Chapter

Electrical Impedance Mammography: Screening and Basic Principles

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Abstract

Nowadays, screening uses the method of X-ray mammography for the early diagnosis of breast cancer. However, as a screening method, X-ray mammography has its limitations, such as age, periodicity of screening, 'dense' mammary gland and dynamic survey (repeated radiation). In order to overpass these limitations, more advanced alternative methods of breast examination should be used, which would be as effective as the 'golden standard.' Characteristics of electroimpedance diagnostics are given. The aim of screening is to detect breast cancer including early breast cancer (tumor size below 1 cm) and to form a survey of high-risk group. In order to reach these aims, the following actions need to be undertaken: search for areas with anomalous conductivity, detection of distorted mammographic scheme and evaluation of age-related electrical conductivity. The application of a scale for age-related breast conductivity with defined percentile limits allows to organize a survey group. Electrical properties of a cancerous tumor differ significantly from those of the surrounding tissues. Statistics of anomalous conductivity in cases of breast cancer is given. The disease development connected with the destruction of epithelial basement membrane is linked with various phenomena occurring in the tumor and the surrounding tissues. Statistics of disrupted mammographic scheme in cases of cancer is given.

Keywords: electroimpedance mammography, breast cancer, survey group, mammary gland structure, age-related electrical conductivity, anomalous conductivity, distorted mammographic scheme

1. Introduction: problems of breast cancer screening

In 1968 James Maxwell Glover Wilson and Gunnar Jungner supported by the World Health Organization published a research named [1]. In 1972 the American Cancer Society together with the National Cancer Institute developed the Breast Cancer Detection Demonstration Project, aimed to perform X-ray mammography breast cancer screening for more than quarter of a million of American women.

Since then, X-ray mammography has become not only the main screening method but also the 'gold' standard in diagnostics. It is important to distinguish the difference between screening tests and early diagnostics. Early diagnostics implies early detection of tumors in patients with symptoms. Screening test means early detection of tumors in patients without symptoms [2]. Nowadays, screening uses X-ray mammography as the method of early diagnostics of breast cancer. However, used as a screening method, X-ray mammography has its limitations and drawbacks. We'll name some problems of the main screening method.

Age. Women aged below 40 usually do not undergo breast cancer screening since sensitivity of mammography is low in this population due to the high density of breast tissue [3]. It was discovered that mammographic screening under the age of 50 is not only less effective than in the elder age but is also related to higher radiation risks [4]. Shifting of screening to the age range below 40 is undesirable since it will lead to the increase of patients' radiation exposure. Age limitations for X-ray mammography are closely related to breast cancer morbidity.

Morbidity. According to the data of the Health and Social Care Information Centre [5], despite screening programs, breast cancer morbidity does not decrease; it remained on the same level for all age groups for 10 years since 2004–2005 till 2014–2015 (**Table 1**). For the sake of solving the problem of morbidity, it would seem only natural to shift the screening framework down along the age scale. But age limitations do not allow for that.

Operational characteristics (sensitivity and specificity). Screening survey is a survey with low prevalence. As a rule, a low-prevalence survey is a preventive checkup. Screening survey is characterized by unrestricted sampling, usually estimated in many thousands, by low prevalence, standardized procedure, significant predominance of healthy patients over patients with pathologies, impossibility to use a reference method and histological verification of diagnosis due to a large number of healthy patients, significant predominance of early stage of disease among the affected patients and impossibility to apply operational characteristics, i.e. sensitivity and specificity. It is impossible to get operational characteristics and incidence data from the screening survey data. Operational characteristics can be received from the examination of patients with symptoms.

Table 2 shows operational characteristics of X-ray mammography received during a 6-year period from a large group of patients with symptoms [6].

Sensitivity of X-ray mammography used for breast cancer diagnostics above 80%, which would satisfy screening requirements, is observed only in the 70–79, 80–89 and 90+ age groups.

Breast density. Breast cancer is often similar to X-ray density of fibroglandular tissue, which makes it difficult to distinguish these tissue types due to the masking effect of dense glandular tissue [7]. It explains the unreliability of X-ray mammography for cancer diagnostics in women with high-density glandular parenchyma, with fibrocystic disease. Women with high mammographic density have higher

Women with cancer detected (rate per 1,000 women screened) by age group

England, 2004-05 to 2014-15 — rates

Age group	2004-05	2005-06	2006-07	2007-08	2008-09	2009-10	2010-11	2011-12	2012-13	2013-14	2014-15
50-54	6.4	6.3	6.4	6.3	6.3	6.3	6.2	6.6	6.7	7.0	6.7
55-59	6.7	6.8	6.7	6.7	6.5	6.2	6.0	6.3	6.6	6.5	6.7
60-64	8.9	8.8	8.5	8.5	8.6	8.6	8.4	8.6	8.9	9.0	8.9
65-70	11.7	11.6	11.3	11.2	10.2	10.1	10.1	10.4	10.3	11.1	11.0
Over 70	16.0	17.0	16.4	15.5	14.5	15.4	14.7	13.9	14.6	15.6	14.8

Source: KC62 (Parts 1 and 3, Table T) Health and Social Care Information Centre - see also Table 9a in Data Tables.

Table 1.
Women with cancer detected by age group.

Diagnostic procedure	Age group (years)	Number of women	Prevalence of breast cancer (%)	Sensitivity (%)	Specificity (%)	ROC area
Mammography	<30	15[a]	40.0	83.3	88.9	0.86
	30–39	1909	4.4	47.6	99.9	0.74
	40–49	4238	5.7	51.2	99.8	0.76
	50–59	2301	8.6	55.6	99.9	0.78
	60–69	1170	14.0	68.9	99.8	0.84
	70–79	925	27.0	79.8	99.3	0.90
	80–89	389	43.0	86.1	97.3	0.92
	90+	56	54.0	86.7	92.3	0.90
	Overall	11003	10.0	66.6	99.7	0.83

ROC, receiver operating curve.
[a]Data should be interpreted with caution as extremely small numbers of patients.

