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Anticarcinogenic effects of selenium

G. N. Schrauzer

Biological Trace Element Research Institute, San Diego (California 92121, USA) and Department of Chemistry, University of California, San Diego, La Jolla (California 92034, USA), Fax + 1 858 794 0212, e-mail: gschrauzer@ucsd.edu

Abstract. Selenium (Se) exerts its anticarcinogenic effects by multiple mechanisms. In the physiological dosage range, Se appears to function as an antimutagenic agent, preventing the malignant transformation of normal cells and the activation of oncogenes. These protective effects of Se seem to be primarily associated with its presence in the glutathione peroxidases, which are known to protect DNA and other cellular components from damage by oxygen radicals. Selenoenzymes are also known to play roles in carcinogen metabolism, in the control of cell division, oxygen metabolism, detoxification processes, apoptosis induction and the functioning of the immune system. Other modes of action, either direct or indirect, may also be operative, such as the partial retransformation of tumor cells and the inactivation of oncogenes. However, the effects of Se in the physiological dosage range are not attributable to cytotoxicity, allowing Se to be defined as a genuine nutritional cancer-protecting agent. The anticarcinogenic effects of Se are counteracted by Se-antagonistic compounds and elements. For maximal utilization of its cancer-protective potential, Se supplementation should start early in life and be maintained over the entire lifespan. In addition, exposure to Se antagonists and carcinogenic risk factors should be minimized by appropriate dietary and lifestyle changes.

Key words. Selenium; cancer; cancer prevention; selenium supplementation; selenium antagonists.

Introduction

The idea that Se is a cancer-protecting trace element is as such not new—the first papers on the subject were published in the late 1960s and early 1970s [1–4], leading to the proposal that 'cancer mortalities in the U.S. and other Western industrialized nations would decline significantly if the dietary selenium intakes were increased to approximately twice the current average amount by the U.S. diet' [5]. The selenium-anticancer hypothesis was subsequently tested in case-control studies. While the majority of these studies were supportive, some produced inconclusive results. Nevertheless, interest in Se as a cancer-protecting agent remained high, resulting in several large-scale human intervention trials in China and in the United States. The results, especially of the American study [6], were encouraging to the degree that it is now believed that perhaps only one additional intervention trial needs to be conducted before selenium supplementation can be officially recommended for cancer prevention [7]. The anticarcinogenic effects of Se were also extensively investigated in laboratory studies. Selenium was shown to exhibit inhibitory effects in various tumor cell lines as well as against chemically induced and transplanted tumors (for reviews see [8, 9]). Several clinical studies involving Se were also conducted. These showed that Se reduces side effects of cancer chemotherapeutic agents and improves the immune status of treated cancer patients, thus indicating that Se holds promise for cancer prevention as well as for tumor therapy. The present review focuses primarily on the role of Se in cancer prevention. Coverage of the literature is not exhaustive; instead, the focus is on topics not treated in other recent reviews.

Ecological and correlational studies

Evidence for cancer-protective effects of Se was initially obtained by means of ecological and correlational studies. Human cancer mortalities were shown to be lower in high- than in low-Se regions of the United States [1,

2], and statistically significant inverse associations were obtained when cancer mortalities were correlated with the blood-Se levels of healthy donors in different U.S. cities, states or counties [3], as well as with the apparent dietary Se intakes in different countries [5]. These and subsequent studies [10–16] suggested a significant protective effect of Se against major forms of cancer at dietary intakes in the range of 200–300 μg/day. As a result of agricultural practices, low Se soil contents and dietary preferences, adult populations in most Western industrialized nations presently reach Se intakes of only one-third of this amount. Intakes of this magnitude still meet the physiological requirement of 70 μg/day [17], but not the higher amounts of Se needed for its protective functions.

Case-control studies

A number of case-control studies were performed from the early 1980s onward. In such studies, Se levels in blood, serum or other indicator organs of healthy subjects are compared with those of cancer cases or of subjects who developed cancer at some time after samples were taken. Such studies have several limitations, one being that Se status is usually assessed on the basis of analyses of only one sample, requiring the assumption that Se status remained constant during extensive periods and was not influenced by the disease. Nevertheless, the majority of these studies showed that serum Se levels or other indices of Se status of cancer patients were lower than those of cancer-free controls. Willett et al. [18], for example, found lower Se levels in serum samples collected from American subjects 1–5 years prior to diagnosis of cancer as compared with those that had remained cancer free during the same period. The association between low serum Se and cancer was the strongest for gastrointestinal and prostatic cancer; low serum vitamin A and E levels compounded the apparent cancer-protective effect of Se.

That low serum Se is a prediagnostic indicator of higher cancer risk was subsequently shown in studies conducted in Finland [19, 20] and Japan [21]. In other nested case-control studies, low serum or plasma Se levels were found to be associated with increased risk of thyroid cancer [22, 23], the presence of premalignant or malignant oral cavity lesions [24] and of colorectal adenomas [25]. Serum Se and vitamin E was also found to be lower in Japanese lung cancer patients and their family members [26]. In three studies, low toenail Se values were associated with higher risks of developing cancers of lung [27], stomach [28] and invasive prostate cancer [29]. Low levels of selenoprotein P, a newly identified indicator of long-term Se status [30, 31], have since also been shown to be associated with significantly increased cancer risk [32]. In four studies [33–36], significantly lower Se levels in plasma, serum or erythrocytes were also observed in breast cancer cases than in controls. Conversely, four prospective studies, one using erythrocyte Se [37], and three employing toenail Se as indices of Se status [38–40], revealed no significant differences between cases and controls. However, in these studies, the Se intakes of most of the subjects tested were below those at which its protective effects would be expected to take effect.

In order to be valid, case-control studies evidently must be carried out with a sufficient number of subjects whose dietary Se intakes are within the protective range; at average or low Se intakes, the protective effect of Se will not be observable. As to toenails, these are relatively imprecise indices of Se status, especially if determined from subjects with closely similar Se intakes. In the prospective study of Hunter et al. [38], cases and controls exhibited mean nail Se levels of 0.823 ± 0.197 and 0.821 ± 0.174 μg/g, respectively, corresponding to Se intakes of 90 ± 20 μg/day, thus for the majority below the protective level. In the two other toenail studies involving Dutch women [39, 40], Se intakes of cases and controls were likewise too low to allow protective effects to be observed.

Because of their low breast cancer incidence and comparatively high dietary Se intakes, Japanese women are more suitable for studies of this kind. In one study [41], the Se contents of healthy Japanese women were 0.285 ± 0.032 ppm, those of newly diagnosed and untreated breast cancer patients, 0.195 ± 0.057 ppm, consistent with an apparent breast cancer protective effect of Se at intakes of 200–300 μg/day. In the breast cancer cases, on the other hand, Se intakes reached only about one-half of this amount and thus corresponded more closely to the Se intakes typically observed in Western industrialized countries.

