is based on the hyperimpedencity and hypoimpedencity of the particular area. This feature showed advancement in breast imaging. However, the device capabilities of self-detection had proved to be highly specific (81.01%) but unfortunately very low in sensitivity (5.88%). Overall PPV and NPV percentages were moderate for all three raters. Thereby, this initial result suggesting that the EIT findings are highly dependent on trained interpreter.

The study focused on population aged 40-year-old and above following the suggestible age for mammogram screening in Malaysia (Al-Naggar and Bobryshev, 2012). Moderate result for sensitivity and specificity may be due to declining breast density among this age group of women (Milanese et al., 2006). As images for EIT depend on the capabilities of the software to map algorithmic calculations of electrical conductivity through breast tissues, low density breast may cause low quality of images (Jossinet and Schmitt, 1999). This study tends to be different from few studies which showed that the sensitivity and specificity of EIT and mammography were almost equal (Prasad et al., 2008; Raneta et al., 2012). Similar findings were gained by Stojadinovic et al. (2005) and they suggested that as EIT is intended for women with nonpalpable lesions, the discrepancy of the findings is may be due to the size of mass that can be captured by EIT. The previous study was done in a younger population as the algorithm calculation of EIT is said to better among younger women with higher density breast (Cherepenin et al., 2002; Prasad et al., 2008).

Another distinct feature of the EIT device from other breast imaging device is the quantitative values available with the device. The values were previously proven to be statistically significant in providing different mammary gland's conductivity with different visual distinctions (Tavares et al., 2012). This study had tried to test the hypothesis that distinct quantitative values will be recorded based on different mammography findings. Thereby, the different values may point towards distribution of tissues at local area of the breast.

Breast cancer is a multifactorial disease with lifestyle plays important key role towards onset of the disease (Lim, 2002). The covariates and co-factors chosen were all based on Gail Model (Gail and Greene, 2000). The univariate analysis done in this study encountered that the risk factors within Gail Model have no significant correlation with different mammography findings in this subjects groups which is relatively similar with the finding in a study within Indian subjects (Challa et al., 2013). Despite that, as the Gail Model had been validated in several studies to be able to predict individual risk in contracting breast cancer, we find it will be very beneficial to use the key risks pointed out by the model as our covariates and cofactors (Hisham and Yip, 2003).

Electrical impedance imaging is not easy as different tissues will have specific range of electrical conductivity. However simplicity of normal breast tissue compounds made it a mission possible. Anatomically the breast is constructed from ducts, mammary glands, adipose tissues and fibrous tissues. There is no way to specifically determine the exact conductivity value of normal breast tissues in vivo, because breast tissues are known to respond to hormonal fluctuation and show changes during different phases of menstrual cycle (Ramakrishnan et al., 2002; Chan et al., 2011). Thereby, rather than focusing in the mean conductivity value of each image, this study focused on the conductive values that appear the most which labelled as extremum value. The extremum value may give a clearer picture the type of tissues that highly present at the breast because each cells have specific range of electrical conductivity.

Besides raw conductive values, the device used in this study also provides advance data of distribution discrimination (%) between the screened breasts with normal histogram of women with the same characteristic. Cut-off point of more than 40% was considered to be at

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risk of abnormalities of the breast. However, the data preinstalled with the software for the normal curve were data from large cohort study taken from Caucasian women. Thereby different continent data was the limitation that should be taken into account. Another interesting feature was the tomogram comparison (%) between left breast and right breast. Cut-off point of more than 20% was used as marker for suspicion of breast abnormalities. Left and right breast can be symmetrical or asymmetrical however it was previously described that the composition of individual breast normally does not discriminate much between the left and the rights breast (Miller and Astley, 1992). These innovative technology application had made screening became easier and based on this data women are capable to decide more accurately on how far they should go in checking for their breast health.

Result of electrical conductivity from this study pointed out that the mean conductivity for extremum values in women with breast abnormalities was far lower than those without significant mammographic findings. The mean extremum value for group 1 was found to be within range of adipose tissue conductivity which was previously described as tissues with low electrical conductivity (Grimnes and Martinsen, 2000). Cumulative evidence up to date supports theories of obesity promotes tumour cell growth (Shahar et al., 2010; Perks and Holly, 2011). Digging deeper inside the cellular phase, there were mammary adipose tissues which comprised of mature adipocytes and progenitor cells as part of the breast composition. These tissues were previously considered as a casual observer at the breast but nowadays had been taken seriously as tissues that may have disease modifying entity (Wang et al., 2012). The capabilities of detecting earlier the presence of high mammary adipose tissue may provide a new strategy for breast cancer prevention.

Anxiety of painful compression during mammography had been part of the reason that many women didn't go for breast imaging or delay their visit for breast imaging (Keefe et al., 1994). Data from this study had shown after years of development in breast imaging, women perception of pain during mammography still remain (Asghari and Nicholas, 2004; Keemers-Gels et al., 2000). Existence of a new imaging tool with much lesser pain may be the answer to boost up the popularity for breast health screening among women worldwide (Fass, 2008).

No present technology satisfies the criteria of an ideal screening tool. However despite EIT being described as a low sensitivity device, it is proven to be specific. Furthermore EIT does show advance feature that may overcome challenges associated with mammography screening. It is a non-invasive device, no radiation involvement, very minimal risk, portable and cost effective for mass screening. Thereby if proven the efficacy of using EIT, it may be a paradigm shift for screening of breast health among women (Misra et al., 2010; Lee et al., 2012). The findings in this study warrant careful consideration as subjects from this study were from specific population. The sensitivity and specificity may not represent general population.

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