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Selenium as a chemoprotective anti-cancer agent: Reality or wishful thinking?

Minireview

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It is generally accepted that selenium (Se) plays an important role in maintaining equilibrium of a healthy organism. It also participates in processes related to carcinogenesis such as inhibition of tumor formation and regression. Scientific data accumulated so far using experimental animal models and from clinical studies devoted to investigating the effects of Se confirm strong relationship or correlation between Se supplementation and tumor frequency of prostate, lungs, liver and colon. However, details of mechanisms of action of Se in modulation of carcinogenesis and cancer prevention are not yet fully elucidated. It is not clear yet whether Se deficiency itself is a cancer risk factor or whether it helps an already present cancer to progress. Additionally, the effects of other factors such as age, gender, life style, geographic location, comorbidities and use of drugs, are not clear. Despite the fact that some positive results were obtained with Se supplementation, it is necessary to verify these findings in more controlled experimental models including clinical studies. At the present time, data related to Se supplementation are not convincing enough as to allow general recommendation for using Se as an effective agent for chemoprevention of cancer.

The goal of this minireview is to highlight present level of understanding of Se biological and prospects of its future clinical use. Information regarding Se, its effectiveness in various experimental models and in clinical tests, including combinations with other bioactive agents and anticancer drugs, is evaluated and summarized.

Key words: selenium, chemoprevention, cancer

Generally, chemoprevention aims at using a chemical substance to reduce the initiation of carcinogenic processes or to reverse these processes. Selenium (Se) is regarded as an essential element playing a key role in human health and its deficiency results in many pathological processes and diseases, including cancer. Attention to Se was drawn when more detailed understanding of Se biology showed that this element is in the structure of selenocysteine, which is necessary for the proper functioning of several enzymes and that, in general, sufficient supplementation of Se as a part of diet leads to inhibition of tumorigenesis and to decreased risk of cancer [1].

Increased interest in Se research led to a discovery of more than 30 selenoproteins. However, the roles of many of these proteins in organisms are not yet elucidated and are still being investigated [2]. Nonetheless, it is already clear that substitution of sulfur for Se yields molecules that are more effective cancer chemopreventive agents, participating especially in processes of carcinogenesis [3]. Furthermore, methylated forms of Se, such as Se-methylselenocysteine, methaneselenenic, or methaneseleninic acid, are usually able to contribute to the cellular protective mechanisms that may result in tumor prevention [4]. Typical examples of such compounds are selenomethionine and selenocysteine (Fig. 1) derived from methionine and cysteine, respectively. These two aminoacids are part of selenoproteins such as glutathione peroxidases, thioredoxin reductases and iodothyronine deiodinases [5] some of which participate in processes of apoptosis, cell growth and modulate cell signaling systems and transcription factors. It is generally accepted that a chemopreventive anticancer effect of Se and Se-containing compounds is based on their ability to act as antioxidants as well as modulate the immune system. Se in se-

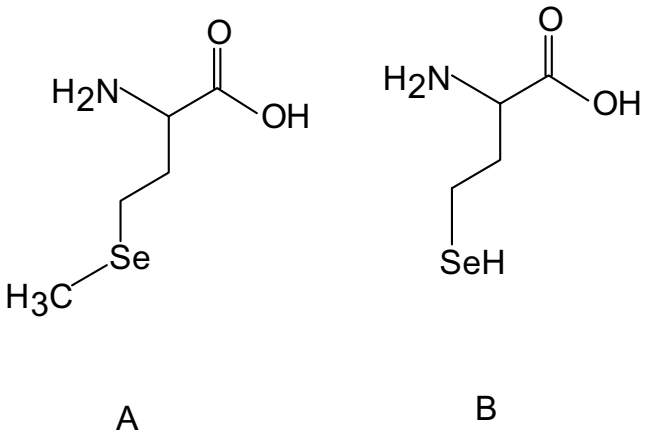

Fig. 1. Chemical structures of selenomethionine (A) and selenocysteine (B)

$$2GSH + H_2O_2 \rightarrow GS–SG + 2H_2O \quad (1)$$

$$GS–SG + NADPH + H^+ \rightarrow 2\,GSH + NADP^+ \quad (2)$$

Fig. 2. An example of a reaction that is catalyzed by glutathione peroxidase (1) and a regeneration of glutathione catalyzed by glutathione reductase (2).