Human intervention trials

The Qidong study (primary liver cancer)

The first human intervention trials to prevent human cancer with Se were performed in Qidong, a region north of Shanghai with a high incidence of primary liver cancer (PLC). In one township, 20,847 inhabitants received table salt fortified with 15 ppm of sodium selenite, providing approximately 30–50 μg of selenium per day for 8 years, resulting in a drop of the PLC incidence to 27.2 per 100,00 population, while in the four surrounding townships maintained on ordinary salt, the PLC incidence during the same period remained at 50.4 per 100,000 population. On withdrawal of Se from the treated group, PLC incidence began to rise [42, 43]. In another trial, 2474 members of families

with high risk of PLC were receiving 200 μg of selenium per day in the form of high-selenium yeast or a placebo. During the 2-year period of study, 1.26% of the controls developed PLC vs. 0.69% in the placebo group ($P < 0.05$). In addition, of 226 HBVsAg carriers, 7 of 113 subjects in the placebo group developed PLC during 4 years, while none of the 113 in the Se-supplemented group did during the same period ($P < 0.05$). In a separate trial, risk populations receiving selenized salt as a source of supplemental Se also showed a significant reduction of the incidence rate of viral infectious hepatitis, a major predisposing PLC risk factor in this region [44].

The Linxian study

An intervention trial was conducted from 1984 to 1991 in Linxian, China, a rural county in Henan Province, where the mortalities from esophageal cancer are among the highest in the world [45]. The aim of this joint Chinese-American study was to test the effects of several minerals (which included selenium) and vitamins at dosages of about two to three times the U.S. Recommended Dietary Allowances against a placebo in a total of 29584 adults. During the period of the study, 2127 of the subjects died from cancer, with cancer of stomach and esophagus accounting for 32% of all cancers. While this study did not provide evidence for cancer-protective effects in groups receiving supplemental retinol and zinc, riboflavin and niacin, and molybdenum and vitamin C, total mortality during the 1986–1991 intervention period was reduced 9%, and cancer mortality by 13% in the group receiving daily supplements of selenium, β carotene and vitamin E, indicating a protective effect of Se in combination with antioxidant vitamins.

The Clark study

The aim of this trial was originally to explore whether supplemental Se could reduce the nonmelanoma skin cancer recurrence in subjects previously treated for nonmelanoma skin cancer [6]. In this fully randomized, placebo-controlled trial, a total of 1312 subjects were enrolled from 1983 to 1993; 75% of the subjects were male, and their average age on enrollment was 63 ± 10 years. Study subjects received either placebo or 200 μg of Se in the form of high Se yeast. The latter contained Se predominantly in the form of selenomethionine, a major nutritional form of Se [46]. In this study, the subject-reported compliance was 82%. However, the true compliance was probably lower and appears to have declined during the conduct of the study, as judged from the measured plasma Se levels of subjects during the trial. Whereas supplemental Se had no effect on skin cancer recurrence, incidence and mortality from cancers in other organs were significantly reduced: in the Se group 70, and in the placebo group 117, of nonepithelial cancers occurred, corresponding to a relative risk of 0.58, and overall cancer mortality was reduced by 56%. The incidence of prostate cancer was reduced by 63%, and colorectal and lung cancer by 58% and 46%, respectively. The observed trend of incidence reduction for prostate, colorectal and lung cancer appears to be related to the ages [47] at which these cancers maximally occur (72.9, 66.1 and 62.3 years).
For cancer at other sites (melanoma, esophagus, bladder, brain, breast, leukemias and lymphomas) case numbers were too small to reach statistical significance.

Diet, selenium and cancer links

In previous studies, international variations of mortality rates for cancers of breast, colon or prostate were associated mainly with the different dietary fat intakes. The low mortalities in Japan, in particular, were attributed to the low dietary fat intake provided by the traditional Japanese diet. Similarly, the increased incidence of these types of cancer among Japanese immigrants was linked to their higher fat consumption as compared with that in their country of origin [48]. Although some animal experiments have supported the dietary fat-cancer hypothesis [49], the association was not observed in all studies and is now viewed as weaker than originally assumed [50]. More recently, phytoestrogens such as found in tofu and miso [51, 52], lycopene [53], β carotene and vitamin E [54] were postulated to lower the risk of hormone-related cancers such as breast and prostate in the Japanese population.
However, mortalities from hormone-unrelated cancers also correlate directly with the dietary fat intakes. In multifactorial correlation studies of male lung cancer mortalities in different countries with the consumptions of 12 major foods, the direct association with the consumptions of fats and oils emerged as statistically most significant [55]. Experimentally, enhancement of mammary tumorigenesis by dietary Se deficiency in rats with a high intake of polyunsaturated fat has been observed [56]. Conversely, a significantly reduced incidence of spontaneous mammary tumors was observed in MMTV-infected mice maintained on an adequately Se-supplemented feed modeled after the traditional Japanese human diet [57]. The presence in fats of substances with estrogenic activity and xenobiotics such as dioxin must also be considered; estrogens counteract the cancer-protecting effects of Se [58], whereas Se protects against dioxin toxicity [59]. The lowering of the dietary Se intakes through the adoption of Western dietary habits by Japanese immigrants living in other countries has since been suggested to be responsible for

their higher risks of cancer of the breast, prostate, lung and colon [60, 61]. Thus, any discussion of the roles of dietary constituents in human cancer development must also include Se.

Metals as Se antagonists

A number of elements that occur in foods, in the drinking water and in the environment (e.g. Cd, As, Zn, Hg, Pb) compete with Se uptake, form unreactive selenides or protein complexes under physiological conditions and/or are inhibitors of Se-dependent enzymes. Many of these elements stimulate oxygen radical production, are mutagenic, inhibit DNA-repair enzymes, exhibit cocarcinogenic activity and stimulate the growth of tumor cells. Exposure to these elements increases the Se requirement. In the following, some of the epidemiological and experimental evidence as to the role of several such elements in carcinogenesis will be presented.

Cadmium and lead

Previous studies have associated occupational exposures of workers to Cd with increased renal, prostate and lung cancer incidence [62, 63]. Direct correlations between the mortalities from major forms of cancer and the levels of Cd in diet, soil and water have also been observed [64–66]. As Cd is widely distributed in foods, the combined intakes of Cd from dietary sources and the water may exceed those of Se, especially in low-Se areas. In New Zealand women, for example, daily dietary Cd intakes expressed in atomic equivalents were three times higher than those of Se [67]. Plasma Se was found to be lower in smokers than in nonsmokers [68], which was attributed to the Cd content of tobacco smoke and interactions of Cd with Se. In rats, exposure to Cd causes increased lipid peroxidation, DNA damage, glutathione depletion and increased excretion of urinary lipid metabolites attributable to the production of reactive oxygen species [69].

