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Selenium's Significance for Human Health and Its Potential Anti-Oncogenic Properties: A Literature Review

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Abstract

Introduction

Selenium (Se), an essential trace element, has attracted considerable attention due to its multifaceted roles in human health, particularly its potential anti-oncogenic properties. This literature review aims to synthesise current knowledge regarding the biological functions of Se, its association with cancer risk, and the efficacy of Se supplementation in the prevention and treatment of cancer. The review provides a critical evaluation of the evidence derived from epidemiological studies, randomised controlled trials (RCTs), and mechanistic investigations, elucidating areas of consensus and divergence within the existing literature. Furthermore, it underscores the roles of Se in additional domains of human health, including cardiology, neurology, and endocrinology.

Methods

A literature review was conducted, based on the PubMed and Google Scholar databases, using keywords “selenium”, “anti-oncogenic”, “cancer treatment”, “cancer prevention”, “human health”. The primary focus was on meta-analyses, double-blind studies, reviews pertaining to specific medical specialities, and research in basic sciences.

Brief description of the state of knowledge

Selenium (Se) is an essential trace element required for optimal physiological functions in organisms. Discovered in 1817, selenium was initially regarded as a toxic element until its beneficial effects were identified in the mid-20th century. The element's biological activity is primarily mediated through selenoproteins, which are crucial for antioxidant defence, immune function, and thyroid hormone metabolism. Epidemiological studies have indicated an inverse relationship between selenium exposure and cancer risk, although the interpretation of these studies is complicated by confounding factors. Randomised controlled trials (RCTs) regarding selenium supplementation and cancer prevention have produced mixed results, underscoring the complexity of selenium's role in this context. Selenium's mechanisms of action involve antioxidant properties, induction of apoptosis in cancer cells, and modulation of various signalling pathways. Evidence suggests that selenium supplementation may enhance chemotherapy efficacy in haematological malignancies, while associations between selenium

levels and specific cancers, such as prostate and breast cancer, require further investigation. Additionally, the health implications of selenium extend beyond oncogenic processes, affecting cardiovascular health, cognitive function, and immune response. As the relationship between selenium and various health outcomes continues to evolve, further research is imperative to determine optimal intake levels, the safety of supplementation, and the intricate interplay of selenium with other health conditions.

Keywords: “selenium”, “anti-oncogenic”, “cancer treatment”, “cancer prevention”, “human health”

Introduction and Current State of Knowledge

Selenium – basic information

Selenium (Se) is classified as an essential trace element, signifying that it is necessary for the proper functioning of organisms, albeit required in minuscule quantities [1]. Selenium belongs to Group 16 (formerly Group VIA) of the periodic table, along with oxygen, sulfur, tellurium, and polonium [2]. Jöns Jakob Berzelius discovered selenium in 1817 while researching chemical compounds responsible for illnesses among workers in a Swedish sulfuric acid factory [3]. Initially, selenium was considered a toxic element. It was not until the second half of the 20th century that its beneficial effects on organisms were recognised, thanks to the studies conducted by biochemists Schwarz and Foltz. They observed that adding selenium-rich yeast to the diet of rats resulted in a reduction of necrotic bodies in the liver and the maintenance of proper liver function [4]. This discovery-initiated research into the beneficial impact of selenium on health.

Selenium's Biological Roles and Essential Functions

Selenium's biological activity is predominantly mediated through its incorporation into selenoproteins [5]. These proteins are involved in various crucial cellular processes, including immune function, antioxidant defence and thyroid hormone metabolism [5], [6]. Some of the most significant selenoproteins [SPs] are glutathione peroxidases (GPx), which play a vital role in protecting cells from oxidative stress caused by reactive oxygen species (ROS) [7], [8].

