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Breast Cancer Relapse Prevention: Role of Anti-Relapsing Immunocorrection

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ABSTRACT

The article focuses on C-C chemokine ligand 5 (CCL5) as a prognostic factor for the breast cancer (BC) progression and presents the effects of the exogenous peptide preparation Arecur in the anti-relapsing immunocorrection programme in patients with BC. The study showed that the anti-relapsing immunocorrector Arecur contributed to a CCL5 expression reduction in patients with luminal A, luminal B, HER2+ and Triple Negative immunohistochemical subtypes of BC. During 60 months of patients' follow-up who took Arecur (N=130), the disease progress was recorded in 10 patients (7.7%), and relapse-free survival made up 92.3%. In the group of patients who were not administered a course of preventive immunocorrection (N=96), the disease progress was recorded in 16 (16.7%), and relapse-free survival composed 83.3%. The presented differences were statistically significant – the hazard ratio HR=0.439 (0.20–0.96), p=0.035, which indicates the risk reduction of BC progression in the study group (Arecur) over the 5-year observation period by 56.1%. The study results allow regarding Arecur as a medicinal product for the routine BC relapse prevention in patients after surgical treatment.

Keywords

CCL5, Breast cancer, Relapses, Exogenous peptides, Arecur, Relapse-free survival.

Introduction

Breast cancer is the most common malignant tumour in women and, unfortunately, survival rates have not changed for the past four decades [1-3]. The optimization schemes of comprehensive treatment of patients with breast cancer have been a subject of ample debatable up to the present day. System adjuvant therapy, including hormone therapy, is used to reduce the relapse incidence and development of distant tumour foci [4-6]. However, in many countries, cyclophosphamide, methotrexate, and 5-fluorouracil remain the standard chemotherapeutic regimen, despite the emergence of new generations of antineoplastic drugs in the arsenal of oncologists [7,8]. Surgery, chemotherapy, radiation therapy and hormone therapy are the main tools of oncologists in the breast cancer (BC) treatment. BC still accounts for 20 percent of all cancer deaths in women [9-11].

Clinically, BC is a heterogeneous disease. Gene expression profiling revealed two major groups based on estrogen receptor (ER) expression: ER-expressing (ER+) breast tumours are more closely associated with hormonal factors than tumours that do not express it (ER-). By the cell line type (luminal or basal / myoepithelial cell compartment), BC is also classified as basal-like or non-basal-like. The first one, also known as triple negative, accounts for about 15% of all BC (Figure 1). It is characterized by the absence of all three hormonal receptors, i.e., ER, progesterone (PR) and human growth factor neu (Her2) receptors, but at the same time it has high expression of basal cytokeratins [12,13].

Several risk factors were identified: non-modifiable factors include elderly age (>65 vs <65 years old), genetic predisposition (including DNA mutations and a family anamnesis of BC), early menarche (<12 years old), late menopause (>55 years old), first pregnancy age over 30 years old, infertility and childlessness, contraceptive use, hormone treatment after menopause, and lack of breastfeeding history. Among the changeable lifestyle factors, the choice of diet and overweight or obesity are associated with various risks of the BC onset and relapse; in particular, obesity is associated with lower overall survival and increased mortality in

women in the postmenopausal period [14-17].

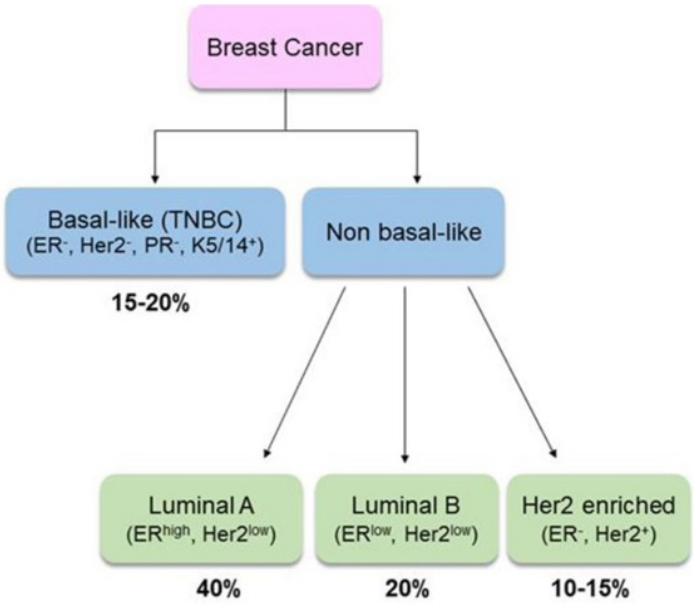

Figure 1: Breast cancer subtypes and relative prevalence. TNBC: triple negative breast cancer [15].