As Se is known to protect against Cd-induced peroxidative damage [70], the development of various types of cancer would also be expected to be dependent on the relative intakes of Cd and Se. In experiments with female mice infected with murine mammary tumor virus (MMTV), Cd abolished the cancer-protecting effects of Se [71]. In male and female patients with cancer and metastatic cancer, Cd/Se ratios in the kidney cortex were found to be elevated [72]. Cd was also elevated in human prostatic cancer tissues, notably the plasma membrane fraction [73]. Other studies showed that Cd stimulates the growth of human prostatic epithelium in vitro at levels between 10^{-9} and 10^{-7} M [74]. As this growth stimulation is inhibited by Se, these findings could account for the protective effect of Se against human prostatic cancer.

Interactions of Pb with Se may similarly increase human cancer risk and could explain the observed direct associations of Pb contents in U.S. water supplies with the mortalities from cancers of stomach, small intestine, large intestine, ovary, kidney, myeloma, all lymphomas and all leukemia [66]. In MMTV-infected mice, low 5 ppm of Pb added to the water supply abolished the cancer protecting effect of 1 ppm Se in the diet [75].

Zinc

Although Zn has a lower affinity for Se, its Se-antagonistic effects are sufficient to reduce or abolish the anticarcinogenic action of Se. Experiments with MMTV-infected mice demonstrated that subtoxic amounts of Zn prevented Se toxicity, and abolished the cancer-protecting effect of Se and accelerated tumor growth [76]. Later investigations provided evidence for interactions of Zn and Se in mice [77] and in rats [78]; Zn and Se were also shown to mutually antagonize dietary Zn and Se absorption [79]. In tumors, significant amounts of Zn were found in the outer, actively growing layer [80], consistent with its role in the promotion of tumor growth. Correlation calculations [67] produced statistically significant direct associations of the apparent dietary zinc intakes in different countries with the mortalities from cancers at all sites, of breast, colon, rectum, ovary, lung, pancreas, leukemia and bladder; significant direct associations were also obtained between these cancer mortalities and observed blood Zn levels of healthy donors sampled in different collection sites of the United States.

Significantly higher levels of Zn and lower levels of Se, Cu and Mn were observed in scalp hair of patients with malignant tumors than in hair of healthy subjects or patients with benign tumors [81], leading these authors to conclude that high hair Zn content indicates increased cancer risk, whereas Se and Mn are protective factors. As meats are major human dietary sources of Zn and Zn uptake is interfered with by plant food constituents such as phytic acid, the relationships of Se and Zn are complex. Obviously, Zn intakes must be adequate for the maintenance of health. However, excessive Zn intakes must be avoided, a fact which should be considered when extradietary Zn supplementation in the absence of established Zn deficiency is contemplated. For further discussion of the Zn-Se antagonism see below.

Arsenic

Arsenic is recognized as an occupational and environmental carcinogen. In areas of Cordoba, Argentina, the use of As-contaminated well water was associated with elevated incidence of skin cancers [82]. In the population exposed to As-containing well water of Taiwan where Blackfoot disease is endemic, elevated bladder, kidney, skin, lung, liver and colon cancer rates have been observed [83]. The apparent oncogenic effects of As are strongly dependent on its chemical form, mode of application and dosage, and are further influenced by interactions with Se. These interactions may be important in the Blackfoot disease-endemic areas, where blood Se levels were found to be lower than in areas free of this disease [84]. Higher As/Se ratios were observed in the scalp hair of miners of the Yunnan tin mine in China who developed lung cancer than in hair of healthy workers [85]. Based on the results of this study, supplemental Se was introduced as a possible means of lung cancer protection [86]. A daily supplement of 300 μg of Se increased blood and hair Se, increased plasma glutathione peroxidase (GSH-Px) activity and reduced the concentration of lipid hydroperoxides. The DNA of lymphocytes of the Se-supplemented subjects were less damaged than those receiving placebo, as evidenced by measurements of unscheduled DNA synthesis. In MMTV-infected mice, additions of arsenite to the drinking water abolished the anticarcinogenic effects of Se and provided evidence for the interaction of As with Se [87].

Chromium

The international correlation calculations [67] also produced statistically significant associations between cancer mortalities and the apparent dietary intakes of chromium. This appeared surprising as Cr, an essential micronutrient, is normally not regarded as a Se antagonist. However, evidence for a mutual interaction between the two elements has been obtained in animal experiments [88]. The physiological effects of Cr depend on its chemical form, dosage and oxidation state. While Cr^{+3} is considered nontoxic, Cr^{+6} in the form of chromate is a recognized mutagen and occupational carcinogen. In experiments with MMTV-infected mice, ppm levels of Cr(III) in the water supply abolished the anticarcinogenic effect of Se [89].

Multiple elements

Significantly higher Cr levels have recently been observed in the blood of Indian breast cancer patients as compared with healthy controls [90]. In these patients, blood Zn and Hg concentrations were also elevated, and blood Se and Hg were directly correlated ($P < 0.05$), indicating an interaction between the two elements. In breast tumor tissue of Indian women from the same area, the concentrations of Zn, Se, Cd and As were significantly higher than in normal tissue (Cr and Hg were not determined) [91]. In American breast cancer tissues, Zn and Se were also elevated, and Cr and Hg were about the same, as compared with normal breast tissue (Cd was not determined) [92, 93]. The accumulation of elements by tumor cells in nonoccupationally exposed subjects evidently depends on element availability and tumor type and is specific enough to discriminate tumor tissues from normal tissues. American breast cancer tissue, for example, was correctly classified with a 9-element linear discriminant function (LDF) involving Ca, Rb, Zn, Cr, Br, As, Mn, Mo and Ni, lung cancer tissue with an 11-element LDF including Ca, V, Fe, Cu, Zn, Se, Br, Sr, Hg, As, and Mo [92]. In lung tissues of Swedish smelter workers dying from lung cancer as compared with workers who died from other causes, elevated levels of Cr, Cd, As, Sb, La and lower levels of Se were observed and the quotient, $[(Sb) + 3(As) + 2(Cd) + 4(Cr) + (Co) + (La)]/[Se]$, was introduced to indicate increased lung cancer risk [94].

The key conclusion to be drawn from these studies is that the cancer-protecting effects of Se are not absolute—they are dependent on the amounts of Se-antagonistic elements at the workplace, in the environment, in foods and in water supplies.