GSH – glutathione, γ-glutamyl-cysteinyl-glycine
GS-SG – glutathione disulfide
NADPH – nicotinamide adenine dinucleotide phosphate (a reducing agent)
$NADP^+$ – oxidized form of NADPH

lenoproteins helps to protect organisms from the consequences of oxidative damage as glycoprotein glutathione peroxidase (EC 1.11.1.9) reduces biological peroxides to alcohols and also reduces free hydrogen peroxide to water [5, 6]. An example of the reaction catalyzed by glutathione reductase is shown in Fig. 2. In most organisms, glutathione peroxidase enzyme is present in different isoforms that differ in cellular location and substrate specificity. The most common is glutathione peroxidase 1 that is generally present in the cytoplasm of majority of mammalian tissues. Hydrogen peroxide is its preferred substrate. Other glutathione peroxidases are glutathione peroxidase 2, 3 and 4. Their concentrations in cells are generally lower compared to glutathione peroxidase 1 [6].

It has been confirmed that the positive effects of Se on human health depends on a chemical form of Se and on its concentration. High concentrations of Se in any chemical form may be cytotoxic and possibly carcinogenic. Se in physiological cellular concentrations exhibits its anti-oxidative properties that is an integral of all ROS-detoxifying selenoenzymes, especially selenocysteine containing enzymes. Cytoprotective effects of these concentrations of Se were observed in various types of cells. It also appears that high concentrations of Se may be used for cancer chemoprevention as the antioxidative effects of selenoenzymes and pro-oxidative effects of some other Se-containing substances in tumor cells may result in a reduction of carcinogenic processes and also in an introduction of some anti-carcinogenic processes [7]. There are many scientific reports published that employ different methodologies for Se identification and quantification. Additionally, these reports are based on detection of different Se-containing substances all of which lead to conflicting conclusions [8].

Genomic stability and/or instability are essential in the determination of an individual's predisposition to carcinogenic processes and consequently to cancer. It has been shown by various epidemiological studies that there is a relationship between nutritional status and cancer risk. These studies stress the importance of inorganic elements, including Se, in ensuring the stability of the human genome [9]. Sodium selenite, an inorganic form of Se, was found to induce various kinds of DNA damage, mainly DNA double-stranded breaks and some other kinds of damages [10, 11] that were not detected after selenomethionine and Se-methylselenocysteine administration [12]. The importance of inorganic Se substances for human organism is not very clear as they are not present in human food in substantial quantities and their biological activity is limited by their low bioavailability. Generally, inorganic forms of Se are more toxic when compared to Se-containing organic compounds [13].

Se as a chemopreventive agent has an ability to increase the therapeutic effects or decrease toxic side effects of some clinically used antineoplastic agents. These allow new treatment options of applying combinations of anti-cancer agents with Se [13]. For example, doxorubicin (DXR) and cyclophosphamide (CP) belong to a class of widely used anticancer agents. However, their therapeutic use is limited by toxicity. Consequently, various attempts have been made to limit these toxic side effects. As indicated above, selenomethionine exhibits protective effects in anticancer therapies because of its antioxidative properties and also because of its ability to modulate processes of DNA repair. In general, selenomethionine causes a decrease in DNA damage of cells exposed to cytotoxic agents [14]. Se inclusion in CP therapy of mice with Erlich ascitic carcinoma led to renewal of activity of antioxidative enzymes, improved hematologic profile of these animals to almost normal and reduced cellular toxicity normally induced by CP. The result of these improvements was an increase in the survival time of experimental mice and generally improved therapeutic efficacy. [15]. Synergistic, in some cases additive, effect of combinations containing Se and cytostatic agents have been documented [16]. Inadequate data have accumulated over time to show that the inclusion of Se into chemotherapeutic regimens leads to a reduction of cytotoxic side effects without lowering antineoplastic activity or overall therapeutic outcomes.

