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Estimation of the prognostic value of some clinical factors and mammographical signs in breast cancer

Ocena wartości prognostycznej wybranych cech klinicznych i objawów mammograficznych w raku piersi

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Summary

Background: The aim of the work is to assess the probability of the breast cancer occurrence on the basis of analysis of the clinical and mammographical factors in women with unpalpable breast tumor.

Material/Methods: In the period from the 1st February 1995 to the 31st August 2000, 163 surgical procedures for the removal of any lesions in the breasts were conducted, after being previously marked by localized needle, in women who earlier underwent mammography exam.Following data was taken into consideration: patients age, type of the breast structure; side of the breast, where the lesion was localized in the mammography exam; localized lesions depending on the quadrant; shape of the lesion; size of the lesion in millimeters; presence and the type of microcalcifications.

Results/Conclusions: 1. The only one population factor, which can be distinguished as characteristic for the women suffering from the breast cancer impalpable in clinical testing, is the age of the patient, because the breast cancer in these women more frequently occurs after 53 years of age. 2. On the basis of our own material the following radiological symptoms characteristic for the breast cancer in mammography exam were stated: the breast cancer is more frequently found in the upper external quadrant; all lesions, which in mammography exam were identified as multifocal and radiologicaly suspected in histopathology exam turned out to be the cancer; pleomorphic microcalcifications are characteristic for the malignant lesions; external outline and the shape of the lesion are the features, which allow to differentiate malignant and benign lesions. 3. The analysis of the material indicates that the greatest probability of the breast cancer occurrence is in case of the four risk factors occurrence simultanosly, and the smallest in case of only one risk factor occurrence.

Key words: breast cancer risk factors • microcalcifications

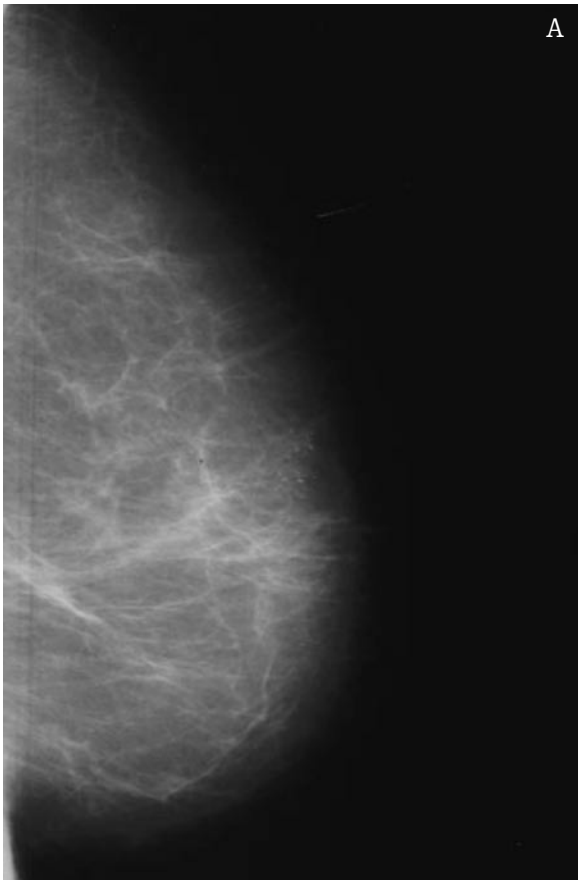
PDF file: http://www.polradiol.com/pub/pjr/vol_71/nr_4/9052.pdf

Background

Breast cancer is one of the most frequently occurring disease in women over the world. It exemplifies about 19% of the whole incidents of the malignant neoplasm in the world. It is also the most frequent occurring malignant neoplasm in women in Poland, as much as 17% of the number of incidents of malignant neoplasm, and about 14% of the total deaths.

One of the methods, which can diminish the number of deaths caused by the breast cancer, is dissemination of mammography tests as it is the only one, that allows to detect the breast cancer not palpable in the clinical examination.

Many years passed from the introduction the first breast X-ray to the screenee. The first information about the breast radiography was published in 1913 in Germany. That information was delivered by the German surgeon Albert Salomon, who conducted about 3000 mastectomies, and later took the X-rays of the breast operated upon and also conducted histopathology tests. He stated that radiological image corresponds with the outline and extensiveness of the tumor. With the assistance of the radiological testing, he distinguished the fibrous and infiltrative forms from the restricted and nodular forms of the breast cancer. Albert Salomon also revealed spotty calcifications typical for the ductal carcinoma, which was not separated as a distinctive pathological unit for many years. Albert Salmon first described cancer impalpable in clinical testing, which was given radiological signs. This form of cancer was accidentally discovered in woman who was operated due to the existence of the palpable big cyst, which was benign in the histological testing. On the specimen next to the described cyst was a small tumor with the processes typical for the fibro carcinoma. Radiologists engaged themselves in breast researches only in the twenties of the twentieth century.



