

Effect of the Interaction Between Selenium and Zinc on DNA Repair in Association With Cancer Prevention

REVIEW

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Cancer is the most common cause of death worldwide. Annually, more than ten million new cancer cases are diagnosed, and more than six million deaths occur due to cancer. Nonetheless, over 80% of human cancer may be preventable through proper nutrition. Numerous nutritional compounds are effective in preventing cancer. Selenium and zinc are essential micronutrients that have important roles in reducing oxidative stress and protecting DNA from the attack of reactive oxygen species. Selenium is an essential trace element that possesses several functions in many cellular processes for cancer prevention. Meanwhile, zinc may have protective effects on tumor initiation and progression, and it is an essential cofactor of several mammalian proteins. Results show that both selenium and zinc provide an effective progression of DNA repair system; thus, cancer development that originated from DNA damage is decreased. Results mostly focus on the separate effects of these two elements on different cell types, tissues, and organs, and their combined effects are largely unknown. This review aimed to emphasize the joint role of selenium and zinc specifically on DNA repair for cancer prevention.

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Key Words: Trace elements, Selenium, Zinc, DNA repair system, Cancer prevention

INTRODUCTION

According to several *in vivo* and *in vitro* studies, adequate nutrition is indeed vital for cells to function properly, given that nutrients have numerous active ingredients, such as proteins, essential minerals, vitamins, and carbohydrates. Clearly, the percentage of deaths, especially cancer deaths, may remarkably reduce by paying attention to healthy nutrition [1].

Selenium and zinc are two essential micronutrients that have well-known functions, such as alleviating oxidative stress and protecting DNA from reactive oxygen species (ROS) attack. Thus, investigation on the role of zinc and selenium micronutrition in preventing neoplastic diseases have gained considerable research interest [1,2].

Numerous dietary compounds have been implicated in the prevention of cancer. Among them, zinc is a key cofactor of many

mammalian proteins that may have protective effects on tumor initiation and progression. Zinc is the most abundant trace intracellular element, playing an important role in both genetic stability and function. Several studies reported that the elderly population of Europe has considerable zinc deficiency as a result of perturbation of zinc homeostasis caused by aging [1,2].

Selenium is another essential trace element that is vital for various cellular processes and also frequently used in cancer prevention. It has an antineoplastic feature, largely because it can inhibit ROS production, thereby preventing oxidative DNA damage [3].

In addition, both selenium and zinc have a role in the efficient progression of DNA repair system, thereby alleviating DNA damage, which could otherwise result in cancer development [4].

Although many *in vivo* and *in vitro* studies were performed to determine the effect of separate administration of these two

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elements on different cell types, tissues, and organs, their joint effects on these tissues and organs are poorly known. Interactions that may have occurred between selenium and zinc as a result of their bioaccumulation in tissues are important, considering that they may have substantial adverse effects not only on ROS generation via disrupting the metallothionein/thionein system, as shown by Maret [5], but also on the DNA repair process.

This review aimed to emphasize the role of selenium and zinc specifically on DNA repair for cancer prevention and chemotherapeutic efficiency and to explain possible interactions between these two elements for their DNA repair role [5]. At first, functions of selenium and zinc in the DNA repair system are discussed separately on a molecular basis, followed by the effect of their possible interaction on the DNA repair system in relation to cancer development.

1. Selenium

Selenium is a trace element that is essential for various cellular processes. At the beginning of the 20th century, selenium was regarded as an undesired element because of its confirmed toxicity [6].

However, in the late 20th century, the vitality of selenium for human nutrition and health remarkably changed. The pioneering work of Schwarz and Foltz [7] revealed that selenium at a low concentration is an essential nutrient; the dietary value of selenium comes from its incorporation into various essential enzymes and proteins, such as the amino acid selenocysteine [7].