In contrast to its use in chemotherapy, Se is being more widely used as a component of various nutritional preparations. Effects of Se in chemoprevention, inhibition and reversal of carcinogenic processes is being extensively investigated. This is due to the fact that various natural sub-

stances are used in conventional tumor therapeutic regimes as adjuvant form of therapy. In this regard, some basic, clinical and epidemiological studies of combinations of Se with other chemoprotective agents, e.g. vitamin E, have revealed a synergistic action compared to each agent alone. Additionally, combinations of Se and other chemoprotective agents investigated by epidemiological, clinical and experimental studies were shown to demonstrate synergistic effect compared to effects for individual constituents of the tested combinations [13]. Se combined with vitamin E is an example of a such combination. Se and vitamin E combination was tested in several cell lines and it was found that the combination led to a modulation of Bax and Bcl-2 enzymes and to the induction of apoptosis [17]. Shortcomings of many similar studies are lack of controls studying interaction of Se with chemotherapeutic agents and lack of data on relevant biomarkers. Furthermore, the majority of published studies were done following only a short-term administration with no long-term Se administration studies to evaluate additional benefits or possible increase of toxicity. Consequently, the credibility of many data on chemopreventive effects of Se and other nutritional agents requires future verification in additional experiments and studies [18]. Such future studies also need to focus on clinical use of Se in tumor chemoprevention and on studying the mechanisms of Se action. Furthermore, determination of the optimal Se concentrations that are beneficial to humans in the short-term and long-term is really essential. Polymorphism in Se-containing proteins in relation to risk of cancer should also be considered in these studies [19] as these can confound the outcomes or interpretation of the data. It should be noted that most of the data recently obtained in clinical tests did not confirm data obtained in *in vitro* and also in *in vivo* experiments in animal models. Caution should therefore be taken when extrapolating data from or between specific experimental models as this may not be possible since chemoprevention is really a multidisciplinary area requiring the cooperation of molecular biologists, medical oncologist, statisticians and nutritional specialists [20, 21]. As a result of the long-term interest in Se for its anticancer properties, this review aims to summarize the progress in selenium-related research and to highlight our current understanding of Se anticancer effects based on pre-clinical and clinical investigations.

Selenium and chemoprevention.

Selenium and chemoprevention of colon cancer. Data from various preclinical and epidemiological studies and from some clinical trials justify consideration of selenium as a potential chemopreventive agent for colon cancer [22]. It has been established that pools of methylselenol and related metabolites play key roles in chemoprevention as they target both endothelial and colon cancer cells [23]. Other possible mechanisms of action of Se that may take place in colon cancer chemoprevention are the inhibition of cyclooxygenase and cytosine methyltransferases, interaction with carcinogens and the activation of p53 [24]. The activation of p53 leads to dependent growth inhibition through induction of G2/M cell cycle arrest and apoptosis [24]. Additionally, it was shown that Se, in combination with calcium and some nonsteroidal anti-inflammatory drugs, has a modest effect in colon cancer chemoprevention [25]. However, despite the fact that this effect is modest, it can be compared with the effect observed with colon cancer screening [25]. The advantage of Se use in chemoprevention is its additional anticancer effect that may be useful in combination with other anticancer agents for colon cancer therapy [13]. There is evidence indicating that Se supplementation decreases a risk of colon carcinoma and the frequency of ademato us polyps in the colon [25]. Despite this the use of Se in chemoprevention of colon cancer is not yet advocated as a standard medical intervention since currently available data are clearly controversial [13] thus detailed and carefully designed basic, clinical and epidemiological investigations are still required [26].