Mechanisms of anticarcinogenic action

The anticarcinogenic actions of Se occur at the systemic, cellular and nuclear level. These actions may also involve the immune system and thus cannot be interpreted by a single mechanism. The anticarcinogenic action of Se also depends on its chemical form, dosage and the nature of the carcinogenic agent. At optimal levels for the prevention of carcinogenesis, Se is effective only prior to, or in the early phases of, malignant transformation. Cells adequately supplied with Se are less susceptible to the damaging effects of endogenously or exogenously generated oxygen radicals, which may attack cellular DNA, cause mutations and the oxidative activation of chemical carcinogens. Oxygen radicals may also attack the DNA of viruses, causing benign strains of Coxsackie B to become pathogenic [95]; by a similar mechanism, nononcogenic viruses could be rendered oncogenic [96].

The protection against oxygen radical damage involves the Se-dependent glutathione peroxidases, thioredoxin reductases and possibly other selenoproteins containing Se in the form of selenocysteine. However, other reactive forms of Se participate in a variety of reactions that are also relevant to its mechanism of anticarcinogenic

action. The detoxification of Se-antagonistic metals through the formation of metal selenides or protein complexes, as well as the methylation of Se, which occurs under normal physiological conditions, belong to this category.

A characteristic of these reactions is that they occur stoichiometrically, causing Se to be physiologically inactivated. Accordingly, to achieve protection against carcinogenic stress factors, Se has to be continuously supplied in amounts above the minimum amounts needed for the prevention of Se deficiency diseases. A short-term Se supplementation for these reasons does not convey long-lasting protection. Thus, animal experiments have shown [97] that for maximum protective effect, Se supplementation has to be maintained over the entire lifespan. Through the methylation of Se to $Se(CH_3)_2$ and $Se(CH_3)_3^+$, biogenic methyl groups are consumed, causing Se to prevent DNA methylation [98], which represents an early stage in benzo[*a*]pyrene carcinogenesis [99]. The methylation of Se depends on oxygen tension. In studies with rat liver cells, $Se(CH_3)_2$-formation from added $^{75}SeO_3^-$ was delayed in an oxygen-rich atmosphere and stimulated under hypoxic conditions [100]. Based on these observations it was suggested that the anticarcinogenic effects of Se would be attenuated under hypoxic conditions and augmented at high oxygen levels [101, 102].

In Se-adequate cells, improved oxygen use results in changes of the GSSG/GSH ratio [103]. The attendant changes of the cellular redox potential may result in a shift of equilibria between active (reduced) and inactive (oxidized) forms of cellular growth factors, transforming zinc-finger proteins or cellular receptors whose activity depends on the presence of surface-SH groups. In these reactions, reactive forms of Se such as $GSSe^-$ GSSeSG and Se-dependent enzymes, namely the thioredoxin reductases, function as biocatalysts. The prooxidant effects of Se at higher dosage levels in the presence of oxygen, which results in the increased production of oxygen radicals, was also suggested to be responsible for some of the anticarcinogenic properties of Se [104]. Cells grown on minimal levels of Se do not become spontaneously malignant and may show higher growth rates than Se-adequate cells. Thus, liver regeneration was accelerated in Se-deficient mice after partial hepatectomy, but the liver cells were qualitatively inferior as compared to those produced by Se-supplemented mice [105]; liver cells adequately supplied with Se show slower growth. Se thus is creating conditions favorable for DNA repair.

At higher levels, additions of Se to cultures of normal and of pulmonary tumor cells resulted in the selective destruction of the tumor cells [106]. In studies with human tumor cells, Se caused partial downregulation, improved contact inhibition and cell adhesion [107], inhibited cell colony formation [108], and induced p53 and apoptosis [109]. In the induction of p53 and of apoptosis, selenodiglutathione, GSSeSG, the initial metabolite of selenite, is believed to be the active species; several other seleno-compounds, e.g. selenomethylselenocysteine and dimethylselenoxide showed lower activity. A role of thioredoxin reductase (whose biosynthesis is induced by addition of Se to culture media in the form of sodium selenite) in the induction of apoptosis has also been considered [110]. The cytotoxic effects of selenite against tumor cells may also be related to the selenite-induced inhibition of microtubule formation [111]. Microtubules consist of polymers of tubulin protein units and are important structural elements of eukaryotic cells which also play a role in dynamic processes such as mitosis and axonal transport; selenite inhibits the polymerization of tubulin through the formation of disulfide bridges between tubulin sulfhydryl groups.

Additions of selenite to cultures of human hepatoma cells resulted in the partial retransformation by inactivation of the oncogene c-*myc* and activation of c-*fos* [112], a gene which regulates the growth and differentiation of normal cells. In experiments with human colon cancer cells, Se inhibited the expression of MAZ, the c-*myc*-activating zinc-finger protein, which regulates the activation of the oncogene c-*myc* [113]. The competition of Se with Zn on MAZ expression provides deeper insights into the nature of the antagonistic interactions between the two elements; similar competitive interactions could also occur with some of the other Se-antagonistic elements and have been suggested as a possible mechanism for metal carcinogenesis [114]. Another mechanism by which Se may prevent carcinogenesis is by inhibiting the activation of the nuclear transcription factor nFκB [115]. The activation/inactivation of NFκB is mediated by redox reactions [116]. In a recent study [117], inhibition of NFκB activation was shown to confer sensitivity to tumor necrosis factor (TNF)-α in human glioma cells. TNF-α is known to have both cytostatic and cytotoxic effects against a variety of tumor cells, but this effect is inhibited by activation of NFκB. Finally, some of the anticancer properties of Se may be associated with its effects on cellular immunity. Again, Se appears to have a variety of effects, such as the stimulation of the proliferation of lymphocytes, the expression of cytokine receptors, the stimulation of activity of NK- and cytotoxic cells [118–123], all of which are essential for the antitumor immunological defense system. The thioredoxin reductases and possibly other selenoproteins or reactive forms of Se may act as regulating biocatalysts in these reactions.

Concluding remarks

The complexity of the mechanisms of anticarcinogenic activity should not detract from the fact that Se is a validated practical means of cancer prevention. While ongoing research will deepen our understanding of its modes of protective action, the available evidence already indicates that a daily extradietary supplement of 200 μg of Se in a nutritional form such as selenomethionine reduces cancer risk. In Se-adequate regions, the desired Se intakes of 200–300 μg of Se/day may be attained through prudent diet choices alone, i.e. by maintaining a high consumption of Se-containing cereals and seafoods. However, for maximal protection, attention to Se alone is insufficient; all other established means of cancer prevention, such as the adherence to healthy lifestyle, avoidance of exposures to known carcinogenic risk factors, the practice of regular self-examination, and periodic medical checkups for early detection, must remain in effect.

