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THE ROLE OF SELENIUM IN CANCER PREVENTION

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Abstract

The aim of the present study was to analyze the scientific documentation about the effects of selenium (Se) in cancer prevention.

Methods. The search for relevant scientific publications was conducted in databases of evidence-based medicine (PubMed and Cochrane Library), specialized search systems (Google Scholar, Cyberleninka, and e-library). Inclusion criteria: studies performed in people published in English, Russian, as well as full versions of articles.

Results. In epidemiological studies conducted in 27 countries in Europe, the United States and Japan, it was found an inverse relationship between the level of Se intake and mortality from leukemia, colorectal cancer, breast, and ovarian cancer. Numerous studies in various countries have confirmed an increase in the incidence of prostate, thyroid, mammary, cervical, lung, oral, digestive, rectal cancer in the presence of Se deficiency in the body. The biochemical role of selenoproteins in the human organism is determined mainly by participation in oxidation-reduction reactions and stabilization of cell membranes in the phase of the damage the cell genetic apparatus (initiation), and tumor transformation (promotion) of certain types of cancers. It was found that supplementation with Se (200-300 µg/day) has preventive effects and decreases mortality rates in persons with a deficit of this trace element.

Conclusion. In the past decades, numerous experimental and clinical studies demonstrate the importance of Se for human health. It is of particular interest that low levels of Se in the blood are paralleled by a significant increase in the incidence of the oncological diseases. Selenium has both antioxidant and prooxidant activity. Prooxidant toxic activity in regard to tumor cells is manifested at increased pharmacological concentrations of Se. The results of the experimental studies show the effect of Se on early stages of carcinogenesis, and also in cancer progression. A significant accumulation of Se in malignant neoplasms has been observed. Further clinical studies are requested to define the roles and indications for the therapeutic use of Se in oncology.

Key words: selenium, cancer, prevention, epidemiology, biochemical mechanisms

Резюме

РОЛЬ СЕЛЕНА В ПРОФИЛАКТИКЕ РАКА

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Целью нашего исследования явился анализ научной литературы о роли селена в профилактике онкологических заболеваний.

Материалы и методы. Поиск соответствующих научных публикаций проводился в базах данных по доказательной медицине (PubMed, Cochrane Library), специализированных поисковых системах (Google Scholar, Cyberleninka, e-library). Критериями включения служили исследования, проведенные на людях. опубликованные на английском, русском языках, а также полнотекстовые статьи.

Результаты. В эпидемиологических исследованиях, проведенных в 27 европейских странах. США и Японии была установлена обратная связь между уровнем потребления Se и смертностью от лейкемии, колоректальным раком, раком молочной железы и яичников. Исследования подтвердили повышение заболеваемости раком простаты, щитовидной и молочной желез, шейки матки, легких, ротовой полости, ЖКТ, прямой кишки при дефиците Se в организме. Биохимическая роль селенопротеинов обусловлена участием в окислительно-восстановительных реакциях и стабилизации клеточных

мембран в фазе повреждения генетического аппарата (инициация) и трансформации (промоция) при определенных видах рака. Длительное применение Se в высоких дозах (200-300 мг/ день) оказывает превентивный эффект и снижает показатели смертности у лиц с его дефицитом.

Заключение. Экспериментальные и клинические исследования показали важность Se для здоровья человека. Установлена значительная связь между повышением заболеваемости раком и низким уровнем Se в крови. Проксидантный эффект Se в отношении раковых клеток проявляется при повышении фармакологической концентрации. Результаты экспериментальных исследований показывают эффект Se на ранних стадиях канцерогенеза, снижение пролиферации опухолевых клеток и индукцию апоптоза. Установлена аккумуляция Se в опухолях. Клинические исследования подтверждают эффективность терапевтического применения Se в онкологии.

Ключевые слова: селен, рак, профилактика, эпидемиология, биохимические механизмы.

Түйіндеме

ІСІК АУРЛАРЫНЫҢ АЛДЫН АЛУДА СЕЛЕННИҢ РОЛІ

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Зерттеудің мақсаты онкологиялық аурулардың алдын-алудағы селеннің ролі туралы ғылыми әдебиеттерді талдау болды.

