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Correlations between Specific and Nonspecific Vaginal Immunity in Women with Breast Cancer in Kazakhstan

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Abstract

Background: The most common malignant tumor in women is breast cancer (BC). The ability of regulatory cells to inhibit cellular immune response as well as to participate in the modulation of antitumor immunity has attracted much interest of scientists. The purpose of this study was to assess the correlation between the specific and nonspecific vaginal immunity in women with BC.

Methods: This was an experimental study. The study involved 278 women, 174 of whom received chemotherapy. The sampling was performed using a universal probe. The qualitative and quantitative assessment of the vaginal microflora was done using the polymerase chain reaction method. Statistical processing of the analysis was performed using the Statistica 10.0 licensed software. The parameters of the immune status before and after chemotherapy were analyzed, and the correlation between the number of cells in the main populations of lymphocytes before and after chemotherapy was investigated.

Results: The study of the correlation between the number of cells of the main lymphocyte populations before and after chemotherapy showed an inhibition of B-lymphocytes (CD3-CD19+) in the study group, as the subpopulations of T-cytotoxic (CD4-CD8+) and CD3+HLA-DR+ (activated E-lymphocytes) were increased in both groups. Direct correlations were observed between local vaginal immunity and the immune status of the examined women in the study group between Megasphaera spp. and Enterobacteriaceae, with a certain population of immunocompetent cells.

Conclusion: It was concluded that impaired biocenosis and suppression of local immune responses in women with BC were the reason for the active involvement of the components of the immune system.

Keywords: Malignant Neoplasms, Immunoediting, Vaginal Immunity, Normal Flora, Obligate Anaerobes, Biocenosis

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Introduction

Breast cancer (BC) is the most common malignant tumor among women worldwide, as well as in Kazakhstan. In the structure of malignancies among women in economically developed countries, BC is the most common, significantly outscoring the proportion of other neoplasms (1). Every year more than 2,000,000 women are diagnosed with BC worldwide (10%-18% of all malignant neoplasms) (2, 3). In the Republic of Kazakhstan, up to 4000 new cases of this oncological disease are diagnosed annually (4). In many malignant neoplasms, various significant

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↑What is "already known" in this topic:
An integrated assessment of the vaginal microbiocenosis and local immunity in patients with cervical intraepithelial tumors was made, where it was proved that the development of cervical tumors is associated with genetically determined significant dysbiotic processes in the vagina with predominant participation of obligate anaerobes and local immune dysfunctions.

→What this article adds:
The present study assesses the correlation between specific and nonspecific vaginal immunity in women with BC.

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immune disorders are observed: a decrease in T-lymphocytes and their subpopulations, number and functional activity of natural killer cells, et cetera. Various populations of cells play an important role in antitumor defense of the body, including both effector and suppressor cells. At present, much attention is paid to the study of regulatory cells, including CD4+ and CD8+ lymphocyte subpopulations as well as NKT cells (5). These cells are able to inhibit cellular immune response as well as to participate in the modulation of antitumor immunity (6-8).

The immune system's interaction with cancer is a delicate balance between immune activation and immune suppression. The dual nature of the interaction between the immune system and the tumor is currently viewed as a dynamic process of immunoediting. An important role in the immune response to a tumor is played by various innate and adaptive immunity cell populations: NK-, T-, NKT-cells, macrophages, and dendritic cells. These populations are heterogeneous and contain both cells with antitumor activity and regulatory (suppressor) cells that promote tumor progression (9-11).

The specific cellular response of the urogenital mucous membranes is formed according to the T cell and B cell humoral pathways. The T cell-mediated immune response is aimed at the destruction of intracellular pathogens and is mediated mainly by CD8+ T-lymphocytes, which are located in the stroma of the vagina, cervix, and uterus under the epithelial layer, and also scattered between epithelial cells (12, 13).

The influence of the immune status, endocrine factors, and some neoplastic processes and their combination on the formation of vaginal dysbiosis was discussed in a number of scientific works. Reproductive health of a woman depends on complex mechanisms of regulation and cooperation between the epithelium of the mucous membrane of the reproductive system, local microflora, and immune cells, which produce biologically active substances and hormonal regulation (14, 15).

The purpose of this study was to assess the correlation between specific and nonspecific vaginal immunity in women with BC.

