HORMONE SENSITIVITY OF TUMOR IN WOMEN WITH BREAST CANCER

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Breast cancer is the most common malignant neoplasm in women. The presence of hormone receptors on malignant cells influences the prognosis and application of the appropriate therapy. The receptor status of estrogen and proestrogen was tested in relation to the age of the patients and clinical stage of disease. The analysis comprised 449 patients with breast cancer, with mean age 56.2±12 years, treated at the Oncology Clinic CC Nis and operated at the Surgery Clinic CC Nis, separated into four groups: I group - 246 patients with ER+/PR+ receptors; II group - 45 patients with ER+/PR- receptors; III group - 20 patients with ER-/PR+ receptors and IV group - 109 patients with ER-/PR- receptors. The clinical stage of the tumor was described as operable, locally advanced and metastasis, plus patient age stratification. The receptor status was determined in 440 patients, while it remained unknown in 9(2%) cases. In regard to the total number of patients, ER+/PR+ is registered in 54.7%, ER+/PR- in 14.0%, ER-/PR+ in 4.5%, and 24.3% in ER-/PR-. The most common is a hormone-sensitive breast tumor (76%) in regard to non-sensitive tumors (24%). From hormone-sensitive tumors, the most common were Er+/Pr+ tumors with 58%, and the least common Er-/Pr+ tumors with 4%. In women younger than 40, hormone non-sensitivity dominates (55%). Hormone-sensitive tumors are more present as the patients are older, and they dominate in patients older than 70. Operable tumors were found in 78.64% of women, locally advanced in 18.18%, and metastasis in 3.18%. Hormone-sensitive tumors are far more often operable and less locally advanced than non-sensitive tumors (Hi=8.2, p<0.01). Metastatic tumors did not show any significant difference in hormone sensitivity. *Acta Medica Medianae 2007; 46(2):25-30.*

***Key words**: breast cancer, hormone sensitive tumors, estrogen, proestrogen*

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Introduction

Breast cancer is one of the biggest health concerns for women. That kind of fear is justified by the fact that breast cancer is the most common sort of malignant tumor which often develops insidiously in the form of a painless tumor and without subjective pains. The patient and her surroundings considerate as a severe and undeserved punishment which leads to a fatal outcome after a lot of suffering and difficulties. It represents the most common malignant tumor in women worldwide and comprises 20% of all neoplasms in women in Europe. Breast cancer is a big social/medical issue/problem because of its frequency and consequences.

There are 10 million people in the world who fall down with cancer every year. Lung cancer is the most common (1.350.000 new patients a year), breast cancer (1.115.000 of women a year) and colon cancer (about a million people). There are huge geographic differences in the number of newly discovered cases, so the there are high risk countries (Northern America and Northern Europe), moderate risk countries (Southern America and Southern Europe) and low risk countries (Asia and Africa) (1).

According to the Cancer Register of Central Serbia (2) and the Malignant Neoplasm Register of Vojvodina (3), there are 30 000 people in whom cancer is discovered every year in Serbia. Breast cancer is the most common malignant neoplasm in women and is of great importance because of continual increase of incidence and mortality. There are about 4000 new cases registered and about 1300 women die (4, 5) each year. Latest statistics show mortality stagnation in regard to morbidity in most countries in the world which is explained by contemporary detection and treatment methods.

There are numerous breast cancer risks which can act pretty early (initiators) and/or later (promoters). The most important are: age, older women who are giving birth to the first child (after 30 years of age), genetic, nutritive and hormone factors, previous breast cancer, changes in breasts (atypical hyperplasia or lobular carcinoma in situ), environment factors (radiation). Despite breast cancer risk factors being known, in 50% of women they are not

detected (5). Genetic factors (BRCA1 and BRCA2 tumor suppressor gene mutation) are responsible for 5-10% breast cancer cases. It is not possible to influence the most important risk factors, such as age and genetic factors, but is possible, to some extent, to influence the reproductive and hormone factors by »healthy way of life« which means healthy nourishment with body weight regulation and regular physical activities.

