Jpn. J. Cancer Res. 87, 1092–1096, October 1996

# Prospective Evaluation of Skin Surface Electropotentials in Japanese Patients with Suspicious Breast Lesions

Mamoru Fukuda,[1,3] Kaname Shimizu,[1] Norihiko Okamoto,[1] Toshihiro Arimura,[1] Tomohiko Ohta,[1] Susumu Yamaguchi[1] and Mark L. Faupel[2]

[1]*First Department of Surgery, St. Marianna University School of Medicine, 2-16-1 Sugao, Miyamae-ku, Kawasaki 216 and* [2]*Biofield Corp., 1225 Northmeadow Parkway, Suite 120, Roswell, Georgia 30076, USA*

**The biofield breast examination (BBE) is a new, noninvasive and cost-effective method for diagnosing breast lesions currently undergoing multicenter evaluation in the USA and Europe. The test analyzes subtle differences in electrical potential caused by dysregulated epithelial proliferation. This report summarizes a prospective evaluation of BBE in a population of 101 patients with suspicious breast lesions scheduled either for open surgical biopsy or fine needle aspiration biopsy. Of the 101 patients included in the study, 49 were found to have a breast malignancy and 52 were found to have a benign breast lesion. BBE correctly identified 44 of 49 biopsy-proven cancers (sensitivity=90%) and correctly indicated no cancer in 31 of 52 biopsy-proven benign cases (specificity=60%). Sensitivity increased to 95% for cancers less than 2.5 cm in size. These results indicate that BBE may be an effective adjunctive test to help to resolve abnormalities discovered by physical examination or other screening methods.**

Key words: Breast lesion — Diagnosis — Biofield breast examination — Electrical potential — Epithelial proliferation

Detection and diagnosis of breast cancer has typically relied on a combination of physical examination, mammography, ultrasound, and tissue sampling techniques such as fine needle aspiration (FNA). In certain clinical situations, these techniques have been supplemented by other methods such as gadolinium-enhanced magnetic resonance imaging (MRI) or computed tomography (CT). Physical examination is one important way in which breast cancer is initially detected. It relies on the subjective interpretation of palpable density differences between breast malignancy and the surrounding parenchyma and its effectiveness is known to diminish as lesion size decreases.[1)] Mammographic screening is capable of detecting smaller lesions, but its relatively low specificity can result in many unnecessary additional imaging studies and biopsies.[2)] Moreover, both physical examination and mammography appear to be less accurate in younger women. Sensitivity of ultrasound in early palpable breast cancer was reported to be higher (77.6%) than that of physical examination or mammography in Japan.[3)] However, use of ultrasound for discriminating suspicious breast lesions has been primarily limited to distinguishing cystic from solid lesions in the USA. MRI and CT are still developmental and are unlikely to be a cost-effective modality in the foreseeable future. Thus, there appears to be a need for a cost-effective way to improve predictive accuracy immediately after initial screening. Recent evidence from clinical trials suggests that the measurement of breast epithelial electrical potentials using an array of signal-specific skin surface sensors may be a useful adjunctive modality for breast cancer diagnosis.[4)] This new technology, termed the biofield breast examination (BBE), is relatively inexpensive and produces an objective and immediate test result. The technology is based on the finding that cell membranes of epithelial tissues are electrically polarized and that the membranes undergo depolarization when the cell is stimulated to proliferate.[5,6)]

Previous clinical evaluation of this approach has occurred both in the USA[7,8)] and Europe.[9)] In these studies, it was shown that breast cancer produced significantly greater electropotential differentials than benign and normal tissue.

The purpose of the present study was to evaluate the effectiveness of BBE in a Japanese population of women with suspicious breast lesions.

## MATERIALS AND METHODS

The BBE diagnostic system consists of an array of sixteen sensors (7 per breast and one each on the axillae), reference sensors on each palm, an electromagnetically shielded cable, and a device platform, which contains the necessary components for filtering out high-frequency (AC) signals, as well as the power supplies and an integrated microprocessor system which controls signal

[3] To whom correspondence should be addressed.

acquisition and processing through a multiplexed analog-to-digital converter/amplifier. During this study, two types of sensors were used. Each of the 16 sensors is sampled 150 times over the course of the less than 1 min measurement period. These 150 individual potentials (in the millivolts range) are averaged under computer control to produce a composite electrical potential reading for each sensor site. Comparisons of averaged voltages are then used to identify regions of relative depolarization and hyperpolarization on the breast surface.