In recent decades, the correlation between specific food items (i.e., alcohol, fruit, vegetables, meat, and soybean products) and BC development was evaluated in several studies [18-24]. However, no consistent and statistically strong association was found, except for alcohol consumption. However, it was suggested that diet may have a substantial influence on the BC treatment outcomes. Pursuant to Dietary Guidelines oriented toward for the general population, accepting a healthy diet based on high consumption of fruit, vegetables, whole grains, poultry and fish, as well as low consumption of red meat, refined food items, sweets and high-fat dairy products – healthy nutrition may improve the overall prognosis and survival of women with a BC diagnosis (stage I, stage II or stage IIIA) [25,26]. Besides, in separate publications, the positive effect on the disease course of various phytotherapy methods, in particular the use of the Canadian herbal tea Essiac, is shown [27,28]. Moreover, there is increasing evidence that physical activity is also associated with a greater likelihood of improved survival.

As it is known, a variety of chemokines and chemokine receptors are found in tumour tissues. One of the most extensively studied chemokines of certain value for predicting cancer progression is the C-C chemokine ligand 5 (CCL5), also known as Regulated upon Activation, Normal T-cell Expressed, and Secreted (RANTES). CCL5 is expressed by T-lymphocytes, macrophages, platelets, synovial fibroblasts, tubular epithelium and some types of tumour cells. CCL5 plays an active role in recruiting many white blood cells to inflammation sites, including T cells, macrophages, eosinophils and basophils. With the support of certain cytokines that are released by T cells, such as IL-2 and IFN-, CCL5 also induces the activation and proliferation of certain natural killer cells.

CCL5, although minimally expressed by normal breast epithelial duct cells, is highly expressed by breast tumour cells in primary tumour sites, regional lymph nodes, and metastatic lesions, indicating that CCL5 expression is acquired during malignant transformation and that CCL5 is of crucial importance in the BC development and/or progression [29-31].

The increased levels of positivity and expression of CCL5 by breast tumour cells are significantly associated with disease progression, relapse and/or metastasis compared with remitters. In this tumour, the main source of CCL5 is tumour cells; however, CCL5 is also expressed by infiltrative leukocytes and mesenchymal stem cells (MSC) of the tumour microenvironment [32].

The functional receptor CCR5 is expressed by a subpopulation of human breast cancer cell lines and demonstrates a functional response to CCL5. The CCL5 expression is closely related to the BC progression, especially triple negative breast cancer (TNBC), and can be an immunotherapeutic target in TNBC [33].

CCL5 supports a malignant breast tumour by changing the equilibrium between leukocyte infiltrates in tumours, resulting in the dominance of cells with activity conducive to the tumour, but not killing it. In fact, CCL5 shifts the balance between various types of leukocytal cells, increasing the number of harmful ones, secreting proangiogenic factors, suppressing the antineoplastic response and inhibiting the antineoplastic activity of T cells.

The CCL5 expression by breast tumour cells is a valuable prognostic factor for identifying patients with BC stage II who are at risk of disease progression. The serum CCL5 levels are increased in patients with BC compared with healthy people and tend to be higher in patients with positive lymph nodes, large-sized tumour, lymphovascular invasion, and multifocal tumours [34].

Average plasma and serum CCL5 concentrations in patients with BC are elevated in patients with positive lymph node. In addition, there are observations that CCL5 levels increased significantly with tumour enlargement. The plasma and serum CCL5 levels correlate with tumour progression. The CCL5 levels in patients with stage I were lower as compared to those in patients with stages II and III.

