

Breast Cancer in Patients with Gene Polymorphisms Associated with Metabolic Syndrome

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ABSTRACT

Each tumor is a combination of several dozen to several hundred potentially highly functional somatic mutation variants, along with a much larger number of potentially highly functional germ mutation variants. The combined action of all gene variations leads to the development and clinical diversity of malignancies. Their changes can lead to violations of gene expression and regulation and the appearance of proteins with altered functional properties. Polymorphism at the phenotype level is explained by the simultaneous existence of both a wild-type allele and a series of mutant alleles in the same population. Mutations change the gene product, and as a result, the functions of the gene product are changed. This can lead to changes in the phenotype.

Materials and methods: Markers are studied (single-nucleotide polymorphisms) in people with malignant neoplasms breast, associated with a metabolic syndrome, and also in representatives of test groups (malignant neoplasm without metabolic syndrome's), allowing predict association development of disease. The results are received thanks to examining of 250 patients.

Results: The association of polymorphism's rs11868035 ($p = 0.01481525$) based on 5 inheritance models' polymorphisms with a risk of development breast cancer glands in patients with a metabolic syndrome in Kazakh populations was identified.

Keywords: Personalized medicine, metabolic syndrome, malignant diseases, breast cancer, single-nucleotide polymorphisms (snp), genetic markers.

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INTRODUCTION

Analysis of factors, characterizing features of tumor development breast, capable to play the role in the pathogenesis diseases, allows to suggest, that breast cancer patients represent a heterogeneous group. In the etiopathogenesis of breast cancer the leading role traditionally assigns to hormonal factors. Alongside with hormonal changes factors, significant role is played by metabolic violations. However, during life simultaneous association of exo-endogenous factors happens. By these exogenous factors are capable to influence the systems of the body in such a way that launches endogenous machinery carcinogenesis's. There are two type of hormonal treatment carcinogenesis's: promoter and genotoxic. Promoters of carcinogenesis contribute to the growth of existing single tumor cells. In the genotoxic variant, hormones or their metabolic products behave like true carcinogens. The risk of converting a promoter variant to a genotoxic one increases when an enhanced hormonal signal is applied to the influence of certain environmental factors (for example, tobacco smoke) and to special periods of ontogenesis that contribute to the formation of so-called "edge effects" of hormones [1, 2].

It is proved that a significant role in the development of hyperplastic processes is played by a violation of the metabolism of sex hormones, a shift in the ratio between their individual fractions [3]. In this regard, special attention is paid to the state of equilibrium between two estrone metabolites: 1 BA-ON-estrone and 2A-ON-estrone [4]. One of them (1 BA-ON-estrone) is a Pro-oncogene, while 2A-ON-estrone has an antitumor effect [5].

It is possible that a violation of the balance between other metabolites of steroid hormones, not only estrogenic, but also androgens, progestins, and glucocorticoids may play a role in the formation and development of the tumor

process in the reproductive organs, including in breast tissues, which are hormone-dependent organs.

The concept of "metabolic syndrome" in Oncology suggests the relationship between metabolic syndrome, as a marker of extra-gonadal steroidogenesis, and cancer of the reproductive system. However, the description of specific clinical and metabolic disorders as manifestations of the metabolic syndrome in cancer of the reproductive system has not yet been completed. There is no clear opinion about the root cause of the metabolic syndrome - whether this condition is genetically predetermined or develops solely due to the influence of environmental factors [6].

A number of researchers believe that the development of the metabolic syndrome is due to the existence of one or a group of interacting genes that can simultaneously stimulate the development of all components of the syndrome [7]. A pathogenetic model that takes into account both the influence of genetic factors (oligo - and polygenic) and the impact of the environment is generally accepted [8]. The complex of causes: genetic defects, environmental influences-as a result, is realized in the development of the key pathogenesis of the metabolic syndrome, which, along with the listed factors, can be caused by hormonal and metabolic disorders [9].

According to scientists' calculations, the processes of glycolysis in tumor cells are about 200 times more intense than in normal tissues. An increase in the level of hormones blocks glycolysis, stimulates insulin resistance of tissues, and causes hyperinsulinemia with the possible development of diabetes [10-12]. The development of oval-shaped melanoma and choroidal nevus is associated with insulin resistance, metabolic syndrome, dyslipidemia, and low serum adiponectin in patients. Low levels of adiponectin and insulin resistance may play the

role of promoters of tumor growth with a more aggressive course and a worse prognosis [13].