The British Journal of Radiology, April 2012

Table 2.
The number of patients attending the symptomatic breast clinic, by age and final diagnosis of either having breast cancer or not having breast cancer.

risk of breast cancer occurrence [8]. It has been proved that high mammographic density can be related to quadruple increase of breast cancer risk [9, 10].

Formation of survey or risk group. According to the definition of the World Health Organization, 'there should be a recognizable latent or early symptomatic stage. The natural history of the condition, including the early stage, should be adequately understood.' With the help of screening, it becomes possible to form breast cancer risk groups. Since ductal carcinoma takes origin from epithelial cells, areas with fibroglandular tissues and large amount of cells are highly susceptible to the increased epithelial proliferation [11]. It is the quantitative estimation of the state of fibroglandular tissue that should be used as the selection criterion allowing to differentiate the norm and the pathology. Patients with the amount of fibroglandular tissue abnormal for their age should become a part of the surveillance group. The existing screening methods do not allow to form breast cancer surveillance groups.

Repetitive examinations. Screening is a dynamic process. Recall of a patient for the screening program may cause anxiety or serious worries about potential illness, the so-called Ulysses syndrome, and lead to repeated radiation exposure [12]. In this connection, it is sensible to use safe screening methods that allow for multiple repetitive examinations. Frequency of examinations especially among high-risk group patients and in cases of hormone replacement therapy is chosen on an individual basis depending on the pathology detected.

Radiation exposure. Glandular tissue in the breast is most susceptible to radiation exposure compared to fat, skin and areola since immature cells are more vulnerable to ionizing radiation exposure [13]. And since ductal carcinoma takes origin from epithelial cells, it leaves one perplexed why X-ray mammography is used in breast cancer screening programs. Mammography has increased risks of radiation-induced breast cancer. Supposedly, low radiation dose is riskier than higher radiation dose [14, 15].

Rupture risk. The mammography procedure carries a risk of rupture of encapsulated cancer tumor, which may occur during the compression of breast tissue, and it may lead to metastases. Modern mammography equipment uses 42 pounds of pressure [16]. It may suffice for the disintegration of capsule and formation of metastases.

Mammography technique. According to the criteria of disease screening, the diagnostic method should be accessible and acceptable for the population [1]. Mammography technique can be evaluated through the analysis of the dose applied, the quality and size of the ray and the specific compression of breast. It has been established that the radiation dose and growth of breast cancer incidence are related [13]. Direct calculations of radiation dose (mGy) for a specific mammary gland are impossible. The difficulty lies in the knowledge of the structure of a specific mammary gland, which is necessary for the calculation of the conversion ratio. For this reason, an average dose is used, which depends on the thickness of the breast. In modern mammographs, the exposition is selected automatically based on the thickness of the compressed breast. Specific compression of the breast is the baseline for a good-quality image. Errors that may occur in the calculation of breast thickness during the compression of breast are related to the compression panel that may get bended and deformed.

These data show the necessity to implement additional effective screening programs for young women including screening with the application of alternative technology in order to lengthen the preclinical detection stage, which would lead to the decrease of breast cancer mortality rate [17]. In order to overcome the existing limitations, it is necessary to use modern alternative methods of breast examination that would be equal to the 'gold' standard in its effectiveness. Electrical impedance mammography is a diagnostic method satisfying the criteria set by the World Health Organization for screening for diseases. MEIK v.5.6, electrical impedance mammograph developed and manufactured by PKF 'Sim-technika,' Russia, uses advanced technologies of imaging and processing of electrical impedance images of breast. It is a noninvasive technology of image creation, it uses 3D-tomography system, it is a form of 'soft-field' tomography, it applies 'non-local' method of tomographic image creation and cross-sectional approach to data collection, it uses back-projection method as the algorithm of image reconstruction, and finally it allows to receive quantitative diagnostic information. The electrical properties of biological tissue as of colloid-dispersed system in an alternating electric field depend on the concentration and behavior of the chemical components of the tissue. The electric properties of a tumor differ significantly from those of the surrounding tissues. The aim of screening is to detect breast cancer including early breast cancer (tumor size below 1 cm) and to form a survey or high-risk group. In order to reach these aims, the following actions need to be undertaken: search for areas with abnormal conductivity, detection of distorted mammographic scheme and evaluation of age-related electrical conductivity.

2. Formation of survey group

Breast cancer risk factors. A notion exists of risk factors for breast cancer development. High breast density is one of the strongest risk factors for breast cancer development. Many of the stated risk factors for breast cancer influence breast density in the long run through hormones. Women with high breast density have higher concentration of estrogen in blood serum than women with lower breast density, and the risk of breast cancer for them is twice as high compared to the low level of circulating estrogens [18]. For women with extremely high breast density, the relative risk of breast cancer is four to eight times higher than high breast density or about two times higher than medium breast density [19]. Relative risk of breast cancer for women with extremely high breast density is 6.0 [with 95% confidence interval, 2.8–12.9], and it is the third risk factor after the patient's sex and age [20]. Search for risk factors, diagnostics and preventive measures for high breast density forms a new field of research.

High breast density. Breast density is inversely proportional to the content of adipose tissue and directly proportional to the content of epithelial and fibrous tissue [21]. With advancing age, breast density decreases, and the breast tissue 'ages' [21]. Serial mammography showed that the initial breast density influences the change of density through life: age-related decrease of high density is stronger than the density decrease in cases of lower density [22]. It was found that there exists a relation between high breast density and hormonal status. The specific features of reproductive anamnesis, menstruation anamnesis, menopausal status, excessive weight and exogenous and endogenous hormones influence breast density. Women with high breast density have higher concentration of estrogen in blood serum than women with lower breast density. Estrogen replacement therapy in pre- and postmenopausal period increases breast density [23–25]. Therefore, 'breast density' marker has higher potential as to being used for the prevention of breast cancer [26].