There is increasing evidence that the tumour development and progression depends not only on cancer cells, but also on cancer-related inflammation arising in the tumour microenvironment. Interactions between inflammatory factors, tumour cells, and components of the immune system involved in the tumour microenvironment are crucial for disease progression. It was suggested that the CCL5 expression by breast tumour cells leads not only to the monocyte migration to the tumour site, but also to an increase in the production and recruitment of proinflammatory cytokines, as well as the recruitment and activation of inflammatory cells, which may contribute to the metastasis formation [35,36].

One of the directions of modern antineoplastic immunotherapy is the use of regulatory exogenous peptides. To solve the

complicated task of harmonizing immune homeostasis, as well as restoring fully-fledged antineoplastic immune surveillance, Arecur was created. Arecur contains biologically active substances, including exogenous peptides, in particular defensin-1 and royal jelly protein-1. Entering the body, exogenous peptides engage in complex and diverse peptide-peptide interactions with human regulatory proteins. It was repeatedly proved that the regulatory peptides of plants and animals are similar in structure and function to those in humans and are able to activate immune reactions in the body. Due to its evolutionarily programmed capability of reacting with other protein structures, exogenous peptides interact with membrane formations: Toll-like receptors, membrane pore receptors, and glycoproteins. Intracellularly, exogenous peptides are able to activate immune cascades: mediate NOD signals for the inflammasome formation; potentiate the caspase enzyme system reactions in stimulating the interleukin synthesis. Exogenous peptides showed positive effects against mixed viral and bacterial infections, in the treatment of cervical intraepithelial neoplasia [37], endometrioma [38], chronic prostatitis [39]; in counteracting circulating tumour cells [40], and also confirmed anti-relapsing efficacy in BC [41] and in patients with hepatocellular carcinoma [42].

Objective

To study the anti-relapsing efficacy of the medicinal product of exogenous peptides Arecur in patients with breast cancer.

Materials and Methods

In total 130 patients with breast cancer aged 34 to 66 years who were treated in the clinic of radiation-induced oncological diseases of the NRCRM of NAMS of Ukraine were included into 4 study groups. Group A1 (N=56) included patients with luminal A cancer, group B1 (N=32) with luminal B, group C1 (N=19) with HER2+ cancer, and group D1 (N=23) with triple negative cancer. The control groups A2, B2, C2, and D2 with similar BC biological subtypes included 44, 22, 16, and 16 patients, respectively, in total there were 98 women.

Tumour size was estimated after measuring its maximum diameter and was classified according to the International TNM classification as T1 (<2 cm), T2 (2-5 cm), T3 (≥5 cm). The supressed menstruation in patients within 1 year prior to the established diagnosis was interpreted as menopause. The histologic type and degree of tumour differentiation was determined in accordance with national standards for the diagnosis and management of malignant neoplasms, based on the recommendations of leading international organizations. The BC molecular subtypes were determined based on the immunohistochemical test results of the ER, PP and Her2/neu expression. All tumours were divided into 4 subtypes: luminal A (Luminal A) ER+ and/or PR+, Her2/neu-; luminal B (Luminal B) ER+ and/or PR+, Her2/neu+; HER2+ (ER- and PR-, Her2/neu+); and TN (Triple negative) ER- and PR -, Her2/neu-.

All patients of the study groups (A1-D1) were operated for BC stage I and IIA – T1N0M0, TisN1M0, T1N1M0, T2N0M0 during the period from January 2013 to October 2014. Patients underwent a subcutaneous radical skin- and nipple-sparing mastectomy. The criteria for selecting patients for these operations were as follows: node-positive BC; mono- and multicentric growth; the absence of a tumour in the skin and the nipple-areolar complex, pectoral muscles, the decentred location of the tumour; the areola edge-tumour distance is at least 4 cm; tumour sizes from 1.5 up to 5 cm; slow and moderate tumour growth rates; lack of conglomerated metastases in regional lymph nodes; lack of distant metastases and severe concomitant diseases.