Apart from its essentiality as a micronutrient, selenium has anticancer properties, as clearly shown in laboratory and clinical studies [8-11]. Selenium in pharmacologically active dietary concentrations can prevent cancer development, especially as a chemoprotector against carcinogenic compounds [3]. However, results of these previous studies are relatively conflicting, probably because different inorganic and organic selenium compounds (i.e., selenite and selenomethionine) and different selenium concentrations were used, as well as studying either with animal models or human subjects [3,9-11].

While selenium at low concentrations has protective effects against cancer development, it may be genotoxic at high concentrations [12]. Its high toxicity can be probably explained by the generation of ROS and subsequent DNA oxidation in vivo [13-17].

In addition to its anticarcinogenic properties, selenium has antimetastatic effects in terms of cell migration, invasion, and angiogenesis, especially in breast, colorectal, melanoma, liver,

lung, prostate, and brain glioma cancers [18].

Selenium has diverse anticancer mechanisms, such as ROS production, thiol modification, chromatin binding/modification, and DNA repair [19]. In this review, we focus on its role in DNA repair mechanism as an anticarcinogen.

2. Anticarcinogenic role of selenium through the DNA repair system

Although carcinogens induce genetic damage by forming covalent DNA adducts, such formation is insufficient to initiate carcinogenesis, which is rather a multistep process. To understand the effect of selenium in this multistep DNA-adduct formation process, researchers performed numerous in vitro studies, mostly with rodents. In these studies, selenium was used in the form of selenite, selenate, 1,4-phenylenebis(methylene) selenocyanate, or diallyl selenide; these different selenium compounds inhibit the initiation of carcinogenesis caused by numerous carcinogens in the colon, lung, liver, and mammary tissues in rats [9]. The possible rationale for this type of carcinogen prevention is that selenium inhibits the cytochrome P450 system Phase I enzymes, which normally convert chemical carcinogens into reactive DNA-attacking adducts.

Moreover, selenium compounds can inhibit carcinogenesis in the late initiation stages, suggesting an additional mechanism of selenium for chemoprevention. This additional chemopreventive mechanism of selenium compounds may be the inhibition of cell growth with induction of tumorigenic cell apoptosis [20,21]. Selenium-mediated apoptosis may prevent the accumulation of carcinogen-induced transformed cells and subsequent clonal expansion of the transformed cell population [22]. In a study conducted with cultured LNCaP prostate cells, researchers focused on the protective role of selenium against genotoxicity generated by multiple chemical agents [23]. When treated with low concentrations of two different selenium compounds (i.e., sodium selenite and selenomethionine), LNCaP cells, which are the wild types of p53 and Rb genes, showed a significant decrease in oxidative DNA damage together with an improved DNA repair capacity after H₂O₂ or UVA treatment.

Overall, selenium prevents carcinogenesis by protecting the genome against oxidative damage and enhancing its repair.

In addition to the selenium's abovementioned anticancer activities such as carcinogen detoxification, inhibition of angiogenesis, and tumor cell invasion, selenium has an immune boosting effect, which may reduce cancer risk; however, studies on selenium and anticancer immunity are limited [24,25]. One of these limited studies was performed by Kiremidjian-Schumacher

et al. [26] in which they used small groups of human subjects receiving either selenium supplementation (200 µg/d) or placebo. They measured cytotoxic T lymphocyte-driven tumor lysis, mitogen-induced proliferation of lymphocytes, and mixed-lymphocyte-reaction proliferation of lymphocytes; all results suggested that selenium supplementation increased lymphocyte performance.

Studies conducted with selenium regarding cancer development are mainly focused on its chemopreventive role in cancer [11]. However, cancer chemotherapeutics is another potential area for selenium's anticancer activity, and selenium has shown remarkable promise in preclinical trials. Recently, colloidal selenium nanoparticles have been used as carriers of chemotherapeutic agents to minimize the adverse effects of chemotherapeutic drugs and also to improve the effectiveness of anticancer activity by generating a synergistic effect between selenium and its chemotherapeutic cargo [27].