Methods

This was an experimental study. Research work was performed in the city of Aktobe in the Republic of Kazakhstan at the Medical Center of West Kazakhstan Marat Ospanov Medical University during 2018-2020. The study involved 278 women with BC from Kazakhstan, with a mean age of 56.7 ± 11.1 years. The women included in the study were divided into 2 observation groups. The study group included 174 patients (62.5%) who received chemotherapy. The control group included 104 patients (37.4%) before chemotherapy. All examined women gave their informed consent to participate in the study.

The qualitative and quantitative composition of the vaginal flora in women with BC was analyzed using the PCR using the Femoflor set of reagents. Materials were collected from the posterior fornix of the vagina. The sampling was done using a universal probe, the working part of which, containing the test material, was cut off or broken off and placed in a disposable Eppendorf tube with a preservative solution (transport medium). These tubes were subsequently delivered to the polymerase chain reaction (PCR) laboratory of the Scientific and Practical Center of the Marat Ospanov West Kazakhstan Medical University, where the qualitative and quantitative assessment of the vaginal microflora was performed using the PCR method based on ddeoxyribonucleic acid (DNA) amplification. The content of microorganisms was expressed as the decimal logarithm of the absolute DNA number (16, 17).

Immunological studies included the determination of lymphocyte subpopulations based on the levels of expression of lymphocyte membrane antigens using a set of monoclonal antibodies specific to differentiation antigens (CD3, CD4, CD8, CD16, CD20, CD25, and CD95). The samples were analyzed using the FacsCalibur flow cytometer (Becton Dickenson) and the CellQuest software. The CellQuest software of the FacsCalibur flow cytometer allows the analysis of up to 50,000 cells in 1 sample simultaneously for several parameters: forward light scattering, side light scattering, and multicolor fluorescence, and to perform a multifactor analysis of cell populations (18, 19).

Statistical processing of this analysis was carried out using the Statistica 10.0 licensed software using the nonparametric Spearman's coefficient to compare the studied groups. The nonparametric Spearman's coefficient was used for independent samples and to assess the relationship between ordinal and quantitative characteristics.

The Spearman rank-order correlation coefficient is a nonparametric measure of the strength and direction of association that exists between 2 variables measured on at least an ordinal scale. This test is used for either ordinal variables or for continuous data that have failed the assumptions necessary for conducting Pearson's product-moment correlation. Methods of descriptive statistics with the calculation of central tendencies and their range were used for quantitative variables. The results were expressed as medians and upper and lower quartiles. Hypothesis testing was used to determine the P value on different stages of research. The significance level for the test was set at $P \leq 0.001$.

Results

The analysis of these results are described in stages in both groups for all parameters of specific immunity, nonspecific immunity, and relationship with immune status (Table 1). The analysis of the immune status after chemotherapy showed that practically all mean levels of cellular immunity according to the reference values of CD3+, CD19-, CD4+, CD8-, IRI, CD3-HLA-DR+, NK(CD16+56+), and CD3+/CD16+56+ were within the physiological normal range in all patients; however, CD3-CD19+ was significantly decreased compared with the reference value in the study group ($P \leq 0.001$); CD4-CD8+ and CD3+HLA-DR+ were significantly increased compared with the reference value in both groups.

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Table 1. Comparative Analysis (Spearman's correlation) of Specific Immunity in Both Groups After Chemotherapy

Markers	Mean Values		P Value
	Study Group	Control Group	
T-lymphocytes (CD3+CD19-)	71.7 [66.3;76.7]	71.4 [65.4;75.8]	0.055
B-lymphocytes (CD3-CD19+)	7.9 [3.7;12.2]	10.4 [7.8;13.7]	0.001
T-helpers (CD4+CD8+)	40.7 [32.4;45.0]	39.0 [32.1;43.7]	0.036
T-cytokines (CD4-CD8+)	31.7[25.8;36.8]	28.5[24.5;35.4]	0.008
IRI	1.3[0.9;1.6]	1.3[1.0;1.7]	0.074
CD3+HLA-DR+(activated T- lymphocytes)	8.7 [4.5;14.8]	6.1 [2.0;13.0]	0.003
CD3-HLA-DR+	13.4 [9.8;15.4]	13.6 [11.5;14.9]	0.045
NK(CD16+56+)-natural killers	11.6[8.0;16.8]	11.3[7.3;18.8]	0.053
T-killers (CD3+/CD16+CD56+)	5.8[3.3;9.0]	6.4[4.5;10.0]	0.003

Note: Me – median, 25% – lower quartile, 75% – upper quartile

The analysis of the vaginal nonspecific immunity showed the following: Peptostreptococcus spp., Gardnerella vaginalis prevailed quantitatively in both groups, which indicated bacterial vaginosis, while the representative of obligate anaerobes, Enterobacteriaceae, showed high values in the control group. The representative of the obligate anaerobes, Lachnobacterium spp., representatives of the mycoplasma group, ureaplasma (urealyticum + parvum) and Mycoplasma genitalium showed high values in the study group, which indicated the presence of bacterial vaginitis and mycoplasmosis or ureaplasmosis.