After surgical treatment, the patients were administered adjuvant chemotherapy, if medically indicated it was combined with hormone therapy according to the FAC or CMF + anastrozole regimen. The patients of study groups A1-C1 were administered a course of anti-relapsing immunocorrection twice a year: using the drug Arecur intramuscularly according to the regimen 1 injection in the morning and 1 injection in the evening for 20 days, then 10-day treatment break and again 20 days of treatment. To reduce the pain with the introduction of 2 mL of Arecur, it was mixed with 2 mL of anaesthetic agent. On completing each anti-relapse course of treatment, the CCL5 expression level in blood serum were measured in patients of the study groups, and this indicator was measured at comparable time intervals twice a year in patients of the control groups. ELISA technique on Quantikine Kits (R&D Systems, Wiesbaden, Germany) was used for the CCL5 analysis.

For descriptive statistics of the CCL5 expression level, the arithmetic mean (M), standard deviation (SD), and mean error (m) were calculated. The qualitative indicators (cases of relapse, metastasis) are presented as the number of observations (n) and (%).

For the quantitative indicators, there was a preliminary evaluation of the normality of distribution provided, which was the basis for the selection of parametric (t-test), or nonparametric criteria (Mann-Whitney test) for comparing indicators between groups. Comparison of the qualitative parameters was performed using the chi-squared test (Pearson's $\chi 2$ squared test).

For the relapse-free survival analysis, the Kaplan-Meier method was used. The analysis was performed using the statistical analysis package STATA 12.

Results and Discussion

Within 60 months of the observation period in study group A1 (Arecur, N=56, histologic type Luminal A), 2 cases of relapse and 1 case of distant metastasis were recorded – the disease progression was recorded only in 3 (5.4%) of 56 patients. These data correlate with the assessment of the CCL5 cytokine expression level: after the 3rd course of immunocorrection, the median of CCL5 expression values began to decrease and this trend persisted throughout the entire subsequent period. In the control group A2 (N=44, histologic type Luminal A), 6 cases of disease relapse were noted, that is, the disease progressed (p=0.151) in 6 (13.7%) of 44 patients. It should be noted that in patients of the control group throughout the entire follow-up period, the CCL5 expression

level remained relatively high (Figure 2). Starting from the 3rd observation period (18 months), the differences between groups A1 and A2 are statistically significant ($p<0.05$) – the 3rd observation period ($p=0.022$), the 4-6th observation periods (24-36 months) – $p=0.001$.

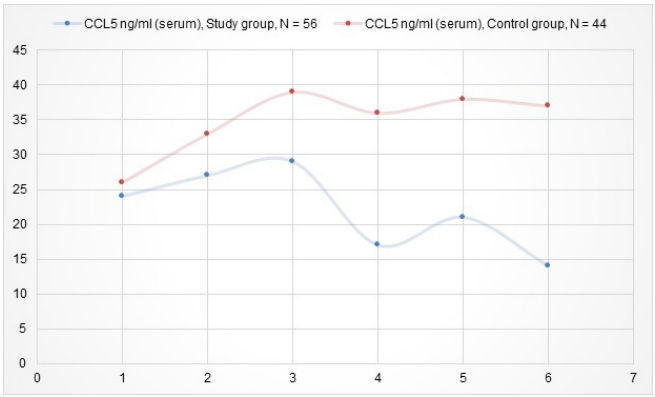

Figure 2: Level of CCL5 expression in dynamics in groups A1 and A2 (histologic type Luminal A).

In study group B1 (Arecur, N=32, histologic type Luminal B), 2 cases of relapse were recorded, and this amounted to 6.3% of patients in this group. In reference group B2 (N=22, histologic type Luminal B), 4 cases of disease relapse were recorded – i.e., disease progress was noted in 18.2% of patients in this group ($p=0.170$). In estimating CCL5 activity, it can be noted that this cytokine systematically decreased in patients of study group and vice versa – significantly increased in the control group (Figure 3). Up to the 3rd observation period (18 months), differences between groups B1 and B2 are not statistically significant ($p>0.05$), and during the 4-6th observation periods (24-36 months), these differences become significant – $p<0.001$.

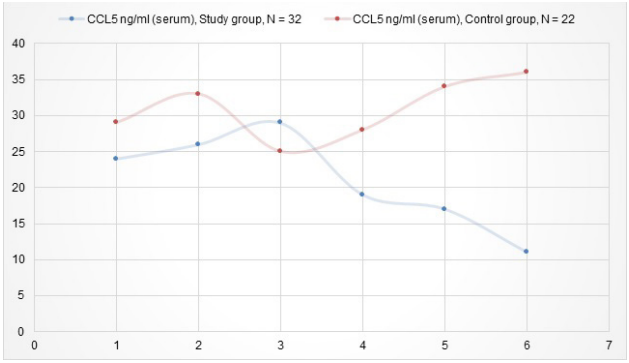

Figure 3: Level of CCL5 expression in dynamics in groups B1 and B2 (histologic type Luminal B).