Methods of breast density estimation. Detecting women with high density of breast is the primary objective for screenings. Today there is no set 'gold' standard for the estimation of breast density. There are several methods for the assessment of breast density. Visual methods are based on the qualitative analysis of breast parenchyma, such as in Wolf's, Tabàr's, Boyde's and BI-RADS classifications. The aim of semiautomatic estimation is to measure breast density. There exist automated systems for the estimation of the area of breast density. Volumetric methods allow to evaluate the actual volume of fibroglandular tissue. It should be noted that various methods of breast density measurement use only X-ray systems. There is a sharp need for additional screening of women with high breast density [27]. Due to the growing interest toward estimation of breast density, new diagnostic methods appear.

Electrical impedance estimation of breast structure. Biological tissue is presented as a colloidal dispersion system. The structure of breast has a number of tissues that fulfill different functions (epithelial tissues, connective tissues, nervous tissue, blood and lymph) and fill the anatomical structures. The electrical properties of tissues are the direct consequence of the tissue structure. The electrical impedance mammograph MEIK v.5.6. with current force 0.5 mA and frequency of 50 kHz allows to evaluate breast structure. The fundamental difference of electrical impedance scanning from other tomography methods is that besides visual evaluation of the image, the electrical impedance mammography provides quantitative information, i.e. the numerical estimation of its anatomical and histological structure. This unique information is used for diagnostic purposes. All other factors equal, the electrical conductivity will depend on the concentration of ions and the amount of cellular elements, and it will decrease as the concentration grows [28]. The electrical conductivity index [IC], which is received during electric impedance scanning, is a quantitative characteristic of breast structure. Low index of electrical conductivity is typical for the breast containing a large amount of cellular elements and high concentration of ions, which corresponds to acinar-ductal type of breast structure. High electrical conductivity index is typical for the breast containing a large amount of fat lobules and connective tissue and low concentration of ions, which corresponds to amorphous structure of the breast. One thousand six hundred thirty-two processed images received from electromammographic examinations of healthy women helped to evaluate, percentile method applied, the structure of breast from the point of view of electrical impedance mammography. **Table 3** shows percentile limits for different types of breast structure in electrical impedance mammography.

Therefore, the electrical conductivity index can be used for the evaluation of breast structure from the point of view of electrical impedance mammography. It is a known fact that the structure of breast defines the breast density. For this reason, the defined ranges of electrical conductivity correspond to different types of 'density' of breast. **Table 4** shows the structure of the breast according to the electrical impedance mammography and types of density according to American College of Radiology [ACR] classification. 'Dense' breast, i.e. the so-called acinar-ductal type, is characterized by low electrical conductivity index. High electrical conductivity index is common for amorphous type of breast [consisting mostly of adipose and connective tissue]. The image shows examples of electrical impedance mammograms of patients from different age groups with different structure of breast: a 25-year-old patient with acinar-ductal type (**Figure 1**) and extreme breast density and 63-year-old patient with amorphous structure and low breast density (**Figure 2**).

Definition	Electrical conductivity	Percentile limits
Amorphous structure	More than 0.66	>90‰
Mixed type with amorphous component prevailing	0.57–0.65	75–90‰
Mixed type	0.30–0.56	25–75‰
Mixed type with acinar-ductal component prevailing	0.22–0.29	10–25‰
Acinar-ductal type prevailing	Less than 0.22	<10‰

Table 3.
Percentile limits for different types of breast structure in electrical impedance mammography.

EIM classification		Electric conductivity	*ACR classification*
Type Ia	Amorphous	above 0,66	Predominantly fat, parenchyma below 25%
Type Ib	Mixed with the predominance of the amorphous component	0,57 – 0,65	
Type II	Mixed	0,30 – 0,56	Fat with some fibroglandular tissue, parenchyma between 25% and 50%
Type III	Mixed with the predominance of the ductal component, high density of the ductal component	0,22 – 0,29	Heterogeneously dense, parenchyma 50-75%
Type IV	Ductal, extremely high density of the ductal component	below 0,22	Extremely dense, parenchyma 75-100%

Table 4.
The structure of the breast according to electrical impedance mammography and types of density according to the American College of Radiology [ACR] classification.

On the **Figure 2** you can find examples of electrical impedance mammograms of the same age group but with different breast structure: 36-year-old patient with acinar-ductal type and high tissue density and 34-year-old patient with amorphous structure and low tissue density (**Figure 2**). In order to form a survey group, it is necessary to determine not only the breast structure but also the correspondence between the structure type and age-related electrical conductivity of the breast.

Electrical impedance evaluation of age-related electrical conductivity of the breast. The application of percentile method for the electrical impedance mammograms of healthy women in the following age ranges, <20, 20–29, 30–39, 40–49, 50–59, 60–69 and >70 years old, allowed to evaluate age-related electrical conductivity of the breast from the point of view of electrical impedance mammography. For each age group, the 5th, 50th and 95th percentile limits of electrical conductivity were calculated. The data can be represented in the form of percentile curves of

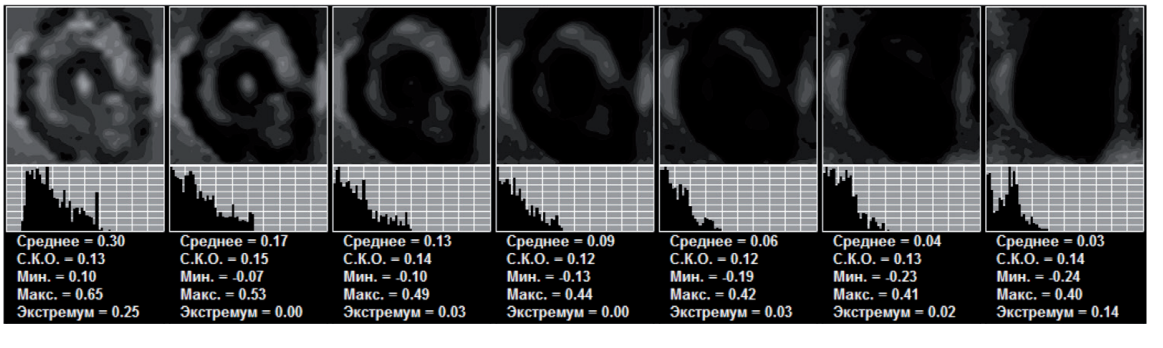

Figure 1.
Type IV (ACR IV). Acinar-ductal type. Extreme tissue density.