All patients were tested in the following manner. The patient was recumbent with the head elevated at approximately 15 degrees for comfort. Use of the diagnostic sensor array entailed placement of sensors contingent on location of the lesion, which was identified as a palpable, mammographic or sonographic abnormality. One sensor was placed over the center of the lesion and four additional sensors were placed over the margins of the lesion superior to, inferior to, medial to, and lateral to the sensor placed over the lesion. Two additional sensors were placed in the center of the two quadrants adjacent to the symptomatic quadrant and one sensor was placed on the ipsilateral axilla. This pattern of sensor placement was then replicated in mirror image form on the contralateral breast and axilla. All breast and axillary potentials were referenced to sensors placed on the thenar eminence of each palm. Fig. 1 shows the pattern of sensor placement for a patient with a lesion in the upper outer quadrant of the right breast. The average voltages for each sensor site are utilized to calculate differences between groups of sensors within the symptomatic breast (symptomatic breast differential) and between breasts (between-breast differential). These calculated differences are referred to as electropotential differentials. An artificial neural network (ANN)[10] was applied prospectively to the data. This ANN was developed for the prospective evaluation of BBE in a double-masked European multicenter study and is a probabilistic network which incorporates 181 neurons in its hidden layer. Once the BBE was completed, the patient underwent various diagnostic tests that may have included FNA or open surgical biopsy (OSB). In this study, only patients whose final diagnosis was obtained either cytologically ($n=24$) or histologically ($n=77$) were included. The results of the BBE were compared with that of FNA or histological diagnosis to obtain sensitivity, specificity, and predictive values for the BBE.

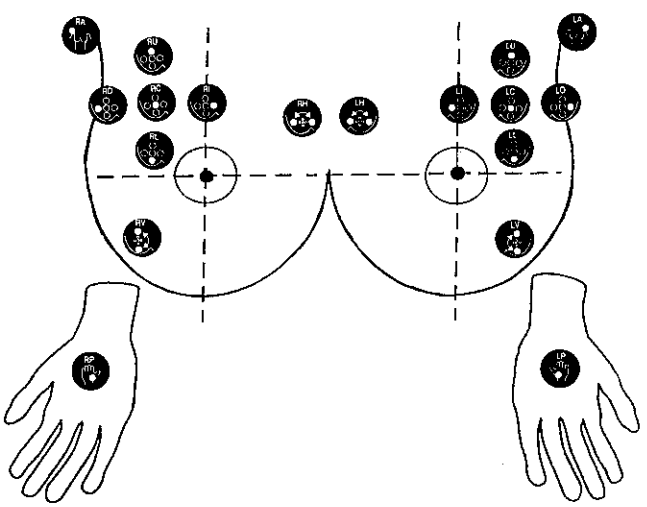

Fig. 1. Diagnostic sensor array in the case of a lesion in the upper outer quadrant of the right breast.

**Statistical analysis** To evaluate electropotential differentials in patients with breast cancer compared to patients with benign lesions, the Mann-Whitney test was used.

## RESULTS

In total, 101 patients were tested with the BBE. Patients ranged in age from 18 to 80 years (median=45). Sixty-six of the patients (65%) were under 50 years of age. Cytological or histological studies revealed that 49 of the patients had breast malignancies (49%), while 52 had benign breast conditions (51%). Forty-eight of the 49 malignancies (98%) were confirmed by histological studies, of which three were noninvasive ductal carcinoma. One malignancy was confirmed by FNA because the patient was referred to another clinic for treatment. Benign lesions consisted of three intraductal papillomas, two adenoses (one sclerosing), one lipoma, 11 fibroadenomas, 9 general fibrocystic/mastopathologic findings,

