ejpmr, 2023, 10(7), 461-466

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

THE INFLUENCE OF METABOLIC SYNDROME ON THE RISK AND PROGNOSIS OF BREAST CANCER (REVIEW)

***Zievedenova S. S. and Mirzaeva M.**

Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology of the Ministry of Health of the Uzbekistan, Tashkent.

***Corresponding Author: Zievedenova S. S.**
Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology of the Ministry of Health of the Uzbekistan, Tashkent.

Article Received on 20/05/2023 **Article Revised on 10/06/2023** **Article Accepted on 30/06/2023**

SUMMARY
Breast cancer and metabolic syndrome remains one of the most urgent problems of modern medicine worldwide. In this review, highlights the molecular pathways that underlie the negative impact of metabolic syndrome on the risk and prognosis of breast cancer. A better understanding of these pathways will help to optimize prevention and treatment of breast cancer in patients with metabolic syndrome.

KEYWORDS: Breast cancer, metabolic syndrome, breast cancer risk and prognosis, the molecular mechanisms.

INTRODUCTION

Breast cancer (BC) and metabolic syndrome (MS) remain one of the most urgent problems of modern medicine, as they reduce the life expectancy of the population.

Worldwide, breast cancer is the most common (22.9%) form of malignant neoplasms in women. In 2008, 458,503 deaths from breast cancer were registered worldwide, which accounted for 13.7% of deaths from malignant tumors among the female population.[1]

MS (Reaven Syndrome, Insulin Resistance Syndrome, Metabolic Syndrome X) is a combination of abdominal obesity, insulin resistance, hyperglycemia, dyslipidemia, arterial hypertension, haemostasis disorders, and chronic subclinical inflammation (International Diabetes Federation, 2005).

In 2005, the International Diabetes Federation named MS as one of the main problems of modern medicine, as it increases the overall mortality of the population. The prevalence of MS has reached pandemic proportions. In economically developed countries, 25–35% of the population of all age groups suffer from MS, this figure increases with age and reaches 42–43.5% among people over 60.[2] The concept of the influence of metabolic disorders on the risk of malignant neoplasms was first expressed by the German biochemist Otto Warburg more than 80 years ago. However, this concept remained unaddressed for many decades. The renewal of interest in it is associated with the introduction of molecular research into oncological practice. Currently, the influence of metabolic disorders associated with obesity, hyperinsulinemia, and MS on the risk of developing and progressing breast cancer has been proven in a number of clinical studies.[3–5]

Our work considers the main molecular mechanisms that explain the negative impact of metabolic disorders on the risk of occurrence and progression of breast cancer in patients with MS.

Theoretical substantiation of the relationship between metabolic syndrome and breast cancer

There are several hypotheses explaining the relationship between MS and breast cancer. The first hypothesis is based on the ability of the adipose tissue of the mammary glands to increase the local concentration of estrogens by peripheral aromatization of androgens. The second hypothesis is based on the mitogenic effect of insulin and insulin-like growth factor (IGF) on the epithelium of the mammary glands. The third hypothesis is on the ability of adipose tissue to perform auto-, para- and endocrine regulation by secreting a large number of substances, the action of which produces various biological effects, including potentially carcinogenic ones.

The role of hormonal imbalance in metabolic syndrome in breast cancer carcinogenesis

Hyperestrogenization in women with metabolic syndrome

Estrogens play a key role in the processes of proliferation and differentiation of the epithelium of the mammary glands, thus they not only regulate the normal growth and development of the latter, but also contribute to the emergence and progression of breast cancer. An increase in the concentration of estrogens and / or the number of

receptors for them in the epithelium of the mammary glands significantly increases the risk of developing breast cancer. The most convincing, but indirect evidence of the role of estrogen in the occurrence of breast cancer in women with MS can be a direct relationship between an increase in their concentration in the peripheral blood and an increase in body mass index in postmenopausal women. It should be noted that this dependence is observed only after the onset of menopause, since hyperestrogenemia as a result of obesity is not typical for premenopausal women.