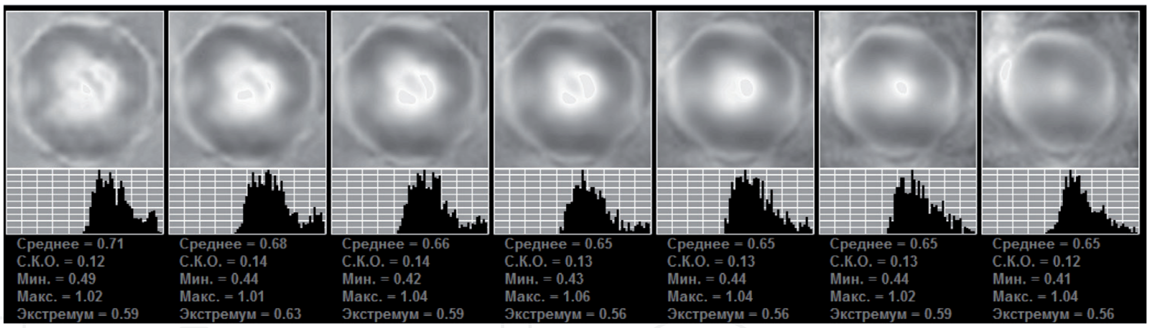

Figure 2.
Type I (ACR I). Amorphous type. Low tissue density.

Age range, years	5 percentile	50 percentile	95 percentile
20-29	0,18	0,28	0,44
30-39	0,16	0,40	0,53
40-49	0,22	0,51	0,63
50-59	0,32	0,58	0,72
60-69	0,43	0,57	0,78
over 70	0,50	0,57	0,64

Table 5.
Diagnostic table of age-related electrical conductivity of breast.

age-related electrical conductivity and in the form of a diagnostic table (**Table 5**). In accordance with the suggested estimations, the values in the 1st percentile corridor [below the 5th percentile] should be treated as significantly lowered, in the 2nd percentile corridor [5–25 percentile] as lowered, in the 3rd and 4th [25–75 percentile] as medium, in the 5th [75–95 percentile] as increased and in the 6th [above the 95th percentile] as significantly increased. In order to form survey groups, it is necessary to use percentile limits of age-related electrical conductivity. The risk group should include the patients who have abnormally low values of age-related electrical conductivity of the breast, i.e. below the fifth percentile, which is the signal of high density of the acinar-ductal component of the breast for this age range. High density of acinar-ductal component is potentially dangerous since it may be combined with insufficient trophic function of connective tissue. It is a known fact that the ground substance of connective tissue plays the main role in the fulfillment of this function. Homeostasis disruption may lead to dystrophic processes including those in the basement membrane. Therefore, this method allows to detect the risk of tumorigenesis in women before the disease manifests itself, and it allows us to form risk groups for monitoring and correction of breast condition.

3. Early diagnostics of breast cancer

The electrical properties of cancer tumor differ greatly from the electrical properties of the surrounding tissues. It was established during several researches that malignant tumors have lower electrical impedance than normal tissues. The results of these studies are given in **Table 6** [29].

S. Haltiwanger published the results of several studies about the specific features of tumor cells that influence their electrical activity:

Authors, year	Frequency range investigated	Nature of study and results
Fricke et al. [29], 1926	20 kHz	They measured the parallel capacitance and resistance of the following excised samples from the breast—fat, gland, mastitis, fibroadenoma and carcinoma They found significantly higher permittivity of the tumor tissue at 20 kHz than the normal or benign tissues.
Singh et al. [30], 1979	100 Hz–100 kHz	They performed in vivo impedance measurements on female breasts with and without tumors. Their results showed that malignant tumors have higher relative permittivity and lower resistance than those of normal breast tissue
Chaudhary et al. [31], 1984	3 MHz–3 GHz	They examined excised normal and malignant breast tissues and found that the conductivity and permittivity of malignant tissues are higher than those of normal tissues, especially at frequencies lesser than 100 MHz.
Surowiec et al. [32], 1988	20 kHz–100 MHz	They conducted in vitro dielectric studies in three different samples of breast tissues—the main tumor tissue, the tissue immediately surrounding the tumor and the peripheral normal tissue. They found that the tumor tissues have a low-frequency (100 kHz) conductivity around 2–4 mS/cm which is higher than the conductivity of normal tissue (below 1 mS/cm) and lower than that of the tissue surrounding the tumor (8 mS/cm).
Morimoto et al. [33, 34], 1990	0–200 kHz	They measured the extracellular and intracellular resistances and membrane capacitance of breast tumors in vivo. They concluded that there are statistically significant differences between normal and cancerous tissues. However, it has been reported that malignant tumors have lowered capacitance compared to benign tumors. This is different from the results of the study conducted by Jossinet [36] and Fricke [33] which have recorded higher capacitance values for malignant tumors.
Jossinet [35], 1996	488 Hz–1 MHz	The study examined six groups of normal and pathological breast tissues in vitro. The variability of impedivity within each group was assessed by statistical methods. It was found that the variability was smaller in adipose tissue, carcinoma and fibroadenoma above 10 kHz.
Jossinet [36], 1998	488 Hz–1 MHz	Using the same data from [35], it was found that the cancerous tissue differed significantly from fibroadenoma and mammary gland tissues by the modulus of impedivity up to 31.25 kHz and from the remaining tissue groups (connective tissue, adipose tissue and mastopathy) by the low-frequency-limit resistivity and the phase angle from 125 kHz to 1 MHz. It was also observed that neither the impedivity nor the low-frequency-limit resistivity nor the fractional power value was different between the groups of normal and benign tissues.
Jossinet et al. [37], 1999	488 Hz–1 MHz	Again using the same excised data collected for previous studies, they defined a set of eight parameters that could differentiate cancerous breast tissues from noncancerous ones. They concluded that a combination of the parameters over various frequencies is necessary for the accurate differentiation among tissues.
Chauveau et al. [38], 1999	10 kHz–10 MHz	They conducted an in vitro study of normal and pathological breast tissues and observed significant differences in their dielectric properties. They have determined three indices based on extracellular resistance, intracellular resistance and membrane capacitance to differentiate between various tissue pathologies—normal, invasive ductal carcinoma (IDC), IDC with stromal reaction and fibrocystic changes.