Table I. Clinical Study Population

| Disease state | Totals | Age range | Patients ≤50 years | Patients >50 years | Non-palpable lesions | Palpable lesions | Size range palpable lesions (cm) |
|---|---|---|---|---|---|---|---|
| Cancer | 49 | 34–80 | 23 | 26 | 1 | 48 | 0.5–13.0 |
| Benign | 52 | 18–71 | 43 | 9 | 7 | 45 | 0.5– 9.0 |
| Total | 101 | 18–80 | 66 | 35 | 8 | 93 | 0.5–13.0 |

Table II. Histopathologic or FNA Results

| Disease state | Number of lesions studied |
|---|---|
| Cancer | 49 |
| Invasive cancer | 45 |
| Ductal carcinoma *in situ* | 3 |
| Cancer by FNA | 1 |
| Benign | 52 |
| Intraductal papilloma | 3 |
| Lipoma | 1 |
| Adenosis | 2 |
| Fibroadenoma | 11 |
| Fibrocystic changes | 9 |
| Miscellaneous benign | 3 |
| Benign by FNA | 23 |

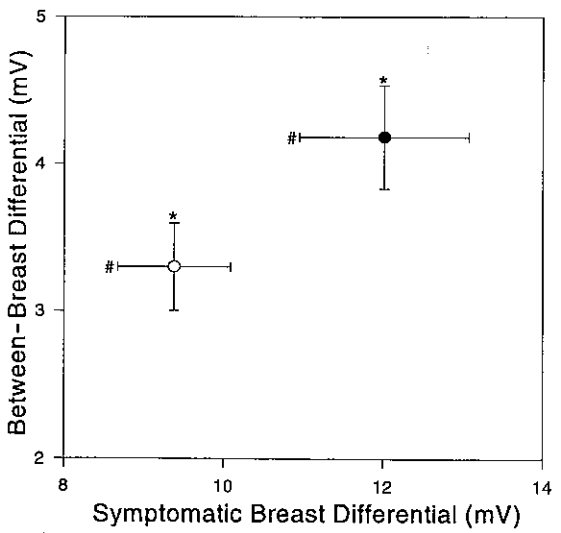


Fig. 2. Mean symptomatic breast differential and between-breast differential in patients with breast cancer are significantly different from those in patients with benign lesions (# Mann-Whitney $P=0.029$, ★ Mann-Whitney $P=0.031$). ○ Benign ($n=52$), ● Cancer ($n=49$).

and 3 miscellaneous benign findings, and there were 23 patients with benign FNAs who did not proceed to OSB. Seven of the benign lesions (13%) and one of the cancers (2%) were nonpalpable. Tables I and II summarize the patients' age and lesion characteristics.

Mean symptomatic breast differential in patients with breast cancer was 12.01 mV as compared with 9.37 mV in patients with benign lesions ($P=0.029$, Mann-Whitney). Mean between-breast differential in patients with breast cancer was 4.18 mV and that in patients with benign lesions was 3.30 mV ($P=0.031$, Mann-Whitney) (Fig. 2).

Table III. Artificial Neural Net (ANN) Results by Sensor Type

| Sensor type | ANN threshold[a)] | Sensitivity | Specificity |
|---|---|---|---|
| A | 0.43 | 90% (36/40) | 59% (24/41) |
| B | 0.41 | 89% (8/9) | 64% (7/11) |
| Total | | 90% (44/49) | 60% (31/52) |

*a*) ANN threshold is the value below which a case is classified as benign and equal to or above which a case is classified as malignant. The threshold varies slightly as a function of the operating characteristics of each type of sensor.

Table IV. Neural Net Value as a Function of Decreasing Proliferation

| Disease state | Median neural net value |
|---|---|
| Carcinoma ($n=49$) | 0.49 |
| Proliferative benign disease ($n=5$) | 0.49 |
| Nonproliferative benign disease ($n=24$) | 0.41 |
| Benign by FNA ($n=23$) | 0.40 |