Oxidative stress is implicated in the development and progression of numerous diseases, including cancer [7]. Furthermore, Se is essential for the activity of other SPs - thioredoxin reductases (TrxRs), which are also involved in redox regulation and cellular defence mechanisms [1]. Iodothyronine deiodinases (DIOs), selenoproteins crucial for thyroid hormone metabolism, are also influenced by Se status [9]. Disruptions in thyroid hormone homeostasis can have significant implications for overall health and may indirectly influence cancer risk [9]. The immune system is also significantly affected by Se status, with Se deficiency leading to impaired immune function [5]. Conversely, adequate Se intake can enhance immune responses, including T-cell proliferation and natural killer cell activity [5].

In light of the above, selenium and its properties have been extensively researched for their impact on human physiology and oncogenesis.

Selenium and Cancer Risk: Epidemiological Studies and Observational Data

Epidemiological studies have consistently shown an inverse association between Se exposure and cancer risk [10]. These studies, however, are observational and susceptible to confounding factors [10], [11]. For instance, higher Se levels may correlate with a healthier lifestyle and dietary habits, making it challenging to isolate the specific effect of Se [11]. Despite these limitations, many observational studies have indicated a protective effect of Se against various cancers, including prostate, lung, colorectal, and bladder cancers [10], [11]. A meta-analysis by Cai et al. [7] found a pooled odds ratio (OR) of 0.78 for high Se exposure, indicating a reduced cancer risk. This protective effect was particularly evident for breast, lung, oesophagal, gastric, and prostate cancers. However, no significant association was found for colorectal, bladder, or skin cancer [7]. Other studies have corroborated these findings, demonstrating that higher serum/plasma Se and toenail Se levels are associated with cancer prevention [7]. Significantly, these studies generally distinguish between Se exposure through diet and Se supplementation, with the former showing more consistent benefits [7].

However, the interpretation of epidemiological data is not without challenges. The studies often rely on different methods for assessing Se exposure and cancer outcomes, leading to inconsistent results [11]. Moreover, assessing Se status relies on various techniques such as serum/plasma levels, toenail levels, or dietary intake, which can lead to differing interpretations [7]. Furthermore, the nonlinear dose-response relationship between Se levels and cancer risk adds complexity to these investigations, suggesting that optimal ranges for protective effects exist [7], [12]. A U-shaped association, where low and high Se intake is

associated with increased cancer risk, has also been reported [12]. This emphasises the importance of maintaining an optimal Se intake within a safe range [12]. The study by Le et al. [12] provides an example of this U-shaped association, identifying a safe intake range of 117.8 μg/day in the Vietnamese population [12].

Selenium Supplementation and Cancer Prevention: Randomized Controlled Trials

While epidemiological studies suggest a protective effect of Se, RCTs have yielded mixed results [10], [13]. Several large-scale RCTs, such as the Nutritional Prevention of Cancer Trial (NPCT) [14] and the Selenium and Vitamin E Cancer Prevention Trial (SELECT) [10], have investigated the efficacy of Se supplementation in reducing cancer risk. The NPCT, which involved Se supplementation with Se-enriched yeast, showed significant reductions in cancer risks in individuals with pre-treatment plasma Se concentrations below approximately 120 ng/ml [14]. However, the SELECT trial, which used selenomethionine, failed to demonstrate a significant reduction in prostate cancer risk [10]. These contrasting findings underscore the complexity of Se's role in cancer prevention and highlight the importance of considering factors such as Se species, dosage, and baseline Se status [10], [13]. The inconsistent results from RCTs may also be attributed to methodological differences, including variations in Se species, dosage, duration of supplementation, and participant characteristics [13].

Furthermore, some studies have even suggested potential adverse effects associated with Se supplementation [10], [13]. Increased risks of non-melanoma skin cancer, high-grade prostate cancer, and type 2 diabetes have been reported in some clinical trials [10]. This highlights the need for caution in recommending Se supplementation as a general cancer preventive measure and underscores the importance of individualised approaches to Se intake [10], [15]. Moreover, a recent study suggested that high-dose selenium supplementation after a prostate cancer diagnosis may actually increase prostate cancer mortality risk [15]. This finding adds further complexity to the interpretation of Se's role in cancer prevention and treatment, particularly in the context of post-diagnosis supplementation [15].