Selenium and chemoprevention of prostate cancer. Prostate cancer represents an attractive target for chemoprevention because of its long latent period before clinical, age-dependent manifestations of the disease. This cancer is also important because of its frequency of occurrence. Several scientific works present data obtained in experimental models indicating that Se is effective in reducing prostate cancer rate and hence, it is now accepted that chemoprevention may play an important role in the prevention of this type of cancer as revealed by the Cancer Prevention Trial started in 2003 [27].

Since the prostate gland is an androgen-dependent organ, androgen signaling plays a key role in prostate cancer and therefore is critical in chemoprevention of this cancer [28]. It has been documented that selenium-containing substances such as MSeA are capable of decreasing the expression of androgen receptors and prostate-specific antigen (PSA). It was also demonstrated that MSeA inhibits the growth of prostate cancer cells through down-regulation of the androgen receptor, primarily by reducing the protein level of the androgen receptor [28]. It was concluded that MSeA's mechanism of prostate cancer inhibition justifies an intervention strategy that would use Se to inhibit prostate cancer progression [28].

As data continues to accumulate on the positive role of Se in prostate cancer prevention, some original Se substances related to the active Se metabolite, selenomethionine, are being investigated for *in vivo* activity. Examples of promising compounds are once again MSeA and methylselenocysteine (MSeC) [29]. It was demonstrated in mice that these compounds clearly delayed cancer lesion progression together with increasing apoptosis and decreasing proliferation of cancer cells thus, effectively inhibiting this model of prostate cancer carcinogenesis [29]. This is generally in agreement with data available on other selenium-containing substances [28].

Furthermore, documented preclinical and epidemiological data supported by phase III trials combining Se with vitamin E have revealed beneficial effects in prostate cancer prevention [27]. Selenium-vitamin E combination is pos-

sibly beneficial to men due to a synergistic action of these substances in arresting cell-cycle, inducing apoptosis and arresting clonal expansion of nascent tumors. As a result of the clear cut benefits of Se chemoprevention in prostate cancer, large scale clinical trials and investigations have been commisioned. The NCI sponsored a phase III trial called 'The Selenium and Vitamin E Cancer Prevention Trial (SELECT)' involving 35,535 men, the results of which were scheduled to be released in 2013 [27, 30]. The potential preventive mechanism of action of Se is to be fully elucidated at the molecular and cellular levels using modern techniques and approaches such as genomics and proteomics. For example, it has already been determined that Se significantly alters genes for cyclin D1, cdk5, cdk4, cdk2, cdc25A and GADD 153 [31]. Some of these studies and their findings should help to determine the optimal chemopreventive dose of Se and also reveal any additional genes that may participate in the chemopreventive processes [32]. In general, these will be predicted to be genes of the phase II detoxification enzymes, apoptotic genes and also genes related to cellular proliferation. Molecular or genetic biomarkers are playing an important role in determining specific molecular events that involve Se [32]. The results of SELECT were recently released ahead of schedule [33]. Unfortunately, they show that there was no decline in prostate cancer. Recommendations of this trial are for additional analyses of the obtained data to be performed to better understand all the processes involved in chemoprevention of cancer by Se with the goal to identify men who may most likely benefit from Se supplementation [33].

There may be two main reasons why SELECT did not detect any decline in prostate cancer incidence. The first reason may be that selenomethionine was used as the source of Se. There is evidence from preclinical studies indicating that selenomethionine has weaker anticancer effects than most other forms of Se [34] and this may be reflected in the SELECT findings. Another reason for the obtained results may be the fact that the men who participated in this trial had relatively high initial levels of Se [33] and consequently, the provided supplementation did not result in a significant decline in prostate cancer incidence.