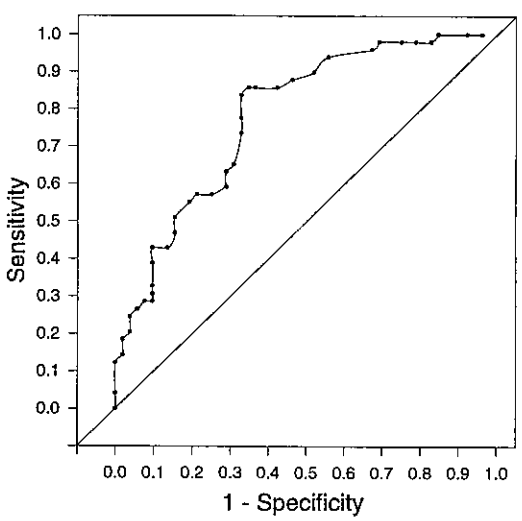


Fig. 3. Receiver operating characteristic curve for BBE. Area under the curve=0.783.

The results of an ANN were applied prospectively to this study's data set and are summarized according to two types of sensors in Table III. The overall sensitivity was 90% (44 of 49 malignancies correctly identified) and the overall specificity was 60% (31 of 52 benign cases correctly identified).

Overall, four of the 52 benign lesions (7%) produced ANN values greater than 0.50, while 15 of the 49 cancers (31%) did. Of the 21 false-positives, there were six (of 11) fibroadenomas, all three intraductal papillomas, two cases of adenosis, four (of 12) fibrocystic/benign lesions, and six (of 23) benign FNA. Four of the false-negative cases were invasive ductal carcinomas and one was a ductal carcinoma *in situ*. The median neural net values by disease state demonstrate a decrease in neural net value with decreasing disease proliferation (Table IV). Only one false-negative case involved a lesion which was less than 2.5 cm. Thus, of the 19 cancers less than 2.5 cm, BBE was positive in 18 cases (sensitivity=95%).

The performance of the BBE also can be represented by the receiver operating characteristic curve. The area under the curve is 0.783, which represents a significant increase in diagnostic performance over chance ($P<0.01$) (Fig. 3).

## DISCUSSION

It has been recognized for a number of years that during cell division, the cell membrane becomes permeable to various ions, including $Na^+$ and $K^+$. These ions are normally maintained in an electrochemical gradient from the cytoplasm to the extracellular space. This gradient dissipates during cell division, resulting in electrical depolarization of the cell membrane.[11] Breast epithelial tissues, which are organized as ducts and lobules to perform transport of ions and water, maintain a gradient across their cell membranes and across the epithelial lining of the ductal-lobular system. Carcinogenesis, which causes disruption of the normal proliferative and apoptotic activity of breast epithelia, can produce transepithelial depolarization, probably as a result of electrical decoupling of the epithelia.[11, 12]

This electrical depolarization, which can occur in the area of proliferative lesions such as breast cancer, produces a penumbra of electrical alterations which is recognized as the "field effect" in many epithelial malignancies,[12] and affects the adjacent quadrant or region. An array of sensors placed on the skin surface of the breast can detect the electrical differentials within the symptomatic breast. Electrical asymmetry is also detected between breasts and in many cases is an additional diagnostic feature of malignancy.[4, 7]

In accordance with previous reports,[7-9] cancers in Japanese women with suspicious lesions produced significantly greater skin surface electropotential differentials than benign lesions. Prospective evaluation of an ANN resulted in a sensitivity of 90% and a specificity of 60%.

Overall, specificity was 60%, though 17 of the 23 (74%) lesions resolved as benign on FNA were designated negative by the BBE. These cases were considered clinically low risk for cancer and were not subjected to OSB, because they had negative FNA. The specificity of the benign lesions that required OSB was 48% (14/29). On the other hand, the BBE often identified proliferative benign lesions such as intraductal papilloma and sclerosing adenosis as false-positives. The median neural net value of these cases was the same as that of the malignant cases. These findings show that BBE is an indicator of dysregulated proliferation in the breast. We therefore consider that false-positive cases should be closely followed, because they might be at increased risk for developing future breast cancer.