Insulin resistance is not just associated with higher morbidity rates, but experimental and clinical models have already been developed that consider the molecular and genetic mechanisms of carcinogenesis in various malignant tumors and cell cultures against the background of insulin resistance and/or metabolic syndrome (MS) [14, 15].

Despite the fact that glucose metabolism is not the only signaling pathway for the effect of polychemotherapy on the tumor cell, oncologists are increasingly studying the quality of life of patients cured of cancer, focusing on the development of the metabolic syndrome in patients who received polychemotherapy and radiation [16, 17].

There is no doubt that there is an increasing cancer risk in postmenopausal women due to metabolic syndrome. More than 90% of cancer patients are over 45 years old. On the other hand, the lifetime risk of neoplasms is approximately 40% for men and about 50% for women [18]. The high incidence of neoplasms among the geriatric category of people, as well as the commonality of many mechanisms of carcinogenesis and aging, allowed us to classify tumors as "normal diseases of aging".

It is not surprising that almost all the "cancer theories" that appeared at different stages of cancer development included attempts to explain the Association of cancer incidence with old age. It seems appropriate to conditionally distinguish 2 groups of hypotheses among such concepts [19].

The first group includes theories that consider the phenomenon of accumulation of somatic mutations as the root cause of cancer. Their essence boils down to the fact that during the life of an organism, various genome disorders accumulate in cells. These genetic damages can occur both spontaneously and under the influence of carcinogens. The reason for the formation of a tumor is the appearance of an oncologically significant mutation (mutations) in a cell, which leads to the initiation of a transformed clone. The probability of the presence of such a genetic event increases steadily throughout the life of the body, so the incidence of tumors in older people is noticeably higher than in young people. If the accumulation of mutations is stimulated by exposure to environmental carcinogens (for example, tobacco smoke) or endogenous metabolites (for example, free radicals), as well as violations in the processes of DNA repair, the disease can manifest itself at a relatively early age [20 - 23].

The second group of hypotheses attached key importance to geriatric disorders of the host organism that contribute to the progression of the tumor clone. In particular, the immunological theory of cancer suggested that malignant cells "escape" from the body's protective factors due to age-related decline of the immune system. Other researchers have focused on hormonal and metabolic shifts that contribute to unregulated proliferation and differentiation processes in the elderly [24].

It is fair to note that modern views on age-related aspects of carcinogenesis recognize both the role of the mutation process as such, and the significance of predisposing (including age-related) changes in the body. However, today's ideas give a central place to the accumulation of genetic damage in the cell, and immunological, hormonal and metabolic disorders are most often considered as auxiliary factors.

Numerous studies have extensively studied the relationship between susceptibility to malignancy and

single-nucleotide polymorphisms (SNP) in excision repair genes. However, many questions remain due to insufficient samples and / or racial differences. The generalized clinical role of SNP genotyping in patients with malignancy is to detect people at high risk of the disease. People who are more likely to develop malignancy may choose to start screening and follow-up at an earlier age or at a higher frequency. In this group, it is also possible to apply preventive measures, including diet, lifestyle correction, and drug prevention.

The definition of SNP allows one to assess the probability of developing malignancy. Currently, they do not play the role of true diagnostic markers. As indicated by Klein *et al.*, there may be other clinical applications of SNP genotyping [25]. Theoretically, it can be used in combination with approved screening programs, increasing the prognostic role [26, 27]. Increasing knowledge about the role of SNP is of great interest, as it can play a crucial role in evaluating new biomarkers. Basic research has already identified several polymorphisms that play a role in the expression or function of hK2, β -MSP, Tmprss2 proteins and others [28 - 30], which can potentially have a significant impact on their role. This leads to the search for new biomarkers that can allow timely detection of the disease in clinical practice, stratify patients by risk groups, and monitor the course of treatment.

The above data show how complex and combined the clinical effects of genetic variation can be. Although these results are very interesting, it should be noted that the study groups of patients are very heterogeneous. This heterogeneity limits the interpretation of genetic variations in such clinical situations. Taking into account the above mentioned, the aim of the study was to determine single-nucleotide polymorphisms in breast cancer patients with metabolic syndrome in the Kazakh population, which allow predicting the risk of developing the disease.

RESULTS AND DISCUSSION

The panel of polymorphisms included polymorphisms localized in different regions of different chromosomes, as well as in different functional regions of genes and intergenic regions. When performing bioinformatic analysis, differences in significance levels were observed when calculating alleles and genotypes for the same polymorphisms. Therefore, it was necessary to evaluate the genotype-phenotype relationship taking into account different inheritance models. 5 inheritance models were used – 1 additive and 4 non-additives. Calculations were also made taking into account the fact that the reference (non-risky) allele may be a major allele (in most cases it is true), but also possibly a minor allele. Therefore, estimates are obtained for 2 variants. The analysis was performed in accordance with the case-control design based on the generalized linear model (GLM).

