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Electrical Potential Measurements in Human Breast Cancer and Benign Lesions

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Abstract
Electrical potentials were measured on the breast and at other sites in 110 women with palpable breast masses. The tumor site was significantly electropositive compared with control sites only when the tumor was a cancer, as determined by a subsequent biopsy; the electrical potentials were not influenced by age or menstrual cycle. The results indicate that, on average, altered electrical potentials detected by a noninvasive measurement on the skin reflect the presence of transformed cells in patients with breast cancer. Previous in vitro studies of breast tissue and breast epithelial cells suggest that the observed effect was due to a change in interstitial K^+ concentration that arose from alterations in the activity of K^+ channels. Electrical potentials may be suitable for diagnosis of individual patients if refinements are made in the measurement technique.

Key Words
Breast cancer
Electrical Potential
Cancer diagnosis
K^+ channels

Introduction

Carcinoma of the breast is the most common cancer in women and the second most common cause of cancer deaths. Early detection through mammographic screening can reduce mortality from breast cancer in women greater than 50 years of age [1], but the false-negative rate can be as high as 80% in women between the ages of 20 and 40 [2].

Because of the prevalence of breast cancer, limitations of diagnostic techniques, and the adverse sequelae of delayed diagnosis, an aggressive approach to the biopsy of breast lesions is the present standard of medical practice. With current screening protocols and biopsy techniques, approximately 10–15% of patients undergoing breast biopsy are found to have breast cancer [3]. Thus, if reliable noninvasive diagnostic techniques could

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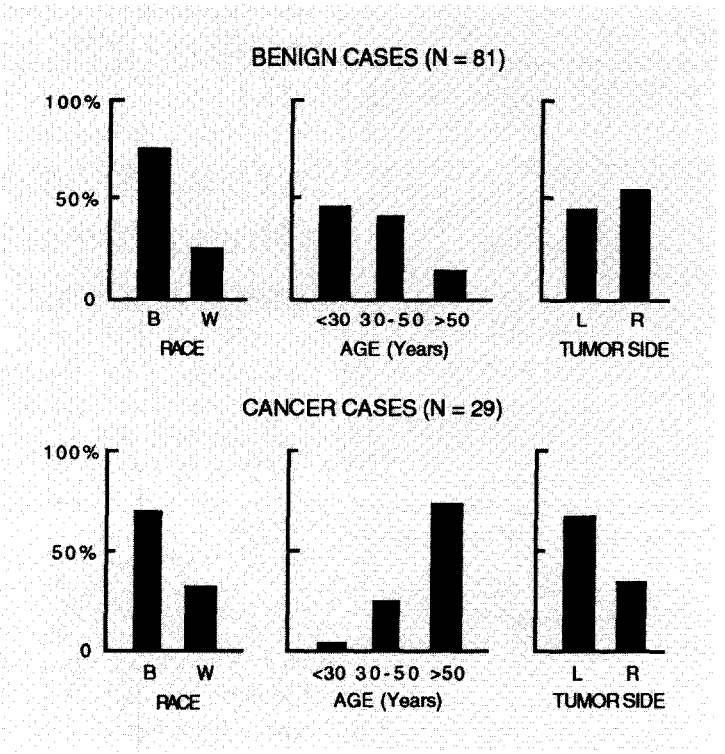

Fig. 1. Characteristics of the study group. B = Black; W = white; L = left; R = right.

be developed, surgery might be avoided in some cases.

Electrical changes may provide a physical basis for distinguishing between normal and cancerous growth. In patients with either cancerous or benign lesions of the face, when the potential was measured at the lesion and at a control position, there was no difference in the benign group but the lesion was significantly more positive in the cancer group [4]. This finding confirmed an earlier result [5] that sites of basal cell carcinomas were significantly electropositive compared with control sites in normal tissue, but that noncancerous lesions yielded no potential difference between the lesion and control sites. In a preliminary study, elevated surface electrical potentials were found to be associated with cancerous lesions beneath the skin in women with palpable breast masses [6]. The aim of this study was to ascertain the relation between surface electrical potential and the presence of cancer of the breast, and to evaluate the possible confounding effects of other factors including age and menstruation.