Table 6.
The results of several researches of the electrical properties of cancer tumor.

1. Cancer cells have cell membranes that exhibit different electrochemical properties and a different distribution of electrical charges than normal tissues [30].

2. Cancer cells also have different lipid and sterol content than normal cells [31].

3. Cancer cells have altered membrane composition and membrane permeability, which results in the movement of potassium, magnesium and calcium out of the cell and the accumulation of sodium and water into the cell [32].

4. Cancer cells have lower potassium concentrations and higher sodium and water content than normal cells [33, 34].

5. The result of these mineral movements, membrane composition changes, energy abnormalities and membrane charge distribution abnormalities is a drop in the normal membrane potential and membrane capacitance.

6. An increase in the intracellular concentration of positively charged sodium ions and an increase in negative charges on the cell coat (glycocalyx) are two of the major factors causing cancerous cells to have lower membrane potential than healthy cells [31].

7. Two of the most outstanding electrical features of cancer cells are that they constantly maintain their membrane potential at a low value and their intracellular concentration of sodium at a high concentration [34, 35].

8. A sustained elevation of intracellular sodium may act as a mitotic trigger causing cells to go into cell division [35].

The results of the researches confirm that electrical conductivity is an appropriate parameter for the differentiation between healthy tissue and tumor tissue. The fundamental difference of electrical impedance scanning from other tomographic methods is that besides visual evaluation of the image, the electrical impedance mammography offers quantitative information [28]. If the diagnostic method under discussion yields a quantitative result, a value is defined, the overpassing of which is deemed to be a sufficient cause for qualitative evaluation, i.e. the so-called differentiation point. It is essential to define a precise differentiation point. The point with electrical conductivity exceeding 3 standard deviations [std] is considered to be the point of differentiation between breast cancer patients and healthy people. The detection of areas with high electrical conductivity exceeding 3 std. outside the lactiferous sinus in electrical impedance mammograms, which differs greatly from the electrical conductivity of normal breast tissue, is used as a diagnostic criteria for the detection of breast cancer [28]. Moreover, sizes of tumors as a rule do not exceed 10 mm.

Figure 3 shows the electrical impedance mammogram of a breast cancer patient with the following parameters: IC = 0.56, std. = 0.12. In the mammogram, at the 3 o'clock position near the areola, a focus without a sharp contour is visualized, its IC being equal to 0.94. Therefore, the IC in the area of interest exceeds the mammogram IC by more than 3 std.

Below X-ray images [fibroadipose involution, the upper external quadrant shows a mass less than 1 cm in size with uneven contour] and ultrasound mammograms [the external quadrant contains a lesion of irregular shape with uneven structure, 7 × 8 mm in size, with vascularization] of the same patient are presented.

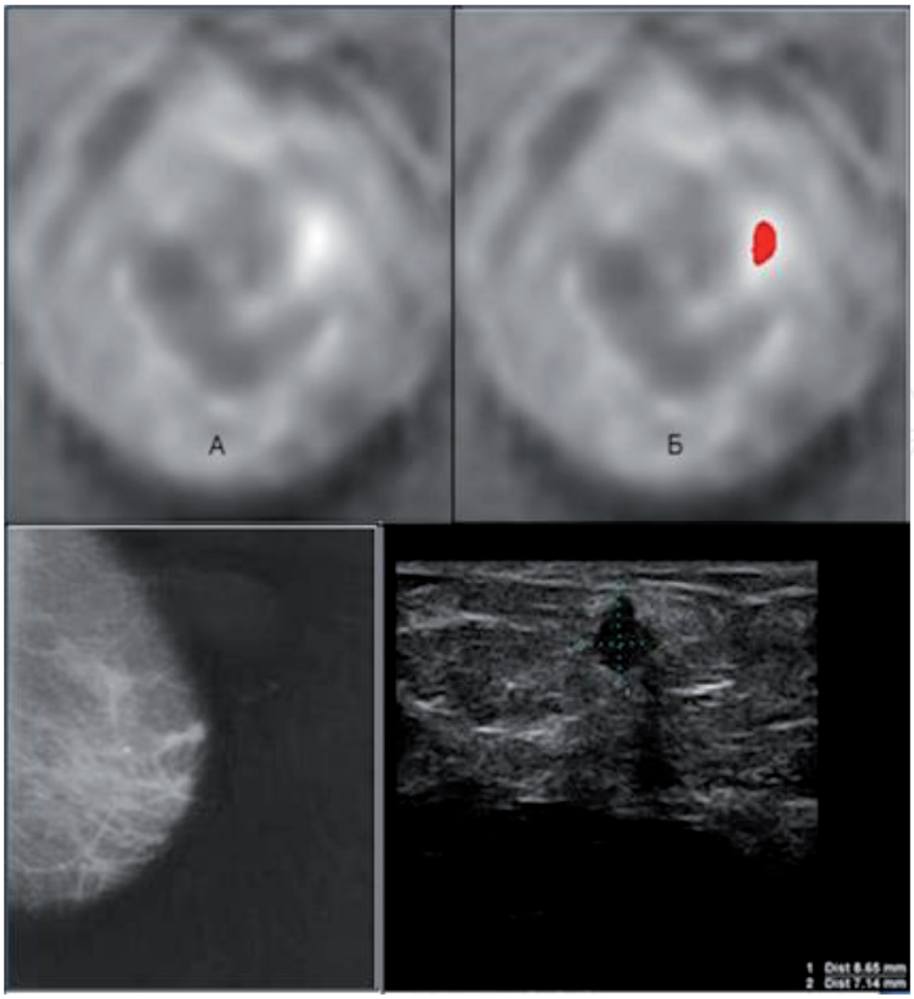

Figure 3.
Upper row: Electrical impedance mammogram of a breast cancer patient. At the 3 o'clock position near the areola a focus without a sharp contour, with abnormal electrical conductivity, is visualized. It is colored red (7 × 10 mm). The lower row shows X-ray and ultrasound images for the same patient.