In study group C1 (Arecur, N=19, histologic type HER2+), 1 case of relapse and 1 case of distant metastasis was observed – disease progression was recorded in 2 (10.5%) of 19 patients. In control group C2 (Arecur, N=16, histologic type HER2+), 1 case of relapse and 2 cases of metastasis were recorded, i.e., disease progress was noted in 18.8% of patients in this group. When assessing CCL5 activity, we saw relatively high numbers of this cytokine in both groups. It is likely that the aggressive type of tumour caused a relatively high percentage of patients with disease progression, however, we may note that in the group with immunocorrection performed using Arecur, this indicator was lower with the presence of statistically significant differences for the 4th ($p=0.040$), the 5th ($p=0.034$) and the 6th ($p=0.001$) observation periods (24-36 months) (Figure 4).

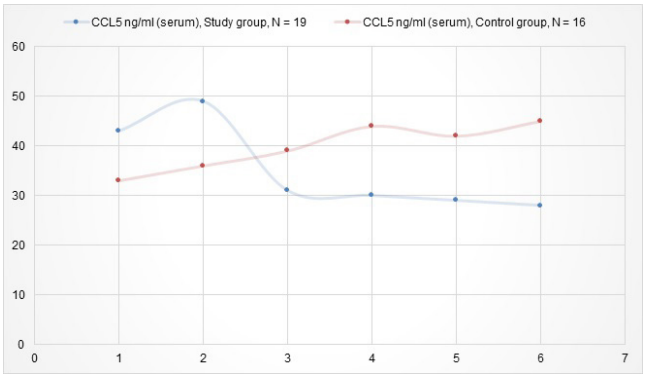

Figure 4: Level of CCL5 expression in dynamics in groups C1 and C2 (histologic type HER2+).

In study group D1 (Arecur, N=23, histologic type Triple Negative), 1 case of relapse and 2 cases of distant metastasis were recorded – thus, 3 (13.0%) of 23 patients had disease progression. These data correlate with the assessment of the CCL5 cytokine expression level: after the 2nd course of immunocorrection, the median of CCL5 expression values began to decrease, and this trend persisted at the following control points. In control group D2 (N=16, histologic type Triple Negative), 3 cases of disease relapse were noted, that is, in 3 (18.8%) of 16 patients, the disease progressed. At the same time, in patients of the control group throughout the entire observation period, the CCL5 expression level not only remained relatively high but also steadily increased (Figure 5). Statistically significant differences ($p<0.05$) between groups D1 and D2 were revealed only for the control points 5 and 6 (30-36 months). The results of measuring CCL5 in all groups are presented in Tables 1 and 2.

Study Group	1	2	3	4	5	6
Group A1 (Luminal A), n=56	24 ± 4,4	27 ± 6,0	29 ± 3,1*	17 ± 2,0*	21 ± 5,1*	14 ± 5,2*
Group B1 (Luminal B), n=32	24 ± 2,0	26 ± 5,2	29 ± 4,1	19 ± 2,2*	17 ± 4,3*	11 ± 2,2*
Group C1 (HER2+), n=19	43 ± 9,0	49 ± 6,3	31 ± 4,3	30 ± 6,4*	29 ± 3,1*	28 ± 3,1*
Group D1 (Triple Negative), n=23	16 ± 2,2	24 ± 4,1	22 ± 3,0	20 ± 4,4	18 ± 5,0*	19 ± 3,0*

Table 1: CCL5 expression levels in study groups, ng/ml.