Methods

Women 15–80 years of age who presented at the Louisiana State University Medical Center breast clinic with a palpable breast mass and who were scheduled for biopsy as a routine part of their clinical care were studied, after approval by the Institutional Review Board. Following informed consent, the patient was placed in a comfortable supine position, the measurement sites were cleaned with alcohol, and electrodes were placed at each site. The electrical potential was measured directly over the tumor and at two ipsilateral control sites defined by either reflection across

the axes that divided the breast into quadrants, or a distance of 2 cm from the tumor site, whichever was greater; electrodes were also placed at the three corresponding sites on the contralateral breast, on the dorsal surface of each wrist, and on the forehead. The patient's feet were placed in 0.9% NaCl, and the electrical potential was measured between a site on the breast, wrist, or forehead, and the feet; the average of the potentials from the control points was used in the statistical analysis.

Silver chloride electrodes were made from silver wire (0.5 mm in diameter) using a direct current (5,000 mA × s/cm^2) in 0.9% NaCl. The chlorided wire was fixed in a polyethylene tube (5 mm in diameter) containing saline agar, and electrical contact with the skin was made via a porous cotton plug saturated with saline, at a contact pressure of about 2,000 Pa. The short-circuit voltages between pairs of electrodes were 1–2 mV (stability, $\leq$100 μV/h); the skin electrical potentials were corrected by subtracting the short-circuit voltages.

The nine electrodes were scanned sequentially (Keithley, 705 Scanner, Keithley Instruments, Cleveland, Ohio, USA), and the potential was measured with an electrometer (Keithley, Model 614, Keithley Instruments). Approximately 20 min were allowed for the voltage readings to stabilize, and the readings after that time were used in all subsequent analyses. Following the electrical measurements, each patient's tumor was biopsied and classified as benign or cancerous on the basis of the pathology report.

The data were analyzed using a one-way ANOVA to determine the dependence of electrical potentials on anatomic location (breast, wrist, forehead), followed by post-hoc tests using Fisher's LSD test. The unpaired and paired t tests were used to compare the breast surface electrical potentials between and within the cancer and benign cases, respectively. The Kolomogorov D statistic was used to test the normality of the data. All statistical tests were performed using SAS (SAS Institute, Austin, Tex., USA) or StatView II (Abacus, Berkeley, Calif., USA), at a significance level of 0.05.

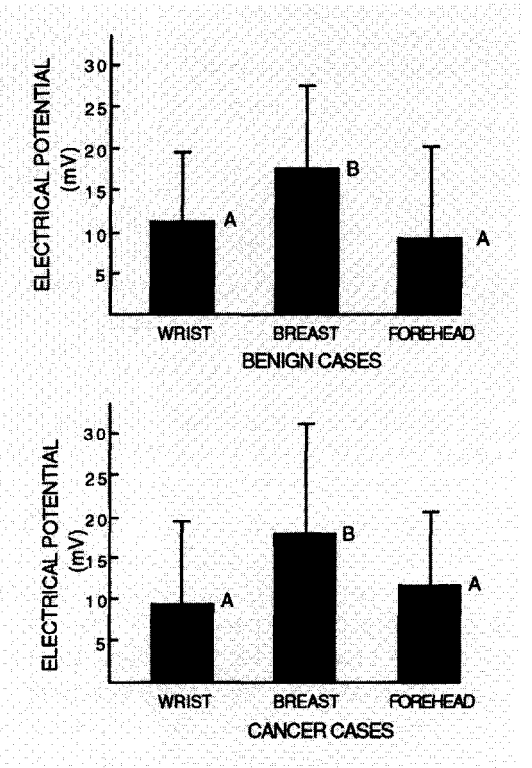

Fig. 2. Surface electrical potential at different locations in the benign and cancer cases. Mean ± SD are shown. Means with differing labels differed at $p < 0.05$.