In several other studies using cultured cells and animal models, the presence of selenium yielded a positive effect on reducing DNA-adduct formation and chromosome breaks, which would otherwise contribute to carcinogenesis. This anticarcinogenic feature of selenium is attributed to being a critical constituent of certain selenoproteins, such as glutathione peroxidases and thioredoxin reductases, which are important for oxidative defense. Aside from its antioxidant activity, selenium may also exhibit protection against DNA damage by increasing the activity of DNA repair enzymes, such as DNA glycosylases, and repair pathways that involve members, such as p53 and BRCA1 [28].

p53 is an important member of these repair pathways, and it is controlled by the ataxia telangiectasia, mutated (ATM) and ATM and Rad3-related (ATR) protein kinases. When different types of cellular DNA damages occur, ATM and ATR respond via phosphorylation of the same substrates. In case of ionizing radiation (IR)-induced DNA double-strand breaks (DSBs), ATM responds as a primary mediator. ATR does not only have a supporting role in the DSB response but also a directing principle response to UV damage. As a result, ATR stops DNA replication [29].

Moreover, p53 has a functional role in G1 cell cycle checkpoint. ATM and ATR kinases control the accumulation and activation of the p53 protein in the center of this checkpoint. p53 expression is maintained at a low level in normally growing cells by MDM2, which provides nuclear export of p53 to the cytoplasm, given that degradation is a general mechanism for regulating p53 levels [30]. Immediately after exposing the IR damage, ATM phosphorylates Chk2 at position T68, which activates p53 via phosphorylation

residue S20. When p53 is phosphorylated at the S20 site, p53/MDM2 interaction is blocked, resulting in p53 accumulation. Thus, MDM2 is a p53 negative regulator. Meanwhile, ATM regulates p53 by phosphorylating MDM2 on S395 [31]. ATR also activates p53 with S20 phosphorylation by the phosphorylating ATR-dependent kinase Chk1 [32]. Activated p53 regulates numerous nuclear DNA repair enzymes that provide cell cycle arrest, DNA repair, and apoptosis in mammalian cells [33] (Fig. 1).

Among the major DNA repair pathways, nucleotide excision repair (NER) is the main way to eliminate bulky DNA lesions such as 6-4 photoproducts and cyclobutane pyrimidine dimers resulted from UV radiation. Likewise, NER repairs platinum-DNA adducts caused by platinum-containing cancer chemotherapeutics [34]. NER has two distinct repair pathways; one is the global genomic repair, and the other is transcription-coupled repair. Both pathways have the following three common steps: recognition of the damaged DNA region, excision of the damage, and resynthesis. The two pathways only differ in the initial recognition step.

In global genomic repair, p53 regulates damage recognition by transcriptionally controlling the DNA damage recognition proteins, namely, the xeroderma pigmentosum complement groups C (XPC) and E (XPE). In a study, p53 transcriptionally forced the expression of p48/XPE/DDDB2, thereby enhancing the global genomic repair [35,36]. Similarly, in a p53- and DNA

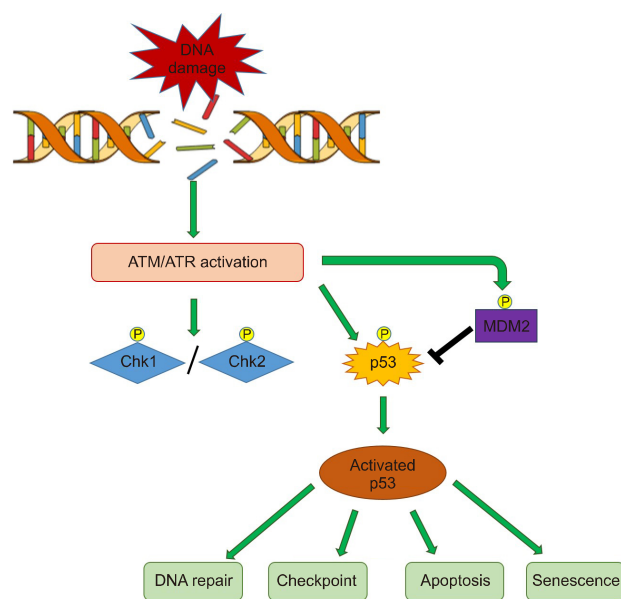


Figure 1. Schematic representation of ataxia telangiectasia, mutated (ATM)/ATM and Rad3-related (ATR) kinase activation and subsequent p53 activity upon DNA damage.

damage-dependent manner, the mRNA and protein expression levels of XPC increased [37].