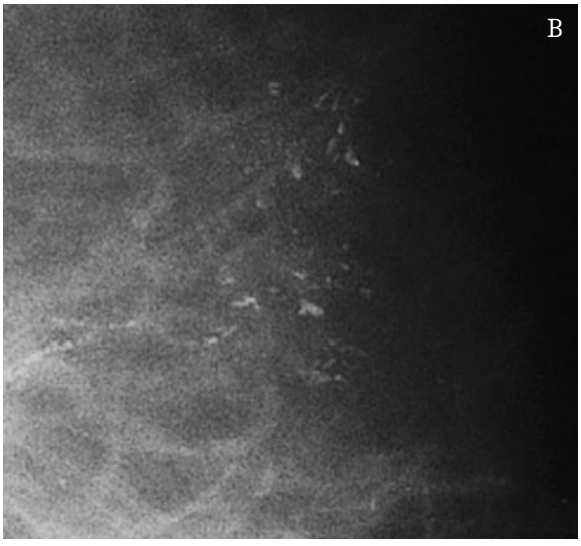


Figure 1 a, b. Microcalcifications without solid center.
Rycina 1 a, b. Mikrozwapnienia bez litego centrum.

Then a number of independent groups of radiologists engage themselves in that direction of researches. First information about the form of radiological researches of the breast was given by Otto Kleinschmidt from the surgical clinic in Leipzig [1].

The aims of the study are:

1. Determination the characteristic features of breast cancer in mammography exam.

2. Assessing the probability of the breast cancer occurrence on the basis of analysis of the clinical and mammographical factors in women with unpalpable breast tumor.

Materials and methods

163 patients who were treated in Oncology Institute in Krakow were put through a retrospective analysis in the period from February 1995 to September 2000. After marking by localized needle, the patient's breast lesion was cut out. In all tested patients focal lesions in the breast were detected during mammography testing. These lesions were impalpable in clinical testing.

The mammography exam was assessed on the basis of BIRADS (Breast Imaging Reporting and Data System) program worked out by the American Society of Radiology (ACR) [2].

Following data was taken into consideration:

1. Type of the breast structure;

2. Side of the breast, where the lesion was localized in the mammography exam;

3. Localized lesions depending on the quadrant;

4. The shape of the lesion;

Figure 2. Round lesions.
Rycina 2. Zmiany okrągłe.

The lesions visible in the mammography were divided into the following groups: the lesions without compact center, that is a clusters of microcalcifications, in the projection of which there was no compact center (Figure 1) and the lesion with processes, eg, radial scar in the projection of which mostly there is no compact center. Besides, there are: round

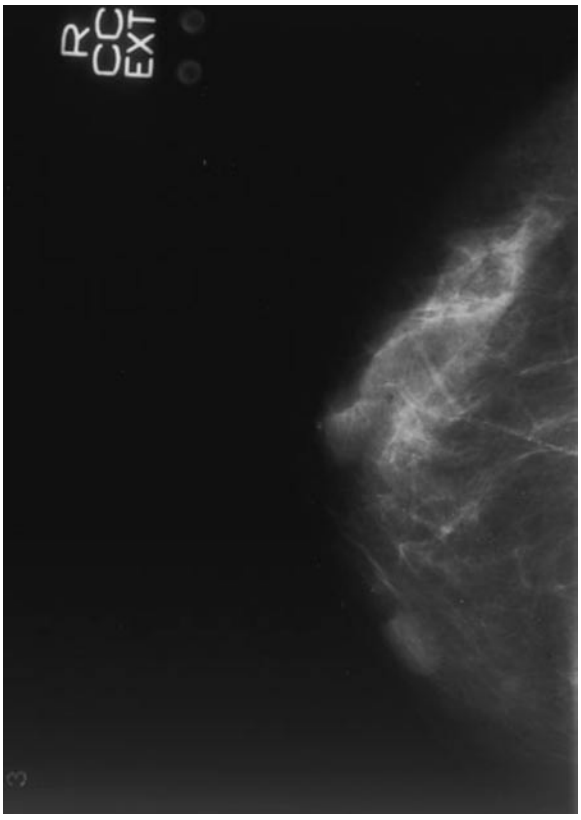


Figure 3. Oval lesions.
Rycina 3. Zmiany owalne.