Selenium's Mechanisms of Action in Cancer Prevention and Treatment

The anti-oncogenic effects of Se are attributed to multiple mechanisms [16], [17]. Its primary role as an antioxidant, through the activity of selenoproteins like GPx, protects cells from ROS-induced damage, thereby reducing the risk of DNA mutations and carcinogenesis.

Se also inhibits cellular proliferation and induces apoptosis in cancer cells [16], [17]. These effects may be mediated through various signalling pathways, such as the JNK MAPK pathway [17]. Furthermore, Se compounds can influence the cell cycle and DNA repair mechanisms, potentially contributing to their anti-cancer activity [16]. However, the precise mechanisms and the specific Se metabolites involved in these effects are not fully understood [14]. Moreover, the effectiveness of Se as a chemopreventive agent can vary depending on its chemical form and concentration [17]. Inorganic Se compounds, such as sodium selenite, can act as pro-oxidants at high concentrations, potentially exhibiting cytotoxic effects against cancer cells and enhancing the efficacy of chemotherapy [18], [19]. This dual role of Se as both an antioxidant and a pro-oxidant highlights the complexity of its biological activity and the need for careful consideration of its dosage and chemical form [16].

Selenium nanoparticles (SeNPs) have emerged as a promising area of research. SeNPs exhibit enhanced bioactivity and reduced toxicity compared to other forms of Se. They demonstrate anticancer effects by inducing apoptosis in cancer cells [4] and are being investigated for their potential to enhance cancer therapy [18]. The efficacy of SeNPs in cancer treatment is attributed to their ability to efficiently penetrate cells, leading to more pronounced effects on cellular processes. However, further research is needed to fully elucidate the mechanisms of SeNPs' anti-cancer activity and determine their optimal dosage and safety profile [4].

Selenium and Hematological Malignancies

Selenium's role in haematological malignancies has been extensively studied [20], [18], [21], [19]. Low Se status is frequently observed in patients with these cancers and is associated with poorer chemotherapy outcomes and survival rates [18], [21]. Selenium supplementation has demonstrated the potential to improve treatment outcomes by augmenting the efficacy of chemotherapy and minimising toxicity to healthy tissues. [20], [18]. In vitro studies have demonstrated that Se compounds possess direct cytotoxic activity against leukaemia and lymphoma cells and can sensitise them to chemotherapy drugs [18]. Se's mechanisms of action in haematological malignancies include inducing apoptosis, cell cycle arrest, and interactions with intracellular signalling pathways [19]. High-dose sodium selenite, in particular, has shown efficacy in inducing apoptosis of lymphoma cells in patients with non-Hodgkin's lymphoma [19]. Clinical trials suggest the potential benefits of Se in improving treatment outcomes [18]. However, more robust, large-scale randomised studies are needed to

confirm these findings and determine optimal dosage and safety profiles [18]. The potential for long-term toxicity associated with selenium compounds, mainly when used in conjunction with chemotherapy or radiation, as well as the risk of developing secondary malignancies, must be taken into account [18].

Selenium in Specific Cancers: Prostate, Breast, and Others

The association between Se and prostate cancer has been particularly well-studied [22], [15]. Observational studies have indicated that lower serum Se levels are associated with an increased risk of prostate cancer [22]. However, RCTs, including the SELECT trial [22], have not shown a consistent preventive effect of Se supplementation. The discrepancy may be due to individual genetic variations affecting selenoprotein function [22]. While Se has potential anti-oncogenic properties through modulation of oxidative stress, cell cycle regulation, and apoptosis induction [22], the complex interplay between Se and other dietary factors, as well as its potential synergistic effects with conventional cancer therapies, needs further investigation [22]. Studies have explored the relationship between Se levels and survival outcomes in prostate cancer patients, with some suggesting that lower Se levels are associated with reduced survival rates. However, more research is required to establish a definitive causal link between Se and prostate cancer prognosis [23].