The biosynthesis of estrogen occurs with the participation of the aromatase enzyme, an isoform of cytochrome P-450, which is synthesized mainly in the ovaries, adrenal glands, muscle and adipose tissue. In postmenopausal women, after ovarian function declines, estrogen-synthesizing function is performed by adipose tissue, including breast adipose tissue.[7] The concentration of estrogen in breast tissue after menopause is 10 times higher than in peripheral blood.[8] There is evidence of a direct relationship between excessive enzyme activity of aromatase in certain areas of the mammary gland and local hyperestrogenization of these areas and the development of a malignant tumor in them.[9]

Insulin resistance and hyperinsulinemia

At the age of 30-40 years, the process of reducing the sensitivity of the hypothalamic centers that regulate the production of somatotropic hormone (STH) to glucose inhibition occurs and further progresses. At a certain stage, this contributes to the hyperproduction of growth hormone, which leads to a decrease in the use of glucose by peripheral tissues and the development of insulin resistance and compensatory hyperinsulinemia. Under conditions of insufficient glucose utilization, free fatty acids become the main energy substrate, the excessive use (oxidation) of which leads to secondary inhibition of GH secretion (somatopause) and the development of obesity.[10] The mechanism of carcinogenesis under conditions of hyperinsulinemia is the malignant transformation of cells due to genetic mutations that occur against the background of hyperproliferation and suppression of apoptosis. Insulin is involved not only in the processes of tumor formation, but also in the processes of tumor progression due to the presence of insulin receptors (IR) on the membranes of normal and tumor cells. After insulin binds to IR, the IR substrate (IRS) is activated, which triggers the mitogen-activated protein kinase (MAPK) and phosphatidylinositol-3-kinase (PI3K) signaling pathways. As a result, this leads to the transition of cells from the G1 period to the S period of the cell cycle, proliferation, and inhibition of apoptosis.[11–14]

In addition to direct, insulin has an indirect mitogenic effect, which is realized by stimulating the synthesis and activation of IGF. IGF, or somatomedins, are formed mainly in the liver, muscle and adipose tissue under the influence of growth hormone. There are 2 types of IGF: IGF-I and IGF-II. Both species take part in the processes of growth and development of the fetus; in the postembryonic period, IGF-I plays a major role in growth regulation. The physiological role of IGF-II in the postembryonic period of development has not yet been established. IGF-I carries out endo-, auto- and paracrine regulation of the processes of growth and development of the body. The concentration of IGF-I in the blood depends not only on the level of growth hormone, but also on a number of other hormones. STH, insulin, sex and thyroid hormones stimulate, and glucocorticoids suppress the production of IGF-I. This feature determines the synergism of the stimulating effect of growth hormone, insulin, sex and thyroid hormones on the processes of cell proliferation and differentiation and the inhibitory effect of glucocorticoids on the processes mentioned above. The mechanism of action of IGF, like insulin, is realized through the activation of MAPK and PDK signaling pathways. Insulin and somatomedins have a similar molecular structure, so insulin can cross-react with IGF receptors (IGF-R) and, conversely, IGF with IR. However, the affinity of insulin for its own receptors is 100-1000 times higher than for IGF-R. Therefore, insulin can stimulate cell proliferation and differentiation by binding to IGF-R only at high concentrations, which is characteristic of hyperinsulinemia.

Also, in hyperinsulinemia, the synthesis of IGF-binding protein by hepatocytes decreases, which increases the bioavailability of IGF, which at high concentrations is able to bind to IR.[11]

The effect of insulin on the risk of development and progression of breast cancer has been proven in several clinical studies.[12] In addition, hyperinsulinemia is an independent prognostic factor for the course of breast cancer, since its presence in this disease significantly reduces overall and recurrence-free survival, regardless of the tumor receptor status.[13]

Synergistic action of insulin and estrogen

Estrogens, interacting with estrogen receptors (ER), stimulate cell proliferation by activating MAPK and PDK signaling pathways. Insulin and IGF-I activate estrogen receptors in the nuclei of breast cancer cells and promote the growth and proliferation of ER-positive human breast cancer cell lines in vitro even in the absence of estradiol.[15,16] In ER-positive breast cancer cells of the MCF-7 line, IGF-I and estrogens have a synergistic effect, increasing the number of mitoses several times compared to the action of one of the factors, however, after the loss of ER, MCF-7 cells lose their ability to divide under the influence of estrogens and /or IGF-I.[17] Thus, insulin, IGF-I and estrogens synergistically stimulate the proliferative processes of mammary epithelial cells. Taking into account the fact that women with MS have hyperinsulinemia and hyperestrogenization, it seems quite logical to state that

there is an increased risk of developing and/or adverse course of breast cancer compared to women without MS due to the synergistic action of insulin, IGF-I and estrogens. However, this hypothesis requires a more detailed study in vivo.