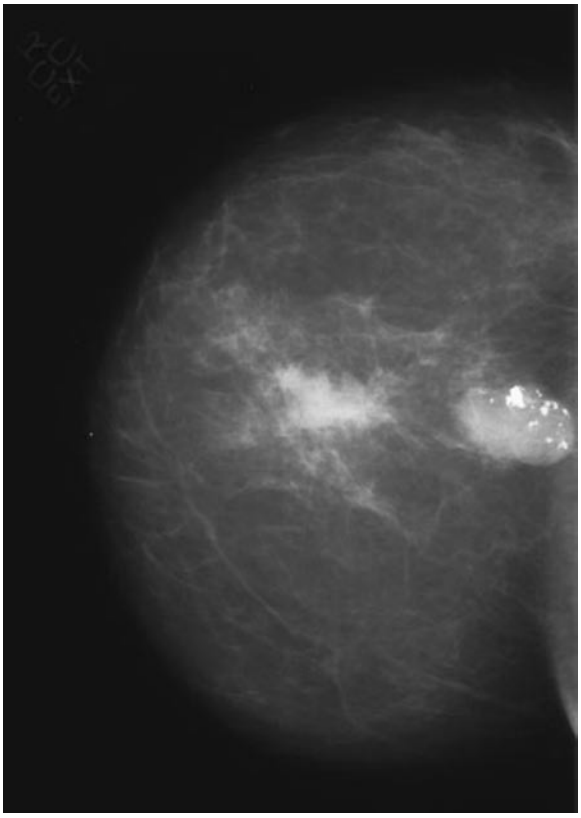


Figure 4. Lobulated lesions.
Rycina 4. Zmiany zrazikowe.

lesions (Figure 2), oval lesions (Figure 3), lobulated lesions (Figure 4), irregular lesions (Figure 5), disorder of the breast architectonics, asymmetry of the glandular tissue.

5. The size of the lesion in millimeters;

6. Presence and the type of microcalcifications.

The microcalcifications were assessed as regards to the shape, density, homogeneity and quantities in the cluster. The microcalcifications present in the mammography exam might be pleomorphic (Figure 6), granular (Figure 7), linear (Figure 8), arch, circinate and "milky calcium" type.

In all patients the age and the medical history of the patient's illness were taken into consideration. Also following population factors were assessed: labors, breast feedings, miscarriages, family factors, as well as the relation to menopause. There were also the following symptoms analyzed and reported by women as: nipple discharge, pain, retraction of the nipple, non-characteristic hardening palpable by the patient as well as lack of the clinical symptoms.

After the revision of the material, the single factor analysis was applied in the work. The statistical significance of the differences, which occur between collections containing the quality data, was assessed by chi-square test. For the quantity variables the t-Student test was applied as well as the non-parametric Mann-Whitney test. The standard deviation for the age of the tested women and the size of the lesions

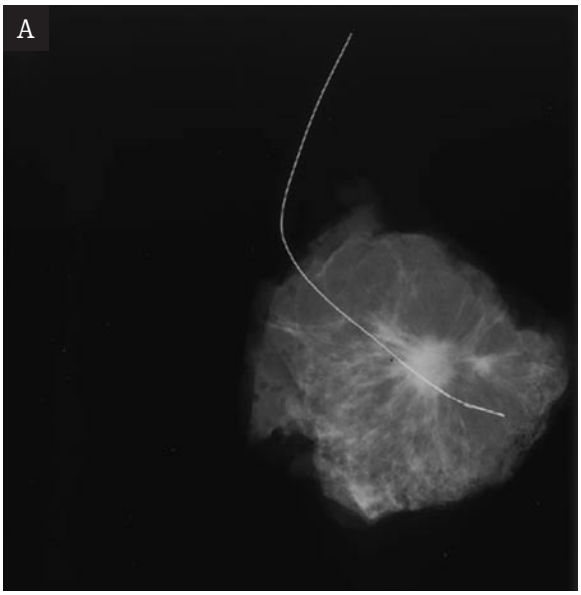


Figure 5 a, b. Lesions with processes.
Rycina 5 a, b. Zmiany z wypustkami.

stated in mammography exam were also calculated. In order to connect the result of the mammography exam with the presence of the malignant lesions and to use this information for the statistical identification of the type of the changes, three methods were used: logistic regression, discriminative analysis as well as classified tree. Significance level was taken at $\propto=0.05$.

Results

In the period from the 1st February 1995 to the 31st August 2000, 163 surgical procedures for the removal of any lesions in the breasts were conducted, after being previously marked by localized needle, in women who earlier underwent mammography exam.