As shown in Figure 1, the correlation analysis in the study group showed that among the representatives of obligate anaerobes, Megasphaera spp. had a medium direct correlation with CD4-CD8+ and CD3+HLA-DR+(activated E-lymphocytes) ($r = 0.5$; $P \leq 0.001$); a medium inverse correlation with the ratio of T-helpers to T-suppressors (IRI), CD3-HLA-DR+ ($r = -0.5$; $P \leq 0.001$); negative weak correlations between Lachnobacterium spp. and T-cytotoxic (CD4-D8+), CD3+HLA-DR+(activated E-lymphocytes) ($r = -0.2$; $r = -0.3$; $P \leq 0.001$), and a positive correlation with IRI ($r = 0.3$; $P \leq 0.001$). The following correlations were observed between Mobiluncus spp. and T-helper (CD4+CD8-) – weak direct ($r = 0.3$; $P \leq 0.001$), and Peptostreptococcus spp. and T-killer CD3+/CD16+56+ – medium direct ($r = 0.4$; $P \leq 0.001$). The representative of the mycoplasma group, Ureaplasma (urealyticum + parvum), showed a negative weak correlation with B-lymphocyte (CD3-CD19+) ($r = -0.3$; $P \leq 0.001$). Figure 2 shows the correlation in the study group between the only representative of the facultative anaerobes, Enterobacteriaceae, and CD3-HLA-DR+ – positive correlation ($r = 0.6$; $P \leq 0.001$).

The following correlation analysis in the control group showed a strong inverse correlation between the representatives of obligate anaerobes: as shown in Figure 3, the correlation between Peptostreptococcus spp. and CD3+HLA-DR+ (activated E-lymphocytes) ($r = -0.6$; $P \leq 0.001$). Figure 4 shows that the correlation between Sneathia spp. and T-cytotoxic (CD4-CD8+) is strong and positive, and between Sneathia spp. and NK (CD16+56+)

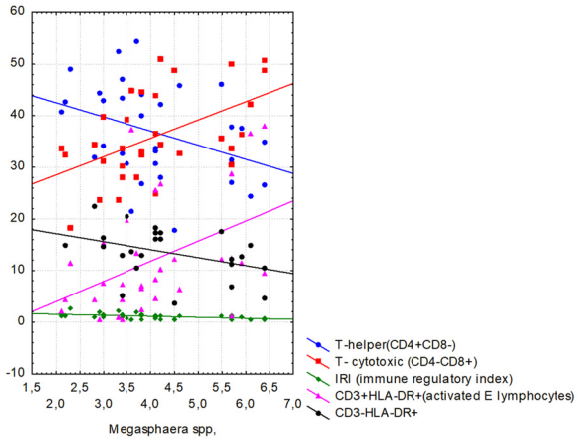

Fig. 1. Correlations Between Specific Immune Markers and Megasphaera spp. in the Study Group

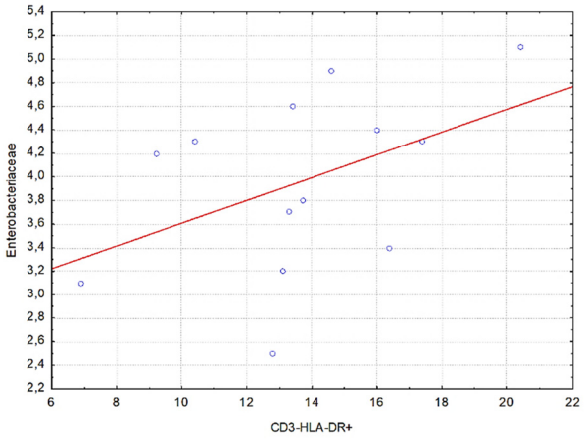

Fig. 2. Correlations Between Immunity and Enterobacteriaceae in the Study Group

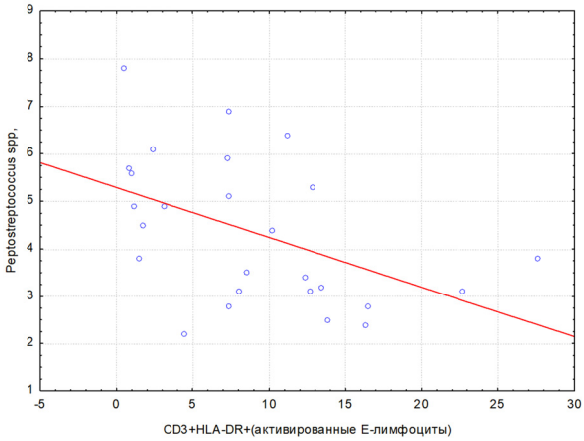

Fig. 3. Correlations Between Immune Markers and Peptostreptococcus spp. in the Control Group