1 Shamberger R. J. and Frost D. V. (1969) Possible inhibitory effect of selenium on human cancer. CMAJ **100:** 682
2 Schrauzer G. N. and Rhead W. J. (1971) Interpretation of the methylene blue reduction test of human plasma and the possible cancer protecting effect of selenium. Experientia **27:** 1069–1071
3 Shamberger R. J. and Willis C. E. (1971) Selenium distribution and human cancer mortality. Crit. Rev. Clin. Lab. Sci. **2:** 211–221
4 Schrauzer G. N., Rhead W. J. and Evans G. A. (1973) Selenium and cancer: chemical interpretation of a plasma 'cancer test'. Bioinorg. Chem. **2:** 329–370
5 Schrauzer G. N., White C. J. and Schneider C. J. (1977) Cancer mortality correlation studies. III. Associations with dietary selenium intakes. Bioinorg. Chem. **7:** 23–34
6 Clark L. C., Combs G. F., Turnbull B. W., Slate E. H., Chalker D. K. et al. (1996) Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. J. Am. Med. Assoc. **276:** 1957–1963
7 Taylor P. R. and Albanes D. (1998) Selenium vitamin E and prostate cancer: ready for prime time? [Editorial]. J. Natl. Cancer Inst. **90:** 184–185
8 Ip C. (1985) Selenium inhibition of chemical carcinogenesis. Fed. Proc. **44:** 2573–2578
9 Milner J. A. (1985) Effect of selenium on virally induced and transplantable tumor models. Fed. Proc. **44:** 2568–2572
10 Cowgill U. (1983) The distribution of selenium and cancer mortality in the continental United States. Biol. Trace Elem. Res. **5:** 336–345
11 Yu S.-Y., Chu Y.-J., Gong X.-G., Hou C., Li W.-G., Gong H.-M. et al. (1985) Regional variation of cancer mortality incidence and its relation to selenium levels in China. Biol. Trace Elem. Res. **7:** 21–29
12 Chen J., Geissler C., Parpia B., Li J. and Campbell T. C. (1992) Antioxidant status and cancer mortality in China. Intl. J. Epidemiol. **21:** 625–635
13 Chu Y.-J., Liu Q.-Y., Hou C. and Yu S.-Y. (1984) Blood selenium concentration in residents of areas in China having a high incidence of lung cancer. Biol. Trace Elem. Res. **6:** 133–137
14 Burguera M., Gallignani M., Alarcon O. M. and Burguera J. A. (1990) Blood serum selenium in the province of Merida, Venezuela, related to sex, cancer incidence and soil selenium. Trace Elem. Electrol. Health Dis. **4:** 73–77
15 Clark L. C., Cantor K. P. and Allaway W. H. (1991) Selenium in forage crops and cancer mortality in U.S. counties. Arch. Environ. Health **46:** 37–42
16 Schrauzer G. N. and White D. A. (1978) Selenium in human nutrition: dietary intakes and effects of supplementation. Bioinorg. Chem. **8:** 303–318
17 Levander O. A., Sutherland B., Morris V. C. and King J. C. (1981) Selenium balance in young men during selenium depletion and repletion. Am. J. Clin. Nutr. **34:** 2662–2669
18 Willett W. C., Polk B. F., Morris J. S., Stampfer M. J., Pressel S., Taylor J. A. et al. (1983) Prediagnostic serum selenium and risk of cancer. Lancet **2:** 130–134
19 Salonen J. T., Alfthan G., Huttunen J. K. and Puska P. (1984) Association between serum selenium and the risk of cancer. Am. J. Epidemiol. **120:** 339–342
20 Fex G., Petterson B. and Akesson B. (1987) Low plasma selenium as a risk factor for cancer in middle aged men. Nutr. Cancer **10:** 221–229
21 Itoh Y. and Kikuchi H. (1997) Serum selenium contents and the risk of cancer. Biomed. Res. Trace Elem. **8:** 75–76
22 Aaseth J., Glattre E., Frey H., Norheim G., Ringstad J. and Thomassen, Y. (1989) Selenium in the human thyroid gland. In: Proc. 6th Internatl. Trace Elem. Symp. 1989, vol. 3, pp. 991–914, Anke M., Baumann W., Bräunlich H., Brückner C. Groppel B. and Grün, M. (eds), VEB Krongreß- u. Werbedruck, Jena
23 Glattre E. M., Thomassen Y., Thorensen S. Q., Haldorsen T., Lund-Larsen P. G., Theodosen L. et al. (1989) Prediagnostic serum selenium in a case-control study of thyroid cancer. Int. J. Epidemiol. **18:** 45–49
24 Toma S., Micheletti A., Giacchero A., Coialbu T., Collecchi P., Esposito M. et al. (1991) Selenium therapy in patients with precancerous and malignant oral cavity lesions: preliminary results. Cancer Detect. Prev. **15:** 491–494
25 Russo M. W., Murray S. C., Wurzelmann J. I., Woosley J. T. and Sandler R. S. (1997) Plasma selenium and the risk of colorectal adenomas. Nutr. Cancer **28:** 125–129
26 Miyamoto H., Araya Y., Ito M., Isobe H., Dosaka H., Takoaka K. et al. (1987) Serum selenium and vitamin E concentrations in patients with lung cancer and their families. In: Toxicology of Metals, pp. 109–110, Brown S. S. and Kodak Y. (eds), Ellis Horwood, Chichester
27 Brandt P. A. van den, Goldbohm A., van't Veer P., Bode P., Dorant E., Hermus R. J. J. et al. (1993) A prospective cohort study on selenium status and the risk of lung cancer. Cancer Res. **53:** 4860–4865
28 Brandt P. A. van den, Goldbohm R. A., van't Veer P., Bode P., Dorant E., Hermus R. J. et al. (1993) A prospective study on toenail selenium levels and risk of gastrointestinal cancer. J. Natl. Cancer Inst. **85:** 224–229
29 Yoshizawa K., Willett W. C., Morris S. J., Stampfer M. J., Spiegelman D., Rimm E. B. et al. (1998) Study of prediagnostic selenium level in toenails and the risk of advanced prostate cancer. J. Natl. Cancer Inst. **90:** 1219–1224
30 Persson-Moschos M., Huang W., Srikumar T. S., Lindeberg S. and Åkesson B. (1995) Selenoprotein P in serum as a biochemical marker of selenium status. Analyst **120:** 833–836
31 Persson-Moschos M., Alfthan G. and Åkesson B. (1998) Plasma selenoprotein P levels of healthy males in different selenium status after oral supplementation with different forms of selenium. Eur. J. Clin. Nutr. **52:** 363–367
32 Persson-Moschos M. E. K., Stavenow L., Åkesson B. and Lindgärde F. (2000) Selenoprotein P in plasma in relation to cancer morbidity in middle-aged Swedish men. Nutr. Cancer **36:** 19–26
33 Capel I. D. and Williams D. C. (1979) Selenium and glutathione peroxidase in breast cancer. IRCS Medical Science: Biochemistry; Cancer; Clinical Biochemistry; Clinical Medicine; Metabolism and Nutrition; Pathology; Reproduction, Obstetrics and Gynecology **7:** 425
34 McConnell K. P., Jager R. M., Bland K. I. and Blotcky A. J. (1987) The relationship of dietary selenium and breast cancer. J. Surg. Oncol. **15:** 67–70