There were five false-negative cases in this study. Most of these cases involved relatively large palpable lesions (median size=3.3 cm). Lesions of this size may be somewhat inactive metabolically and often have significant areas of necrotic tissue. In evaluating any new breast cancer diagnostic test, detection of cancers which are small is more important for improving the current clinical situation. It is notable that for smaller cancers (<2.5 cm), BBE was accurate in 18 of 19 cases (sensitivity=95%). These results compare favorably with diagnostic mammography or sonography, which showed sensitivity of 57.9% or 77.6%, respectively, in palpable breast masses less than 2cm in size in Japanese women.[3]

The initial results reported here support the preliminary indications from studies in the USA and Europe that BBE may be an effective adjunct to physical examination and mammography in the diagnosis of suspicious breast lesions. The test is noninvasive, and results indicate high sensitivity. In addition, BBE can provide an immediate test output and requires relatively little time for technician training. The operating characteristics of BBE suggest that it should be used immediately after suspicious findings by palpation or on a screening mammogram. The sensitivity and specificity of the test are such that in a population with a prevalence of 20% or less, the negative predictive value would be greater than 95%. Because the BBE has both high sensitivity and high negative predictive value, the majority of patients with benign breast lesions could then be spared the additional tests, time and psychological trauma associated with resolution of their diagnosis by current modalities.

It is possible that BBE might be able to select those patients who would most benefit from additional diagnostic work-up, including surgical biopsy. BBE also could provide a novel means to identify patients at increased risk for developing breast cancer, as well as detecting early breast cancer.

*(Received May 9, 1996/Accepted July 24, 1996)*

REFERENCES


1) Cardona, G., Cataliotti, L., Ciatto, S. and Rosselli Del Turco, M. Reasons for failure of physical examination in breast cancer detection — analysis of 232 false-negative cases. *Tumori,* **69,** 531–537 (1983).
2) Kopans, D. B. The positive predictive value of mammography. *Am. J. Rad.,* **158,** 521–526 (1992).
3) Ueno, E., Tohno, E., Tsunoda-Shimizu, H., Aiyoshi, Y., Morishima, I., Ishikawa, T., Fukusawa, M., Yazawa, T. and Yashiro, T. Clinical diagnosis of early breast cancer. *Jpn. J. Cancer Chemother.,* **21,** 140–147 (1994).
4) Faupel, M. L. and Hsu, Y.-S. Dedicated systems for surface electropotential evaluation in the detection and diagnosis of neoplasia. *In* "Electropotentials in Clinical Assessment of Breast Neoplasia," ed. Dixon, D. M., pp. 37–44 (1996). Springer-Verlag, Berlin.
5) Marino, A. A., Iliev, I. G., Schwalke, M. F., Gonzalez, E., Marler, K. C. and Flanagan, C. A. Association between cell membrane potential and breast cancer. *Tum. Biol.,* **15,** 82–89 (1994).
6) Chapman, L. M. and Wondergen, R. Transmembrane potential and intracellular potassium ion activity in fetal and maternal liver. *J. Cell. Physiol.,* **121,** 7–12 (1984).
7) Weiss, B. A., Ganepola, G. A., Freeman, H .P., Hsu, Y.-S. and Faupel, M. L. Surface electrical potentials as a new modality in the diagnosis of breast lesions — a preliminary report. *Breast Dis.,* **7,** 91–98 (1994).
8) Crowe, J. P. and Faupel, M. L. Use of non-directed (screening) arrays in the evaluation of symptomatic and asymptomatic breast patients. *In* "Electropotentials in Clinical Assessment of Breast Neoplasia," ed. Dixon, D. M., pp. 57–62 (1996). Springer-Verlag, Berlin.
9) Dickhaut, M., Schreer, I., Frischbier, H.(German data) and Merson, M. (Italian data) The value of BBE in the assessment of breast lesions. *In* "Electropotentials in Clinical Assessment of Breast Neoplasia," ed. Dixon, D. M., pp. 63–69 (1996). Springer-Verlag, Berlin.
10) Cross, S. S., Harrison, R. F. and Kennedy, R. L. Introduction to neural networks. *Lancet,* **346,** 1075–1079 (1995).
11) Sachs, H. G., Stambrook, P. H. and Ebert, J. D. Changes in membrane potential during the cell cycle. *Exp. Cell Res.,* **83,** 362–366 (1974).
12) Goller, D. A., Weidema, W. F. and Davies, R. J. Transmural electrical potential difference as an early marker in colon cancer. *Arch. Surg.,* **121,** 345–350 (1986).