The effect of hyperinsulinemia on the concentration of sex hormone-binding globulin

An increase in the concentration of insulin and IGF-I associated with MS leads to a decrease in the level of sex hormone-binding globulin (SHBG) in the peripheral blood.[18] The main function of SHBG is to bind circulating estrogens and testosterone, so when its concentration decreases, the amount of bioavailable sex hormones increases. In postmenopausal women, the risk of breast cancer is directly proportional to the concentration of bioavailable sex hormones and inversely proportional to the level of SHBG. This relationship is not seen in premenopausal women.[19]

SHBG can directly affect breast cancer cells by inhibiting estradiol-associated cell proliferation and neutralizes the anti-apoptotic effect of estrogens in the MCF-7 human breast cancer cell line.[20,21] Thus, SHBG, being a regulator of the bioavailability of sex hormones, plays one of the key roles in blocking the proliferative and antiapoptotic effects of estrogens on the mammary gland epithelium.

Role of adipokines in breast cancer carcinogenesis

In vitro studies have shown that the addition of adipose tissue during the cultivation of human breast cancer cell lines leads to an increase in cell proliferation and invasive potential, promotes angiogenesis, and suppresses apoptosis.[22,23] This effect of adipose tissue on breast cancer cells is realized due to its ability to produce biologically active substances - adipokines.

Adipokines (adipocytokines, adipose derived hormones) are biologically active substances that are produced by white adipose tissue cells and are involved in the regulation of cellular metabolism. Currently, the biological effects of most adipocytokines have been studied and it has been established that the following play the main role in the occurrence and progression of breast cancer: leptin, adiponectin (APN), tumor necrosis factor a (TNF-a) and interleukin-6 (IL-6).

Leptin is a hormone-like substance of the cytokine class, the main physiological function of which is appetite suppression (anorexigenic action). It is believed that leptin acts on the hypothalamus by blocking the synthesis and secretion of neuropeptide Y, which causes hunger. Congenital leptin deficiency in humans leads to the development of a severe form of alimentary obesity. However, in most cases, obesity is accompanied by a decrease in the sensitivity of hypothalamic receptors to the anorectic action of the hormone and thus causes compensatory hyperleptinemia. Leptin is also involved in many other processes, from reproduction and lactation to cell proliferation and differentiation.[6]

It has been experimentally proven that the addition of leptin during the cultivation of T47D.[24,25] and MCF-7.[26,27] cell lines of human breast cancer stimulates cell proliferation. By activating leptin receptors (Lep-R), which are expressed by breast cancer cells, this adipokine stimulates cell proliferation, migration, and invasion, and also suppresses apoptosis through MAPK-, STAT3-, and P13K-signaling pathways.[24-28] In addition to the direct mitogenic effect on the epithelium of the mammary gland, lep- tin stimulates the local synthesis of estrogens due to the aromatization of androgens; directly activates a-estrogen receptors (ERa), blocks their proteosomal degradation induced by ICI 182780, thereby reducing the effectiveness of breast cancer hormone therapy.[29]

Clinical studies have shown that the presence of Lep-R in breast cancer cells is associated with the presence of unfavorable prognostic factors for the course of the latter (large tumor size, the presence of metastases in regional lymph nodes), which in turn leads to a decrease in overall and relapse-free survival of patients.[30,31]

APN is an adipocytokine that is synthesized exclusively by adipocytes and has a pronounced anti-inflammatory and insulin-sensitizing effect.[32] Two types of APN receptors have been found in the human body: AdipoR1 and AdipoR2. AdipoRl express cells of various tissues, including the epithelium of the mammary glands. The highest amount of AdipoR2 was found in hepatocytes.[33] The role of APN in carcinogenesis has not been fully studied, however, the results of clinical studies indicate an increase in the risk of breast cancer with a decrease in the concentration of APN in blood plasma in patients with MS.[34,35] The mechanism of anticarcinogenic action is associated with the activation of adenosine monophosphate-activated protein kinase, which leads to cell retention in the Gl phase of the cell cycle, suppression of proliferation, and activation of apoptosis.[36] In addition, APN reduces the production of reactive oxygen species, inhibits MAPK activation, inhibits cell proliferation,[37] and inhibits tumor angiogenesis in vitro.[38]