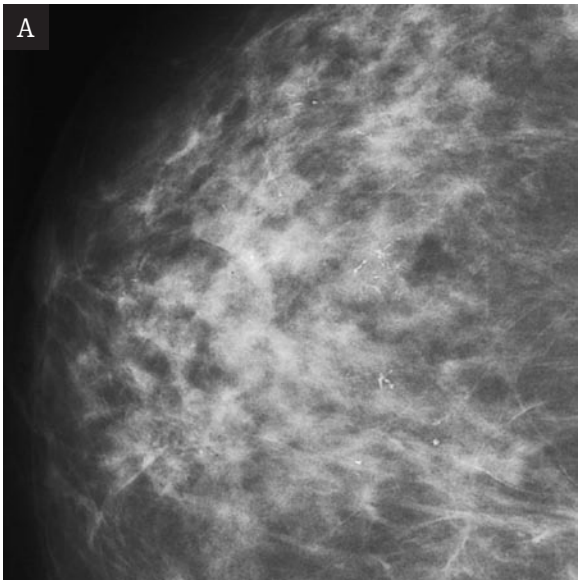
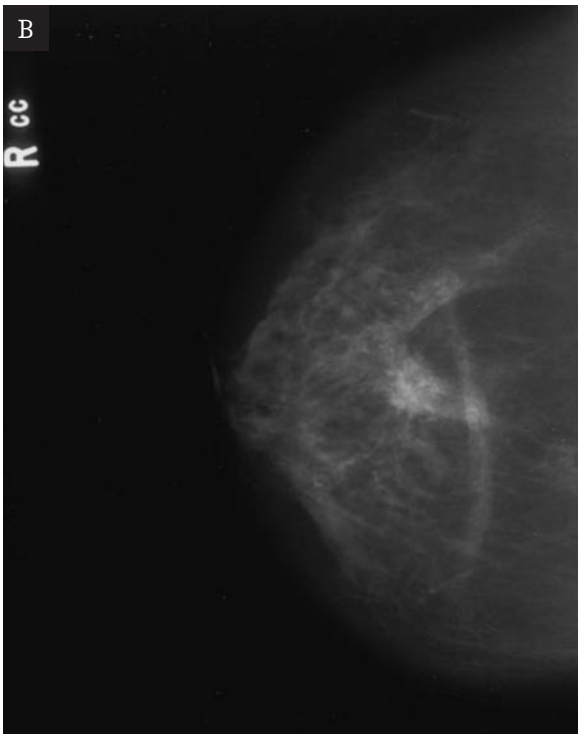
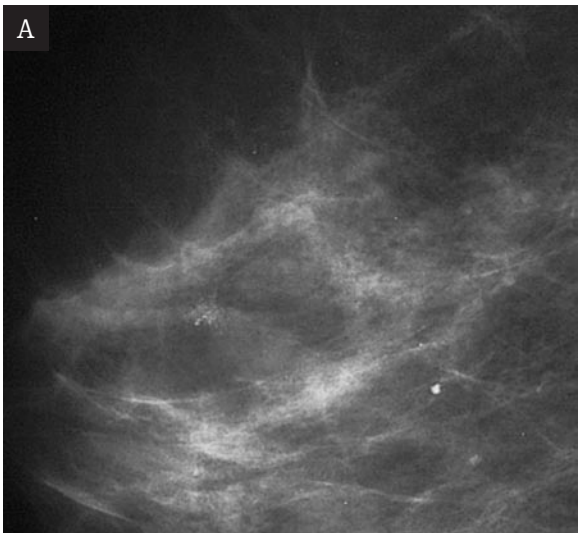


Figure 6 a, b. Pleomorphic microcalcifications.
Rycina 6 a, b. Mikrozwapnienia różnokształtne.



Among population features only the age of the women suffering from the breast cancer was statistically significant. Other features like: labors, breast feeding, miscarriages, family factors and relation to the menopause are not statistically significant in the tested group of patients. Also the clinical symptoms reported by women in the tested group of patients were not statistically significant.

The patients qualified for the surgical procedure were from 35 to 87 years of age. Average age of women who were operated due to the suspected lesion in the breast visible in the mammography exam was 53 years. The first table shows the breast cancer occurrences, depending on the age of the patient.