Breast cancer is a hormone-dependant tumor prototype and 1/3 of the patients will positively respond to the endocrine therapy. In evaluation of hormone-sensitivity degree, important factors are estrogen receptors (ER) and proestrogen receptors (PR), for there are new treatment possibilities by applying medicaments which »block« the receptors. The importance of their determination is stressed by the latest references for individual therapy approach in breast cancer patients (6).

Having in mind that breast cancer risk can not be eliminated, secondary prevention is necessary which includes early detection pro-grams and screening programs. Screening means an organized application of the screening test in healthy population and opening of illness cases which are still not recognizable (7). Programs for early detection aim at: health enlightenment of people, education of health care workers, references for early detection, etc.

For breasts of younger women, an important diagnostic method (after the physical examination) is the ultrasound, because its sensitivity and characteristics at that stage are higher than mammography. The reason for this is the fact that the majority of the breast size in generative stage represents a hyperechogenous glade tissue, while in the menopause the gland and the parenchyma are replaced with hypoechogenous fatty tissue. In older women they are complementary, but because of the examination being a simple one and satisfactory sensitivity, mammography is preferred.

According to the EU references, breast screening should be done by mammography examination of women aged 50-69 years each 2-3 years by organized invitation and monitoring of women. Mammography is a breast x-ray used for more precise confirmation of changes in the breast tissue, as well as for detection of those minor changes which can not be registered during the palpable examination. Application of this screening in Europe and the USA reduced mortality by 20-30 %.

Aims

Having in mind breast cancer being so frequent, morbidity and mortality in women and the predictive importance of the hormone status for the prognosis of the illness and application of the appropriate therapy, the objective was to determine the estrogen and proestrogen receptor status in regard to age of the patients and clinical stage of disease.

Material and methods

The general method is comparing of data acquired by retrospective analysis of medical documents and hospital registers.

There were 449 breast cancer patients analyzed, operated at the Surgery Clinic CC Nis, who carried on with their treatment at Oncology Clinic CC Nis.

According to the hormonal status, all patients were divided into four groups:

- **I group** - 246 patients with ER+/PR+ receptors
- **II group** - 45 patients with ER+/PR- receptors
- **III group** - 20 patients with ER-/PR+ receptors
- **IV group** - 109 patients with ER-/PR- receptors.

During data analysis, patients were classified by age, and those younger than 36 years of age were specially dealt with at the moment of giving the diagnosis.

Patients from all four groups were analyzed in regard to the clinical tumor stage, defined as operable, locally advanced or metastasis.

All participants were analyzed at the Oncology Clinic CC Nis. The observation study comprised patients treated at the Clinic from January 2003 to December 2005.

Data were processed by using standard descriptive statistic methods (mean value, standard deviation and percentage). The results were analyzed by using appropriate tests, depending on the size of the group, type of indication and distribution type. The strategic processing was done within and among defined groups.

There were several test types: Student t test for pared and non-pared causes, Hi^2 test, Mantzel Haencel test and Fisher test of exact probability.

Statistics was done by the use of Excel 7.0 and SPSS 11.0 in Windows 98 operative system, which presented data through tables and diagrams.

Results

Within three-year period of monitoring (2003-2005) at the Oncology Clinic, there were 449 breast cancer patients treated. The receptor status was determined in 440 patients, but it was unknown in 9 (2%) patients. In regard to the total number of analyzed patients, ER+/PR+ was registered in 54.7%, ER+/PR- in 14.0%, ER-/PR+ in 4.5% and 24.3% of patients was not hormone sensitive. General data of the examined patients and hormone sensitivity to disease is shown in Table 1.

Average age of the breast cancer patients is 56.2±12 years, and Student T-test did not show any significant difference concerning the age of the patients which belong to analyzed groups. Non-parametrical analysis of Mantzel Haencel test did not either confirm any difference concerning the place of living (Table 1).