TNF-a is a pro-inflammatory cytokine that is synthesized by macrophages, lymphocytes, and adipocytes. For a long time it was believed that the secretion of TNF-α by macrophages causes tumor necrosis.[39] However, the role of TNF-a in carcinogenesis has recently been revised. It has been established that this cytokine is actively involved in the induction of carcinogenesis and tumor progression.[40,41] TNF-a stimulates the formation of cyclooxygenase-2 (COX-2), an enzyme involved in the synthesis of prostaglandins. The latter activate epithelial growth factor, vascular endothelial growth factor, and IGF-I, which stimulate cell proliferation.[40,42,43] It has been clinically proven that an

increase in the concentration of TNF-α in the blood serum is associated with a decrease in the overall survival of cancer patients.[44]

IL-6 is a pro-inflammatory cytokine that is produced under physiological conditions by macrophages and T-lymphocytes and stimulates the maturation of B-lymphocytes. In obesity, the level of IL-6 in peripheral blood increases due to synthesis in adipocytes.[45] After IL-6 binds to its own receptors, MAPK, STAT3, and P13K signaling pathways are activated,[46] the role of which in carcinogenesis is described above. IL-6 also stimulates local estrogen synthesis due to androgen aromatization,[47] An interesting fact is that in the early stages of IL-6 inhibits the progression of breast cancer, however, an increase in its concentration in the blood serum of patients with metastatic breast cancer significantly worsens the prognosis of the latter.[48]

DISCUSSION

Taking into account all of the above, the negative impact of metabolic disorders caused by MS on the risk of occurrence and prognosis of the course of breast cancer is beyond doubt. Therefore, adequate correction of MS can be an additional direction of special treatment, as well as a measure of primary and secondary prevention of breast cancer.

As noted above, in postmenopausal women with MS, local hyperestrogenization is observed, which is a consequence of excessive synthesis of the aromatase enzyme by adipose tissue. Therefore, a possible method of preventing breast cancer in postmenopausal MS patients is the use of antiestrogen and aromatase inhibitors. Currently, antiestrogens such as tamoxifen are the first-line drugs in the treatment of ER-positive breast cancer. The direct mechanism of action of tamoxifen is due to its ability to cause proteosomal degradation of ERa. In addition, the antimitogenic effect of tamoxifen is realized by reducing the concentration of IGF-I in the peripheral blood.[49] However, since leptin can reduce the effectiveness of antiestrogen, the use of aromatase inhibitors in breast cancer patients with hyperleptinemia may be more effective. Although there are currently no clinical data to support this hypothesis.

Recently, metformin has been of great interest to oncologists. The results of several retrospective clinical studies indicate a more favorable prognosis for breast cancer in patients with type 2 diabetes treated with metformin.[50–52]

Leptin is a potential therapeutic target for the prevention and treatment of breast cancer. A pegylated leptin receptor antagonist (PEG-LPrA2) has been developed, the efficacy and safety of which is being tested in animals.[53]

The use of acetylsalicylic acid and other COX-2 inhibitors is another possible method of prevention, as it reduces the risk of breast cancer, which is due to the leveling of the mitogenic effect of pro-inflammatory cytokines (TNF-a, IL-6).[54-57]

Data on the mechanism of the effect of hyperinsulinemia and an increase in the concentration of IGF-I on carcinogenesis became the basis for the development of targeted drugs that block IGF-I receptors. These drugs are currently undergoing clinical trials.

