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Invited Review

Selenium in the prevention of colorectal cancer

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SUMMARY

Colorectal cancer remains a major cause of cancer related mortality and morbidity. Therefore, primary chemoprevention would be a desirable option. Recently, the trace element selenium (Se), has been evaluated in clinical trials, as a possible chemopreventive agent, in cancer. Several possible mechanisms for its potential anticarcinogenic effects have been proposed, however the exact mechanisms, by which selenium compounds exert these properties, is largely unknown.

Results from epidemiological studies have been mixed and inconclusive. The true nature of the association between selenium deficiency and incidence of colorectal adenomas or cancer remains controversial. However, the limited clinical data suggest a potential benefit of Se supplementation. Yet, more conclusive evidence is needed before any dietary recommendation can be decided.

Key words: Colorectal cancer, adenomas, prevention, selenium, selenoproteins, selenomethionine

Colorectal cancer is one of the most common cancers and a major cause of cancer related mortality and morbidity, in Western lifestyle countries. Primary prevention has received considerable attention, since colorectal carcinogenesis involves a sequence of molecular and cellular events, during the transition from normal mucosa to adenoma and subsequently to carcinoma. In that aspect, specific chemical compounds have been used in clinical trials to prevent, inhibit or reverse colorectal carcinogenesis.[1]

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Recently, the trace element selenium (Se), has been evaluated in clinical trials, as a possible chemopreventive agent, in cancer. This mineral is taken up by plants from the soil and it is mainly ingested by humans, in bread, cereals, fish, poultry and meat.[2] A typical dietary intake ranges from 80 to 166 μg/day and the safe upper limit of intake is considered to be 400 μg/day. However, dietary selenium intakes vary between different geographical regions, because of soil diversity - low soil content of selenium in volcanic regions - and for unknown reasons, in some parts of Europe. In addition, bioavailability and tissue distribution after ingestion, is different between variable organic and inorganic forms of selenium.[3] Inorganic selenium compounds (e.g. selenite) are highly active, but they have a narrow safe range of intake in humans, and they show potential genotoxicity in long-term use.[4] Methylation of selenium produces less toxic forms and is a major pathway for Se metabolism in microbes, plants and animals.[5] A dose of 200μg/day is considered to be the optimal dose in chemoprevention trials, based on preclinical, efficacy and safety data.[6-7]

So far, all the known functions of Se as an essential nutrient, in animals are attributed to a number of mammalian selenoproteins, that represent potential molecular targets for nutritive selenium supplementation. Gastrointestinal glutathione peroxidase (GI-GPx) and selenoprotein P (SePP) are selenoproteins, abundantly expressed in normal colon mucosa.[8] Selenoproteins are selenocysteine containing proteins, where selenocysteine is specifically incorporated through a unique co-translational mechanism.[9-10] However, non-specific incorporation of Se into proteins, occurs through substitution of selenomethionine for methionine.[5] Selenomethionine, is an organic compound that was considered to be the major component of high-selenium yeast, used in chemoprevention studies.

MECHANISMS OF SE ANTICARCINOGENIC EFFECTS

Several possible mechanisms for the potential anticarcinogenic effects of selenium have been proposed, however the exact mechanism by which selenium compounds exert these properties, is largely unknown.

Evidence suggest that it affects key cellular events of tumorigenesis, such as cell proliferation and apoptosis, with a variety of complex possible mechanisms.[11]

According to cellular studies, monomethylated forms of Se were effective at very low concentrations to induce apoptosis and cell cycle arrest, in transformed cells. This action appears to be an attractive mechanism of chemoprevention, since it causes deletion of carcinogen-initiated cells and suppression of clonal expansion of a transformed cell population.[12-13] In that initial demonstration of Se-induced apoptosis, DNA damage was involved. Later on, studies with methylated forms of Se have shown that, apoptosis can be triggered by Se, independent of DNA damage and separate from a functional p53,[14] implying that other mechanisms must be involved. Recently, studies implicate cell cycle cdk2 or cell signaling protein kinases to be potential targets of Se metabolites.[15] Additionally, preclinical studies, suggest that in human colonic carcinoma cell lines, selenium inhibits the enzyme DNA cytosine methyltransferase 1, that is increased in tumor progression, in association with regional hypermethylation.[16]