In a study conducted with selenomethionine as selenium source, selenium could only regulate and enhance DNA repair in cells with wild-type p53 [38]. For an efficient DNA damage protection, selenium requires redox factor 1 (Ref-1), which interacts with p53 to reduce p53 cysteine residues; this reduction requires an enzyme, that is, selenoprotein-containing thioredoxin reductase [38-40].

In another study, primary, low-passage mouse embryonic fibroblasts that are wild type or null for p53 genes were used to test the differential effects of selenium before exposure to UV radiation or UV-mimicking chemotherapy drugs; then, seleno-L-methionine pretreatment of cultured cells was performed. This pretreatment induced DNA repair response and prevented subsequent DNA damage by UV radiation or UV-mimicking chemotherapeutics only in cells with wild-type p53, not in p53-null cells [41].

In conclusion, selenium enhances DNA damage response by increasing the expression levels of DNA repair proteins. Another remarkable point is the p53 dependency of selenium to exhibit all these DNA repair-improving features, considering that selenium did not induce the initial recognition step of NER without p53. Hence, selenium only protects genetically normal cells from DNA-damaging chemotherapeutics but has no protective effect on p53-null or p53-mutant cells [41]. Thus, selenium can be used in combination with cancer chemotherapeutics because of its protective effect on tissues from dose-limiting toxicity. Furthermore, selenium takes the advantage of not protecting p53-null or p53-mutated cancer cells from DNA damage, given that its DNA repair-enhancing activity is p53 dependent.

3. Zinc

Zinc has well-known functions in several cellular processes, such as reproduction, cell proliferation, immune function, and protection against free radicals [42,43]. Being the most abundant trace element, zinc generally participates in protecting genetic stability and function [44]. In *in vivo* and *in vitro* studies, zinc was predominantly found in cell nucleus, indicating a role for regulating gene expression [45]. Moreover, zinc has an effect on DNA by chromatin structure recruitment, DNA replication, and DNA repair [46]. Zinc is an essential component of more than 3000 transcription factors with zinc-finger DNA-binding domains. It is also a cofactor for more than 300 enzymes, such as copper/zinc superoxide dismutase (CuZnSOD) and various DNA repair proteins [47]. Clearly, zinc is vital for many cellular

processes ranging from oxidative stress to DNA damage repair.

Antioxidant function of zinc can be first attributed to being a component of CuZnSOD enzyme, which is the cell's leading defense enzyme against ROS attack. Second, zinc is the antagonist of redox-active transition metals, such as copper or iron, and it prevents the oxidation of proteins' sulfhydryl groups. This effect of zinc on sulfhydryls can protect sulfhydryl-containing proteins (e.g., tubulin and zinc-finger proteins), alanyl tRNA synthetase from thiol oxidation, and disulfide formation. Enzymes are inactivated if zinc is eliminated [43,48,49].

Another antioxidant mechanism for zinc is its regulation of metallothionein metabolism. Metallothionein is a scavenger antioxidant protein with small molecular weight, and it regulates zinc homeostasis. Zinc directly binds and activates metal transcription factor 1, causing the induction of cysteine-rich metallothionein protein expression.

However, the only effect of zinc on DNA stability does not involve its antioxidant feature. Zinc also takes role in gene expression regulation via zinc-finger transcription factors, which are especially important for the regulation of DNA repair genes. Many DNA repair proteins contain zinc-finger domains [50].