35 Hardell L., Danell M., Ängqvist C.-A., Marklund S. L., Fredriksson M., Zakari A.-L. et al. (1993) Levels of selenium in plasma and glutathione peroxidase in erythrocytes and risk of breast cancer. A case-control study. Biol. Trace Elem. Res. **36:** 99–108

36 Subramaniam S., Shyama S., Jagadeesan M. and Dhyamala Devi C. S. (1993) Oxidant and antioxidant levels in the erythrocytes of breast cancer patients treated with CMF. Med. Res. Sci. **21:** 79–80

37 Meyer F. and Verreault R. (1987) Erythrocyte selenium and breast cancer risk. Am. J. Epidemiol. **125:** 917–919

38 Noord P. A. H. van, Collette H. J. A. and Waard F. de (1987) Selenium levels in nails of premenopausal breast cancer patients assessed prediagnostically in a cohort-nested case-referent study among women screened in the DOM project. Int. J. Epidemol. **16:** 318–322

39 Hunter D. J., Morris J. S., Stampfer M. J., Colditz A., Speizer F. E. and Willett W. C. (1990) A prospective study of selenium status and breast cancer risk. J. Am. Med. Assoc. **264:** 1128–1131

40 Veer P. van't, Wielen R. P. J. van der , Kok F. J., Hermus R. J. J. and Sturmans F. (1990) Selenium in diet, blood, and toenails in relation to breast cancer: a case control study. Am. J. Epidemiol. **131:** 987–994

41 Schrauzer G. N., Molenaar T., Mead S. and Kuehn K. (1985) Selenium in the blood of Japanese and American women with and without breast cancer and fibrocystic disease. Jpn. J. Cancer Res. (Gann) **76:** 374–377

42 Yu Sh.-Y., Zhu Y. J., Li W. G. (1997) Protective role of selenium against hepatitis B virus and primary liver cancer in Qidong. Biol. Trace Elem. Res. **56**: 117–124

43 Yu Sh.-Y., Zhu Y.-J., Li W.-G., Huang Q.-S., Zhi-Huang C., Zhang Q.-N. et al. (1991) A preliminary report of the intervention trials of primary liver cancer in high risk populations with nutritional supple-mentation of selenium in China. Biol. Trace Elem. Res. **29**: 289–294

44 Yu Sh.-Y., Li W.-G., Zhu Y.-J., Yu W.-P. and Hou C. (1989) Chemoprevention trial of human hepatitis with selenium supplementation in China. Biol. Trace Elem. Res. **20**: 15–22

45 Blot W. J., Li J.-Y., Taylor P. R., Guo W., Dawsey S., Wang G.-Q. et al. (1993) Nutrition intervention trials in Linxian, China: supplementation with specific vitamin/mineral combinations, and disease-specific mortality in the general population. J. Natl. Cancer Inst. **85**: 1483–1492

46 Schrauzer G. N. (1998) Selenomethionine and selenium yeast: appropriate forms of selenium for use in infant formulas and nutritional supplements. J. Medic. Food **1:** 201–206

47 Waterhouse J. A. H. (1974) Cancer Handbook of Epidemiology and Prognosis, Churchill Livingstone, Edinburgh

48 Kodama M., Kodama T., Miura S. and Yoshida M. (1991) Nutrition and breast cancer in Japan. Anticancer Res. **11:** 745–754

49 Freedman L. S., Clifford C. and Messina M. (1990) Analysis of dietary fat, calories, body weight and the development of mammary tumors in rats and mice: a review. Cancer Res. **50:** 5710–5719

50 Prentice R. L., Pepe M. and Self S. G. (1989) Dietary fat and breast cancer: a quantitative assessment of the epidemiological literature and a discussion of methodological issues. Cancer Res. **49:** 3147–3156

51 Herman C., Adlercreutz T., Goldin B. R., Gorbach S. L., Höckerstedt K. A. V., Watanabe S. et al. (1995) Soybean phytoestrogen intake and cancer risk (1995). J. Nutr. **125:** 757S–770S

52 Messina M., Barnes S. and Setchell K. D. (1997) Phytooestrogens and breast cancer. Lancet **350:** 971–972

53 Rao A. V., Fleshner N. and Agrawal S. (1999) Serum and tissue lycopene and biomarkers of oxidation in prostate cancer patients. Nutr. Cancer **33:** 159–164

54 Singh R. B., Nioaz M. A., Rastogi V., Beegom R. and Singh N. K. (1997) Diet, antioxidants and risk of cancer: a case control study. J. Nutr. Environ. Med. **7:** 267–274

55 Schrauzer G. N. and Nichols W. L.(1987) Selenium, dietary fats and male lung cancer mortality. In: Toxicology of Metals, pp. 107–108, Brown S. S. and Kodama Y. (eds), Ellis Horwood Chichester

56 Ip C. and Sinha D. K. (1981) Enhancement of mammary tumorigenesis by dietary selenium deficiency in rats with a high polyunsaturated fat intake. Cancer Res. **41:** 31–34

57 Welsch C. F., Goodrich-Smith M., Brown C. K., Greene H. D. and Hamel E. J. (1981) Selenium and the genesis of murine mammary tumors. Carcinogenesis **2:** 519–522

58 Schrauzer G. N., Molenaar T., Kuehn K. and Waller D. (1989) Effect of simulated American, Bulgarian and Japanese human diets and of selenium supplementation on the incidence of virally induced mammary tumors in female mice. Biol. Trace Elem. Res. **20:** 169–178

59 Hassan M., Stohs S. J., Murray W. J. and Birt D. F. (1985) Dietary selenium, glutathione peroxidase activity and toxicity of 2,3,7,8-tetradichlorobenzo-p-dioxin. J. Toxicol. Environ. Health **15:** 405–415

60 Tsugane S., Souza J. M. P. de, Costa M. L., Mirra A. P., Gottlieb S. L. D., Laurenti R. et al. (1990) Cancer incidence rates among Japanese immigrants in the City of Sao Paulo, Brazil, 1969–78. Cancer Causes Control **1:** 189–193