Data from another trial investigating the effects of a combination of Se and vitamin E supplementation are somehow more encouraging. The SU.VI.MAX trial comprised 5,141 men, randomized to take either a placebo or a supplementation with nutritional doses of vitamin C, vitamin E, beta-carotene, Se and zinc daily for 8 years. The overall finding of this trial was that "there was a moderate, albeit insignificant reduction in prostate cancer rate associated with the supplementation" [35]. Prostate cancer reduction was statistically significant in men with normal values of PSA but not in men with elevated PSA [35]. Obviously, these two trials, SELECT and SU.VI.MAX, indicate that a huge need for further data gathering exists to fully realize the possible benefits of Se in chemoprevention. The currently available data are not sufficient to draw meaningful conclusion on the benefits of Se supplementation in men to decrease the risk of prostate cancer [36]. Indeed, the latest data from SELECT state that "selenium or vitamin E, alone or in combination at the doses and formulations used, did not prevent prostate cancer in this population of relatively healthy men" [37].

Selenium and breast and ovarian cancer chemoprevention. Considerations of Se as a chemopreventive agent in breast cancer are based on *in vitro* and *in vivo* animal studies as well as data from female breast-cancer patients. As in other cancer cases, laboratory and preclinical data are more positive than clinical results when Se is used for chemoprevention of breast cancer patients. Similar to prostate cancer, hormone-related signaling plays an important role in breast cancer cells [38]. Estrogen plays an essential role in the development and differentiation of various estrogen target tissues possessing estrogen receptors (ER). It was found that Se is capable of decreasing the levels of ER mRNA expression in MCF-7 cells while increasing ER mRNA expression in MDA-MB231 human breast cancer cells [38]. Furthermore, it has been shown that sodium selenite protects cells from chromosomal damage and gene mutations caused by UV radiation [39]. This protection depended on functional BRCA1 activity. It was also shown that supplementation of Se may lead to prevention or increased repair of DNA damage with participation of a specific selenoprotein (GPx-1). These laboratory findings will definitely be useful in future breast cancer prevention studies.

Even more relevant to chemoprevention is the fact that *in vivo* data show a synergistic action of organic selenium in the form of MSeC with tamoxifen in adjuvant therapy as well as in chemoprevention of breast cancer using MCF-7 breast cancer xenografts [40]. MSeC in combination with tamoxifen and also alone produced significant decrease in ER, cyclin D1 and in microvessel density. It also increased apoptotic activity in tumor tissue [40]. Consequently, ER positive breast cancer patients clearly seem to benefit from Se – tamoxifen adjuvant therapy and high risk patients may possibly also derive benefit from this combination as chemoprevention. However, it was revealed that interactions of Se with other metals may prevent positive outcomes. For example, lead (Pb) abolishes the anticarcinogenic effect of Se while Pb toxicity is counteracted by inactivation of Se [41]. Generally, Se stimulates detoxification of toxic metals such as arsenic, copper, nickel, cobalt, chromium, manganese, zinc, cadmium, tin, lead, mercury etc. in many organisms [42, 43, 44]. *In vivo* experiments showed that prolonged exposure to these metals abolished the cancer preventive activity of Se and hence the antagonistic activities of these elements should be taken into account when studying Se as a cancer chemoprotective agent.

Breast cancer chemopreventive effects of Se were documented in a study [45] investigating women with constitutional heterozygous mutations of the BRCA1. These women have significant risk of breast and ovarian cancers as their DNA are susceptible to breaks. It is being predicted that preventive intervention for this group of women should reduce chromosome damage resulting in a decreased rate of cancer. In this

trial [45], orally administered Se significantly reduced the observed frequency of chromosome breaks in mutated BRCA1 gene carriers to the level similar to non-carriers. In this case, Se seems to be a suitable option for cancer chemoprevention in this specific population group.

Data on ovarian cancer chemoprevention and Se is much more scarce compared to those on other types of cancer probably because no connection has been found between Se and the incidence of ovarian cancer. A multicenter study published in 2004 [46] based on data from 442 ovarian cancer patients diagnosed in 1994 and 2,135 controls found no association of ovarian cancer with Se supplementation. A similar conclusion was reached in a newer study published in 2008 [47] which involved 133,614 postmenopausal women.