In addition to medication, in order to reduce the risk and improve the prognosis of the course of breast cancer, in patients with MS, normalization of body weight, diet, and increased physical activity are important.[58,59]

REFERENCES

1. World Cancer Report. International Agency for Research on Cancer. 2008. http://www.iarc.fr/en/publications/pdfs-online/prev/handbook7/index.php. Retrieved, 2011-02-26.
2. International Diabetes Federation Epidemiology Task Force Consensus Group. The IDF consensus world wide definition of the metabolic syndrome. International Diabetes Federation. Brussels, 2005. (Available at: www.idf.org/webdata/docs/IDF Metasyndrome definition.pdf).
3. Agnoli C., Berrino F., Abagnato C.A. et al. Metabolic syndrome and postmenopausal breast cancer in the ORDET cohort: a nested case-control study. Nutr Metab Cardiovasc Dis, 2010; 20(1): 41—8.
4. Lipscombe L.L., Goodwin PJ., Zinman B. et al. The impact of diabetes on survival following breast cancer. Breast Cancer Res Treat, 2008; 109(2): 389—95.
5. Pasanisi P., Berrino F., De Petris M. et al. Metabolic syndrome as a prognostic factor for breast cancer recurrences. Int J Cancer, 2006; 119(1): 236—8.
6. Alimkhodzhaeva L. T. Immunomorphological changes in breast tumors during neoadjuvant chemotherapy under conditions of artificial hyperglycemia. Tumors of the female reproductive system, 2008; (2): 35-37. (In Russian)
7. Grodin J.M., Siiteri P.K., MacDonald P.C. Source of estrogen production in postmenopausal women. J Clin Endocrinol Metab, 1973; 36(2): 207—14.
8. van Landeghem A.A., Poortman J., Nabuurs M., Thijssen J.H. Endogenous concentration and subcellular distribution of estrogens in normal and malignant human breast tissue. Cancer Res, 1985; 45(6): 2900—6.
9. Bulun S.E., Simpson E.R. Breast cancer and expression of aromatase in breast adipose tissue. Trends Endocrinol Metab, 1994; 5(3): 113—20.
10. Dieli-Conwright CM, Mortimer JE, Schroeder ET, Courneya K, Demark-Wahnefried W, Buchanan TA, Tripathy D, Bernstein L. Randomized controlled trial to evaluate the effects of combined progressive exercise on metabolic syndrome in breast cancer survivors: rationale, design, and methods. BMC