Results

A total of 81 patients with benign disease were studied, consisting of 37 patients with fibrosis, 36 with fibroadenoma and 8 with other types of benign lesions. There were 29 patients in the cancer group, consisting of 24 patients with ductal carcinoma and 5 with other cancer. Pertinent characteristics of both groups are listed in figure 1. Electrical potential measurements varied with anatomic location in both the benign [$F(2,700) = 34.8$, $p < 0.001$] and cancer cases [$F(2,246) = 9.7$, $p < 0.001$]; the breast was significantly more electropositive than the wrist or forehead in both groups (fig. 2). The mean electrical potential at the tumor site did not differ between the cancer and control cases ($p = 0.065$), but when the tumor potential was referred to either the contralateral or ipsilateral control value, the resulting differences in electrical potential

Table 1. Comparisons of surface electrical potentials between cancer and benign cases

Measurement site	Cancer cases, mV	Benign cases, mV	p
Tumor (T)	21.4±12.4	17.1±10.3	NS (0.065)
Contralateral control (CL)	16.8±15.3	18.5±11.1	NS
Ipsilateral control (IL)	17.4±12.8	16.9±8.9	NS
T – CL	4.5±9.4	−1.6±9.3	<0.05
T – IL	4.0±9.1	0.1±6.8	<0.05

Values are the mean ± SD. NS = Not significant (unpaired t test).

were significantly more positive in the cancer cases (table 1).

Differences in electrical potential were also evaluated within each group (table 2). The tumor site was significantly electropositive compared with either the ipsilateral or contralateral controls in the cancer cases, but not in the benign cases. Moreover, when the electrical potential at the tumor site was referred to the control value of the involved breast, the difference in potentials was significantly higher than its control value (table 2) in the cancer but not benign cases.

The electrical potential at the tumor site is shown in relation to age in figure 3; no correlation was found in either patient group. Proportionately more cancers occurred among postmenopausal women (fig. 4), as expected from the age distributions in the cancer and benign cases; however, no relation was observed between menstrual status or timing of the menstrual cycle and tumor electrical potential in either patient group (fig. 4).

Table 2. Comparisons of surface electrical potentials within cancer and benign cases

Measurement site	Cancer cases mV	Benign cases mV
Tumor (T)	21.4±12.4	17.1±10.3
Contralateral control (CL)	16.8±15.3	18.5±11.1
p	<0.05	NS
Tumor (T)	21.4±12.4	17.1±10.3
Ipsilateral control (IL)	17.4±12.8	16.9±8.9
p	<0.05	NS
T – IL	4.0±9.1	0.1±6.8
*T – *IL	− 0.1±7.9	0.9±7.3
p	<0.05	NS

Values are the mean ± SD. T – IL = Difference in surface electrical potential between tumor site and ipsilateral control sites; *T – *IL = similar difference formed from measurements at the sites on the noninvolved breast that corresponded anatomically to the measurement sites in the breast that contained the lesion; NS = not significant (paired t test).

Discussion

Vascular-related streaming potentials and neural activity may contribute to the genesis of the electrical potentials, but they arise primarily from Nernst potentials across various tissue membranes [7]. Electrical potentials measured in the wrist and forehead (both relative to the feet) were similar (fig. 2), in general agreement with previous observations that the magnitude of the potential was unrelated to electrode separation [4, 5, 7, 8]. The negligible role of circuit length is consistent with the view that the potentials were primarily deter-

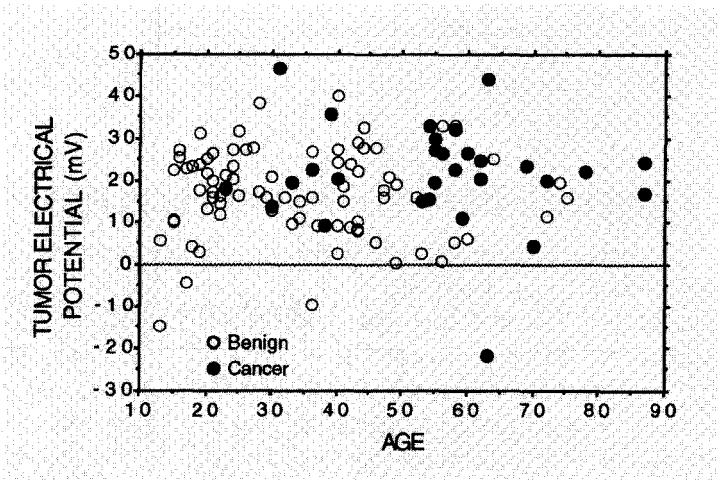

Fig. 3. Electrical potential at the tumor site in relation to patient age.

