The role of Vitamin D3 in breast cancer prevention: A literature review

Relevance: Breast cancer is one of the most common malignancies with a high mortality rate worldwide, including in Kazakhstan. Despite modern advanced diagnosis and treatment methods, breast cancer remains one of the top three “killer cancers.” Treatment with immunoglobulins and modern targeted chemotherapy agents is efficient but does not reduce breast cancer incidence. High treatment cost, antitumor drug resistance occurring during therapy, and significant side effects of chemotherapy urge the importance of prophylactic actions to prevent the tumor disease.

The purpose of the study was to review the Vitamin D3 role and potential in breast cancer prevention.

Results: The analysis of the literature reviews and original articles accessing the Vitamin D3 role in breast cancer pathogenesis and the study of the main anti-tumor mechanisms of Vitamin D3 action emphasize the need for large randomized prospective studies to determine the actual Vitamin D3 role in breast cancer pathogenesis and its possible inclusion in antitumor therapy regimen.

Conclusion: The results obtained evidence on the Vitamin D3 adjuvant potential in breast cancer treatment.

Keywords: Breast cancer (BC), Vitamin D3, cancer prevention.

Introduction: In 2018, 4,648 new cases of breast cancer (BC) were registered in the Republic of Kazakhstan. Over five years, from 2014 to 2018, BC incidence increased by 12.2%. The average national mortality from BC remains quite high – 6.8 per 100,000 population, emphasizing the urgency of solving the BC problem in the country and the need for further research to identify its risk factors [1]. BC has a multifaceted etiology. Lifestyle and nutrition play an important role in addition to genetic predisposition. For many years, researchers are studying the role in cancer prevention of vitamins involved in metabolic control, defensive mechanisms in the body, and antitumor activity.

In many cases, oncologists recommend that patients with cancer reduce exposure to the sun. How justified is it from the perspective of the effect on the vitamin D3 level? A 12-week prospective cohort study in two regions of Australia in chemotherapy-naive BC patients showed a significant and faster vitamin D3 deficiency in those patients compared to healthy women [2]. Welsh notes the vitamin D3 reduced content and dysfunction during carcinogenesis [3].

The purpose of the study was to review the Vitamin D3 role and potential in breast cancer prevention.

Materials and Methods:
The 2010-2020 data obtained from the PubMed database were analyzed by keywords “breast cancer” and “vitamin d3”. The analysis revealed 52 review articles. This literature review includes 33 literary sources. These original scientific articles and reviews analyze the results to assess the vitamin D3 role in BC pathogenesis.

Results:
Numerous studies point at the relationship between the vitamin D3 level and the risk of BC. According to Rossi M. et al., women with a high vitamin D content in the diet are at a lower risk of developing BC [4]. A study conducted in Ireland in 2001-2011 included 5,417 women with BC aged 50-80. Those 2,581 women who started vitamin D3 supplements immediately after being diagnosed with BC showed a 20% reduction in the risk of cancer death. Women who started taking vitamin D3 supplements within 6 months after establishing the diagnosis showed a 49% reduction in BC progression risk (HR=0.51, 95% CI=0.34-0.74; p<0.001) [5].

A meta-analysis conducted by German scientists in 2014 on the results of five studies involving 4,413 BC patients showed that a high D3 level of 1,25 (OH) (>75 η mol/L) reduces the risk of death from BC by 42% (HR= 0.58, 95% CI=0.38-0.84) [6].

In a review published in 2016, E.T. Jacobs referred to four rigorous meta-analyses that included both case-control and prospective studies of the relationship between circulating 25 (OH) D concentrations and BC risk [7-10]. The authors mention the differences in the results obtained depending on the study type and design. A statistically significant reverse causality between 25 (OH) D and BC was found mainly in case-control studies. In contrast, prospective studies have shown no significant causality between 25 (OH) D and BC incidence. The researchers concluded that the vitamin D3 role in BC pathogenesis requires more careful study [11].