Cancer, 2014 Apr 3; 14: 238. doi: 10.1186/1471-2407-14-238. PMID: 24708832; PMCID: PMC3985576.
11. Giovannucci E., Harlan D.M., Archer M.C. et al. Diabetes and cancer: a consensus report. CA Cancer J Clin, 2010; 60(4): 207-21.
12. Michels K.B., Solomon C.G., Hu F.B. et al. Type 2 diabetes and subsequent incidence of breast cancer in the Nurses' Health Study. Diabetes Care, 2003; 26(6): 1752-8.
13. Goodwin PJ., Ennis M., Pritchard K.I. et al. Fasting insulin and outcome in early- stage breast cancer: results of a prospective cohort study. J Clin Oncol, 2002; 20(1): 42-51.
14. Grimberg A., Cohen P. Role of insulin-like growth factors and their binding proteins in growth control and carcinogenesis. J Cell Physiol, 2000; 183(1): 1-9.
15. Moschos S.J., Mantzoros C.S. The role of the IGF system in cancer: from basic to clinical studies and clinical applications. Oncology, 2002; 63(4): 317-32.
16. Sachdev D., Yee D. The IGF system and breast cancer. Endocr Relat Cancer, 2001; 8(3): 197-209.
17. Clarke R.B., Howell A., Anderson E. Type I insulin-like growth factor receptor gene expression in normal human breast tissue treated with oestrogen and progesterone. Br J Cancer, 1997; 75(4): 251-7.
18. McTiernan A., Rajan K.B., Tworoger S.S. et al. Adiposity and sex hormones in postmenopausal breast cancer survivors. J Clin Oncol, 2003; 21(10): 1961 —6.
19. Zeleniuch-Jacquotte A., Shore R.E., Koenig K.L. et al. Postmenopausal levels of oestrogen, androgen, and SHBG and breast cancer: long-term results of a prospective study. Br J Cancer, 2004; 90(1): 153-9.
20. Fortunati N., Fissore F., Fazzari A. et al. Estradiol induction of cAMP in breast cancer cells is mediated by foetal calf serum (FCS) and sex hormone-binding globulin (SHBG). J Steroid Biochem Mol Biol, 1999; 70(1-3): 73-80.
21. Catalano M.G., Frairia R., Boccuzzi G., Fortunati N. Sex hormone-binding globulin antagonizes the anti-apoptotic effect of estradiol in breast cancer cells. Mol Cell Endocrinol, 2005; 230(1): 31-7.
22. Manabe Y., Toda S., Miyazaki K., Sugihara H. Mature adipocytes, but not preadipocytes, promote the growth of breast carcinoma cells in collagen gel matrix culture through cancer-stromal cell interactions. J Pathol 2003; 201(2): 221-8.
23. Iyengar P., Combs T.P., Shah S.J et al. Adipocyte-secreted factors synergistically promote mammary tumorigenesis through induction of anti-apoptotic transcriptional programs and proto-oncogene stabilization. Oncogene, 2003; 22(41): 6408-23.
24. Hu X., Juneja S.C., Maihle N.J., Cleary M.P. Leptin - a growth factor in normal and malignant breast cells and for normal mammary gland development. J Natl Cancer Inst, 2002; 94(22): 1704-11.
25. Laud K., Gourdou I., Pessemesse L. et al. Identification of leptin receptors in human breast cancer: functional activity in the T47-D breast cancer cell line. Mol Cell Endocrinol, 2002; 188(1-2): 219-26.
26. Dieudonne M.N., Machinal-Quelin F., Serazin-Leroy V. et al. Leptin mediates a proliferative response in human MCF7 breast cancer cells. Biochem Biophys Res Commun, 2002; 293(1): 622-8.
27. Okumura M., Yamamoto M., Sakuma H. et al. Leptin and high glucose stimulate cell proliferation in MCF-7 human breast cancer cells: reciprocal involvement of PKC-alpha and PPAR expression. Biochim Biophys Acta, 2002; 1592(2): 107—16.
28. Bjorbaek C., Uotani S., da Silva B. et al. Divergent signaling capacities of the long and short isoforms of the leptin receptor. J Biol Chem, 1997; 51(272): 32686-95.
29. Ando S., Catalano S. The multifactorial role of leptin in driving the breast cancer microenvironment. Nat Rev Endocrinol, 2012; 8(5): 263-75.
30. Karaduman M, Bilici A, Ozet A, Sengul A, Musabak U, Alomeroglu M. Tissue leptin levels in patients with breast cancer. J BUON, 2010 Apr-Jun; 15(2): 369-72. PMID: 20658737.
31. Jarde T., Caldefie-Chezet F., Damez M.et al. Leptin and leptin receptor involvement in cancer development: a study on human primary breast carcinoma. Oncol Rep, 2008; 19(4): 905-11.
32. Ouchi N., Kihara S., Funahashi T et al. Reciprocal association of C-reactive protein with adiponectin in blood stream and adipose tissue. Circulation, 2003; 107(5): 671-4.
33. Yamauchi T., Kamon J., Waki H. et al. The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. Nat Med, 2001; 7(8): 941-6.
34. Ye J, Jia J, Dong S, Zhang C, Yu S, Li L, Mao C, Wang D, Chen J, Yuan G. Circulating adiponectin levels and the risk of breast cancer: a meta-analysis. Eur J Cancer Prev., 2014 May; 23(3): 158-65. doi: 10.1097/CEJ.0b013e328364f293. PMID: 23929213.
35. Miyoshi Y., Funahashi T., Kihara S. et al. Association of serum adiponectin levels with breast cancer risk. Clin Cancer Res, 2003; 9(15): 5699-704.
36. Igata M., Motoshima H., Tsuruzoe K. et al. Adenosine monophosphate-activated protein kinase suppresses vascular smooth muscle cell proliferation through the inhibition of cell cycle progression. Circ Res, 2005; 97(7): 837-44.
37. Ouedraogo R., Wu X., Xu S.Q. et al. Adiponectin suppression of high-glucose- induced reactive oxygen species in vascular endothelial cells: evidence for involvement of a cAMP signaling pathway. Diabetes, 2006; 55(6): 1840-6.
38. Brakenhielm E., Veitonmaki N., Cao R. et al. Adiponectin-induced antiangiogenesis and antitumor activity involve caspase- mediated endothelial cell

