International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Scholarly Publisher
RS Global Sp. z O.O.
ISNI: 0000 0004 8495 2390

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ARTICLE TITLE	THE IMPACT OF SELENIUM SUPPLEMENTATION ON HUMAN HEALTH AND THE COURSE OF DISEASES, INCLUDING BREAST CANCER PREVENTION AND TREATMENT
DOI	https://doi.org/10.31435/ijitss.3(47).2025.3709
RECEIVED	24 July 2025
ACCEPTED	10 September 2025
PUBLISHED	22 September 2025
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THE IMPACT OF SELENIUM SUPPLEMENTATION ON HUMAN HEALTH AND THE COURSE OF DISEASES, INCLUDING BREAST CANCER PREVENTION AND TREATMENT

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ABSTRACT

Introduction and purpose: Selenium is a trace element that plays a huge role in the human body. It acts mainly through enzymes—selenoproteins—which protect cells from oxidative stress, participate in thyroid hormone metabolism, and also have anti-inflammatory properties. The aim of this review is to discuss the impact of selenium levels and the effects of selenium supplementation on human health, including breast cancer prevention and treatment.
Description of the state of knowledge: Selenium supplementation plays an important role in thyroid diseases and may influence the development and course of type II diabetes, neurological and psychiatric diseases. Selenium and its supplementation have been shown to influence female and male fertility, as well as the course of pregnancy and the health of the mother and fetus. Selenium is involved in the activation of the immune system and has the ability to modulate lipid metabolism, which is beneficial in cardiovascular diseases. Research is ongoing on the effect of selenium supplementation in the prevention and treatment of cancer, including breast cancer. Some studies show a reduction in incidence and improved prognosis in patients supplementing with selenium.
Conclusions: Current data from numerous studies indicate the benefits of selenium supplementation, especially in patients with selenium deficiency. Further detailed clinical and experimental studies on large groups of patients are needed to confirm the effectiveness and clearly determine the potential benefits or harms associated with selenium supplementation in various health conditions.

KEYWORDS

Selenium, Selenoproteins, Human Diseases, Breast Cancer

CITATION

Ziomek Weronika, Koss Magdalena, Bebrysz Elżbieta, Bartnik Piotr, Baran Jarosław, Dębek-Kalinowska Karolina, Palmi Jan, Dunder Ida, Biszewski Mateusz, Drabik Aleksandra. (2025) The Impact of Selenium Supplementation on Human Health and the Course of Diseases, Including Breast Cancer Prevention and Treatment. *International Journal of Innovative Technologies in Social Science*. 3(47). doi: 10.31435/ijitss.3(47).2025.3709

Introduction and Aim

Selenium is one of the most important trace elements necessary for the proper functioning of the human body. As a component of selenoproteins, it performs important functions, is responsible for maintaining redox balance and regulating inflammatory processes. Selenium also has broad immunomodulatory and neuroprotective properties. There is growing interest in the potential benefits of selenium supplementation in the prevention and treatment of many chronic diseases, including thyroid disorders, cardiovascular diseases, metabolic disorders, and certain cancers.

The aim of this article is to provide an overview of the current state of knowledge on selenium supplementation, its impact on human health, the course of diseases with a focus on breast cancer.

Material and Methods

The review was based on articles from PubMed and Google Scholar databases. Key search terms were: selenium, selenoprotienes, human diseases, breast cancer. Articles written since 2020 were selected, of which 1 was older (2017). This time frame was chosen to ensure that the article was as up-to-date as possible.

Description of the state of knowledge

Selenium

Selenium is a trace element that plays an important role in the body. In nature, it occurs in two forms: organic as selenocysteine and selenomethionine, and inorganic as selenate and selenite. Compared to the inorganic form, the organic form is associated with better bioavailability (inorganic 80-85%, organic 90-95%)

and less toxicity - a fact that may be important when developing new supplements and guidelines for selenium supplementation. [1]

Absorption of selenium occurs mainly in the duodenum of the small intestine. The mechanism of absorption depends on the form of selenium, e.g.: selenite is absorbed by simple diffusion, while selenate is absorbed by sodium selenate cotransport and active sodium transport pump. Selenium deficiency is more common in patients with malabsorption syndrome, mainly caused by surgical resections of the stomach and small intestine. [2] Selenomethionine, the main nutritional form of selenium, cannot be synthesized by higher organisms. Selenomethionine synthesis is based on plants and fungi. [3]