Table 1. General data of the examined patients

Receptor characteristics	No.	(%)	Age (years)	Place	
				City	Village
Er+/Pr+	246	54.7	55.5±11.9	154	92
Er+/Pr-	65	14.5	57.4±9.02	46	19
Er-/Pr+	20	4.5	54.2±15.1	9	11
Er-/Pr-	109	24.3	57.6±11.9	65	44
Not specified	9	2.0	67.4±7.7	4	5
total	449	100.0	56.2±12	278	171

Table 2. Clinic stages and receptor status

Stage	Er+/Pr+	Er+/Pr-	Er-/Pr+	Er-/Pr-	Total
Operative	207	49	16	74	346
Locally advanced	33	13	4	30	80
Metastasis	6	3	0	5	14
Total	246	65	20	109	440

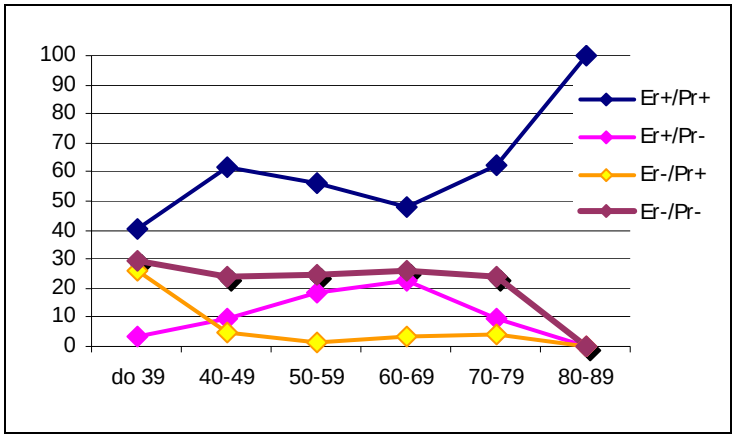

Diagram 1. Hormone status and age of patients with primary breast cancer

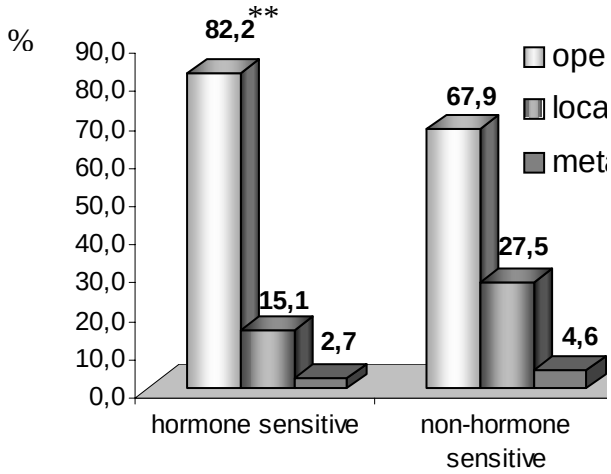

Diagram 2. Clinical stage and tumor hormone status

In analyzed women breast hormone sensitive tumor was the most common one (ER+/PR+, ER+/PR-, ER-/PR+) (76%) in regard to non-sensitive (Er-/Pr-) tumors (24%). From hormone sensitive, mostly there were the Er+/Pr+ tumors presented with 58%, while the least frequent was Er-/Pr+ tumor, presented with only 4% ,.

Age structure of the patients and the combination frequency of hormone status with the rise in regard to age of the patients is shown in Diagram 1.

From Diagram 1 one can see that the majority of the patients were in the group aged 40-49 and 60-69. The least number of patients was in the group of 80-89 years of age.

It is notable that in women younger than 40 years of age, hormone non-sensitivity dominates, and is present in about 55% of all cases. As the age advances, the frequency of the hormone non-sensitive tumors falls, while the number of the hormone sensitive tumors, which completely dominate in patients older than 70 years of age, rises.