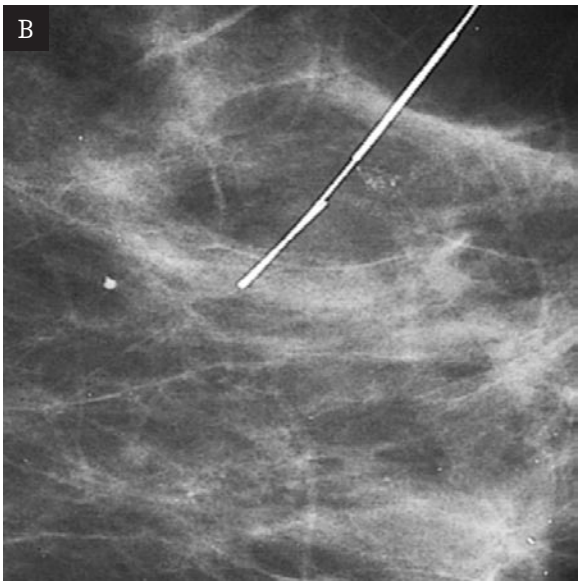
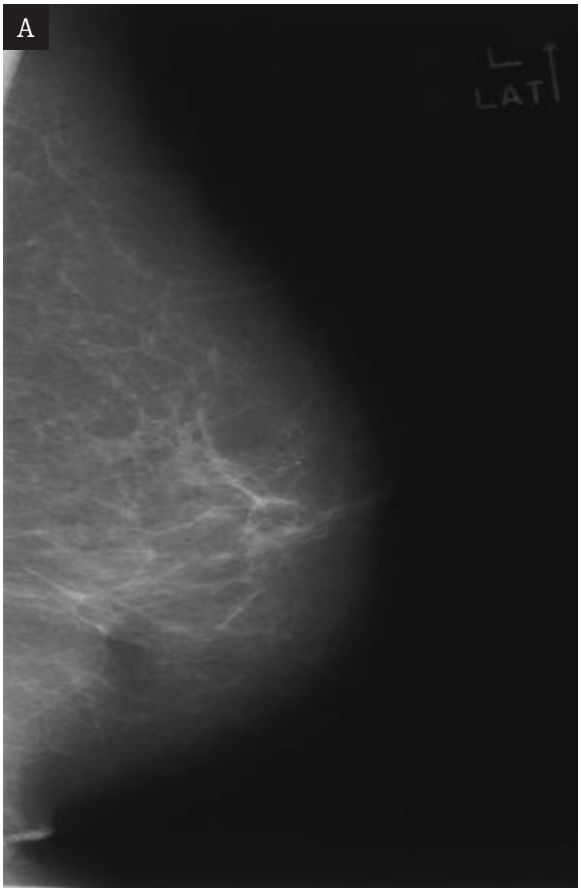


Figure 7 a, b. Granular microcalcifications.
Rycina 7 a, b. Mikrozwapnienia ziarniste.



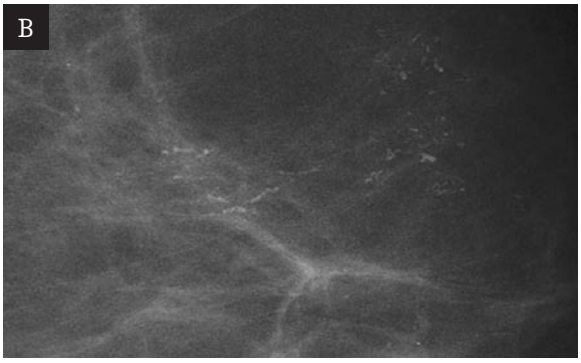


Figure 8 a, b. Linear microcalcifications.
Rycina 8 a, b. Mikrozwapnienia linearne.

The average women's age who have malignant lesions in the breasts comes to 56,5 years and the standard deviation comes to 9.6 years. Average women's age who have benign changes in the breast comes to 53,2 years and the standard deviation comes to 9.5 years. P-value from t-student test comes to 0,0338 and from Mann-Whitney test to 0,0228.

P value for the chi-square test equal to 0,0679, which indicates that in older women malignant changes were detected more frequently then the benign ones.

The first figure shows distribution of benign and malignant changes in the breast depending on age (Figure 9).

The benign lesions more frequently occur in women under 53 years of age and the malignant changes are more often

Table 1. Women's age and breast cancer occurrence.
Tabela 1. Częstość występowania raka piersi w zależności od wieku.

Variable	Malignant		Benign		p-value from the t-student test	p-value from Mann-Whitney test
	Average	Standard deviation	Average	Standard deviation		
Age	56.5	9.6	53.2	9.5	0.0338	0.0228

Table 2. The occurrence of benign and malignant changes in breast, depending on woman's age.
Tabela 2. Występowanie zmian łagodnych i złośliwych w sutku w zależności od wieku.

Patient's age	Benign lesions %	Malignant lesions %	Total
Women under 53 years of age	52 64.2	29 35.8	81
Women over 53 years of age	41 50.0	41 50.0	82
Total	93	70	163

noted in women over the age of 53 years. The average age for women who have malignant lesion is equal 56,5 years of age, and the average age for women who have benign lesion is equal 53,2 years of age. Median for the tested group of women is equal 54 years of age.

The only mammography features statistically significant turned out to be:

1. Localisation of the lesion in the breast depending on the quadrant;

Table 3 shows that the localisation of the lesion in the external quadrant and the multifocal lesion in mammography exam are statistically significant features, connected with the frequent occurrence of malignant changes (p-value for chi-square test equals 0,0011).

2. The lesion's shape;

Table 4 shows that the changes with processes are characteristic for the breast cancer. This is statistically significant feature. P- value for chi-square test equals 0,0000.