For the last few years, clinical studies have been held in different countries determining the potential of electrical impedance mammography in breast cancer diagnostics. All these studies used electrical impedance computer mammograph MEIK v.5.6, abnormal electrical conductivity being the diagnostic criterion [28].

Sachin Prasad and colleagues performed a study to determine the diagnostic efficiency of 3D electrical impedance tomography [EIT] compared to mammography (mg) and ultrasonography (USG) in breast imaging [36]. A group of 88 patients with various breast complaints was examined using combined mammography and ultrasonography [MG & USG] or either of these modalities alone. The same patients were then examined using the 3D EIT imaging system MEIK. The study revealed that there was no overall significant difference in sensitivity between MG-USG [p = 0.219] and MG-EIT [p = 0.779] and USG-EIT [p = 0.169].

O. Raneta and colleagues [37] performed a study to analyze the possibilities of electrical impedance tomography [EIT] application in the differential diagnosis of pathologic lesions of the breast either solely or in combination with MMG/USG [37]. A group of 870 eligible women with suspected pathological breast lesion discovered by mammography [MMG] or ultrasound examination [USG] were recommended to pass histological examination to verify the diagnosis. The sensitivity of MMG increased from 87.8% when using it as an independent method to 94.5% with EIT added. The sensitivity of USG increased from 86.7% when used as an independent method to 93.3% with EIT added. The results of the study showed that the use of EIT in addition to MMG/USG can improve the sensitivity of these methods and increase the rate of early detection of breast cancer with minimal economic costs and time input of highly qualified staff.

Daglar and colleagues [38] performed a study to compare the usefulness of the breast electrical conductivity measures performed in a surgical examination room against conventional breast screening modalities for identifying the symptomatic lesions of the breast tissue [38]. A group of 181 patients were examined with ultrasonography [USG], mammography [MG] and electrical impedance scanning [EIS] modalities, which were followed up for 24 months to clarify the lesion tumor progression relationship. EIS exhibited compatible sensitivity [81.2%], accuracy [84.6%] and PPV [81.8%] rates with USG in BI-RADS 4 subgroup, combination of these modalities raised sensitivity rates to 92.31%, accuracy and PPV to 100%. EIS results in BI-RADS 3 subgroup were pointed out 77.8% specificity and 87.5% NPV rates. Breast electrical impedance measures should be useful to reduce the number of the unnecessary follow-up and biopsy rates in the clinical setting.

Xu Feng and colleagues [39] performed a study to investigate the diagnostic accuracy of electrical impedance tomography [EIT] for benign and malignant breast diseases in comparison to conventional ultrasonography and mammography [39]. A total of 121 patients with 126 breast lesions who underwent ultrasonography mammography and EIT were enrolled in the study. All of these lesions were confirmed by pathological biopsy. The accuracy, sensitivity, specificity, positive predictive value and negative predictive value of EIT, ultrasonography and mammography were calculated with histology used as the 'gold' standard. The accuracy of EIT, ultrasonography and mammography were 75.4, 81.7 and 76.1%, respectively. The sensitivity was 76.8, 94.6 and 74.4%, respectively. The specificity was 74.3, 71.4 and 77.6%, respectively. The accuracy, sensitivity and specificity of EIT combined with ultrasound in the diagnosis of breast lesions were 91.3, 98.2 and 85.7%, respectively. The accuracy [$\chi 2 = 4.896$, $P = 0.027$] and specificity [$\chi 2 = 4.242$, $P = 0.039$] were significantly higher on EIT than ultrasound. The accuracy, sensitivity and specificity of EIT combined with mammography were 95.5, 97.4 and 93.9%, respectively, which were significantly higher than those of mammography [$\chi 2 = 13.474$, $P < 0.001$; $\chi 2 = 8.573$, $P = 0.003$; $\chi 2 = 5.333$, $P = 0.021$]. Used together with ultrasound or mammography, the electrical impedance tomography could be a valuable complementary examination in the diagnosis of breast diseases. Furthermore, EIT could provide very useful additional information for metabolic assessment of mammary glands, which may be used for early screening of breast diseases.

Blanca Murillo-Ortiz and colleagues [40] performed a study to know the effectiveness of the electrical impedance mammography for the detection of mammary carcinoma in 615 women from 25 to 70 years of age [40]. The sensitivity and specificity of the electrical impedance mammography (MEIK) was 85 and 97%, respectively.

Therefore, the studies showed high level of sensitivity and specificity, which allows to use abnormal electrical conductivity as the diagnostic criterion in screenings for early detection of breast cancer.

4. Distorted mammographic scheme in cases of breast cancer

Distortion of normal mammographic scheme appears in case of structural changes, such as pathological shadows and microcalcifications. These focal changes can be easily detected with the help of medical equipment checking the density of tissue. But along with focal changes, breast cancer can reveal itself through diffuse changes of breast structure, which also leads to the disruption of normal mammographic scheme, and this can be detected with electrical impedance mammography.

For X-ray diagnostics, diffuse changes are a difficult matter since they do not change the density of breast tissue.