Number of patients and their receptor status in regard to the clinical stage of disease in breast cancer is shown in Table 2. Operable tumors were found in 78.64%, locally advanced in 18.18%, and metastasis in 3.18%.

The variance analysis shows that there is a significant difference in the frequency of clinical stages among patient groups with different receptor combinations ($F=3.75$, $p<0.05$). Post-hoc analysis shows that there is the difference among groups with ER+/PR+ and ER-/PR- (Tuckey HSD, $p<0.05$), i.e. ER+/PR+ tumors were more often operable (Table 2).

Hormone sensitivity and clinical stages of disease are shown in Diagram 2.

Hormone sensitive tumors (ER+/PR+, ER+/PR-, ER-/PR+) were operable in 82.2% and locally advanced in 15.1%. Non-sensitive tumors were operable in 67.9% and locally advanced in 27.5%. Mantzel- Haencel test confirmed that hormone sensitive tumors are considerably more often operable, less likely locally advanced than non-sensitive tumors ($Hi=8.2$ $p<0.01$). Metastasis tumors did not show any significant difference in hormone sensitivity ($p=NS$) (Diagram 2).

Discussion

Breast cancer, having in mind its epidemic and biological characteristics, is the most important malignant disease in women. Each year, there are 4000 women registered with breast cancer in Serbia and 1300 die.

World Health Organization estimates that in this century every 8th woman on the planet will have this illness. The number of the newly registered is in constant increase and it amounts to 1-2% a year worldwide, while in our country, that number have increased this year by 10% in regard to 2003. Incidence spike is more and more moving towards younger women. Ten years ago, breast cancer was discovered in women aged about 65 years and today about 55 years. According to the Institute of Oncology and Radiology in Belgrade, the mean of patients is 56 years and it is identical to the mean age of our patients. Women with breast cancer in the USA, Australia, South American countries, etc. are of average age 50 years (8).

An important prognostic and predictive factor of breast cancer is estrogen and proestrogen receptor status. Majority of receptors indicate a positive response to endocrine therapy. About 70% of primary breast cancer have positive estrogen receptors, while 30% are negative (9). Positive receptor status correlates with favorable prognostic characteristics, including a low level of cell proliferation and histological proof of tumor differentiation (10).

Results of various studies show that about 70% of the primary breast cancer express estrogen receptors, while 30% are ER-negative (11), which is not vastly different from the results of women in our study, where ER+ 69.27%, ER- 30.73% and PR+ 4.45 %.

Lower level of expression ER+ 32.1% in breast cancer is found in women in India. This can be partially explained by breast cancer being more frequent in younger women with high grade of tumor, for they are almost ten years younger than in Western countries (12). On the contrary, Lou's studies from China result in 73, 5% ER+ and 65, 5 % PR+.

The published results of Barns and his associates in European population is about 50% of cancer ER+/PR+, 25% is ER-/PR-, 20% is ER+/PR- and about 5% is ER-/PR+. Our results are not significantly different apart from (ER+/PR- 15% and ER+/PR+ 55%).

There is an unusual result of the research conducted in India which allows a high level of proestrogen receptors ER-/PR+ (21,1% compared to 5%). This model of a receptor status was significant in patients with soft tissue and metastasis of CNS. The results confirm that this is a biologically and clinically defined subgroup which requires further detailed analysis and estimates (3).

In our group ER+/PR+ cancer amounted to 55%, with significantly higher presence of 70,3% in patients over 50 years of age in regard to the data from the literature which shows 49%, which can be explained by the number of patients included in the research. The concentration of ER-/PR- was more visible in younger patients, which correlates with the literature data.

Positive breast cancer receptors are more often in postmenopause - 80, 3%, while the receptor of the negative is more often found in younger age groups - 41, 2%. This result finding is a result of differences in hormone status or biologic differences of cancer of observed patient groups. Higher presence of concentration ER-/PR+ of the primary breast cancer in postmenopause in regard to premenopause can be the result of higher concentration of estrogens and higher saturation ER of endogen estradiol (14).