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natural killers is strong and negative (r = -0.5; P ≤ 0.001). A weak but significant negative correlation was observed between Gardnerella vaginalis and CD3+HLA-DR+ (activated E-lymphocytes) (r = -0.3; P ≤ 0.001).

Figure 5 also shows the correlation between the only representative of facultative anaerobes Streptococcus spp. and T-cytotoxic (CD4-CD8+), which was a significant direct medium correlation, while for IRI there was a significant inverse strong correlation (r = 0.5; r = -0.6; P ≤ 0.001).

This was confirmed in our study by the fact that the development of an imbalanced immune response in tumors of the reproductive system affected the nonspecific vaginal immunity, with a predominance of representatives of obligate anaerobes with inflammation in the form of bacterial vaginosis (Table 2).

Discussion

The study of the relationship between specific immunity and nonspecific vaginal immunity markers showed a correlation between obligate anaerobes Megasphaera spp. and the main populations of lymphocytes, which were involved in the immune response to the infection and were directly involved in the destruction of infected cells (20). This was confirmed in our study and this fact indicated a significant decrease in the immune regulatory index (IRI) regarding a quantitative increase in Megasphaera spp. in the vaginal flora, which indicated the occurrence of bacterial vaginosis in patients in the study group. T-activated lymphocytes with the CD3+HLA-DR+ phenotype are the markers of late activation and immune hyperreactivity and a decrease in these parameters indicates a weakening of the body's defenses and the development of a hypoimmune state (21). If T-helpers are up to 0.4*100, the clinical picture can be transient and reversible. In our patients, it manifested itself as a correlation between these parameters and representatives of the vaginal biocenosis Megasphaera spp. and Enterobacteriaceae in women with BC, following long-term chemotherapy.

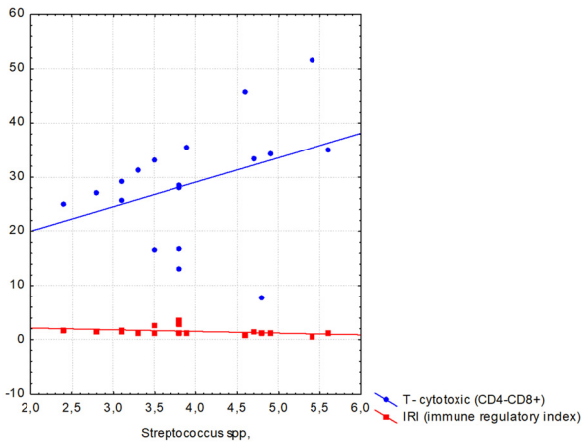

Fig. 4. Correlations Between Cellular Immunity and Streptococcus spp. in the Control Group.

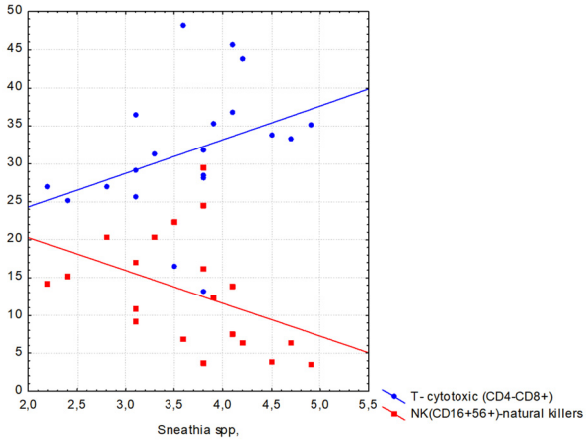

Fig. 5. Correlations Between Immune Markers and Sneathia spp. in the Control Group.