A meta-analysis of 68 studies published in 2018 pointed at the protective effect of vitamin D3 in BC. Ac-
According to the authors, the case-control studies showed a 35% reduction in the risk of BC formation (OR=0.65, 95% CI=0.56-0.76) as compared to the cohort studies – by 15% (RR=0.85, 95% CI=0.74-0.98). Notably, the protective relationship of vitamin D3 against BC with a 33% reduction in the risk of the disease remained only in premenopausal women (OR=0.67, 95% CI=0.49-0.92) [12]. Similar data were obtained from a meta-analysis published by Hossain et al. 2019 where vitamin D3 deficiency was directly linked to the BC risk [13].

A systematic review of Cochrane by Cardoso et al. (2014) involved patients taking vitamin D3 in various forms (cholecalciferol, ergocalciferol, alfacalcidol, or calcitriol) regardless of the dose, duration, and administration route. The patient data was compared to the placebo group of healthy adults receiving no treatment and adults with stabilized chronic diseases not associated with vitamin D3 metabolism. The analysis showed no conclusive evidence of vitamin D3 supplementation’s influence on cancer risk. However, there is a risk of type I errors due to small sample sizes and significant dropouts during the studies. Supplemental cholecalciferol resulted in a 12% reduction in cancer mortality (95% CI:2-22%), while the administration of other vitamin D3 forms reduced all-cause mortality by 7% (95% CI:2-12%). A combined administration of cholecalciferol and calcium supplements increased the incidence of kidney stone disease [14].

Vitamin D3 is a precursor of the potent steroid hormone calcitriol, and, unlike other vitamins, it has its receptor in tissues and its carrier protein. Therefore, vitamin D can be classified as a D-hormone able to generate and modulate biological responses in target tissues due to gene transcription regulation [15]. The effect of vitamin D on proliferation, apoptosis, and cell differentiation is one of the most studied issues in searching for mechanisms of this effect and evaluation of recent-year epidemiological studies. They have shown the vitamin D deficiency impacts the mortality of several non-communicable diseases, including cancer, namely BC, prostate, and colon cancer [16-21].

Vitamin D receptors are present in cells of various organs and tissues, and tumor cells. This fact, and the regulatory effect of vitamin D on cells without these receptors, suggest vitamin D inhibitory effect on proliferation, metastasis, neoangiogenesis, and invasion [22-24]. This means that D3 blood serum level may be associated with cancer risk prevention effect.

In his review of BC chemical prevention using vitamins and microelements, Mokbel et al. cited Simboli-Campbell et al., who indicated two main mechanisms of vitamin D3positive antitumor effect: an anti-proliferative effect of cell growth inhibition by suppressing signals stimulating the growth of receptors in breast tissue, and a pro-apoptotic effect that promotes the natural death of breast cells. Other researchers report similar findings [25-28].

Studying the mechanisms of vitamin D3 effect on the tumor process, Santos et al. (2017) indicated that vitamin D3 inhibits glycolysis, which is essential for cancer cells to maintain energy balance, growth, and survival. By inhibiting glycolytic enzymes, vitamin D3 reduces glucose uptake, induces apoptosis while significantly reducing cell viability. These vitamin D3 effects are consistent with a decrease in the expressed rapamycin (mTOR) that regulates glycolysis and cancer cell survival [29].

In their further studies of the vitamin D3 antitumor effect, these authors testified that vitamin D3 significantly reduces BC aggressiveness. Metastatic cancer cells have to acidify the extracellular environment to maintain an optimal pH for their growth, invasion, and metastasis. This process required overexpression of the V-H + -ATPase proton pump on the plasma membrane, which is in turn associated with high glycolytic flux, mTORC1 activation, and hypoxia. The V-H + -ATPase overexpression is peculiar to more aggressive BC phenotypes with more active metastasis, as evidenced by the studies on tumor models of different BC phenotypes, MB231 and MCF-7. Vitamin D3 inhibits the proton pump by suppressing the V-H + -ATPase function and expression in BC cells. Therefore, vitamin D3 is considered a non-toxic and widely used compound that significantly reduces cancer aggressiveness [30]. The above results evidence a therapeutic and prophylactic role of vitamin D3 in BC [29, 30].