Selenium and chemoprevention of lung cancer. As the major cause of lung cancer is cigarette smoking, lung cancer is probably one of the most preventable types of cancer. However as of now, no chemical substance is recommended for use as a chemopreventive agent but Se represents a possible candidate for serving as a nutritional supplement that would help prevent this and other cancers. Our current understanding of its molecular biology is being paid considerable attention. An excellent review [48] already addressed the involvement of selenoproteins in lung cancer. The conclusion is that Se would affect not only carcinogenesis but also tumor progression and development of metastasis. The majority of investigations concentrate on the levels and activity of glutathione peroxidase (GPx) because *in vivo* experiments using established carcinogens show that this enzyme is important in preventing processes of carcinogenesis [49, 50]. Many new organic substances are being tested for their ability to surpass 'traditional' inorganic sources of Se in diets since it is now clear that various selenium-containing substances are not the same in their cancer chemopreventive effects and that the structures of these substances are a major determinant of their cellular effect [51]. 2-Aryl/alkyl selenazolidines (Fig. 3.) are an example of synthetic organic compounds with an efficacy preventing carcinogenesis of lung tumors [50]. Recently, STAF [Sec tRNA gene transcription activating factor] (Sec = selenocysteine), a transcription activating factor for several RNA Pol III- and RNA Pol II-dependent genes that control the expression of all selenoproteins, was investigated using transgenic mice [52]. The expression of selenoproteins in these transgenic mice was most significantly affected in tissues with the Sec tRNA levels reduced the most. It was shown that the selenocysteine tRNA STAF-binding region played a key role in ensuring adequate selenocysteine tRNA status, expression of selenoproteins and in early age survival of the experimental animals [52].

In 1990, the possibility of preventing lung cancer with Se was investigated in 40 persons in China sampled from a population with an extraordinarily high lung cancer incidence [53]. The amount of Se supplemented was 300 μg daily for one year. It was concluded that this supplementation was beneficial to participants who started the study with inadequate amounts of

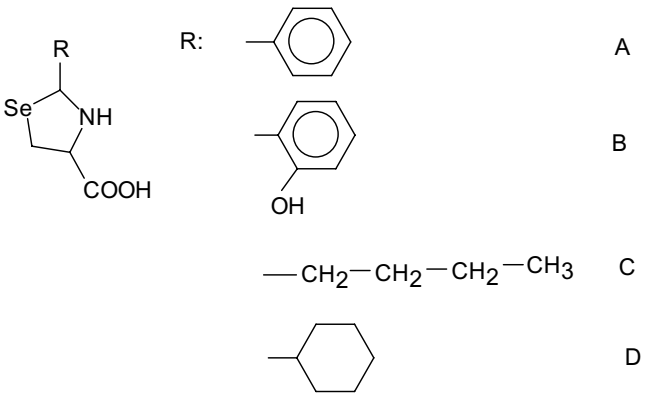

Fig. 3. Structure of organic selenium-containing compounds with chemopreventive activity: A) 2-phenylselenazolidine-4-carboxylic acid; B) 2-(2'-hydroxyphenyl)selanazolidine-4-carboxylic acid; C) 2-butylselenazolidine-4-carboxylic acid; D) 2-cyclohexylselenazolidine-4-carboxylic acid.

Se in their diet. Unfortunately, detailed follow up was not done in this cohort. Another study was also recently performed in China using various combinations of vitamins and minerals, including Se in 29,584 people [54]. This study participants took their supplements for more than 5 years and Se was provided to them in combination with carotene and vitamin E. The duration of the trial was from 1986 to 2001. No reduction in lung cancer mortality was observed in participants, including those taking selenium-containing combination [54]. Recent study of 424 patients [55] was based on "The Nutritional Prevention of Cancer (NPC)" study, in which participants were given 200 or 400 μg of Se per day. The results of this study revealed that Se supplementation decreased the risk of lung and some other cancers but there was an increased risk of non-melanoma skin cancer [55]. The overall conclusion of this study [55] was that 200 μg of Se per day decreased total cancer incidence by 25% which appears contradictory to other studies. Future trials, with better controls and involvement of additional nutritional factors are required before meaningful recommendations on Se supplementation in lung cancer can be made with confidence. .