Operable cancers are ER+ in 78, 6% in regard to ER- 21, 4%, while locally advanced are ER+ 62, 5%, and metastasis 64, 2%. Data from the literature show that the size of tumor does not correlate with ER/PR status (15).

Breast cancer in younger patients is, according to conducted research results, significantly more aggressive. It is usually detected in the advanced stage and requires aggressive therapy. One of the reasons for bad diagnosis is that in patients of this age, the more common receptor is negative breast cancer which is not sensitive to hormone therapy.

There were only 27 (6%) women in our research younger than 40 operated from breast cancer with ER/PR status. From the total number of the patients with receptors, 70, 3% were hormone sensitive, which is statistically significant and does not correspond to data from many studies. The reason for this may be a small number of patients in the research group, but also the criteria for detecting positive cancers' receptor, which are modified and in a great number of studies represent only an evident expression ER cancers (16).

There are data in the literature which show a favorable therapeutic effect of the hormone therapy in 10% negative receptor cancers (17), which is explained by an extra receptor, insufficiently explained mechanism of hormone therapy.

Conclusion

- The level of steroid estrogen and proestrogen breast cancer receptors is in positive correlation with patients' age.
- There is no statistically significant difference concerning the patients age of the researched groups.
- Positive ER/PR is significantly present in postmenopause patients, contrary to negativity in premenopause.
- Operable cancers are receptor ER positive in 78,6% cases, in regard to receptor ER negative (21,4%).

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HORMONSKA SENZITIVNOST TUMORA KOD BOLESNICA SA RAKOM DOJKE

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Karcinom dojke je najčešća maligna neoplazma kod žena. Prisustvo hormonskih receptora na malignim ćelijama utiče na prognozu i primenu adekvatne terapije. U radu je ispitivan estrogen i progesteron receptorski status u odnosu na starost bolesnica i klinički stadijum bolesti. Analizirano je 449 bolesnica obolelih od karcinoma dojke, prosečne starosti 56.2±12 godina, lečenih na Klinici za onkologiju KC Niš i operisanih na Klinici za hirurgiju KC Niš, podeljene u četiri grupe: I grupa - 246 bolesnica sa ER+/PR+ receptorima; II grupa - 45 bolesnica sa ER+/PR- receptorima; III grupa - 20 bolesnica sa ER-/PR+ receptorima i IV grupa - 109 bolesnica sa ER-/PR- receptorima. Klinički stadijum tumora je definisan kao operabilni, lokalno uznapredovali i metastatski, pri čemu je izvršena i starosna stratifikacija bolesnica. Receptorski status je određen kod 440 bolesnica, dok kod 9(2%) nije poznat. U odnosu na ukupan broj ispitanica ER+/PR+ je registrovan kod 54.7%, ER+/PR- kod 14.0%, ER-/PR+ kod 4.5%, a 24.3% kod ER-/PR-. Najčešće je zastupljen hormonosenzitivni tumor dojke (76%) u odnosu na nesenzitivne tumore (24%). Od hormonosenzitivnih najčešće su bili zastupljeni Er+/Pr+ tumori sa 58%, a najređe Er-/Pr+ tumori sa 4%. Kod žena mlađih od 40 godina dominira hormonska nesenzitivnost (55%). Sa starošću bolesnica dolazi do porasta učestalosti hormono-senzitivnih tumora, koji dominiraju kod bolesnica starijih od 70 godina. Operabilni tumor je nađen kod 78.64%, lokalno uznapredovali kod 18.18%, a metastatski kod 3.18%. Hormonosenzitivni tumori su značajno češće operabilni a ređe lokalno uznapredovali od nesenzitivnih tumora (Hi=8.2, p<0.01). Metastatski tumori nisu pokazivali značajniju razliku u hormonskoj senzitivnosti. *Acta Medica Medianae 2007;46(2):25-30.*

Ključne reči: *karcinom dojke, hormon senzitivni tumori, estrogen, progesteron*