Vitamin D3 is a known participant in minerals and bone homeostasis. In the past, it was mainly used to treat osteoporosis and rickets. In recent years, vitamin D3 immunomodulatory activity was established. It can play a certain role in several diseases, including autoimmune diseases. Immunological and rheumatological diseases were studied first, but the current focus is on the interaction between vitamin D3 and tumor cells [31].

A study by Bouvard et al. on the treatment of osteoporosis in 450 postmenopausal women suffering from luminal BC treated with aromatase inhibitors for ten years showed vitamin D3 deficiency in 11.3% of cases. According to the study results, the age at the time of cancer diagnosis (HR=1.07, P≤0.01) and vitamin D3 deficiency (HR=1.85, P=0.04) was associated with increased risk of mortality for that patient group. This correlates with the response to osteoporosis treatment with bisphosphonates in the case of vitamin D3 inclusion in women receiving aromatase inhibitors for BC. Vitamin D3 inclusion in the treatment regimen for bone metastases led to a 50% reduction in the risk of recurrence and mortality. According to the authors, vitamin D3 receptors in BC cells act as nuclear transcription factors. They regulate gene activity and determine the prognostic role of vitamin D3 in BC [32].

Bone softening, a complication in treating bone metastases, is another important factor in the vitamin D role in cancer patients. In BC, osteoporosis (bone softening) and bone metastases are very frequent, so this problem is urgent. Studies have shown that a lack of vitamin D3 is a risk factor for developing jaw osteo-
necrosis associated with bisphosphonates. In vitamin D3 deficiency, oral and parenteral bisphosphonates should not be used until this deficiency is eliminated. Not all doctors are aware of this fact. Osteonecrosis in patients receiving treatment with bisphosphonates without correcting the vitamin D3 level is quite frequent in recent years. This can be explained by the wide availability of bisphosphonates and the lack of doctors’ vigilance regarding vitamin D3 level control. Administering bisphosphonates without vitamin D control often leads to osteonecrosis of the lower jaw bone. All cancer patients, in particular cancer patients with nutritional deficiencies, should be monitored for the vitamin D3 status and receive adequate vitamin D3 supplementation [33].

Conclusion:
The accumulated data on the vitamin D3 role in the human body, its correlation with the development and course of cancer pathologies suggest a promising role of vitamin D3 deficiency correction in cancer prevention and complex treatment. However, not all studies prove the correlation of low vitamin D3 levels with BC incidence and poor prognosis. This issue requires large prospective randomized studies.

References:
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Сут безі қатерлі ісігінің алдын алуға Д3 дәруменің ролі: Әдебі шолу

Выводы: Был вклад бойынша, оның ішінде Қазақстан-Республикасында сут безі қатерлі ісігі (СБҚІ), Д3 дәрумені, аткырған және сүт безі қатерлі ісігінің Д3 дәруменің рөлі: әдебі шолу

АКТУАЛЬНОСТЬ: Во всём мире и в Казахстане рак молочной железы (РМЖ) является одним из наиболее распространённых злокачественных заболеваний с высоким уровнем смертности. Несмотря на современные передовые методы диагностики и лечения, РМЖ остаётся в тройке лидеров «раков-убийц». Как и другие виды злокачественных заболеваний с высоким уровнем смертности. Высокая стоимость лечения, устойчивость к противоопухолевым препаратам, развивающаяся в процессе терапии, и, наконец, побочные эффекты химиотерапии подчеркивают важность проведения профилактических мероприятий, позвоночущих предотвратить развитие опухолевого заболевания.

Цель настоящего обзора — оценить значение и место витамина Д3 в профилактике рака молочной железы: Обзор литературы

Роль витамина Д3 в профилактике рака молочной железы: Обзор литературы

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Сут безі қатерлі ісігінің алдын алуға Д3 дәруменің ролі: Әдебі шолу

Опциетнін: Бұғыры алып бойынша, оның ішінде Қазақстан-Республикасында сут безі қатерлі ісігі (СБҚІ), Д3 дәрумені, аткырған және сүт безі қатерлі ісігінің Д3 дәруменің рөлі: әдебі шолу

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