Материалдар мен әдістер. Дәлелді медицина деректер базасында (PubMed, Cochrane Library), мамандандырылған іздеу жүйелерінде (Google Scholar, Cyberleninka, электронды кітапхана) тиісті ғылыми жарияланымдарды іздеу жүргізілді. Зерттеуге қосу критерийлері адамдарда жүргізілген зерттеулер. Ағылшын, орыс тілдерінде жарияланған, сондай-ақ толық мәтінді мақалалар.

Нәтижелері. 27 еуропалық елдерде жүргізілген эпидемиологиялық зерттеулер жүргізілді. АҚШ пен Жапонияда селен тұтынуы мен лейкемиядан өлім, колоректальды қатерлі ісік, сүт безі және аналық безі қатерлі ісігі ауруы арасында кері байланыс орнатылды. Зерттеулерде селен жеткіліксіздігі кезінде простата обыры, қалқанша безі және сүт бездері, жатыр мойны, өкпе, ауыз қуысы, асқазан-ішек жолдарында қатерлі ісіктің өсетіні расталды. Селенопротеиндердің биохимиялық рөлі қатерлі ісік ауруларының белгілі бір түрлерінде тотығу-тотықсыздану реакцияларына қатысып, генетикалық аппараттың зақым келтіру фазасында (инициация) және трансформация (промоция) жасуша мембранасының қалпына келтірілуіне қатысуымен байланысты. Жоғары дозада (200-300 мг / тәу) селенді ұзақ уақыт бойы қолдану қатерлі ісіктің алдын-алуының тиімділігіне ие және оның тапшылығы бар адамдарда өлімді азайтады.

Қорытынды Эксперименттік және клиникалық зерттеулер селеннің адамның денсаулығына маңыздылығын көрсетті. Қатерлі ісік ауруы мен қандағы селен деңгейі төмендеуі арасындағы маңызды байланыс анықталды. Селеннің ісік жасушаларына қатысты прооксидантты әсері селеннің фармакологиялық концентрацияның артуымен байланысты. Эксперименттік зерттеулердің нәтижелері селеннің канцерогенездің ерте сатыларында ісік жасушаларының пролиферациясын төмендетіп, апоптоздың индукциясына әсерін көрсетеді. Ісіктерде Se жинақталуы анықталады. Клиникалық зерттеулер онкологиядағы Se емдеудің тиімділігін растайды.

Түйінді сөздер: селен, рак, алдын алу, эпидемиология, биохимиялық механизмдер.

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Introduction

It is commonly claimed that it was first discovered in 1957 that selenium (Se) is an essential nutrient for animals [69, 28, 34], with the discovery being independently made by Klaus Schwarz (1914-1978) and Calvin M. Foltz [50] and by

E.L. Robert Stokstad (1913–1995) [65]. It was because of the work published in 1957 that the importance of Se as one of the essential nutrients soon became recognized among biochemists, veterinarians, and human nutrition scientists, but Schwarz, Foltz, and Stokstad were not the first ones to

discover the role of Se as a nutrient. Alvin L. Moxon (1909 - 2007) and colleagues had shown already in 1941 that Se stimulated the growth of chicks [45, 28]. Despite the discoveries in 1957, the animal industry did not rush to demand its use as a feed supplement [28].

There was some delay before it was realized that severe Se deficiency among animals was widespread in some parts of the world, including New Zealand, parts of the United States, Norway, Sweden, and Finland, and that this affected various species, including chicks, sheep, and pigs [69, 34, 43], with impairment of the immune system leading to lethal coccidiosis in chicks is one of the problems [28, 29], and also lethal heart disease in various species [69, 34]. Veterinarians also realized that there is a close interaction between Se and vitamin E, with severe deficiency of vitamin E and Se often leading to the same symptoms. Although there were also some diseases more specifically associated with deficiency of only one of these nutrients, and the requirement of vitamin E is enhanced if the Se intake was low and vice versa [69, 34]. It was, moreover, also soon discovered by veterinarians that there is an interaction between these nutrients and polyunsaturated fatty acids (PUFAs), with a high intake of polyunsaturated fatty acids enhancing the nutritional requirement for vitamin E [40, 74]. Also, it was very early realized by veterinarians that the three-way interaction between Se and vitamin E was caused by the proneness of PUFAs to peroxidation, with PUFA peroxidation also leading to the enhanced destruction of vitamin E, while vitamin E and Se both were antioxidant nutrients that protected against peroxidation processes *in vivo*. The explanation why Se functioned as an antioxidant nutrient became apparent with the discovery by Rotruck and collaborators in 1973 that glutathione peroxidase (GPX) is a Se-dependent enzyme [47]. Since then, several different Se-dependent antioxidative enzymes have been discovered [26, 17, 42, 37, 70, 6, 63, 30, 33, 36, 66, 75, 79].