4. Regulatory function of zinc in the DNA repair process

Both base excision repair (BER) and NER systems have zinc-finger or zinc-associated proteins. Zinc-finger motifs function in protein-protein and protein-nucleic acid interactions in several proteins, such as the DNA repair system members. The role of Zn(II) ion in this motif is that it binds to cysteine thiolates and histidine imidazole groups, thereby maintaining the structure and function of the domain. As a result of the oxidation of thiolate donors, Zn(II) can be substituted with other metal ions or can be released from the protein structure, finally distorting the zinc-finger motif. Concordantly, certain carcinogenic metals (e.g., cadmium, nickel, and arsenic) and potential carcinogens (e.g., lead), as well as endogenous oxidative substances, may disturb zinc-finger domains and inhibit the function of protein. Thus, this reactivity can be an alternative molecular mechanism in carcinogenesis [51].

As clearly depicted, zinc nutrition deficiency can be an important risk factor for DNA damage and subsequent cancer development because it is a key component of proteins functioning in antioxidant mechanism, DNA repair, and p53 protein expression. In a study examining the effect of zinc deficiency on DNA damage and expression of DNA repair enzymes in primary human lung fibroblasts, intracellular zinc

was depleted by different ways, such as growing cells in a zinc-deficient medium, thereby exposing cells to an intracellular zinc chelator [52]. Microarray analysis data revealed that genes related to oxidative stress and DNA repair were upregulated, whereas other DNA repair genes were downregulated. In addition, zinc deficiency caused oxidative stress, p53 overexpression, and generation of single-strand breaks on DNA. Thus, zinc deficiency does not only cause oxidative stress-mediated DNA damage but also disrupts the DNA repair ability of cells [52].

Hence, the tumor suppressor protein p53 is the key regulator of the DNA repair process. This protein is important in cell cycle progression, apoptosis, and DNA repair [53]. One of the major functions of p53 is to arrest the cell cycle in G1 phase, allowing cells to properly repair its DNA before cytokinesis. More than 50% of human malignancies contain a p53 mutation of which the majority are found in the DNA-binding domain gene-coding region [54-56]. Given that this binding region contains a zinc-binding domain, p53's binding ability to DNA targets significantly declines in case of zinc deficiency [57]. Importantly, p53 is a transcription factor that has to have the ability to bind to DNA promoter regions to control certain events, such as DNA repair. Zinc-deficient cells cannot increase p53 expression because this p53 is, in fact, dysfunctional and cannot regulate the expression of DNA repair genes.

Same research group also investigated the effect of low zinc concentration on the expression of an important BER enzyme, that is, apyrimidinic endonuclease (APE) [58]. Oxidative DNA damage is primarily repaired by the base excision system [50]. In this pathway, APE (also known as Ref-1) cleaves the damaged sites in DNA. It is a multifunctional protein that also participates in controlling the DNA-binding activity of various transcription factors, such as AP-1 and P53, involved in carcinogenesis [59]. In zinc-deficient cells, same as in cancer cells, APE expression elevates, likely because of DNA damage caused by low intracellular zinc [57,60].

To demonstrate the importance of zinc concentration on DNA stability by analyzing changes in global gene expression and transcription factor-binding abilities in prostate tissue, researchers used normal prostate epithelial cells. In such cells that were grown in zinc-deficient media, more single-strand DNA breaks were present than those in cells grown in media with adequate amount of zinc for 7 days [61]. DNA repair genes such as the tumor protein p73, MRE11 meiotic recombination 11 homolog A, X-ray repair complementing defective repair in Chinese hamster cells 4, and breast cancer 2 were downregulated at first onset. Western blot also revealed that nuclear p53 levels were

upregulated in zinc-deficient cells. However, the binding activity of p53 did not significantly change, indicating the impaired function of zinc-containing proteins involved in DNA repair [61].

As evidently depicted in the previous sections, both selenium and zinc are essential for the proper regulation of different DNA repair processes, such as BER and NER. Hence, an interaction between selenium and zinc may be present on the progression of DNA repair.