In breast cancer, similar trends are observed [24], [25]. Low serum Se levels have been associated with increased mortality, with patients in the lowest quartile of Se exhibiting significantly lower 10-year survival rates. The antioxidant and immunomodulatory properties of Se may mediate its protective effect against breast cancer [24]. Moreover, research has indicated that the combination of selenium supplementation with other therapeutic modalities, such as fish oil and doxorubicin, may improve therapeutic outcomes in cases of triple-negative breast cancer [25]. This combination therapy can modulate the expression of selenoproteins and fatty acid receptors, influencing multiple anti-cancer signalling pathways. However, more research is needed to validate these findings in more extensive clinical trials and to determine optimal treatment regimens [25].

Other cancers, such as laryngeal, lung, colorectal, ovarian, kidney, and melanoma, have also shown associations with Se status [26], [27], [28], [29], [30]. Low Se levels are often linked to increased mortality or reduced survival rates in these cancers [26], [28], [29]. The mechanisms underlying these associations are likely multifactorial, involving Se's roles in antioxidant defence, immune response, and regulation of cellular processes [26], [28], [29].

However, the particular species of selenium and the optimal intake levels for each type of cancer necessitate further investigation [31].

Selenium Deficiency and Cancer Rehabilitation

Selenium deficiency is prevalent among cancer patients undergoing treatment. The prevalence rates vary depending on the cancer type and may range from 36% to 90% [32]. This deficiency can impair immune function and increase susceptibility to infections, negatively impacting the patient's ability to tolerate treatment and recover from cancer therapy. In cancer rehabilitation settings, Se supplementation has effectively corrected selenium deficiency and improved quality of life. A daily intake of 600 μg of Se has been reported to be beneficial in improving physical and emotional functioning among cancer patients undergoing rehabilitation. Maintaining adequate Se levels during and after cancer treatment may be crucial for enhancing long-term health outcomes in cancer survivors [32].

Selenium Speciation and Bioavailability

The biological effects of Se are significantly influenced by its chemical form or speciation. Different Se species exhibit varying bioavailability and metabolic fates. Organic Se compounds, such as Se-methylselenocysteine, are generally considered more bioavailable and potent than inorganic forms, like selenite or selenate. The anti-tumour effects of Se-methyl selenocysteine have been demonstrated in animal studies [31]. However, human studies investigating the specific effects of different Se species on cancer risk and treatment outcomes are limited. Further research is needed to elucidate the particular Se species and their contributions to the observed health benefits, particularly in human studies [31].

Selenium and Thyroid Cancer

The relationship between selenium and thyroid cancer has also been explored. Meta-analyses have suggested a link between lower serum Se levels and increased thyroid cancer risk. The antioxidant properties of selenoproteins, particularly GPx, may play a protective role by reducing oxidative stress, which is implicated in thyroid carcinogenesis. However, the results vary depending on geographical location and measurement methods. Further studies are necessary to fully elucidate the role of Se in thyroid cancer prevention and treatment [33].

Selenium and Other Health Conditions

Beyond cancer, Se plays a role in various health conditions. Se deficiency has been associated with Keshan disease and Kashin-Beck disease [34], highlighting its importance for overall health. Keshan disease is a form of juvenile cardiomyopathy that exhibits clinical characteristics akin to idiopathic dilated cardiomyopathy (DCM), yet it is distinctly associated with specific geographic regions. This condition predominantly affects young women of reproductive age and children between the ages of 2 and 10 years. If left untreated, Keshan disease can lead to cardiovascular atrophy. Although it once posed a significant public health challenge, the condition is now primarily managed through public health interventions, notably involving selenium supplementation [35]. Kashin-Beck disease is a geographically localised bone and joint disorder attributed principally to deficiencies in selenium, iodine, and other environmental factors. This condition predominantly affects children, leading to deformities in cartilage and bone. Treatment protocols involve supplementation with selenium and iodine, while preventative measures encompass avoiding mycotoxins and providing access to clean water [3].