Selenium and chemoprevention of skin cancer. Morbidity and mortality related to skin cancers are very high and Se seems to be a suitable candidate that may help to prevent them. Many studies dealing with chemopreventive activity of Se in skin cancer have been done and published. For example, it has been shown recently in mice that Se in various forms very effectively inhibits skin carcinogenesis [56, 57].

As a result of promising basic research data, a large number of clinical and epidemiological studies have been conducted. Unfortunately, the conclusions from all these studies are not very encouraging as they do not support the basic research data. This is possibly due to the fact that in real life studies, conditions are not as controlled as in basic

research and the selection of human subjects has more variables. A trial conducted in 1996 in the USA [58] addressed the question as to whether Se supplementation will lead to increased cancer incidence, namely basal and squamous cell carcinomas of the skin. It was concluded, based on the evaluation of 1312 patients that 200 μg Se daily did not significantly affect the incidence of both types of skin cancer. Additionally, The Nutritional Prevention of Cancer Trial that investigated the effect of Se (200 μg daily in the form of yeast) on followed individuals at high risk of nonmelanoma skin cancer demonstrated ineffectiveness of Se supplementation in chemoprevention of basal cell carcinoma and an increased risk of squamous cell carcinoma and total nonmelanoma skin cancer among participants [59]. Finally, Se supplementation was tested in organ graft recipients as they are known to have many pre-malignant and malignant skin lesions linked to HPV [60]. Again, Se supplementation did not prevent the occurrence of these types of skin lesions.

Selenium and liver cancer chemoprevention. Primary liver cancer is a common malignancy with a poor prognosis. The role of antioxidant with possible chemopreventive action has been considered in this malignancy. Oxidative DNA damage plays a role in initiation of hepatocarcinogenesis. This process is regulated or affected by various substances with antioxidative and chemopreventive potential. These substances possess an ability to inhibit carcinogenic processes in the liver and the inclusion of Se leads to an overall synergistic anticarcinogenic effect [61]. A few basic research data and several clinical investigations in human subjects have been reported regarding the use of Se as a chemoprotective agent in hepatocarcinomas.

An *in vivo* study [62] in rats with diethylnitrosamine-induced hepatoma tested the effects of Se enriched diet (in the form of selenized malt or sodium selenite) on tumors. This diet showed efficiency in preventing the formation of hepatoma nodules and in delaying a decrease in serum levels of insulin, glucagon and thyroid hormones. Another *in vivo* study found that a change in the expression of selenoproteins either suppresses or promotes tumorigenesis but this process depends on the genotype and cell type [63]. Thus, Se supplementation and also dietary Se may result in chemopreventive effect or in carcinogenicity. Because of this, it is necessary to determine more precisely who would benefit from Se supplementation and who will not [63]. This finding may have general implications for other types of cancer. For example, only a partial chemopreventive effect was reported for selenomethionine in mice [64] as it inhibited gene expression and reversed up-regulation of several inflammation-controlling genes and modified response to oxidative stress. All of these changes resulted in a reduction of incidence of large tumors. A positive hepatocellular carcinoma chemopreventive effect of Se was also reported in Syrian hamsters [65]. Positive relationship between high serum concentrations of Se and the risk of liver cancer has been reported even in humans [66].

Conclusion

This review discusses options of using Se for chemoprevention of cancer and compares results from basic laboratory experimental models with obtained clinical and epidemiological data. Future prospects of a broader use of Se in cancer chemoprevention are discussed based on our current knowledge and information.