One of the human nutrition scientists who very early became interested in the possible role of Se in human nutrition was Douglas Van Anden Frost (1910-1989) [21, 22, 43]. While an early animal experiment had led to the belief that Se was carcinogenic, Frost was convinced that it was, on the contrary, an anticarcinogen. He collaborated with the young biochemist Raymond Shamberger, who demonstrated protective effects of Se in animal experiments [55] and also together with Frost and with other collaborators later carried out geographic epidemiological studies, showing that there was an inverse correlation between total deaths from cancer and the average Se intake, comparing different states in the United States [56, 57, 58]. Shamberger found, moreover, that there is an enhancement of peroxidation in carcinogenesis [60] and that the secondary lipid peroxidation product malondialdehyde is mutagenic [59]. Shamberger and coworkers found, moreover, that there was also a similar geographic association as had been seen for cancer between cardiovascular death rates and Se intake when comparing different states in the United States [61]. This was confirmed in a subsequent investigation, using Se concentrations in human blood from pooled blood bank samples in different states instead of an estimate of the dietary intake of Se in the different states.

The aim of the present study was to evaluate the scientific documentation about the role of Se in cancer prevention.

Materials and methods

The search for relevant scientific publications was conducted in databases of evidence-based medicine (PubMed and Cochrane Library), specialized search systems (Google Scholar, Cyberleninka, and e-library).

Inclusion criteria: studies performed in people published in English, Russian, as well as full versions of articles. Preference was given to studies of high methodological quality (systematic reviews and surveys of studies of various designs), in the absence of which the publications of the results of cross-sectional studies were taken into account.

Studies were obtained by searching for the following keywords (date of search: September 29, 2018): selenium and biochemical mechanisms, selenium, and oncology treatment, selenium, and oncology prevention. In total, 753 literary sources were found, 79 of which were selected for analysis.

Results and discussion.

Epidemiological studies of Se effects in cancer prevention.

Protective role of Se in the chemically induced tumor cells was established in 1949 [10]. After 20 years, the first report appeared on the relationship between Se content in plants and mortality from some malignant tumors [56]. It was revealed that mortality from cancer in people living in areas of the United States with a high concentration of Se in feed crops is significantly lower than in areas with a low content of this microelement [59, 8]. In epidemiological studies conducted in 27 countries in Europe, the United States and Japan, it was found an inverse relationship between the level of Se intake and mortality from leukemia, colorectal cancer, breast cancer, and ovaries [53]. Similar results were obtained in China, where the content of Se in the soils of different regions varies from inadequate to toxic [78].

Soon it was established that the level of Se determined in the patients for the previous five years before the diagnosis of malignant tumors of the gastrointestinal tract, lung, prostate, lymphomas, was significantly lower than that in the healthy people [73]. Numerous studies in various countries have confirmed an increase in the incidence of prostate, thyroid, mammary, cervical, lung, oral, digestive, rectal cancer in the presence of low Se status [49, 43, 11, 25, 48, 31, 77]. Selenium supplementation reduced the incidence of tumors by more than 35% [12]. Clinical trials in the US have shown that in the elderly, Se intake reduced the risk of oncological diseases by 65% [53]. Epidemiological study NPC (Nutritional Prevention of Cancer) was conducted in 1983-1993 in the US regions with a low Se level in the soil. In the study, 1,312 people with skin cancer received 200 µg of Se (in the form of yeast) or a placebo daily. Results of the study demonstrated no decrease in the incidence of skin cancer but the reduction in lung cancer risk by 48%, colorectal cancer by 58%, prostate cancer by 63%, and decrease the incidence of cancer generally by 37% and cancer deaths by 50% [9]. In the group of people who continued to take Se for 7.4 years, new cases of prostate cancer were reduced by 52% (PCa), colorectal cancer by 54%, and lung cancer by 26% compared to placebo group [13]. If concentration of Se in the blood plasma did not exceed 105.2 µg/l, the total risk of cancer was reduced by 49%, at a concentration of Se in the range from 105.2 to 121.6 µg/l, this risk was reduced by 30%, and with a Se