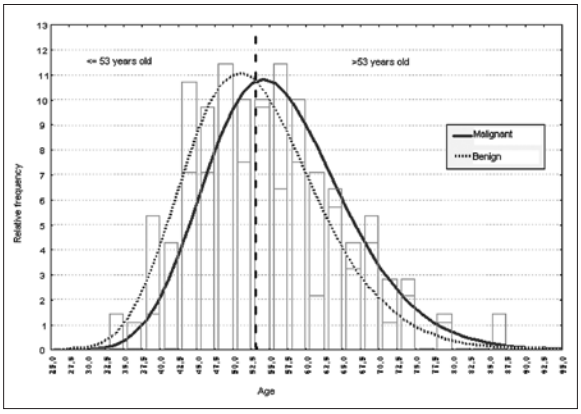


Figure 9. Distribution of the malignant and benign changes in the breast, depending on age.
Rycina 9. Rozkład zmian złośliwych i łagodnych w sutku w zależności od wieku.

3. Microcalcifications;

On the basis of the table 5, it can be stated that pleomorphic micrcalcifications are the most suspected for cancer.

Table 3. Localisation of lesion in mammography exam and probability of breast cancer occurrence.
Tabela 3. Umiejscowienie zmian w sutku a prawdopodobieństwo wystąpienia raka.

Localisation of the lesion in mammography	Benign lesions		Malignant lesions		Total
	Number of patients	%	Number of patients	%	Number of patients
Central	9	90.00	1	10,00	10
Internal quadrants	23	71.88	9	28.12	32
External quadrants and on the quadrants boarder line	61	53.04	54	46.96	115
Multifocal changes	0	0.00	6	100.00	6
Total	93		70		163

Table 4. External outline of the lesion in mammography and probability of breast cancer occurrence in women.
Tabela 4. Zewnętrzny obrys zmiany a prawdopodobieństwo wystąpienia raka sutka.

External outline of the lesion	Benign lesion		Malignant lesion		Total
	Number of patients	%	Number of patients	%	Number of patients
The lesions with processes	36	41.38	51	58.62	87
Blurring limited	22	66.67	11	33.33	33
Lesions with good limitation	35	81.40	8	18.60	43
Total	93		70		163

Table 5. The analysis of the type of microcalcifications in mammography exam and the frequency of breast cancer occurrence in women.
Tabela 5. Typ mikrozwapnień w badaniu mammograficznym a częstość występowania raka sutka.

Microcalcifications	Benign lesion		Malignant lesion		Total
	Number of patients	%	Number of patients	%	Number of patients
Linear	2	50.00	2	50.00	4
Pleomorphic (diversiform)	29	46.77	33	53.23	62
Granular	13	76,47	4	23.53	17
'Milky calcium" type	2	100.0	0	0.00	2
Circular	1	100.0	0	0.00	1
Total	47		39		86

Table 6. Pleomorphic microcalcifications and frequency of breast cancer in women.
Tabela 6. Mikrozwapnienia różnokształtne , a częstość wystepowania raka sutka.

Microcalcifications	Benign lesion		Malignant lesion		Total
	Number of patients	%	Number of patients	%	Number of patients
Others or deficiency	64	54.40	37	36.60	101
Pleomorphic	29	46.80	33	53.20	62
Total	93		70		163

Table 7. The risk of breast cancer depending on selected clinical and radiological parameters.
Tabela 7. Ryzyko wystąpienia raka sutka w zależności od wybranych czynników klinicznych I mammograficznych.

Variable	Categories	Number of observations	Relative risk	p
Patient's age	Up to 53 years of age	81	1,00	–
	Over 53 years of age	82	2,35	0,0298
External outline of the lesion	Remaining	87	1,00	–
	Spicular	76	15,37	0,0000
Microcalcifications	Deficiency or others	101	1,00	–
	Pleomorphic	62	6,36	0,0003

This is also statistically significant feature (p=0.0119). In the table 6 the tested women are divided into 2 groups. The first group consists of women in whom in the breast mammography exam pleomorphic calcifications were affirmed and women without microcalcifications or women who have other remaining types of microcalcifications like: linear, granular, "milky-calcium" type and circular.

From the table 6 it follows that the occurrance of pleomophic microcalcifications turned out to be an essential factor, which increases probability that the change affirmed in the mammography testing is the malignant change (p= 0,0269). The remaining mammography features are not statistically significant.

After an initial assessment of the identification factors, the multifactorial model of logistic regression was built by way of application of the perineal regression procedure. For the final model the following variables were used: age, location of the lesion depending on the quadrant, the shape of the lesion and the occurrence of the microcalcifications in mammography exam. The foregoing model is illustrated in the table 7.

Final logistic regression equation allows the calculation of neoplasm's probability for the different combinations of prognostic factors. Adequate equation has the following form:

$$P(Y=1)=\frac{\exp(-3,83761)+0,848602*W+1,308351*U+2,71289*Z+1,83606*R}{1+\exp(-3,83761)+0,848602*W+1,308351*U+2,71289*Z+1,83606*R}$$

where explanatory variables zero – 1 indicate:

W – age over 53,
U – location in external quadrants or multifocal lesions,
Z – spicular lesion,
R – pleomorphic micricalcifications.