Control Group	1	2	3	4	5	6
Group A2 (Luminal A), n=44	26 ± 5,0	33 ± 1,2	39 ± 3,0	36 ± 5,0	38 ± 2,7	37 ± 4,1
Group B2 (Luminal B), n=22	29 ± 5,4	33 ± 2,0	25 ± 2,9	28 ± 1,0	34 ± 1,4	36 ± 2,5
Group C2 (HER2+), n=16	33 ± 2,9	36 ± 4,1	39 ± 4,1	44 ± 1,4	42 ± 5,0	45 ± 1,9
Group D2 (Triple Negative), n=16	18 ± 3,0	21 ± 3,2	26 ± 4,3	24 ± 2,8	31 ± 2,2	33 ± 2,7

Table 2: CCL5 expression levels in control groups, ng/ml.

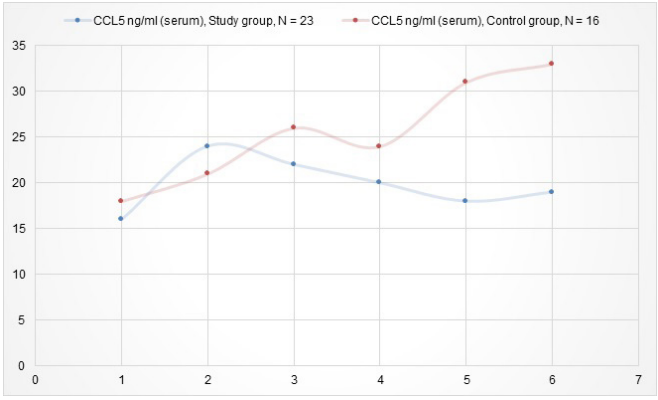

Figure 5: Level of CCL5 expression in dynamics in groups D1 and D2 (histologic type Triple Negative).

During the observation period of 2014–2019, in groups A1-D1 (130 patients), disease progress was recorded in 10 patients (7.7%), and relapse-free survival made up 92.3%. In groups A2-D2 (a total of 96 patients), disease progress was recorded in 16 (16.7%), and relapse-free survival was 83.3%. The differences were statistically significant – the hazard ratio HR=0.439 (0.20–0.96), p=0.035, which indicates the progression risk reduction in groups A1-D1 (Arecur) for a 5-year observation period by 56.1%. The relapse-free survival analysis results are shown in Figure 6.

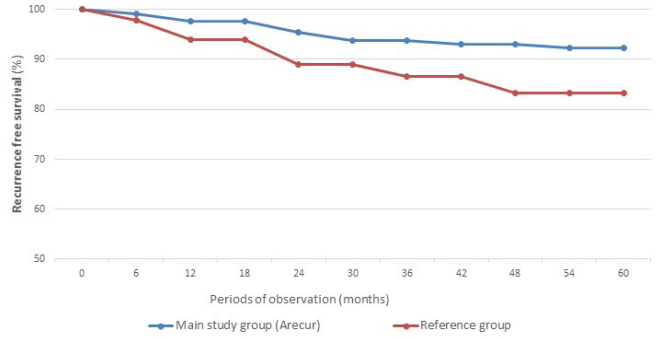

Figure 6: Curves of recurrence free survival of patients with breast cancer in the main study group (Arecur) and the reference group (Kaplan-Meier curves analysis).

Conclusion

The experience of anti-relapsing immunocorrection in patients with breast cancer indicates that the harmonization of immune homeostasis with the help of the exogenous peptide drug Arecur improves the relapse-free survival and improves the disease prognosis.

It should be emphasized that owing to the use of peptides of the Arecur drug, it was possible to reduce and control for a long time the expression of CCL5 factor, a key marker of disease aggressiveness and a predictor of relapses and metastases; and, moreover, the improvement in the prognosis of the disease course occurred in patients with all breast cancer biotypes.

Considering the results obtained, Arecur may be reasonably regarded as a drug for the routine BC relapse prevention in patients after surgical treatment. The studies of the anti-relapsing immunocorrection efficacy in oncological practice, in our opinion, should be continued.