Se's antioxidant properties may also offer protection against heavy metal toxicity (arsenic, cadmium) by reducing their accumulation and mitigating oxidative stress. The interaction of Se with other essential elements, like chromium and vanadium, suggests a complex interplay affecting human health [34]. Additionally, Se deficiency has been linked to impaired cardiovascular function [35], [36], with low Se levels associated with higher readmission rates for heart failure [36]. This phenomenon can be elucidated through multiple avenues of investigation. Selenium deficiency has been associated with compromised mitochondrial function and elevated production of reactive oxygen species, both of which can lead to myocardial injury. Additionally, the activity of several key selenoproteins is affected by selenium status. Among these, Selenoprotein P (SELENOP) plays a vital role in transporting selenium in the bloodstream and maintaining selenium levels within the brain. Reduced levels of SELENOP have been correlated with an increased risk of rehospitalisation and mortality in individuals experiencing acute heart failure. Selenoprotein S (SELENOS) is involved in managing the endoplasmic reticulum's stress response and regulating inflammation, suggesting its protective function for cardiovascular health; a deficiency in SELENOS may elevate the risk of heart failure. Selenoprotein T (SELENOT), which is situated in the endoplasmic reticulum, is essential for adaptation to stressful environments, and its insufficiency may contribute to the development of cardiac dysfunction [1][35][36][38].

Moreover, selenium supplementation has demonstrated the potential to enhance outcomes in Graves' orbitopathy, a condition associated with thyroid disorders [37]. These findings underscore the multifaceted role of Se in human health beyond its potential anti-oncogenic properties [38]. Furthermore, selenium deficiency is linked to cognitive decline and neurological disorders [39], with selenoproteins playing critical roles in neuroprotection. Selenium's antioxidant properties may reduce oxidative stress, implicated in neurodegenerative diseases like Alzheimer's, Parkinson's, and Huntington's [40]. The relationship between Se species in cerebrospinal fluid and the conversion from mild cognitive impairment to Alzheimer's dementia highlights the complexity of selenium's effects on brain health. Different selenium species may have varying effects, with some potentially contributing to neurodegeneration [40]. The significance of selenium in maintaining brain health and its potential implications for neurodegenerative and oncogenic processes warrant further investigation [38].

Conclusion

The importance of selenium for human health is indisputable, given its integral role in various essential biological processes that govern physiological functions. A substantial body of evidence suggests that selenium possesses potential anti-oncogenic properties, primarily attributed to its antioxidant activity and immunomodulatory effects. However, the findings from clinical trials investigating the protective role of selenium in cancer prevention and treatment have produced inconsistent results, reflecting the complexity surrounding its application in this context.

The multifaceted nature of selenium’s involvement in oncology is underscored by the varying biological effects exhibited by different forms of selenium, the existence of U-shaped dose-response relationships, and the potential adverse effects associated with elevated doses. To fully understand the mechanisms underlying selenium's actions, it is imperative that further research is conducted to delineate optimal intake levels that are tailored to different population groups and specific cancer types. Additionally, it is vital to assess the long-term safety and efficacy of selenium supplementation as part of comprehensive cancer prevention and treatment protocols.

Innovative developments in the utilisation of selenium nanoparticles (SeNPs) present a promising approach to cancer therapy; however, extensive research is still required to ascertain their effectiveness and safety profile in clinical settings. An integrative framework that takes

into account individual genetic predispositions, dietary practices, and lifestyle factors is essential for optimising selenium intake and exploiting its potential therapeutic benefits for human health while simultaneously minimising associated risks.

The complex interactions between selenium, its associated selenoproteins, and various health conditions—including cancer—demonstrate the need for continued investigative efforts. Such research is crucial for deepening our understanding of selenium's impact on health outcomes and formulating personalised interventions for cancer prevention and treatment.

Disclosure

Author's contribution:

Conceptualisation: AF, AK

Methodology: WF, AD

Software: AF, BU

Check: JRD, JL

Formal analysis: AM, MJ

Investigation: MN, AK

Resources: BU, JL

Data curation: MJ, WF

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