As the disease develops, which leads to the destruction of the basement membrane of the epithelium, the lesion and surrounding tissues may undergo various phenomena followed by changes of electrical properties of the tumor mass:

- Edema and softening of fibrous connective tissue
- Slimming, hyalinosis, calcification
- Appearance of purulent areas
- Lymphocytic infiltration of tissue

Therefore, tumor growth is naturally accompanied by the changes of electrical properties of tumor and surrounding tissues. The criteria of distortion of normal mammographic scheme in cases of breast cancer are changes of contour, anatomical changes, local changes of electrical conductivity and change of comparative electrical conductivity. As previously stated, the electrical impedance method gives a possibility of quantitative imaging [28]. Quantitative analysis of an electrical impedance image allows to receive a histogram of electrical conductivity distribution and compares it with reference values. As a rule, distorted mammographic scheme in case of breast cancer is accompanied by changes of electrical conductivity of breast tissues. This phenomenon facilitates visual and quantitative interpretation of the lesion and can be used for diagnostic purposes. **Figure 4** shows several variants of distorted mammographic scheme in cases of breast cancer and their visual evaluation [1, contour deformation; 2,4, thickening of contour; 3, anatomic distortion; 5,6, local changes].

For the classification of a patient (healthy or affected), test of differences in the form of distributions [λ criterion], i.e. Kolmogorov-Smirnov test in Dx modification, is used [41]. This criterion, which is a nonparametric test, allows to determine the statistical value of differences in the distribution of any normal or abnormal features, including the distribution of electrical conductivity in electrical impedance tomograms. For the assessment of informativeness of distribution divergence, Kulback informativeness measure is applied [41]. High informativeness of the detected differences allows to refer the patient with high degree of probability to one class or the other (e.g. norm or cancer). In case of breast cancer, histogram of affected breast gets displaced, and Dx criterion exceeds 40% (**Figure 5**).

Table 7 shows the comparative electrical conductivity data for patients with breast cancer, benign changes, for healthy patients and for those with different types of breast structure; the data was received during clinical studies in the hospitals of Russia. It is evident that divergence of histograms of electrical conductivity distribution by more than 40% is observed only in cases of breast cancer, and actually divergence of histograms of electrical conductivity distribution by more than 30% in the majority of cases is observed during oncological processes in the breast.

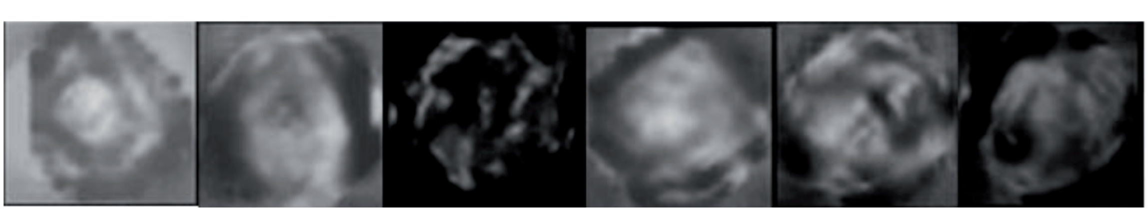

Figure 4.
Several variants of distorted mammographic scheme in cases of breast cancer.

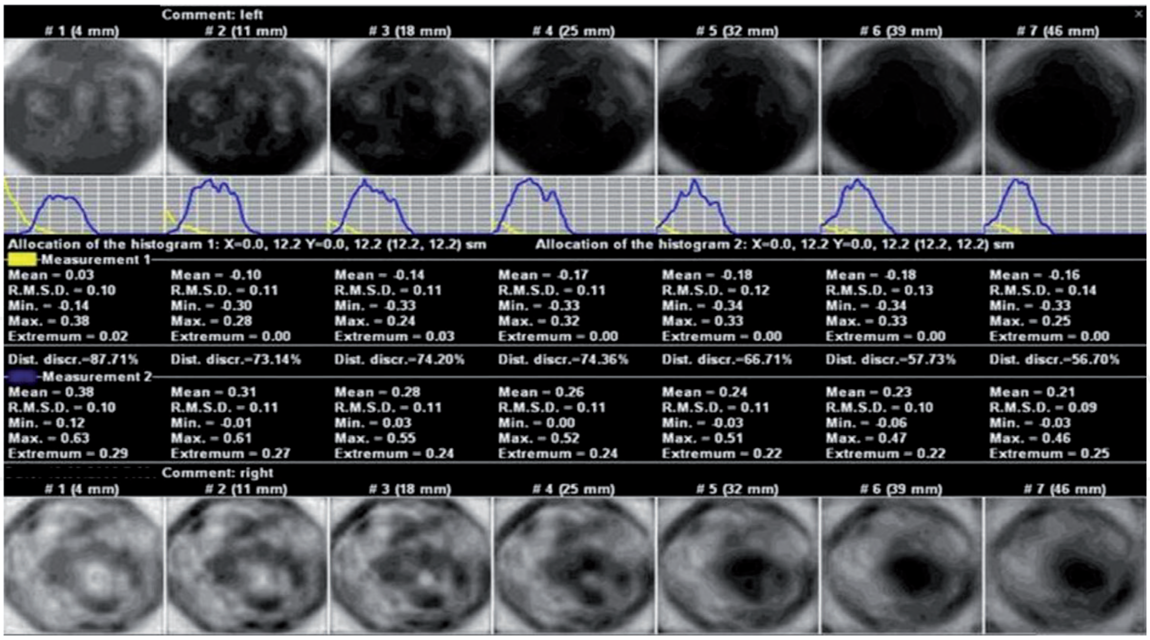

Figure 5.
Upper row, EIM. Seven scan planes. Breast cancer. Bottom row, EIM. Seven scan planes. Healthy breast. The second row shows the divergence between the histograms of electrical conductivity distribution of the affected and healthy breast.