The results of statistical analysis of the genotype-phenotype association were obtained both without gender and age, and with gender and age, including the odds ratio and 95%CI. For each polymorphism, genotype-phenotype calculations were performed in two variations (either common or minor). This is due to the fact that it is necessary to determine which allele is risky, i.e. it is associated with the risk of developing diseases. The "default" calculations (group - common) imply that minor alleles are risky. You can expect that in most cases this may be true. However, there are situations where the risk allele is a major one for the population and the minor allele is a reference one for the calculation.

A study conducted in breast cancer patients with metabolic syndrome showed statistically significant differences in the replacement of single-nucleotide bases of the rs11868035 polymorphism ($p = 0.01481525$). According to the literature, case-control studies have identified a link between the minor allele (T-allele) rs11868035 and the risk of developing type 2 diabetes using an additive logistic regression model [31]. The minor T-allele rs11868035, was significantly associated with an increased risk of type 2 diabetes. These data are confirmed by International HapMap [32], where data were obtained on a high correlation of equilibrium coupling between rs11868035 and the G952G variant ($D'=1$ and $r^2=0.87$), which allowed the authors to suggest that the associations found in the study may be caused by rs11868035, and the G952G variant or the SREBF1c gene variant. The study [33] found a statistically significant association of sreb1c and rs11868035 polymorphisms with plasma triglyceride levels. Significant differences in genotype distribution and the frequency of rs11868035 minor alleles were observed between early onset amyotrophic lateral sclerosis (ALS) in women and the control group ($P = 0.001$ and $P = 0.002$). The minor "G" allele rs11868035 was associated with a reduced risk of amyotrophic lateral sclerosis in women (OR = 0,74 [0,59-0,93]) [34].

SREBF1 target genes are involved in cholesterol biosynthesis, unsaturated fatty acid biosynthesis, triglyceride biosynthesis, phospholipid synthesis, and lipid capture [35]. SREBF 1c rs11868035 polymorphism is associated with an increased risk of developing non-alcoholic fatty liver disease with impaired glucose metabolism and lipoprotein metabolism [36]. SREBP-1c modulates genetic predisposition to the full range of health risks associated with liver function, significantly affecting several stages of metabolism in the liver and outside the liver. SNP rs11868035, which is associated with impaired glucose and lipoprotein and adiponectin homeostasis in response to fat intake, correlated with the severity of steatosis and necroinflammation, as well as the presence of non-alcoholic steatohepatitis.

One of the significant risk factors for the development of malignant breast tumors is the background pathology of the liver, where inactivation of female sex hormones occurs, in particular estrogen, which is one of the most studied factors causing the development of breast cancer. Activation of fatty acid synthetase expression and fatty acid synthesis is common in breast cancer. Proteins that bind the Sterol regulatory element (SREBP) also regulate transcription factors involved in lipid metabolism. SREBP-1c expression is induced in the liver and adipose tissue by insulin and fasting and is crucial for the nutritional regulation of lipogenic gene expression. In contrast, increased fatty acid metabolism during the transformation of human breast epithelial cells and breast cancer cells *in vitro* is due to increased signaling by MAP kinase and PI3 kinase, which increases sreb1c levels. Sreb1c mRNA and fatty acid synthetases have been shown to be increased by H-ras transformation of MCF-10a breast epithelial cells and both are reduced by exposure to MCF-7 breast cancer cells with a MAP kinase inhibitor, PD98059, or PI3 kinase inhibitor. MRNA levels for fatty acid synthetase and SREBP-1c in human primary breast cancer samples show a significant increase than levels for SREBP-1a and SREBP-2, and are significantly correlated with each other, indicating regulation of SREBP-1c and fatty acid synthetase in breast cancer.

Literature data confirm the correlation between the replacement of single-nucleotide bases in the rs11868035 polymorphism, the presence of metabolic disorders and the risk of breast cancer in women of the Kazakh population.

CONCLUSION

As a result of the analysis based on 5 models of inheritance of polymorphisms and the risk of developing breast cancer in patients with metabolic syndrome in the Kazakh population, an association of polymorphism rs11868035 was revealed ($p = 0.01481525$). This marker can be used to predict the risk of developing breast cancer in a group of patients with breast cancer, but the study results are limited by the sample size. More research is needed to obtain conclusive evidence.