Sources of selenium

Selenium concentrations vary among foods: animal origin > vegetables > cereals > fruits. [3] Meat is a source of relatively high amounts of Se (selenium content ranges from 0.08 to 0.7 μg/g). Particularly rich in selenium are offal (animal organs - livers, kidneys, hearts). Vegetables and fruits contain selenium in amounts less than 0.1 μg/g. Brazil nuts are a good source of the element. Cereals are a major source of selenium, even though their selenium content is relatively low. [1,3] Other sources of the micronutrient include eggs, milk and dairy products, fish and seafood, and mushrooms. The amount of selenium contained in foods can vary depending on a number of factors, including the soils and growing conditions in which the crops used to make bread and cereals are grown, the feed consumed by animals, and the processing of these foods for human consumption.

Selenoproteins

Selenium exerts its biological function through selenocysteine and selenomethionine. The human genome encodes 25 selenoproteins. These are proteins that contain selenocysteine in their active sites, essential for their activity. [3,4,5] Selenoproteins are found in various organs and tissues and have different specific substrates and functions. Among the most important selenoproteins are:

- glutathione peroxidases(GPX) are antioxidant enzymes with a key role in protecting cells from oxidative stress. They are responsible for the reduction of hydrogen peroxide (H2O2) to water, which prevents oxidative damage to cells; they catalyze the reduction of lipid peroxides, protecting cell membranes, and maintain the balance of glutathione in cells [1,6]
- thioredoxin reductases (TXNRD) are key enzymes in the thioredoxin system that have important functions in regulating the redox state in the cell and protecting against oxidative stress. The main functions of TXNRD include - reduction of oxidized thioredoxin (Trx) to its reduced form, allowing it to carry out reduction reactions again, regulation of inflammatory processes and apotosis [5]
- Iodothyronine deiodinases (DIOs) play a key role in thyroid hormone metabolism by controlling their activation and inactivation at the cellular and systemic levels. DIO1 and DIO2 convert inactive thyroxine (T4) into biologically active triiodothyronine (T3), while DIO3 inactivates thyroid hormones: converting T4 to rT3 and T3 to inactive T2. DIO3 has an important protective function against excessive tissue exposure (especially during development) to active thyroid hormones. [1,5]
- Selenoprotein P (SELENOP) is responsible for the transport of selenium from the liver to other tissues, exhibits activity similar to glutathione peroxidase, protects cells from oxidative stress

Supplementation

Although selenium is present in very low concentrations in the human body, selenium deficiency can cause dysfunction in various systems, which is why supplementation of this element in people with selenium deficiency can play such a great role in human health. With proper doses, supplementation with this element is associated with a better prognosis and a reduced risk of developing many diseases. Supplementation should take into account the patient's baseline selenium concentration. Excessive supply should be avoided. Supplementation should be considered mainly in patients with low selenium intake or low plasma selenium levels. According to studies, selenium intake of 55 μg/day or more reduces the risk of cancer. In adults, maximum saturation of selenoprotein P occurs at a serum selenium level of about 110 μg/L. [7] In 2022. EFSA's Panel on Nutrition, Novel Foods and Food Allergens (NDA), concluded that a tolerable upper intake level (UL) for selenium of 255 μg Se/day is safe for adult men and women (including pregnant and lactating women). During the study, a non-linear U-shaped relationship was observed between selenium concentration/supplementation and beneficial effects. Individuals with low baseline selenium levels at the start

of the study may benefit from supplementation; however, those with adequate or high baseline status or with too much supplementation may experience negative effects. [4] At high intakes above 330 to 450 μg/day, selenium can cause toxic effects, affecting the liver, peripheral nerves, skin, nails and hair. [7]

Selenium supplementation in thyroid disease

Selenium is a trace element essential for the synthesis of thyroid hormones. Enzymes such as glutathione peroxidase (GPX), thioredoxin reductase (TXNRD) and iodothyronine deiodinase (DIO), play an important role in human thyroid function - affecting increased antioxidant activity (IL-10, SOD and TAC), reduced inflammatory and oxidative activity (IL-2, MDA, IFN-γ and TNF-α), and help manage oxidative stress in thyrocytes. [8,9,10].