References

1. Stewart RL, Updike KL, Factor RE, et al. A Multigene Assay Determines Risk of Recurrence in Patients with Triple-Negative Breast Cancer. Cancer Res. 2019; 79: 3466-3478.
2. Baum M, Buzdar A, Cuzick J, et al. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early stage breast cancer. Results of the ATAC (Arimidex, Tamoxifen Alone or in Combination) trial efficacy and safety update analyses. Cancer. 2003, 98: 1802-1810.
3. Bian L, Yi Liu, Tao Wang, et al. Prediction value for dynamic changes of circulating tumor cell in therapeutic response and prognosis of Chinese metastatic breast cancer patients. Zhonghua Yi Xue Za Zhi. 2014; 94: 265-268.
4. Beije N, Jager A, Sleijfer S. Circulating tumor cell enumeration by the CellSearch system the clinician's guide to breast cancer treatment. Cancer Treat Rev. 2015; 41: 144-150.
5. Keller PJ, Arendt LM, Skibinski A, et al. Defining the cellular precursors to human breast cancer. Proc Natl Acad Sci USA. 2012; 109: 2772-2777.
6. Wang D, Xu J, Shi G, et al. Molecular markers' progress of breast cancer treatment efficacy. J Cancer Res Ther. 2015; 1: C11-C15.
7. Yu F, Yao H, Zhu P, et al. let-7 regulates self renewal and tumorigenicity of breast cancer cells. Cell. 2007; 131: 1109-1123.
8. Zhang M, Atkinson RL, Rosen JM. Selective targeting of radiation-resistant tumor-initiating cells. Proc Natl Acad Sci USA. 2010; 107: 3522-3527.
9. Kasimir-Bauer S, Bittner AK, König L, et al. Does primary neoadjuvant systemic therapy eradicate minimal residual disease? Analysis of disseminated and circulating tumor cells before and after therapy. Breast Cancer Res. 2016; 18: 20.
10. Sørlie T, Perou CM, Tibshirani R, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci USA. 2001; 98: 10869-10874.
11. Ursaru M, Jari I, Naum A, et al. Causes of Death in Patients with Stage 0-Ii Breast Cancer. Revista medico-chirurgicala a Societatii de Medici si Naturalisti din Iasi. 2015; 119: 374-378.
12. Visser LL, Groen EJ, van Leeuwen FE, et al. Predictors of an Invasive Breast Cancer Recurrence after DCIS A Systematic Review and Meta-analyses. Cancer Epidemiol Biomarkers Prev. 2019; 28: 835-845.
13. Sparano JA, Robert J. Gray, Peter M. Ravdin, et al. Clinical and Genomic Risk to Guide the Use of Adjuvant Therapy for Breast Cancer. N Engl J Med. 2019; 380: 2395-2405.
14. Cronin-Fenton D. Opioids and breast cancer recurrence. Curr Opin Support Palliat Care. 2019; 13: 88-93.
15. De Cicco P, Catani MV, Gasperi V, et al. Nutrition and Breast Cancer A Literature Review on Prevention, Treatment and