5. Importance of selenium and zinc interaction on DNA repair regarding cancer prevention

In addition to agents that directly or indirectly induce DNA damage, several agents, such as metal compounds, nickel, arsenic, cobalt, and cadmium, can directly interfere with the DNA repair process and especially inhibit the BER/NER pathways, thereby increasing the negative outcomes of DNA damage. Target molecules for these metal ions may possibly be the zinc-finger domains of DNA repair proteins [62,63]. Furthermore, zinc-finger motifs may be sensitive not only for toxic metal ions but also for some trace elements, such as selenium. In a study performed with two zinc-finger repair proteins, namely, bacterial formamidopyrimidine DNA glycosylase from the BER pathway and xeroderma pigmentosum group A protein (XPA) involved in NER, certain reducible selenium compounds decreased the activity of zinc-finger motifs and induced the release of zinc from these motifs [64].

These findings indicate that reducible selenium compounds may interfere and inhibit DNA repair response via the oxidation of zinc fingers in DNA repair proteins as well as in the transcriptional regulators of DNA repair genes, such as p53 [50]. In another study, osteosarcoma and lymphocytes treated with reducible selenium compounds clearly lost their abilities to repair UV-induced DNA damages, such as chromosome deletions and chromatin breaks [65]. Therefore, selenium may directly inhibit DSB repair and transcription-coupled repair systems.

Conversely, according to some other study results, DNA repair capacity increases in selenomethionine-treated human fibroblast cells exposed to UV radiation, and selenomethionine has a protective role against UV-induced DNA damage in keratinocytes [66,67]. The reason for these conflicting results might be the difference and complexity of forms and doses of selenium compounds. Moreover, these differences about selenium compounds have widely varied effects on DNA integrity and DNA repair processes; these effects include SH group oxidation and zinc release from zinc fingers in DNA repair proteins.

Although the effects of selenium + zinc supplementation on

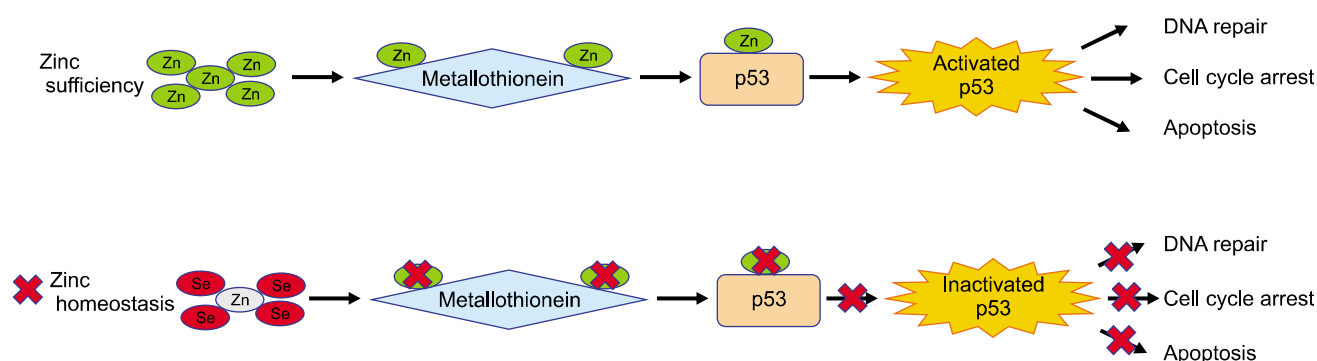


Figure 2. Selenum-mediated impairment of zinc homeostasis and consequent dysregulation of metallothionein system.

the bioaccumulation and interaction of these two elements in tissues have remained unreported, selenium + zinc supplementation model is frequently used in different neoplastic diseases, especially in prostate cancer [68]. However, cellular and molecular studies show that selenium and zinc may interact with each other, allowing selenium to exert its antioxidant or pro-oxidant function interchangeably through differences in the levels of released zinc [69]. Impairment of zinc homeostasis can also be mediated by selenium, resulting in the disruption of the metallothionein system, which is very important in the oxidoreductive metabolism of cells. Metallothioneins are low-molecular-weight, sulfhydryl-rich proteins that bind zinc predominantly. The binding of zinc ions allows metallothionein to play a central role in oxidoreductive cellular metabolism, cellular zinc distribution, and homeostasis [70]. Thus, when zinc homeostasis is disrupted by selenium, the metallothionein system is dysregulated, thereby losing its antioxidant feature. The downstream effect of the metallothionein system dysregulation is the modulation of transcription of the DNA repair gene p53 (Fig. 2).