61 Karita K., Tsugane S., Hamada G. S., Watanabe S. and Laurenti R. (1994) Serum selenium levels in middle-aged Japanese men in Sao Paulo, Brazil, and five areas of Japan. Biomed. Res. Trace Elem. **5:** 77–84

62 Friberg L., Nordberg G. and Piscator M. (1977) Cadmium. In: Toxicology of metals, vol. 2, pp. 124–163, Springfield, VA

63 Stokinger, H. E. (1981) The metals. In: Patty's industrial hygiene and toxicology, 3rd ed., vol. 11A, Toxicology, Clayton G. D. and Clayton F. E. (eds), New York, Wiley-Interscience, John Wiley & Sons, pp. 1493–2060

64 Bako G., Smith E. S. O., Hanson J. and Dewar R. (1982) The geographical distribution of high cadmium concentrations in the environment and prostate cancer in Alberta. Can. J. Public Health **73:** 92–94

65 Berg J. W. and Burbank F. (1972) Correlations between carcinogenic trace metals in water supplies and cancer mortality. Ann. N.Y. Acad. Sci. **199:** 249–252

66 Schrauzer G. N., White D. A. and Schneider C. J. (1977) Cancer mortality correlation studies. IV. Associations with dietary intakes and blood levels of certain trace elements, notably Se-antagonists. Bioinorg. Chem. **7:** 35–56

67 Robinson M. F., McKenzie J. M., Thomson C. D. and Rij A. L. van (1973) Metabolic balance of zinc copper cadmium iron molybdenum and selenium in young New Zealand women. Br. J. Nutr. **30:** 195–205

68 Bagchi D., Bagchi E., Hassoun E. A. and Stohs S. J. (1996) Cadmium-induced excretion of urinary lipid metabolites, DNA damage, glutathione depletion and hepatic lipid peroxidation in Sprague-Dawley rats. Biol. Trace Elem. Res. **52:** 143–154

69 Ellingsen D. G., Thomassen Y., Aaseth J. and Alexander J. (1997) Cadmium and selenium in blood and urine related to smoking habits and previous exposure to mercury vapor. J. Appl. Toxicol. **17:** 337–343

70 Sugaware N. and Sugawara C. (1984) Selenium protection against testicular lipid peroxidation from cadmium. J. Appl. Biochem. **6:** 199–204

71 Schrauzer G. N.(1987) Effects of selenium antagonists on cancer susceptibility: new aspects of chronic heavy metal toxicity. In: Toxicology of Metals, pp. 91–98, Brown S. S. and Kodama Y. (eds), Ellis Horwood, Chichester

72 Shamberger R. J.(1978) Antioxidants and cancer. VIII. Cadmium-selenium levels in kidneys. In: Trace Element Metabolism in Man and Animals, vol. 3, pp. 391–392, Kirchgessner M. (ed.), Arbeitskreis für Tierernährungsforschung Weihenstephan, Freising-Weihenstephan

73 Brys M., Nawrocka A. D., Miekos E., Zydek C., Foksinski M., Barecki A. et al. (1997) Zinc and cadmium analysis of human prostate neoplasms. Biol. Trace Elem. Res. **59:** 145–152

74 Webber M. M. (1985) Selenium prevents the growth stimulatory effects of cadmium on human prostatic epithelium. Biochem. Biophys. Res. Comm. **127:** 871–877

75 Schrauzer G. N., Kuehn K. and Hamm D. (1981) Effects of dietary selenium and lead on the genesis of spontaneous mammary tumors in mice. Biol. Trace Elem. Res. **3:** 185–196

76 Schrauzer G. N., White D. A. and Schneider C. J. (1976) Inhibition of the genesis of spontaneous mammary tumors in C3H mice: effects of Se and of Se-antagonistic elements and their possible role in human breast cancer. Bioinorg. Chem. **6:** 265–270

77 Eybl V., Sykora J. and Mertl F. (1986) In vivo interaction of selenium with zinc. Acta Pharmacol. Toxicol. Suppl. **59:** 547–548

78 Chmielnicka J., Zareba G., Witasik M. and Brzesnicka E. (1988) Zinc-selenium interaction in the rat. Biol. Trace Elem. Res. **15:** 267–276

79 House W. A. and Welch R. M. (1989) Bioavailability of and interactions between zinc and selenium in rats fed wheat grain intrinsically labeled with ^{65}Zn and ^{75}Se. J. Nutr. **119:** 916–921

80 Ujiie S., Itoh Y., Kikuchi H. and Wakui A. (1994) Zinc distribution in malignant tumors. Biomed. Res. Trace Elem. **5:** 81–82

81 Xu Z. and Wang C. (1999) Relationship between tumor and trace elements in hair. Guangdong Weiliang Yuansu Kexue **6:** 24–27

82 Besuschio S. C., Perez Desanzo A. C. and Croci M. (1980) Epidemiological associations between arsenic and cancer in Argentina. Biol. Trace Elem. Res. **2:** 41–55

83 Chen C.-J., Chuang Y.-C., Lin T.-M. and Wu H.-Y. (1985) Malignant neoplasms among residents of a Blackfoot disease-endemic area in Taiwan: high-arsenic artesian well water and cancers. Cancer Res. **45:** 5895–5899

84 Lin S. M. and Yang M. H. (1988) Arsenic, selenium and zinc in patients with Blackfoot disease. Biol. Trace Elem. Res. **15:** 213–221

85 Wang W., Xu H., Xiang S. and Guo L. (1988) A study of the relation of the Se/As ratio in the hair of workers to lung cancer at the Yunnan Tin Mine. In: Proc. Internatl. Symp. on Environmental Life Elements and Health, Chinese Academy of Sciences, Beijing, P.R.C., p. 216

86 Yu S.-Y., Mao B. L., Xiao P., Yu W. P., Wang Y. L., Huang C. Z. et al. (1990) Intervention trial with selenium for the prevention of lung cancer among tin miners in Yunnan, China. Biol. Trace Elem. Res. **24:** 105–108

87 Schrauzer G. N., White D. A., McGinness J. E., Schneider C. J. and Bell L. J. (1978) Arsenic and cancer. Effects of the joint administration of selenium and arsenic on the genesis of spontaneous mammary tumors in mice. Bioinorg. Chem. **9:** 245–253

88 Czauderna M. and Rochalska M. (1989) Interaction between selenium and chromium and distribution of zinc, rubidium, cobalt and iron in mice given chromate ions and selenium compounds. J. Radioanal. Nucl. Chem. **134:** 383–392