apoptosis. Proc Natl Acad Sci USA, 2004; 101(8): 2476-81.
39. Carswell E.A., Old L.J, Kassel R.L. et al. An endotoxin-induced serum factor that causes necrosis of tumors. Proc Natl Acad Sci USA, 1975; 72(9): 3666-70.
40. Kulbe H., Thompson R., Wilson J.L. et al. The inflammatory cytokine tumor necrosis factor-a generates an autocrine tumor- promoting network in epithelial ovarian cancer cells. Cancer Res, 2007; 67(2): 585-92.
41. Davies F.E., Rollinson S.J., Rawstron A.C. et al. High-producer haplotypes of tumor necrosis factor a and lymphotoxin a are associated with an increased risk of myeloma and have an improved progression-free survival after treatment. J Clin Oncol, 2000; 18(4): 2843-51.
42. Ihnatko R, Kubes M. TNF signaling: early events and phosphorylation. Gen Physiol Biophys, 2007 Sep; 26(3): 159-67. PMID: 18063842
43. Balkwill F. TNF-a in promotion and progression of cancer. Cancer Metastasis Rev, 2006; 25(3): 409-16.
44. Il'yasova D., Colbert L.H., Harris T.B. et al. Circulating levels of inflammatory markers and cancer risk in the health aging and body composition cohort. Cancer Epidemiol Biomarkers Prev, 2005; 14(10): 2413-8.
45. Kishimoto T Interleukin-6: from basic science to medicine - 40 years in immunology. Annu Rev Immunol, 2005; 23(1): 1 —21.
46. Schafer Z.T, Brugge J.S. IL-6 involvement in epithelial cancers. J Clin Invest, 2007; 117(12): 3660—3.
47. Purohit A., Newman S.P., Reed M.J. The role of cytokines in regulating estrogen synthesis: implications for the etiology of breast cancer. Breast Cancer Res, 2002; 4(2): 65-9.
48. Bachelot T., Ray-Coquard I., Menetrier- Caux C. et al. Prognostic value of serum levels of interleukin 6 and of serum and plasma levels of vascular endothelial growth factor in hormone-refractory metastatic breast cancer patients. Br J Cancer, 2003; 88(11): 1721 —6.
49. Helle S.I., Holly J.M., Tally M. et al. Influence of treatment with tamoxifen and change in tumor burden on the IGF-system in breast cancer patients. Int J Cancer, 1996; 69(4): 335-9.
50. Wolf I., Sadetzki S., Catane R. et al. Diabetes mellitus and breast cancer. Lancet Oncol, 2005; 6(2): 103—11.
51. Goodwin PJ., Stambolic V., Lemieux J. et al. Evaluation of metformin in early breast cancer: a modification of the traditional paradigm for clinical testing of anti-cancer agents. Breast Cancer Res Treat, 2011; 126(1): 215-20.
52. Jalving M., Gietema J.A., Lefrandt J.D. et al. Metformin: taking away the candy for cancer? Eur J Cancer, 2010; 46(13): 2369—80.
53. Otvos L.J., Kovalszky I., Scolaro L. et al. Peptide-based leptin receptor antagonists forcancer treatment and appetite regulation. Biopolymers, 2011; 96(2): 117—25.
54. Terry M.B., Gammon M.D., Zhang F.F. et al. Association of frequency and duration of aspirin use and hormone receptor status with breast cancer risk. JAMA, 2004; 291(20): 2433—40.
55. Zhang Y., Coogan P.F., Palmer J.R. et al. Use of nonsteroidal anti-inflammatory drugs and risk of breast cancer: the Case-Control Surveillance Study revisited. Am J Epidemiol, 2005; 162(2): 165—70.
56. Garcia Rodriguez L.A., Gonzalez-Perez A. Risk of breast cancer among users of aspirin and other anti-inflammatory drugs. Br J Cancer, 2004; 91(3): 525—9.
57. DuBois R.N. Aspirin and breast cancer prevention: the estrogen connection. JAMA, 2004; 291(20): 2488—9.
58. McTiernan A., Irwin M., Von Gruenigen V. Weight, physical activity, diet, and prognosis in breast and gynecologic cancers. J Clin Oncol, 2010; 28(26): 4074—80.
59. http://repository.tma.uz/xmlui/handle/1/7104