It has been studied that underlying thyroid diseases may be deficient in selenium, among other things, so selenium supplementation may show promise for the prevention or treatment of these diseases. [8,10]

Many studies have been conducted on selenium supplementation for Hashimoto's disease. Huwiler VV et al. 2024 conducted an updated systematic review and meta-analysis of randomized controlled trials (RCTs) examining the effects of selenium supplementation on Hashimoto's disease. They showed a significant reduction in TSH levels after selenium supplementation for patients not treated with thyroid hormones. In the case of patients taking thyroid hormones, it was difficult to interpret TSH, since the level depended mainly on the doses of hormone replacement. However, a consistent reduction in TPOAb levels, observed after several months of selenium supplementation, was noted in both groups of patients. This reduction may be related to the antioxidant and anti-inflammatory role of selenoproteins. There was no statistically significant effect on fT4, fT3, T4, T3, TGAb, thyroid volume. Selenium supplementation was well tolerated, as evidenced by the lack of significant differences in adverse events between the selenium and placebo groups. [8] Selenium supplementation has shown particular promise in euthyroid or subclinical hypothyroid subjects, with a protective effect of Se observed in reducing the development of overt hypothyroidism. [11]

Selenium supplementation is also being studied in the context of Graves' disease and thyroid orbitopathy. A study by Gallo D et al. found that selenium and vitamin D supplementation facilitated the restoration of euthyroidism during Metimazole treatment. [12] Other studies have observed an alleviation of symptoms associated with hyperthyroidism and an improvement in patients' quality of life. However, there are no clear conclusions or clinical indications on the effect of supplementation on Graves' disease. Promising results, however, have been provided by studies of selenium supplementation in patients with thyroid orbitopathy, suggesting that selenium may improve quality of life and the course of orbitopathy, and may protect against progression to a more severe form of the disease. [9,13] Selenium has been shown to have beneficial effects on orbital fibroblasts, can inhibit the release of pro-inflammatory factors and hyaluronic acid, reduce the toxic effects of reactive oxygen radicals, and directly affect sympathetic tension in the opercular muscles and reduce inflammation in the eyelid muscles. [9]

It is advisable to individualize supplementation decisions, especially in populations with selenium deficiency or high levels of antithyroid antibodies, and to conduct further research on this topic.

Selenium supplementation during preconception and pregnancy

Selenium is an important micronutrient associated with the proper functioning of the gonads, and has implications for female and male fertility, fetal development, pregnancy complications and the health of the baby after birth.

Selenium in the ovaries is localized in healthy pre-ovulatory follicles in close contact with the pre-ovulatory oocyte, which may play a preparatory role for subsequent fertilization and embryo development. [14] Selenium deficiency may be associated with implantation failure, miscarriage. It can also be a cause of unexplained infertility. In in vitro studies in animal models, the addition of selenium to culture media has been shown to improve embryo development and survival, which is associated with reduced reactive oxygen species and less DNA damage. [14] Selenium has also been shown to control the development of granulosa cells and the biosynthesis of one of the major female sex hormones, 17-estradiol (E2) in adult ovaries in vitro. [1]

Selenium also plays an important role in male fertility. In the testes, selenium is found in the seminal tubule, where sperm are produced, as well as in the interstitial space, where testosterone production occurs and where the blood supply is located. [14] Selenium improves the activity of glutathione peroxidase, which protects sperm from oxidative damage to their cell membranes and DNA. [14] In selenium-supplemented men, sperm quality parameters including sperm count, morphology and motility improved compared to the control

group. [1] These findings confirm that selenium supplementation can have a positive impact on male reproductive health by reducing oxidative stress.

During pregnancy, selenium levels in the blood drop mainly due to transport to the developing fetus. Studies suggest that Se deficiency is associated with an increase in inflammatory factors,and this is associated with a variety of pregnancy disorders, including miscarriage, preeclampsia, gestational diabetes, pregnancy-induced hypertension, neural tube defects, postpartum depression, premature rupture of membranes and preterm labor. [15,16] Many studies confirm that selenium supplementation during pregnancy is important for reducing maternal oxidative stress and has beneficial effects for both mother and fetus. To optimize the antioxidant potential of GPX, serum Se levels should ideally reach about 100 μg Se/L. [16] A study by Mesdaghinia E. et al. observed that selenium supplementation reduced the risk of pregnancy complications in women at risk for intrauterine growth restriction. [17]. Selenium supplementation helps reduce postpartum thyroid dysfunction. [15] It also influences the growth of the placenta, which partly explains its effects on fetal growth and development, as well as developing the mammary gland, improving lactation performance and colostrum composition.