Table 8. The probability of malignant neoplasm depending on the tested risk factors.
Tabela 8. Prawdopodobieństwo wystąpienia zmiany złośliwej w zależności od wybranych czynników ryzyka.

W	U	Z	R	Probability
■				0,05
	■			0,07
			■	0,12
■	■			0,16
■			■	0,24
		■		0,24
	■		■	0,33
■		■		0,43
■	■		■	0,54
	■	■		0,54
		■	■	0,67
■	■	■		0,74
■		■	■	0,83
	■	■	■	0,88
■	■	■	■	0,95

After providing of all combinations of zeros and ones in the place of hidden explanatory variables, we receive the evaluations of probability, illustrated in the table 8.

From the table 8 it follows that with the one risk factor, the probability of the malignant neoplasm occurrence is in the range from 0,05 to 0,1. With the two risk factors, which occur simultaneously, the breast cancer probability is in the range from 0.16 to 0,43. In the case of three or four risk factors occurring simultaneously, probability of the breast cancer occurrence hesitates within the limit from 0,54 to 0,95.

Discrimination analysis is the method which allows to recognize the mechanism, which causes that the collection of objects brakes up into subgroups. This kind of division relates to the value of explanatory variables. In our issue we are dealing with the division into two groups (malignant/ non-malignant). With the help of discrimination analysis we can find expressions for so-called classification functions, which connect the occurrence of the risk factors with the group belonging.

Classification functions for the non-malignant class has the following form:

Non – malignant = -3,01377+2,380318* W + 3, 84592 *U + 2,35457 * Z + 2,16486 * R

For the malignant class equation is taking the following form:

Table 9. Confusion matrix for the identification based on logistic regression.
Tabela 9. Wyniki prognozowania typu zmiany przy pomocy modelu regresji logistycznej.

Assessment in histology	Prognosis		Percent of correctly classified
	Non-malignant	Malignant	
Non-malignant	68	25	73,1
Malignant	14	56	80,0

Malignant = -6,71489 + 3,26899 . W + 5,05481 . U + 5,16496 . Z + 3,82375 . R.

For each woman the value of both classification functions is calculated and the greater of these values indicate to which of the groups (malignant/non-malignant) a given woman must be classified (in the sense of the prognosis). After conducting of this procedure for 163 patients included in that analysis, the following results of "diagnosis" were received and they are illustrated in the table 9.

On the basis of the above-mentioned analysis, the mammography's sensitivity is 0,80 and specificity 0,73. The negative predictive value comes to 0,83 and the positive predictive value comes to 0,69.

Classifying trees is the method, which by the way of the consecutive decision making, based on diagnostic variables, can lead to conforming the object to a certain quality class. In this paper the approach was used to predict the kind of neoplasm (malignant/non-malignant). We used the diagnostic variables, which predictive significance was proved in logistic regression. The classifying tree was obtained by the CART method and is illustrated in the Figure 10.

From the Figure 10 it follows that the tree contains four decision nodes. First analysed change has the same shape as the lesion affirmed in mammography exam. If the lesion has an irregular shape, we are moving in the decision tree to the left and in the case of the other shape we are moving to the right. In case of the lesion with the irregular shape, its location is assessed depending on the quadrants. External or multifocal location of the lesion indicates its malignant nature and

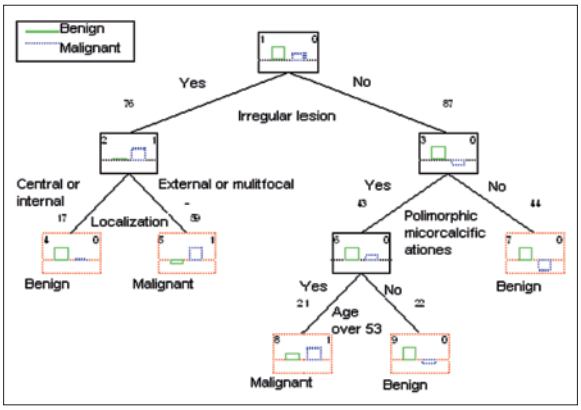


Figure 10. Classification tree for mammography results.
Rycina 10. Drzewo klasyfikacyjne dla wyników mammograficznych.

internal or central location indicates its benign nature. If the lesion is not irregular, we check for pleomorphic microcalcifications. If not, so the image is in advocacy of its benign nature. In case of the pleomorphic microcalcifications occurrence, in women up to 53 years of age benign lesions predominate but in older women the lesions are malignant. The table of decisions making by the use of the decision tree, on the analysed group of patients is as follows:-

Table 10. Confusion matrix for the classification tree classifier.
Tabela 10. Wyniki prognozowania typu zmiany przy pomocy drzewa klasyfikacyjnego.