content of more than 121.6 $\mu\text{g/l}$ it was reduced only by 20% [9]. These data were the basis for conducting a SELECT study involving 35,533 people. The nutritional supplements contained 200 $\mu\text{g/day}$ of Se in the form of L-selenomethionine and vitamin E (400 IU/day of α -tocopherol). After 5.5 years, persons received Se alone or in combination with vitamin E, showed no differences in the incidence of lung cancer, prostate cancer, colorectal cancer, or the incidence of other diseases compared to those who received placebo. After analysis, the absence of a positive effect was associated with the use of various forms of Se: Se yeast enriched in the study of NPC and L-selenomethionine in the SELECT study [27, 44, 46]. Furthermore, baseline plasma Se values in subjects enrolled in the SELECT study (mean value 135 $\mu\text{g/l}$) were higher than in those in the NPC trial. At the same time, the increase in the availability Se for the population of Finland as a result of the State Program for the correction of microelements deficiency was accompanied by a significant decrease in cancer mortality [2]. In subsequent years, the results of seven epidemiological studies were published, including about 2000 people with low, medium and high content Se in populations. In populations with low levels of Se in the plasma, it was found a high incidence of cancer not only the prostate gland, but also in other localizations: tongue, esophagus, stomach, colon, liver, lung, mammary gland, pancreas, uterus, kidneys, bladder, skin, and blood system. The protective role of high intake of Se in the prevention of prostate cancer has been confirmed in six controlled, double-blind, randomized trials [72, 46, 7, 76, 68, 35].

These results aroused the interest in the intensive study of the mechanisms for Se inclusion in processes associated with the prevention and suppression of tumor cell transformation.

Biochemical mechanisms of Se in cancer prevention.

Biochemical role of selenoproteins in the human organism is determined mainly by participation in oxidation-reduction reactions and stabilization of cell membranes in the phase of the damage the cell genetic apparatus (initiation), and tumor transformation (promotion) of certain types of cancers [14]. In the case of deficiency of Se (less than 0.02 mg/kg/day), the synthesis of these proteins is strongly suppressed. If there is a deficient dietary Se intake, the activity of GPX and its concentration in the serum decreased, this makes it possible to use the activity of this enzyme as a marker of the Se status of the organism [3]. Decreasing the GPX level reduces the resistance of the organism to oxidative stress [20].

Selenium is also a part of the enzyme iodothyronine-5-deiodinase involved in the conversion of thyroxine (T4) to triiodothyronine (T3). It indicates a link between Se and metabolism of thyroid hormones and iodine. More recently, isoforms of Se-dependent thioredoxin reductase (TrxR 1-3) were isolated and identified [67]. Its main biological function is catalysis of oxidation/reduction of SH-groups in the specific protein thioredoxin, which is responsible for the maintenance of the oxidation-reduction homeostasis. The increase in TrxR content in tissues and serum is caused by activated metabolites of oxygen and can be used as an indicator of the oxidative stress in the tissues. TrxR1 is involved in the regulation of "redox-sensitive" transcription factors, such as tumor suppressor p53, induced by hypoxia

factor (HIF) and the transcription factor of AP-1 (activating-protein-1), which both are responsible for changing the oxidation-reduction balance. This balance determines the participation of the TrxR-enzyme in the proposed anti-tumor action of Se [23]. The protective effect of Se in the prevention of carcinogenic and toxic effects of heavy metals and arsenic was found [1].

More than 50% of oncological patients have an impaired or changed protein p53 function. If DNA is damaged p53 either stimulates DNA repair or activates apoptosis in the case of irreversible disorders. The Trx enzyme system promotes the induction of p53 and DNA repair [16]. The action of Se-containing enzymes is associated with multifarious possibilities of anticancer effects such as oxidative stress, detoxification, and metabolism of carcinogens, induction of apoptosis and cell proliferation, methylation and reduction of DNA, control of cell segmentation and inflammation, production of hormones, and immune function [18, 15]. Selenium has antimutagenic action, suppresses the expression of oncogenes, inhibits the activity of protein kinase C, inhibits angiogenesis, and increases the activity of antineoplastic clones of natural killers by stimulating Interleukin-1 and interleukin-2 production [54, 24].

A specific feature of the metabolism of Se in the organism of the oncological patient is its accumulation in the tumor and reduction of its concentration in the blood [41]. In viable tumor tissue, Se concentration is 5-10 times greater than in necrotic one [5]. Selenium has a pronounced toxic action on tumor cells [51]. The toxicity of some Se compounds, such as selenocysteine and isoselenocyanates, may contribute to antitumor actions. Synthesis of new Se redox active compounds that may be added to existing drugs is also an area of research. Of particular interest is a modification of existing molecules with redox-active Se [39].