CONCLUSION

As vital components of nutrition, approximately 40 micronutrients are needed for a healthy human diet. Deficiency of micronutrients (i.e., vitamins B12, B6, niacin, vitamin C, vitamin E, iron, and zinc) seriously disrupts DNA integrity through generating single-strand breaks/DSB and/or oxidative damage, leading to cancer development [71]. These micronutrient deficiencies may be as detrimental as the DNA-damaging agents, such as UV radiation and several chemicals; in some cases, such deficiencies are even more dangerous [72]. Therefore, selenium-generated deficiency in zinc homeostasis most likely has a significant impact on DNA stability and DNA repair ability of cells.

Considering the multifaceted effect of selenium on intracellular antioxidant/pro-oxidant mechanisms, signaling pathways and DNA repair processes largely depend on both its different forms and different concentrations. Selenium can possibly make various interactions with other molecules, such as zinc, leading to positive or negative results on the abovementioned intracellular mechanisms. The reducible forms of selenium can interfere and inhibit the DNA repair process by oxidizing the zinc fingers of DNA repair genes as well as the transcriptional regulators of DNA repair genes. Depending on the concentration of selenium, zinc homeostasis may be interrupted; thus, the antioxidative metallothionein system is disrupted, leading to oxidative DNA damage and cancer. Therefore, controlling the balance between these two essential trace elements is extremely important.

Considering that different forms of selenium compounds are frequently used as pharmaceutical supplements at high doses, their possible pro-oxidant and DNA repair inhibitory effect needs great attention in terms of interaction with intracellular zinc. Moreover, selenium + zinc supplements are prescribed especially for the prevention of certain neoplastic diseases, such as prostate cancer. Using selenium + zinc preparations decreases the bioavailability of zinc in prostate tissue, and the highest zinc bioavailability is achieved by treating animals only with zinc [73]. This result also supports the findings of other studies implicating the presence of an adverse interaction between selenium and zinc.

In addition to pharmaceutical selenium preparations, recently, colloidal selenium nanoparticles have been used as a chemopreventative agent and also as a carrier of chemotherapeutic agents to minimize the adverse effects of chemotherapeutics and also to improve the effectiveness of anticancer activity by generating a synergistic effect between selenium and its chemotherapeutic cargo [27]. Thus, choosing appropriate dose and form of selenium is indeed important.

To sum up, selenium and zinc are two essential trace elements that are both vital micronutrients for human diet. However, selenium is in close interaction with zinc, leading to oxidation and release of zinc from zinc-finger motifs, especially in the DNA-binding sites of DNA repair proteins depending on selenium's different forms and different concentrations; thus, this interaction poses a risk for unrepaired DNA damage and subsequent cancer development. In selenium- and zinc-rich diets, their supplements and also selenium-nanocarriers of chemotherapeutics are frequently used for their anticancer features. Their interaction in cells in terms of negative effects of this interaction on their bioaccumulation, bioavailability, and functions regarding impairments in DNA repair should be given importance. Otherwise, using inappropriate forms and concentrations of selenium compounds may cause disruption of zinc homeostasis, driving cells to a cancerous state as a result of unrepaired and accumulated DNA damage. Thus, additional experimental studies in vivo, in vitro, and also on human subjects are necessary to avoid a cancer-prone cellular environment while trying to prevent it. By this way, more efficient and beneficial dietary supplement combinations can be designed, aiming to provide protection against carcinogenesis and also to increase the effectiveness of used chemotherapeutics.

ETHICAL APPROVAL

This article does not contain any studies with human participants or animals performed by any of the authors.

CONFLICTS OF INTEREST

No potential conflicts of interest were disclosed.

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