Another chemopreventive mechanism, that has been recently proposed, involves Se catalysis of reversible cysteine/disulfide transformations that occur in a number of redox-regulated proteins, including transcription factors. An Se-facilitated deactivation of such proteins, that allow a time-limited activation, would allow normalization of critical cellular processes in the early stages of transformation.[5] Additionally, the important oxidative metabolism of the n-6 polyunsaturated fatty acids, arachidonic and linoleic acids are linked with selenium, in colorectal tumorigenesis.[17] In four human colon cancer cell lines, selenomethionine inhibited their growth in a time and concentration dependent manner, partly mediated by a COX-2 dependent mechanism.[18] Recent data, suggest that the link between selenium and the oxidative metabolism of linoleic and arachidonic acids extends to another metabolic enzyme family involved in colorectal tumorigenesis, the lipoxygenases (LOXs). 15-LOX-1 which has anti-tumorigenic effects and COX-2 that has pro-tumorigenic effects in the colorectum exert opposing effects on the selenoprotein thioredoxin reductase. This, selenomethionine containing, enzyme catalyses the reduced nicotinamide adenine dinucleotide phosphate (NADPH)-dependent reduction of thioredoxin and other oxidised cell constituents. Enhanced thioredoxin reduction could have beneficial effects in oxidative stress, which is considered to be a key factor for DNA damage, however possible adverse effects are considered. Thioredoxin reductase shows increased activity with Se supplementation in the nutritional to the supranutritional range and it is involved in the prevention, intervention and repair of damage caused by hydrogen peroxide-based oxidative stress[19]. Other functions of thioredoxin reductase may be relevant to cell signalling pathways. So far, in vitro studies, have shown inhibitory effects of Se on the thioredoxin system correlated with growth inhibition by Se, but in vivo data regarding the functional status of the thioredoxin / thioredoxin reductase system during selenium chemoprevention is lacking.[3] However, it would be interesting to clarify whether or not selenoproteins are obligatory agents of Se anticancer activity, in knockout models that preclude selenoprotein synthesis.[5]

CLINICAL AND EXPERIMENTAL DATA

In animal models of colorectal tumorigenesis, selenium compounds have been shown to inhibit the development of adenocarcinomas, especially in combination with low-fat diet.[20]

However, it is not known whether selenoproteins or low molecular weight selenocompounds are responsible for this activity. Currently, Irons et al provided evidence that the lack of selenoprotein activity increases colon cancer susceptibility.[21] Furthermore, in that study, low molecular weight selenocompounds reduced preneoplastic lesions independent of the selenoprotein genotype. Yet, irrespective of the form of Se that exerts antineoplastic effects, Finley et al, emphasized the need to study Se in food forms, and not extrapolate from previous studies using pure chemical forms in cancer inhibition studies. It was also demonstrated that foods with high Se bioavailability are not necessarily the most efficacious for cancer incidence reduction.[22]

Apart from animal studies, Se compounds have been associated with preventive effects in ecologic studies.[23] However, results from other observational studies have been mixed, inconclusive and based predominantly on small studies.[24-25] A number of the epidemiological studies showed a statistically significant or suggestive protective association, while an approximately equal number showed a null or suggestive harmful association, between

Se and colorectal adenomas or cancer.[17]

In addition, a variety of studies have addressed whether selenium deficiency contributes to the development of colorectal neoplasia.[26-28] Early et al, measured total plasma selenium and plasma selenoproteins in colorectal cancer and adenoma patients.[26] No selenium deficiency was found compared to controls. In the study of Psathakis et al, mean serum selenium levels did not differ significantly between colorectal cancer patients and disease free controls, although tumour patients showed significantly lower glutathione peroxidase activities.[27] Patients with a low selenium level showed a significantly lower mean survival time, and cumulative cancer-related survival rate. However, it was declared uncertain by the authors, whether the low selenium status was a consequence or a causative factor for the development and course of malignancy.