The use of selenium in oncology.

In recent years, clinical data confirming the importance and effectiveness of the therapeutic application of Se in oncology have appeared. Se therapy should be performed in the oncological patients due to a deficit of this microelement [52]. Chemotherapy, as well as radiation therapy, may exacerbate a pre-existing Se deficiency, which increases the severity of toxic side effects. Adequate Se status optimizes the functions of the glutathione system in the tumor cells, increases their sensitivity to chemotherapy and radiation therapy, and simultaneously reduces the toxicity of therapeutic measures to normal cells [64]. It was revealed a positive correlation between the initial level of Se, its therapeutic dose and the results of chemotherapy of lymphoma (life expectancy, response to chemotherapy). The introduction of Se supplementation in cancer therapy can give new opportunities for the treatment of this disease [4].

Adjuvant therapy by selenium nitrate at a dose of 0.2 $\mu\text{g/kg/day}$ for 7-day chemotherapy showed an increase in apoptosis in lymphoma cells and the effect of synergy (decrease in the sizes of supraclavicular and cervical lymph nodes and spleen, and bone marrow infiltration) [32].

To assess the effect of Se and zinc in chemotherapy of gastrointestinal cancer the randomized clinical trial was performed. In 70% of patients treated with Se 200 $\mu\text{g/day}$ and zinc Zn 21 mg/day for 50 days, there was no

deterioration in the status of nutrition; weakness was significantly decreased, and improved appetite appeared, while in the placebo group, 80% of the patients had significant decreases in the levels of total protein, albumin, prealbumin, and of body weight [19]. Results of another study demonstrates that use of Se in the yeast form (200 µg/day) for 2-3 months in the patients with ovarian cancer led to a decrease of the chemotherapy side effects (cisplatin 100 mg/m² and cyclophosphamide 600 mg/m² every 3 weeks), such as hair loss, abdominal pain, weakness and loss of appetite [62].

The multicenter randomized trial was performed in the patients with cervical and uterine cancer (n = 81). Patients of the study group received sodium selenite in the dose 500 µg/day of radiotherapy and 300 µg/day without irradiation for five weeks. Total radiation dose was 45-50 Gy (single dose 1.8-2.0 Gy), the total dose of Se was 15.9-18 mg. The concentration of Se in the blood increased from 62.8 to 86 µg/l. Significant results were achieved for the incidence of complications (diarrhea, changes in blood tests, and body weight) in comparison with a control group (20.5% vs. 44.5% in the control group, 5-year survival rates were 92 and 83%, respectively) [38]. In the all mentioned clinical studies, there were not any adverse effects of Se in the used doses and terms of application.

Conclusion.

In recent decades, numerous experimental and clinical studies demonstrate the importance of Se for human health. Based on the epidemiological studies it has been established a significant correlation between the high incidence of various cancers and low (suboptimal) levels of Se in the blood. It has been observed that supplementation with Se (in the dose range 200-300 µg/day) has preventive effects and decreases mortality rates in the persons with a deficit of this microelement.

However, the observations reviewed in the present paper indicate a two-stage model for chemoprevention, reflecting two roles of Se in anticarcinogenesis: First, Se acts as an essential nutrient providing the catalytic center of antioxidant enzymes (nutritional dose range), and secondly, Se compounds appear to be a source of cytostatic metabolites produced from supra-nutritional doses of some forms of the element. The latter effect was observed already by Wassermann and coworkers [71] and has been reproduced experimentally in numerous animal and cellular studies. Selenium has both antioxidant and prooxidant properties. Prooxidant toxic activity with regard to tumor cell growth is manifested at unphysiologically high (pharmacological) doses of Se (above about 200 µg/day). The results of the several experimental studies show the effect of pharmacological doses of Se on early stages of carcinogenesis, as well as in the proliferation of the malignant cells. It has been observed a significant accumulation of Se in malignant neoplasms. In conclusion, further clinical studies are of utmost importance to confirm and define the effectiveness of the therapeutic use of Se in oncology.

Authorship Contributions:

Björklund G.: concept and design, literature search, analysis or interpretation, writing.

Aaseth J.: interpretation, writing.

Pivina L.M.: literature search, analysis or interpretation, writing.

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