	Number of patients	Comparative electric conductivity (affected – normal gland)					
		<20%	20-30%	30-40%	40-50%	50-60%	>60%
Cancer	310	101 (33%)	67 (22%)	44 (14%)	37 (12%)	26 (8%)	35 (11%)
Healthy	161	157 (98%)	4 (2%)	0	0	0	0
Healthy acinar-ductal type	20	18 (90%)	1 (5%)	1 (5%)	0	0	0
Healthy amorphous type	32	28 (88%)	2 (6%)	2 (6%)	0	0	0
Benign	68	59 (87%)	7 (10%)	2 (3%)	0	0	0

Table 7.
Percentage distribution of healthy patients, patients with benign changes and breast cancer depending on the percentage of comparative electrical conductivity of the breasts.

EIM	ACR
Common scale	BI-RADS categories
No score	BI-RADS 0 poor image
0–1	BI-RADS 1 lesion is not defined
2–3	BI-RADS 2 benign tumors—routine mammography
4	BI-RADS 3 probably benign findings
5–7	BI-RADS 4 suspicious abnormality—biopsy
>8	BI-RADS 5 highly suggestive of malignancy—treatment/biopsy

Table 8.
EIM scale and ACR BI-RADS.

During the oncological process, natural changes of general and local electrical conductivity occur. And distortion of normal mammographic scheme may occur at an early stage of the disease. This is the reason why this criterion is included in the EIM scale of breast cancer diagnostics [41].

A scoring scale used for the evaluation of mass lesions in the breast by means of electrical impedance mammography allowed to relate the information received with BI-RADS ACR categorization (**Table 8**). The EIM scoring scale allowed to standardize the description of mass lesions examined by means of electrical impedance mammography and to use the patient follow-up algorithm developed by the American College of Radiology.

Therefore, the distortion of normal mammographic scheme along with abnormal electrical conductivity is one of the most frequent diagnostic indicators of breast cancer.

5. Discussion

Sensitivity and specificity are operational characteristics that allow to evaluate the effectiveness of a diagnostic method. Operational characteristics are influenced by several factors: size and area of pathology, age of patients in the groups under study and prevalence in the group under study. In the process of sensitivity and specificity calculation, the disease prevalence in the group is not taken into account. It is a significant benefit since it gives a possibility to spread the data received in a group of people onto other groups, with different prevalence. However, it is also a drawback of evaluation. The diagnostic test data should be spread cautiously onto groups of people that differ significantly from the group under study.

The calculation method used for operational characteristics such as sensitivity and specificity has its own peculiarities in cases of low and high prevalence.

Low-prevalence studies. As a rule, studies with low prevalence are preventive checkups. Screenings are low-prevalence studies as well.

Characteristics of screenings:

- Unrestricted population of sampling group, as a rule including many thousands of people
- Low prevalence
- Standard methodology
- Significant prevailing of healthy patients over patients with pathologies
- Impossibility to use reference method and histological verification of the diagnosis due to a large number of healthy patients
- Significant prevailing of patients with early stages of disease from among the number of those with revealed pathologies
- Impossibility to apply operational characteristics: specificity and sensitivity

High-prevalence studies. Studies performed in a diagnostic department of a specialized clinic are high-prevalence studies.

Characteristics of a diagnostic study:

- Restricted sampling population, several dozens of respondents

- High prevalence
- Standardized methodology
- Significant prevailing of patients with pathologies over healthy ones
- Significant prevailing of patients with progressing disease over those with early stages
- Use of referential method and histological verification of diagnosis
- Application of operational characteristics: sensitivity and specificity

Medium prevalence, which can be called an intermediate link, is a study held in a diagnostics department of a general practice clinic.

Characteristics of a diagnostic study:

- Unrestricted sampling population and timing
- Medium prevalence
- Standardized methodology
- Prevailing of healthy patients over patients with pathologies
- Full range of disease manifestation: from early-stage patients to patients with progressing disease
- Use of referential method and histological verification of diagnosis
- Application of operational characteristics: specificity and sensitivity

Is it correct to spread operational characteristics received from the second and third examples onto the screening?

1. Spreading the estimations received in high-prevalence conditions onto low-prevalence conditions should be done with caution. High-prevalence spectrum of disease manifestations differs from low-prevalence spectrum. Since diagnostic centers accumulate patients with a certain disease, in the structure of high-prevalence cases of progressing disease dominate significantly over early stages of disease.

2. Since every stage of disease has its own symptoms or specific criteria, for every stage the diagnostic criteria should have their own operational characteristics.

3. Operational characteristics are determined on the basis of restricted sample group of patients with verified diagnoses. Since reference tests, as a rule, are indifferent for the respondents, in such studies the number of persons not affected by the disease under study is minimal. In case of data spreading, it can influence the expected number of false-positive and false-negative results.

4. The optimal study for receiving operational characteristics of the method used from the point of view of patient selection, prevalence level, from the point of view of commonality of the methodology used and the usage of the reference

method and histological verification is not a low-prevalence study, such as screening, and is not a high-prevalence study as inpatient examination but a study held in an imaging room for the prevalence typical for the settlement. Shifting of operational characteristics in the situation of medium prevalence is preferable since it has a well-balanced data set.

Electrical impedance mammography is a tool for primary breast cancer screening. It is confirmed by its high informativeness, safety for the staff and patient, portability and mobility. Operational characteristics (sensitivity and specificity) are determined on a restricted sample group, the so-called high- and medium-prevalence group, with the use of reference method (X-ray mammography) and verified diagnosis. The studies were held in oncological centers and clinics. The study on a group of patients with high and medium prevalence demonstrated high sensitivity and specificity of the electrical impedance mammography. The received operational characteristics can be spread onto groups of patients with low prevalence and be used during planning of screening studies. It allows to use the electrical impedance mammography for primary breast cancer screening of big groups of population with low prevalence. The electrical impedance mammography fulfills its functional screening tasks without ionizing radiation and other potentially hazardous means. It can be used to perform examinations for women of all age groups in outpatient departments, schools, clinics for women, maternity hospitals and sanatoriums, i.e. in the gathering places for women. In such a way, the problem of organization of mass screening for women can easily be solved.

Conflict of interest

The authors declare no conflict of interest.

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