In the control group, the picture of the vaginal

Table 2. Correlation Between Immune Markers and Representatives of Vaginal Microflora in Both Groups With Breast Cancer

Immune markers	Representatives of Vaginal Microflora											
	Study group								Control Group			
	Enterobacteriaceae	Lachnobacterium spp	Megasphaera spp,	Peptostreptococcus spp,	Mobiluncus spp	Ureaplasma	Mycoplasma genitalium	Streptococcus spp,	Gardnerella vaginalis	Sneathia spp,	Peptostreptococcus spp	Atopobium vaginae
T-cytotoxic (CD4-CD8+)		-0.2	0.5					0.5		0.5		
T-helper (CD4+CD8-)			-0.4		0.3							
CD3-HLA-DR+	0.6		-0.4									
CD3+HLA-DR+(activated E-lymphocytes)		-0.3	0.5						-0.3		-0.6	
T-killers CD3+/CD16+56+				0.4								
B-lymphocytes (CD3-CD19+)			-0.4			-0.3						
NK(CD16+56+)-natural killers										-0.5		
IRI		0.3	-0.5		-0.2			-0.6				

Note: P ≤0.001 was the significance level for all correlations.

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biocenosis regarding this flora, such as Peptostreptococcus spp., Sneathia spp., and Streptococcus spp., changed with an increase in response to the inhibition of T-activated lymphocytes with the CD3+HLA-DR+ phenotype, IRI, and NK (CD16+56+)-natural killers at baseline in the examined women with BC before chemotherapy, and this indicates that in the acute phase of this pathology, the immune response is correspondingly reduced. Whereas in the control group, high values of the representative of obligate anaerobes, Enterobacteriaceae, had no correlations; and in the study group, the strong, direct correlation made it possible to consider it a late marker of cellular and nonspecific immunity. The results of this study in the control group in terms of correlation levels, among the presented vaginal biocenosis of Peptostreptococcus spp. and Gardnerella vaginalis, revealed an inverse correlation between CD3+HLA-DR+ and Peptostreptococcus spp., which may be considered an early marker of nonspecific immunity.

Based on the studies performed in Russia (Yekaterinburg authors) and in Europe, an integral assessment of the vaginal microbiocenosis and local immunity in patients with cervical intraepithelial tumors was made, where it was proved that the development of cervical tumors is associated with genetically determined significant dysbiotic processes in the vagina, with predominant participation of obligate anaerobes and local immune dysfunctions (22).

The authors from the Amsterdam Institute for Infection and Immunity state that bacterial vaginosis-associated Megasphaera spp. bacteria induced the maturation of dendritic cells and increased the levels of proinflammatory cytokines (23), which contradicts our results. This is because of the fact that Megasphaera spp. produced both direct and negative correlations with a subpopulation of T-lymphocytes in the study group.

The experimental study at the Chinese Research Institute of Hong Kong on mouse models with colorectal cancer showed that Peptostreptococcus spp. attached to the mucous membrane and accelerated the oncogenic response in vitro and in vivo (24). In our study, Peptostreptococcus spp. affected a subpopulation of T cells with inverse correlation (in vivo) (25).

Conclusion

The function of the immune system is to preserve and maintain beneficial bacteria in the vagina alive. The mechanisms of interactions between the immune system and normal microbiota remains unclear, but there is no doubt that the microbial biocenosis and the immunity of the vaginal mucosa function together. It is important to emphasize that the effects of microbial products are rather systemic than local. Neoplastic processes in the mammary glands are associated with genetically determined significant dysbiotic processes in the vagina with a predominant participation of obligate anaerobes and local immune dysfunctions. Among anaerobes, the most important are Megasphaera spp., Streptococcus spp., Sneathia spp., Peptostreptococcus spp. and Enterobacterium spp. The variety of leading pathogens requires a comprehensive study of vaginal microbiocenosis and local immunity in patients with BC, with a correction of identified disorders to improve treatment outcomes. The components of the immune system (T-cytotoxic (CD4-CD8+) and CD3+HLA-DR+(activated E-lymphocytes)) are actively involved in maintaining nonspecific vaginal immunity, based on molecular genetic studies in women with BC, as manifested by an impaired biocenosis and depression of local immune responses.

The biocenosis of the vagina, together with the suppression of normal flora, indicates the prevalence of the representatives of obligate anaerobes: Megasphaera spp., Enterobacteriaceae, and Peptostreptococcus spp. in response to changes in the subpopulation of T cells associated with a decrease in immunobiological protection, creating conditions for the implementation of the pathogenic action of biocenosis, which further exacerbates the immunological failure. The presence of multiple correlations between biocenosis parameters and cellular immune status indicates the presence of a general immune response of the body and requires further in-depth study of these correlations.

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Conflict of Interests

The authors declare that they have no competing interests.

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