It is obvious from the data accumulated on Se chemopreventive potential that there is still a lot to be learned. The bulk of the obtained data clearly indicate that Se is no panacea and just increasing its general plasma concentrations through supplementation would definitely not benefit all potential cancer patients. Indeed, in some cases Se supplementation could lead to an increased risk for some cancer as documented for prostate cancer in men with elevated PSA values [28], nonmelanoma skin cancer [59] and liver cancer [65].

On the other hand, clinical investigations succeeded in identifying some population groups and certain cancers that clearly benefit from Se supplementation. These are colon cancer patients [22], prostate cancer men with near normal PSA values [35], and breast cancer ER positive patients (especially in combination with tamoxifen), [40]. Se decreases significantly the risk of breast cancer in women with mutated BRCA1 gene [45] and also the risk of lung cancer in individuals with inadequate Se concentrations in their body [53]. Se supplementation, in general, does not prevent or affect (positively or negatively) the risk of ovarian cancer in the general population [46, 47] as well as the risk of many types of skin cancers [58].

It seems to be clear that further investigations of Se chemopreventive anti-cancer potential have to be considered before its use in humans. These include studying Se concentrations and dietary intake of Se in targeted population as well as concentrations of many metals, such as lead, arsenic, copper etc. It should be kept in mind that just having or achieving a high Se concentration in the body does not automatically provide protection against all types of cancer as seen in men with initially high PSA values. The conclusions that can be drawn from the accumulated data so far are: 1) to keep Se dietary intake, and consequently Se body concentration at physiological level, and 2) in cases where the cancerous processes are at the beginning, to consider reactions of the particular cancer type to an increased Se supplementation and selenium-cancer therapy interactions.

Attention is also being paid, with varying degree of success, to combining Se with other bioactive substances. Se combinations with vitamin E and other antioxidants are an example of combinations regarded by many as rational and successful [27, 30, 35, 52, 55]. However, it was shown in a large population of American men (35,533) that Se or vitamin E alone or in a combination do not act to prevent prostate cancer [37]. As this did not confirm results published earlier, Se and vitamin E supplementation was not recommended to patients for prostate cancer prevention [67] until the credibility of the earlier results is verified [18].

New findings from *in vivo*, clinical and epidemiological studies indicate a need to re-orient these investigations towards more specific work involving elucidation of mechanisms of antioxidative processes as these mechanisms differ in preventing cellular oxidative stress [68]. At present, our understanding of the biological role of Se is limited. It is necessary to devote more time and resources towards understanding of gene polymorphism and their varying regulation in the clinical setting. For example, gene expression profiles in target tissues in rats with increased or normal Se intake were compared using DNA microarray technique. It was revealed that chemoprevention by Se changed the expression of many genes important for cell cycle regulation, tumor growth regulation, metabolism and apoptosis [69]. In these studies, it became clear that many Se-induced changes in gene expression were related to the experimental models or systems used. These differences could have important or serious implications when applied in a clinical setting [69]. Furthermore, it is highly likely that other factors, such as genotype, general health status and Se status, play a role in chemoprotection [33]. The conflicting results from clinical studies have led to the hypothesis that Se supplementation may result in significant and observable cancer chemoprevention only in Se deficient population [30]. Since the majority of clinical studies were performed in heterogeneous populations and very often used only limited number of subjects with differing confounding factors that may have affected the outcomes, scientists and clinicians should take these conclusions and recommendations with extreme caution as they are of limited validity. On the other hand, it is possible that a therapeutic benefit of Se, especially in combination with other anticancer agents may be to decrease the dose of the primary drug leading to decreased toxic side effects and improved therapeutic outcome [13, 14, 15, 16, 70].

In general, the results from the numerous cancer chemoprevention studies of Se are not convincing at the present time. As improved and more sensitive research tools and techniques continue to be developed, further *in vitro* and *in vivo* experiments need to be done. Clinical studies should examine Se effects in healthy volunteers as well as in well screened and selected patients with fewer confounding factors so that any results obtained can be better interpreted and broad conclusions drawn. Unfortunately, based on the currently available data, it is not possible to recommend the use of Se for cancer chemoprevention.

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