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REFERENCES

- Berstein L. M. Oncoendocrinology of Smoking, Saint Petersburg, 1995.
- Toniolo P. et al. // J. Natl. Cancer Inst. 1995. V.87. P.190—195.
- Kiselev V. I., Lyashenko A. A. Molecular mechanisms of regulation of hyperplastic processes, Moscow: Dimitrade Grafik Gruppov, 2005, 348 p.
- Kiselev V. I., Sidorova I. S., Unanyan A. L. et al. Hyperplastic processes of female reproductive system organs: theory and practice: monograph. Moscow: Medpraktika-M, 2011. 468 p. (in Russian)
- Berstein L. M. Hormonal carcinogenesis. St. Petersburg: Science, 2000. 199 p. (In Russ.)
- Perova N. V., Metelskaya V. A., Mamedov M. N., Oganov RG Methods for early detection and correction of the metabolic syndrome/ disease Prevention and health promotion. 2001. Vol. 4 (1). Pp. 18-31.
- Boitsov S. A., Goloshchapov A.V. the Relationship of the main parameters of metabolic cardiovascular syndrome with the degree of impaired carbohydrate metabolism and the severity of abdominal obesity in men. // Arterial hypertension. - 2003. - Vol. 9, No. 2. - Pp. 32-39.
- Borch-Johnsen K. The new classification of diabetes mellitus and IGT: a critical approach // Exp Clin Endocrinol Diabetes. - 2001. - Vol. 109. Suppl 2. - P. 86-93.
- Roydberg, G. E., Metabolic syndrome, Moscow: MED-press-inform, 2007, 224 p.
- Arshanskaya E. G., Semochkin S. V., Rumyantsev A. G. Quality of life of adolescents and young adults with long-term remissions of Hodgkin's lymphoma. Basic research and clinical practice. - 2014. - Vol. 7, No. 2. - P. 184-191.
- Hartman A., de Winkel M. L., van Beek R. D. et al. A randomized trial investigating an exercise program to prevent reduction of bone mineral density and impairment of motor performance during treatment for childhood acute lymphoblastic leukemia [Electronic resource] // *Pediatr. Blood and Cancer*. — 2009. — Vol. 53, № 1. — P. 64–71. — URL: doi: 10.1002/pbc.21942.