The results of the study indicate that selenium levels and glutathione peroxidase activity, correlate with anthropometric parameters of the newborn, such as birth weight, length and APGAR score at birth, especially in pregnancies with a physiological course. [18] The findings provide consistent evidence that selenium deficiency in pregnancy may be a risk factor for ADHD and ASD features. Research on this topic should be confirmed by further studies on this topic. [18] Selenium deficiency has also been linked to the development of cretinism, as it shows a direct relationship with iodine in the body during hormone conversion. [19]

The optimal dose and duration of supplementation in pregnancy is still the subject of ongoing research to better tailor guidelines and recommendations for taking selenium during pregnancy. [20]

Selenium supplementation in cardiovascular disease

Oxidative stress impairs endothelial cell function, contributing to the onset and progression of some cardiovascular diseases. Studies prove that active selenoprotein redox GPxs and TrxRs protect the cardiovascular system by preventing or modulating oxidative stress and oxidative lipid modification, reducing inflammation, and reducing platelet aggregation, which are major risk factors for coronary heart disease. [3] Suboptimal selenium levels (<100 μg/L) are common in more than 70% of patients with heart failure and have been associated with lower exercise capacity, lower quality of life and worse prognosis. Clinical trials evaluating selenium supplementation in patients with HF have shown improvements in clinical symptoms (NYHA class), left ventricular ejection fraction and lipid profile. [5] It has been studied that subjects with confirmed selenium deficiency with D-dimer levels above the median relative to baseline had significant benefits from selenium supplementation at 200 μg/day along with CoQ10 200 mg/day, resulting in lower cardiovascular mortality compared to the placebo group. [21] In two Finnish observational studies, low serum selenium levels (<45 μg/L) were associated with an increased risk of cardiovascular death. [7] In another study, 24-week selenium supplementation in hemodialysis patients with diabetes had beneficial effects on markers of insulin metabolism, total cholesterol, LDL cholesterol, HDL cholesterol, CRP cholesterol and GSH cholesterol compared to placebo. [22] Yet another study found that Se supplementation increased GPx1 activity in whole blood and reduced mortality after myocardial infection with Coxsackie B3 virus. [6] Several studies suggest that patients with selenium levels <100 μg/L should be focused on, as they may benefit most from supplementation. [5]

Selenium supplementation in diabetes

In light of recent studies, selenium supplementation may also bring positive effects in patients with insulin resistance and type II diabetes. Mechanisms for the benefits of selenium supplementation include reduced oxidative stress, improved selenoprotein function (including glutathione peroxidase), modulation of inflammatory processes, and beneficial effects on insulin sensitivity. [29] According to a 2022 study, selenium supplementation significantly reduces fasting insulin levels and the HOMA-IR insulin resistance index. [30] A study by Mohammadparast V et al. on selenium supplementation in combination with probiotics reports that it leads to a significant reduction in fasting glucose (by an average of 4.02mg/dL), insulin (-2.50mIU/mL) and the HOMA-IR insulin resistance index (-0.59). An increase in the QUICKI insulin sensitivity index was also observed at that time. [31]

Indications are that the effects of supplementation are most pronounced in those with low baseline selenium levels or deficiency, while in those with normal or elevated selenium saturation, the effects may be less pronounced or even negative. Moderate doses of selenium up to 200 μg/day have the greatest benefit in lowering glycemia, while doses above this range do not improve the effect, and in some studies high doses may be associated with the risk of adverse metabolic effects. [29,32]

Due to the paucity of research in this aspect, no guidelines for clinical practice can be firmly established; therefore, further, larger, longer, pragmatic studies are needed to reach a decisive conclusion. [29]

Selenium supplementation in neurological and psychiatric diseases

Selenium supplementation, effectively raises selenium levels in serum, plasma or cerebrospinal fluid, and improves the activity of glutathione peroxidase (GPx), a key antioxidant enzyme that protects brain tissues from oxidative damage. It is recognized that improving selenium status and selenoenzyme activity may have the effect of reducing oxidative stress and inflammation in the central nervous system, which underlies the pathogenesis of Alzheimer's disease and cognitive impairment. In studies involving supplementation with selenium inclusive or selenium together with other micronutrients, improvements in cognitive function and performance on cognitive tests have been observed in patients with MCI, as well as increases in Mini-Mental State Examination (MMSE) scores in patients with Alzheimer's disease. [23] Selenium supplementation has neuroprotective effects. It turns out that starting supplementation even after an incident of cerebral ischemia (ischemic stroke), shows long-term and multidirectional neuroprotective effects. This means that selenium significantly reduces damage and improves survival of nerve cells after hypoxic-ischemic brain damage. [24] A study by Leiter O. et al. noted that selenium administration, either by infusion or oral supplementation, stimulates neurogenesis, increasing proliferation and differentiation of precursor cells in the hippocampus of adult individuals. The mechanism is based on the activation of selenium transport by selenoprotein P (SEPP1) into neurons, which promotes their regeneration and the formation of new nerve cells. The supply of the micronutrient mimics the neuroprotective effects of exercise - it counteracts cognitive impairment resulting from aging or damage to the hippocampus. [25]