Recurrence. Nutrients. 2019; 11: 1514.
16. Sun YS, Zhao Z, Yang ZN, et al. Risk factors and preventions of breast cancer. Int. J. Biol. Sci. 2017; 13: 1387-1397.
17. Giles ED, Wellberg EA, Astling DP, et al. Obesity and overfeeding affecting both tumor and systemic metabolism activates the progesterone receptor to contribute to post-menopausal breast cancer. Cancer Res. 2012; 72: 6490-6501.
18. Mourouti N, Kontogianni MD, Papavagelis C, et al. Diet and breast cancer A systematic review. Int. J. Food Sci. Nutr. 2015; 66: 1-42.
19. Protani M, Coory M, Martin JH. Effects of obesity on survival of women with breast cancer Systematic review and meta-analysis. Breast Cancer Res. Treat. 2010; 123: 627-635.
20. Kwan ML, Weltzien E, Kushi LH, et al. Dietary patterns and breast cancer recurrence and survival among women with early-stage breast cancer. J. Clin. Oncol. 2009; 27: 919-926.
21. Rock CL, Doyle C, Demark-Wahnefried W, et al. Nutrition and physical activity guidelines for cancer survivors. CA Cancer J. Clin. 2012; 62: 243-274.
22. Aune D, Chan DS, Vieira AR, et al. Fruits, vegetables and breast cancer risk A systematic review and meta-analysis of prospective studies. Breast Cancer Res. Treat. 2012; 134: 479-493.
23. Fung TT, Chiuve SE, Willett WC, et al. Intake of specific fruits and vegetables in relation to risk of estrogen receptor-negative breast cancer among post-menopausal women. Breast Cancer Res. Treat. 2013; 138: 925-930.
24. Masala G, Assedi M, Bendinelli B, et al. Fruit and vegetables consumption and breast cancer risk The EPIC Italy study. Breast Cancer Res. Treat. 2012; 132: 1127-1136.
25. Farvid MS, Stern MC, Norat T, et al. Consumption of red and processed meat and breast cancer incidence A systematic review and meta-analysis of prospective studies. Int. J. Cancer. 2018; 143: 2787-2799.
26. Anderson JJ, Darwis NDM, Mackay DF, et al. Red and processed meat consumption and breast cancer UK Biobank cohort study and meta-analysis. Eur J Cancer. 2018; 90: 73-82.
27. Zick SM, Sen A, Feng Y, et al. Trial of Essiac to ascertain its effect in women with breast cancer TEA-BC. J Altern Complement Med. 2006; 12: 971-980.
28. Olaku, OO, White JD. Herbal therapy use by cancer patients: a literature review on case reports. European journal of cancer. 2011; 47: 508-514.
29. Aldinucci D, Colombatti A. The inflammatory chemokine CCL5 and cancer progression. Mediators Inflamm. 2014.
30. Walens A, DiMarco AV, Lupo R, et al. CCL5 promotes breast cancer recurrence through macrophage recruitment in residual tumors. Elife. 2019; pii: e43653.
31. Soria G, Ben-Baruch A. The inflammatory chemokines CCL2 and CCL5 in breast cancer. Cancer Letters. 2008; 267: 271-285.
32. Mi Z, Bhattacharya SD, Kim VM, et al. Osteopontin promotes CCL5-mesenchymal stromal cell-mediated breast cancer metastasis. Carcinogenesis. 2011; 32: 477-487.
33. Lv D, Zhang Y, Kim HJ, et al. CCL5 as a potential immunotherapeutic target in triple-negative breast cancer. Cellular & Molecular Immunology. 2013; 10: 303-310.
34. Dehqanzada ZA, Storrer CE, Hueman MT, et al. Assessing serum cytokine profiles in breast cancer patients receiving a HER2/neu vaccine using Luminex technology. Oncology Reports. 2007; 17: 687-694.
35. Zhang Y, Yao F, Yao X, et al. Role of CCL5 in invasion, proliferation and proportion of CD44+/CD24- phenotype of MCF-7 cells and correlation of CCL5 and CCR5 expression with breast cancer progression. Oncology Reports. 2009; 21: 1113-1121.
36. Yaal-Hahoshen N, Shina S, Leider-Trejo L, et al. The chemokine CCL5 as a potential prognostic factor predicting disease progression in stage II breast cancer patients. Clinical Cancer Research. 2006; 12: 4474-4480.
37. Kurchenko AI, Beniuk VO, Potebnya GP, et al. The role of exogenous peptides in the renewal of a full immune reaction in the conditions of the second immunodeficiency. Women's health. 2017; 1: 89-97.
38. Melnikov SM, Tatskyi OF. A new look at endometriosis: the role of restoring of full immune surveillance over ectopic cells of the endometrium. Women's health. 2017; 7: 99-107.
39. Zaseda YI, Tatskyi OF. The effect of tissue accumulation of exogenous peptides is the key to understanding the mechanisms of harmonization of the immune homeostasis of patients with chronic bacterial prostatitis. Health of the man. 2017; 1: 51-56.
40. Lytvynenko OO, Tatskyi OF. Effective prophylaxis of breast cancer recurrence the role of exogenous peptides MHP in the restoration of the immune homeostasis. Clinical Immunology. Allergology. Infectology. 2017; 3: 51-57.
41. Lytvynenko O, Konovalenko V, Tatskyi O, et al. Effectiveness of Breast Cancer Recurrences Prophylaxis by Means of Exogenous Peptides Results of 24 Months Supervision. Rep Cancer Treat. 2018; 2: 39-46.
42. Shypulin V, Stoliarova O, Konovalenko V, et al. Study of the Exogenous Peptide Effect on the TGF-β1 Expression-A Risk Factor for the Hepatocellular Carcinoma Recurrence. American Journal of Biomedical and Life Sciences. 2019; 7: 73-78.