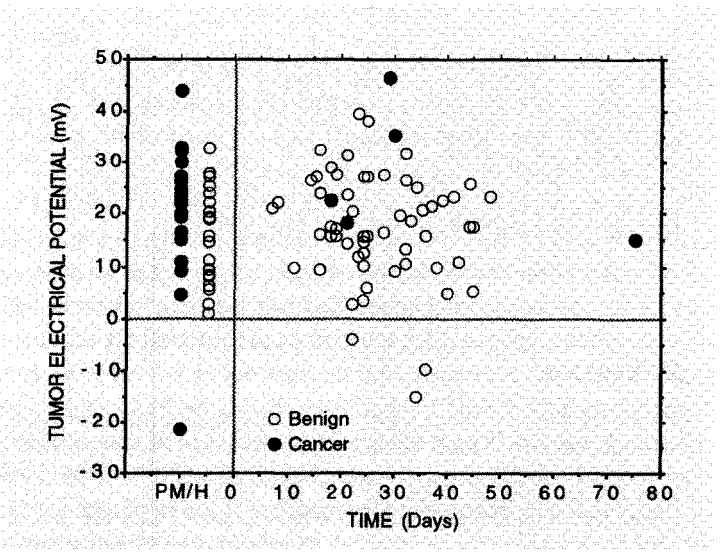

Fig. 4. Electrical potentials at the tumor site in relation to menstrual cycle. PM/H = Postmenopausal or hysterectomy patients. Time was measured from the beginning of the menstrual cycle.

mined by Nernst potentials generated in the vicinity of the electrodes. The influence of processes at the reference electrode was eliminated by analyzing potential differences between sites on the breast (tables 1, 2).

Benign tumor sites were not electrically distinct from the contralateral control site, but the tumor-site potential was significantly electropositive when the tumor was a cancer (table 2). Further, the potential difference between the tumor site and the ipsilateral control was significantly elevated only in the presence of cancer (table 2). These results indicated that electrochemical events at anatomically paired locations were similar in the absence of cancer, but different in its presence. The association of cancer with a local electropositivity was consistent with the results found when the effect of the disease on the difference in electrical potential between the lesion and control sites was

studied; both T – CL and T – IL were significantly elevated only in the presence of cancer (table 1). It can be concluded, therefore, that, on average, the presence of a cancer was correlated with a local electropositive maximum when compared with either the involved or contralateral breast.

Decreased intracellular K^+ concentration occurred during oncogenesis in mouse mammary tissue [9], and this observation could account for the observed association between elevated electrical potentials and cancer. Decreased intracellular K^+ suggests a higher extracellular K^+ level, and the cancer site would therefore tend to be electropositive compared with a control site in normal tissue because addition of relatively few K^+ could produce electrical potentials comparable in magnitude to those reported here [10]. Evidence for the altered kinetics of transmembrane K^+ channels was found in a study involving the effects of K^+ channel blockers on normal and transformed breast epithelial cells [11]: K^+ flow was altered in transformed breast epithelial cells, as determined by the differential effects of K^+ channel blockers on cell membrane potential.

Tumor diameter and depth both influenced the electrical potentials; if control sites were chosen after a determination of these parameters from a suitable mammogram, rather than irrespective of them as in this study, more reliable measurements could be obtained. An increased number of measurements from each breast and consideration of various patient characteristics such as the stage of the disease and the presence of metastases would also increase the precision of the technique. Incorporation of these various improvements might reduce the variance in the data, thereby permitting use of electrical-potential measurements for diagnosis of specific cases.

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