Assessment in histology	Prognosis		Percent of correctly classified
	Non-malignant	Malignant	
Non-malignant	69	24	74,2
Malignant	14	56	80,0

With the classification tree the identification is much better, because the mammography exam sensitivity equals 80% and specificity equals 74%. A positive predictive value equals 70% and negative predictive value equals 83%.

Conclusions

On the basis of our material analysis the following suggestions can be formulated:

1. The only one population factor, which can be distinguished as characteristic for the women suffering from the breast cancer impalpable in clinical testing, is the age of the patient, because the breast cancer in these women more frequently occurs after 53 years of age.

2. On the basis of our own material the following radiological symptoms characteristic for the breast cancer in mammography exam were stated:

   a. the breast cancer is more frequently found in the upper external quadrant;

   b. all lesions, which in mammography exam were identified as multifocal and radiologicaly suspected in histopathology exam turned out to be the cancer;

   c. pleomorphic microcalcifications are characteristic for the malignant lesions;

   d. external outline and the shape of the lesion are the features, which allow to differentiate malignant and benign lesions.

3. The analysis of the material indicates that the greatest probability of the breast cancer occurrence is in case of the four risk factors occurrence simultanosly, and the smallest in case of only one risk factor occurrence.

4. The mammography exam is the best method of the breast cancer detection, also in case of impalpable cancers in clinical testing.

Discussion

The mammography exam conducted in appropriate time intervals allows to detect the breast cancer in the early stage. The quantities of detected cancers in mammography exam depends on doctor's experience, mammography's quantities, the patient's age and type of the breast structure. Therefore, the probability of malignant lesion detection differentiate in the mammography images [3, 4].

The average age of the patients of the tested group comes to 53 years. In the literature average age for the patients suffering from the early breast cancer varies from 51 to 59 years of age. The majority of researches stated the age of over 55 years of age. And the age of 57 is stated by Skiles at al. and Cote at al. [5, 6], 55.5 years Burbank at al. [7], 55 years Iwaszkiewicz at al. [8]. The lower average age for the patients suffering from the breast cancer is stated by: Wesołowska at al. [2], Schabot at al. 51 years of age and Stomper at al. [9, 10]. In the group of patients tested, the breast cancer more frequently occurred after 53 years, which is fully confirm in the available literature [11].

The researches conducted revealed that the breast cancer most frequently was located in the upper exterior quadrant. 45% of lesions were located in that quadrant, which is similar to the literature's data. Stomper at al. [9] stated that 51% of the multifocal lesions visible in mammography were located in the upper external quadrant. Also Cote at al. [12] stated that 48% focal lesions are located in the upper external quadrant.

In our material all multifocal changes visible in mammography exam after histologic verification appeared to be malignant. On the base of our material and the literature's findings, it can be stated that the most frequent microcalcifications clusters are arranged in multifocal forms, which are the first sign of intraductal and plug cancers. Microcalcifications in the intraductal cancer are located along the milk ducts, that is why in mammography exam they might be seen in the form of many microcalcification clusters [13, 14].

In the tested group of patients who suffer from the early breast cancer stated that the lesions with the processes and with an irregular external outline are characteristic for the breast cancer. Statistically it is a significant feature. (chi – square p-value equals 0,0000). Among 163 women the changes with processes appeared in 87 patients, from which in 51 (59%) the breast cancer appeared and in 36 patients (41%) the benign lesions occurred. The literature stated that the lesions of irregular shape with the processes are characteristic for the breast cancer. [10].

In our material the pleomorphic microcalcifications occurred in case of 62 women, which is 72%, in whom the breast cancer occurred in 33 women (53%). The occurrence of the pleomorphic microcalcifications proved to be the essential factor, which increases the probability that the lesion affirmed in mammography was the malignant one (chi – square p-value equals 0, 0378).

The similar data was noted in the literature. Tabar at al. [15] stated that pleomorphic microcalcifications in about 72% are associate with the breast cancer. The granular microcalcifications are associated with the breast cancer only in 19%, but circular and regular in 10%. The similar data is given by other authors like: Wesolowska at al., Iwaszkiewicz at al. as well as Liberman at al. [2, 8, 16]. According to the literature's findings the intraductal cancer is very often visible in mammography exam in the microcalcification forms, most often of different forms, ramifying into the shape of the letter V or U. About the microcalcifications' malignancy decides their quantity and saturation in the cluster [17]. The pleomorphic microcalcifications sometimes occur in benign lesion like: fibroparenchyma, intraductal proliferation or tubular proliferation connected with fibrosis. In these cases microcalcifications imperceptibly differ on saturation, location and shape. Mammography exam alone can not distinguish the benign microcalcifications from the malignant microcalcification so the histopathologic exam is necessary as a decisive answer.

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