Selenium, through its antioxidant and anti-inflammatory properties, can support the therapy of psychiatric disorders, e.g. depression, anxiety disorders, bipolar disorder or schizophrenia, and improve the prognosis in these patient groups. Supplementation should be considered especially in individuals at risk of Se deficiency or with an increased need for this element (e.g., postpartum women) - individuals with these disorders often have increased oxidative stress and chronic inflammation, neurotransmitter abnormalities that can affect the severity of psychiatric symptoms. [26] In addition, an inverse relationship between GPx activity in blood and structural grades of brain atrophy has been observed in a population of patients with chronic schizophrenia, suggesting a potential link between redox dysregulation and neurodegeneration. [4]

Selenium supplementation and immunity

Selenium also plays an important role in the functioning of the immune system. Selenium supplementation stimulates the activation of various immune system cells, including T lymphocytes, macrophages, NK cells, dendritic cells and neutrophils. Low blood selenium levels are associated with a weakened immune system. [27] Selenium participates in the regulation of both innate and acquired immunity, supporting the body's immune responses. [1] Selenium's protective effects on the immune system are mediated by selenoproteins with redox functions, such as glutathione peroxidase (GPx) and thioredoxin reductase (TXNRD). They protect immune cells from oxidative stress and damage caused by oxygen free radicals. Selenium regulates inflammation by affecting macrophage polarization, promoting their transition from a pro-inflammatory M1 phenotype to an anti-inflammatory M2 one. Selenium improves T-cell proliferation and differentiation and stimulates T-cell-dependent immune responses. Multinomic analyses have shown that Crohn's patients are deficient in selenium, which promotes excessive differentiation of Th1 cells - the type of T cells responsible for the pro-inflammatory immune response characteristic of the disease. Selenium supplementation significantly reduced the development of symptoms and the course of Crohn's disease in experimental models by suppressing excessive activation of Th1 cells and thus the inflammatory process. Selenium supplementation can significantly reduce IFN-γ expression in Th1 cells. [28] In animal models and clinical studies, selenium deficiency has been shown to be associated with atrophy of lymphoid organs (lymph nodes, spleen, thymus) and impaired immune response. [1]

Selenium supplementation and cancer

The role of selenium supplementation has also been found in the context of fighting cancer. It exerts its effects primarily by maintaining normal redox homeostasis and error-free protein folding, mainly through the selenoproteins glutathione peroxidases (GPxs), thioredoxin reductases (TrxRs) and selenoprotein P (SelP, SeP or SELENOP), which prevent DNA mutagenic stress. [4] Other functions include modulation of gene expression, redox and hormonal regulation of metabolism, and a role in DNA repair and cell signaling pathways. Selenoproteins act at various key levels: inhibiting cell proliferation, stimulating apoptosis, arresting the cell cycle, through redox modification of protein thiols and methionine mimicry in critical proteins. [4] Selenium can inhibit angiogenesis (formation of new vessels for the tumor) and metastasis. It interacts with a number of molecular pathways by, among others, reactions involving selenoenzymes (e.g., glutathione peroxidase), activates immune cells (e.g., M1 macrophages and CD8+ lymphocytes), and enhances the production of pro-inflammatory cytokines such as interferon-gamma. [33] Selenium proves itself as a potential chemosensitizer and radiosensitizer - enhancing the effectiveness of standard chemotherapy/radiotherapy while protecting healthy cells from the toxic effects of anticancer drugs. Experimental work suggests that selenium may mitigate the side effects of cancer therapies. [34] Supplementation has been shown to have a bidirectional (bimodal) dose-dependent effect in the context of cancer: At low, physiological doses, selenium acts as an antioxidant, promoting the survival and proper functioning of immune cells. This supports cancer prevention effects. In contrast, high, pharmacological doses exhibit pro-oxidant effects - inducing redox signaling and cell death, including cancer cells. Thus, selenium may not only have a prophylactic effect, but also support cancer therapy. [33]

Selenium supplementation in the prevention and treatment of breast cancer

Breast cancer ranks among the leading causes of cancer-related deaths in women worldwide (approximately 600,000 deaths per year). [35] Research is constantly underway to improve existing therapies, reduce toxicity, and improve their efficacy (e.g., through combination therapy with other anticancer substances). New therapies are also being sought. Low selenium levels have been linked to a high incidence of several different types of cancer, including breast cancer, as well as cancer mortality. [36] As a result, studies have been conducted for years examining the impact of selenium levels and supplementation in this group of patients.