Recently, studies have suggested that increased selenium status may decrease the risk of advanced adenomas, either in a geographical area with a low selenium status, in subjects less than 60 years of age[28] or particularly among the high-risk group of recent smokers.[29] In the study of Connelly-Frost et al, high selenium was associated with a reduced prevalence of colorectal adenomas, as well.[30] In addition, other studies, demonstrated an inverse association between serum levels of selenium and adenoma risk.[31-32] Jacobs et al.[32] reported a pooled analysis of three randomized trials of dietary or nutrient interventions in preventing colorectal adenomas. None of these trials tested selenium as an intervention. Individuals in the highest quartile of plasma selenium concentration had 34% lower odds of developing metachronous adenoma, compared with those in the lower quartile of plasma selenium. In contrast, the nested case-control study by Wallace et al. did not indicate a clear association between serum Se concentrations and adenoma recurrence.[33]

So far, the true nature of the association between selenium deficiency and incidence of colorectal adenomas or cancer remains controversial. Yet, it is possible that an individual who is not selenium deficient overall, might develop selenium deficiency in certain tissues, such as the colon. However, Charalabopoulos, et al.[34] reported increased Se concentration in the cancerous compared to healthy tissue. Knowing the antioxidant action of Se, it might be hypothesized that this finding is part of the defence mechanism against the neoplastic process. Another recent study examined the expression of selenoproteins in colorectal adenomas, compared to normal tissue. The expression of GI glutathione peroxidase, an isoform of GSH-Px that is expressed predominately in the GI tract, was elevated in adenomas compared to normal tissue, whereas Se-P expression was lower in adenomas.[35] Therefore, it can be assumed that an altered expression of selenoproteins, in colorectal tissue might affect the progression of normal tissue to adenoma.

However, regardless of the association of colorectal cancer or adenomas with selenium deficiency, it is possible that selenium supplementation might help to prevent colorectal cancer. The most compelling evidence for such an issue, comes from the Nutritional Prevention of Cancer (NPC) Trial carried out by Clark and coworkers in the USA.[36] That was the first double-blind, placebo-controlled intervention trial in the western population, designed to test whether selenium supplementation could reduce the risk of cancer. A total of 1312 individuals with previously resected non-melanoma skin cancers were randomized to placebo or 200 μg selenium per day in yeast, taken for an average of 4.5 years. Although, there was no effect on the primary end-point, being the development of skin carcinomas, this study found significantly reduced overall cancer mortality and incidence rates in Se-supplemented patients. On analyzing individual cancers, a significantly reduced risk of developing colorectal cancer was observed in the selenium group (RR: 0.42; 95% CI, 0.18-0.95; $p=0.03$). Additionally, colorectal cancer deaths were 60% less frequent among individuals who were assigned to selenium.[36]

Recently, Reid et al[37] evaluated the association of selenium supplementation and colorectal adenoma, in a sample of patients of the above mentioned trial and found reduced risk among participants with low baseline selenium level.

Selenium has also been tested in combination with β-carotene, vitamin A, vitamin C and vitamin E, in two trials, that evaluated polyp reccurence. The development of colorectal adenoma was significantly reduced in the trial of Hofstad et al.[38] However, these trials were associated with high risk of bias.[39]

In addition, it should be mentioned that studies on adenoma reccurence, have many potential limitations and may not reflect the true consequences on the development of colorectal adenoma or cancer in the general population.

At present, the role of selenium in the prevention of colorectal cancer has yet to be defined. The limited clinical data suggest a potential benefit of Se supplementation, but more conclusive evidence is needed before any dietary recommendation can be decided. Hopefully, ad-

vances in our understanding of colorectal carcinogenesis and selenium mechanisms may potentially lead to the development of new interventions.

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