- 12 Gurney J. G., Kaste S. C., Liu W. et al. Bone mineral density among long-term survivors of childhood acute lymphoblastic leukemia: results from the St. Jude Lifetime Cohort Study // *Pediatr. Blood and Cancer.* — 2014. — Vol. 61, № 7. — P. 1270–1276. — URL: doi: 10.1002/pbc.25010.
- 13 Lowas S., Malempati S., Marks D. Body mass index predicts insulin resistance in survivors of pediatric acute lymphoblastic leukemia // *Pediatr. Blood and Cancer.* — 2009. — Vol. 53, № 1. — P. 58–63. — URL: doi: 10.1002/pbc.21993.
- 14 Zharkov P. A., Rumyantsev A. G., Novichkova G. A. Venous thrombosis in children with malignant neoplasms (literature review) // *Russian Journal of pediatric Hematology and Oncology*, 2015, no. 1, pp. 66-74.
- 15 Jarfelt M., Fors H., Lannering B., Bjarnason R. Bone mineral density and bone turnover in young adult survivors of childhood acute lymphoblastic leukaemia // *Eur. J. Endocrinol.* — 2006. — Vol. 154, № 2. — P. 303–309
- 16 Campbell L. K. et al. Executive function, coping, and behavior in survivors of childhood acute lymphocytic leukemia // *J. of Pediatric Psychology.* — 2009. — T. 34. — № 3. — P. 317–327.
- 17 Butler R. W. et al. Interventions to improve neuropsychological functioning in childhood cancer survivors // *Developmental Disabilities Research Reviews.* — 2008. — T. 14. — № 3. — P. 251–258.
- 18 Ries L.A.G., Kosary C.L., Hankey B.F., Hurray A., Miller B.A., Edwards B.K. (eds). SEER cancer statistics review, 1973-1993: tables and graphs, National Cancer Institute. Bethesda, 1996.
- 19 Anisimov V.N. Age as a risk factor in multistage carcinogenesis // In "Comprehensive Geriatric Oncology" (eds. Balducci L., Lyman G.H., Ershler W.B.), Harwood Academic Publishers. - 1998. - P. 157-178.
- 20 Anisimov V.N. Age as a risk factor in multistage carcinogenesis // In "Comprehensive Geriatric Oncology" (eds. Balducci L., Lyman G.H., Ershler W.B.), Harwood Academic Publishers. - 1998. - P. 157-178.,
- 21 G. Cortopassi, Liu Y. Genotypic selection of mitochondrial and oncogenic mutations in human tissue suggests mechanisms of age-related pathophysiology // *Mutat. Res.* - 1995. - Vol. 338. - P. 151 - 159.,
- 22 Nusbaum N.J. The aging/cancer connection // *Am. J. Med. Sci.* - 1998. - Vol. 315. - P. 40 - 49.,
- 23 Vijg J., Wei J.Y. Understanding the biology of aging: the key to prevention and therapy // *J. Am. Geriatr. Soc.* - 1995. - Vol. 43. - P. 426 - 434.
- 24 Anisimov V.N. Age as a risk factor in multistage carcinogenesis // In "Comprehensive Geriatric Oncology" (eds. Balducci L., Lyman G.H., Ershler W.B.), Harwood Academic Publishers. - 1998. - P. 157-178.
- 25 Klein RJ, Hallden C, Gupta A, et al. Evaluation of multiple risk-associated single nucleotide polymorphisms versus prostate-specific antigen at baseline to predict prostate cancer in unscreened men. 2012;61(3):471–477.
- 26 Gudmundsson J, Besenbacher S, Sulem P, et al. Genetic correction of PSA values using sequence variants associated with PSA levels. 2010;2(62)62ra92
- 27 Loeb S, Carter HB, Walsh PC, et al. Single nucleotide polymorphisms and the likelihood of prostate cancer at a given prostate specific antigen level. 2009;182(1):101–105.
- 28 Helfand BT, Loeb S, Hu Q, et al. Personalized prostate specific antigen testing using genetic variants may reduce unnecessary prostate biopsies. 2013;189(5):1697–1701.
- 29 Heidenreich A, Aus G, Bolla M, Joniau S. EAU guidelines on prostate cancer. 2008; 53:31–45.
- 30 Cooperberg MR, Carroll PR, Klotz L. Active surveillance for prostate cancer: progress and promise. 2011;29(27):3669–3676.
- 31 A.H. Harding, R. J. F. Loos, J. Luan, S. O’Rahilly, N. J. Wareham & I. Barroso Polymorphisms in the gene encoding sterol regulatory element-binding factor-1c are associated with type 2 diabetes. // *Diabetologia* 2006, volume 49, pages 2642–2648.
- 32 A haplotype map of the human genome. The International HapMap Consortium* // *Nature*, 2005, Oct 27; 437(7063): 1299–1320.
- 33 Vargas-Alarcon G, Gonzalez-Pacheco H, Perez-Mendez O, Posadas-Sanchez R, CardosoSaldaña G, Ramirez-Bello J, et al. SREBF1c and SREBF2 gene polymorphisms are associated with acute coronary syndrome and blood lipid levels in Mexican population. *PLoS ONE* 14(9): e0222017. <https://doi.org/10.1371/journal.pone.0222017>.
- 34 Xiao Qin Yuan et al. Association analysis of SNP rs11868035 in SREBF1 with sporadic Parkinson's disease, sporadic amyotrophic lateral sclerosis and multiple system atrophy in a Chinese population. // *Neurosci Lett.* 2018, Jan 18; 664:128-132. doi: 10.1016/j.neulet.2017.11.015. Epub 2017 Nov 8.
- 35 Shimano H. Sterol regulatory element-binding proteins (SREBPs): transcriptional regulators of lipid synthetic genes. *Prog Lipid Res.* 2001;40(6):439–452. doi: 10.1016/S0163-7827(01)00010-8; Bauer S, Wanninger J, Schmidhofer S, Weigert J, Neumeier M, Dorn C, et al. Sterol regulatory element-binding protein 2 (SREBP2) activation after excess triglyceride storage induces chemerin in hypertrophic adipocytes. *Endocrinology.* 2011;152(1):26–35. doi: 10.1210/en.2010-1157.
- 36 Musso G, Bo S, Cassader M, De Micheli F, Gambino R. Impact of sterol regulatory element-binding factor-1c polymorphism on incidence of nonalcoholic fatty liver disease and on the severity of liver disease and of glucose and lipid dysmetabolism. *Ame J Clin Nutr.* 2013;98(4):895–906. doi: 10.3945/ajcn.113.063792.