An analysis of NHANES data involving more than 25,000 women, conducted between 1999 and 2020, found that higher dietary selenium levels were associated with a statistically significant reduction in breast cancer risk. [37] A study by Cheng J et al. also confirms a protective, causal relationship between higher blood selenium levels and a lower risk of breast cancer, especially in women with low baseline selenium levels. [38] A study conducted in Poland, a country low in soil selenium, examined the effect of selenium levels on 10-year survival in breast cancer patients. It was then confirmed that low selenium levels may contribute to poorer survival in women - the 10-year survival rate was 57.1% for women with selenium levels in the lowest quartile, compared to 86.7% for women in the highest quartile. [36]

One study has shown that selenium - whether used supplementally or pharmacologically - may be a potential adjuvant therapy in patients with HER2-positive trastuzumab-resistant breast cancer through a bidirectional effect: overcoming treatment resistance by affecting the Akt pathway and beclin-1 autophagy (a combination that results in marked inhibition of resistant cell growth when used with trastuzumab alone) and inhibiting proliferation. [39]

Triple-negative breast cancer (TNBC) is a very aggressive subtype due to the fact that human epidermal growth factor receptor 2 (HER2), progesterone (PR) and estrogen (ER) receptors are not molecularly expressed. TNBC is characterized by significant invasiveness, high metastatic potential and an unfavorable prognosis. Studies have shown that selenium compounds increase the cytotoxicity of anticancer drugs i.e. (trastuzumab, bevacizumab, doxorubicin and paclitaxel) against TNBC cells, which may lead to better control of tumor growth and reduce its pathological features, such as excessive proliferation and potential for metastasis (by inhibiting angiogenesis, among others). [35]

Selenium supplementation (e.g., selenomethionine) may be a valuable strategy to counteract doxorubicin-induced cardiomyopathy by increasing GPX4 activity, reducing polyunsaturated fatty acids and their oxidation products in cardiomyocytes. [40] In selenium-deficient patients, supplementation is associated with a significant reduction in radiotherapy toxicity. [41]

Not all studies support the effect of selenium supplementation on reducing breast cancer risk. A study in which participants - women at high risk of breast cancer - received 200 μg of selenium daily (usually in the form of selenomethionine) for 36 months found no measurable benefit in modifying breast cancer risk biomarkers. Routine supplementation is not recommended for women at increased risk of breast cancer if they are not deficient in this element. [42] During cancer treatment, it is worth monitoring selenium levels because therapy, including chemotherapy, can significantly affect selenium concentrations and oxidant-antioxidant balance. [43]

At this stage, it is recommended that selenium concentrations be monitored and supplementation potentially considered in deficient individuals, especially in regions with low levels of selenium in the soil and population, as research on the effect of selenium supplementation in prevention and treatment is inconclusive. The results do not support the use of selenium supplementation as a general prevention strategy for breast cancer. Benefits may apply to selected subpopulations (e.g., premenopausal women or those with specific selenoprotein gene variants). [44] The protective or neutral effect of selenium supplementation may depend on individual genetic profile. [45] Caution, regular assessment of selenium status and origin, and avoidance of excessive supplementation without a specific indicated need are recommended.

Conclusions:

Many scientific studies prove the improvement of fertility and pregnancy, as well as

the beneficial effect of supplementation on the prevention, course, and prognosis of many diseases. The effects of supplementation are best in people with a deficiency of this element, which is why it is recommended to individualize the decision to supplement. The authors of the studies emphasize that more detailed clinical and experimental studies on large groups of patients are necessary to confirm the effectiveness and safe dosage of selenium.

Disclosure

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All authors have read and agreed to the published version of the manuscript

Funding Statement: This research received no external funding
Institutional Review Board Statement: Not applicable
Informed Consent Statement: Not applicable
Data availability statement: Data sharing is not applicable to this article
Conflict of interest: The authors declare no conflict of interest.

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