89 Schrauzer G. N. (1979) Trace elements in carcinogenesis. Adv. Nutr. Res. **2:** 219–244

90 Singh V. and Garg A. N. (1998) Trace element correlations in the blood of Indian women with breast cancer. Biol. Trace Elem. Res. **64:** 237–245

91 Garg A. N., Weginwar R. G. and Sagdeo V. (1990) Minor and trace elemental contents of cancerous breast tissue measured by instrumental and radiochemical neutron activation analysis. Biol. Trace Elem. Res. **26/27:** 485–496

92 Sky-Peck H. E. (1989) Distribution of trace elements in normal and neoplastic human tissues by energy dispersive x-ray fluorescence. In: XRF and PIXE Applications in Life Sciences, pp. 31–47, Moro R. and Cesareo R. (eds), World Scientific, Teaneck, NJ

93 Schrauzer G. N. (1995) Inorganic element levels in neoplasia. In: Handbook of Metal Ligand Interactions, pp. 1060–1067, Berthon G. (ed.), Marcel Dekker, New York

94 Gerhardsson L., Brune D., Nordberg I. G. F. and Wester P. O. (1985) Selenium and other trace elements in lung tissue in smelter workers. Relationship to the occurrence of lung cancer. Br. J. Industr. Med. **42:** 617–624

95 Beck M. A., Kolbeck P. C., Rohr L. H., Shi Q., Morris V. C. and Levander O. A. (1994) Benign human enterovirus becomes virulent in selenium-deficient mice. J. Med. Virol. **43:** 166–170

96 Taylor E. W., Nadimpalli R. G. and Ramanathan C. S. (1997) Genomic structures of viral agents in relation to the biosynthesis of selenoproteins. Biol. Trace Elem. Res. **56:** 63–91

97 Schrauzer G. N., McGinness J. E. and Kuehn K. (1980) Effects of temporary selenium supplementation on the genesis of mammary tumors in female inbred C3H/St mice. Carcinogenesis **1:** 199

98 Cox R. (1985) Selenite: a good inhibitor of rat liver DNA methylase. Biochem. Int. **10:** 63–69

99 Flesher J. W., Myers S. R. and Stansbury K. H. (1990) The site of substitution of the methyl group in the bioalkylation of benzo-[*a*]-pyrene. Carcinogenesis **11:** 493–496

100 Garberg P. and Hoegberg (1985) The role of hypoxia in selenium metabolism. Biochem. Pharmacol. **36**: 1377–1379

101 Schrauzer G. N. (1992) Selenium: mechanistic aspects of anticarcinogenic action. Biol. Trace Elem. Res. **33:** 51–62

102 Schrauzer G. N. (2000) Sauerstoff und Selen in der Onkologie. Biochemische und Praktische Aspekte. Z. Onkol./J. Oncol. **32:** 17–22

103 LeBoeuf R. A., Laishes B. A. and Hoekstra W. G. (1985) Effects of selenium on cell proliferation in rat liver and mammalian cells as indicated by cytokinetic and biochemical analysis. Cancer Res. **45:** 5496–5504

104 Spallholz J. E. (1994) On the nature of selenium toxicity and carcinostatic activity. Free Radical Biol. Med. **17:** 45–64

105 Vogl S., Goldberg M., Ruhenstroth-Bauer G., Otter R. and Wendel A. J. (1987) Biological efficacy of partial hepatectomy and hepatopoietin in long-term selenium-deficienc mice. Hepatol. **4:** 212–217

106 Yu S. Y., Ao P., Wang L. M., Huang S. L., Chen H. C., Lu X. P. et al. (1988) Biochemical and cellular aspects of the anticancer activity of selenium. Biol. Trace Elem. Res. **15:** 243–255

107 Pung A., Mei Z. and Yu S. Y. (1987) Differential effects of selenium on the proliferation of human pulmonary adenocarcinoma cells and human embryonic lung diploid cells *in vitro*. Biol. Trace Elem. Res. **14:** 29–42

108 Caffrey P. B. and Frenkel G. D. (1991) Inhibition of cell colony formation by selenite: Involvement of glutathione. Mol. Pharmacol. **39:** 281–284

109 Lanfear J., Fleming J., Wu L., Webster G. and Harrison P. R. (1994) The selenium metabolite selenodiglutathione induces p53 and apoptosis: relevance to the chemopreventive effects of selenium? Carcinogenesis **15:** 1387–1392

110 Gallegos A., Berggren M., Gasdaska J. R. and Powis G. (1997) Mechanism of the regulation of thioredoxin reductase activity in cancer cells by the chemopreventive agent selenium. Cancer Res. **57:** 4965–4970

111 Leynadier D., Peyrot V., Codaccioni F. and Briand C. (1991) Selenium: inhibition of microtubule formation and interaction with tubulin. Chem.-Biol. Interact. **79:** 91–102

112 Yu S.-Y., Lu X. P., Liao S. D. (1990) The regulatory effect of selenium on the expression of oncogenes associated with the proliferation and differentiation on tumor cells. In: Metal ions in Biology and Medicine, pp. 487–489, Collery P., Poirier L. A., Manfait M. and Etienne J. C. (eds), John Libbey Eurotext, Paris

113 Nelson K. K., Bacon B. and Christensen M. J. (1996) Selenite supplementation decreases the expression of MAZ in HT29 human colon adenocarcinoma cells. Nutr. Cancer **26:** 73–81

114 Sunderman F. W. Jr and Barber A. M. (1988) Finger-loops, oncogenes and metals. Ann. Clin. Laborat. Med. **18:** 267–288

115 Makropoulos V. and Bruening T. Schulze-Osthoff (1996) Selenium-mediated inhibition of transcription factor nFκB and HIV-1 LTR promoter activity. Arch. Toxicol. **70**: 277–283

116 Flohé L., Brigelius-Flohé R., Saliou C., Traber M. and Packer L. (1997) Redox regulation of nFκB activation. Free Rad. Biol. Med. **22:** 1115–1126

117 Otsuka G., Nagaya K., Mizuno M., Yoshida J. and Sao H. (1999) Inhibition of nuclear factor κB activation confers sensitivity to tumor necrosis factor-α by impairment of cell cycle progression in human glioma cells. Cancer Res. **59:** 4446–4452

118 Kiremidjian-Schumacher L. and Stotzky G. (1987) Selenium and immune responses. A review. Environ. Res. **42:** 277–302

119 Kiremidjian-Schumacher L., Roy M., Wishe H. I., Cohen M. W. and Stotzky G. (1990) Selenium and immune cell functions. I. Effect on lymphocyte proliferation and production of interleukin-1 and interleukin-2. Proc. Soc. Exp. Biol. Med. **193:** 136–142

120 Kiremidjian-Schumacher L., Wishe H. I., Cohen M. W. and Stotzky G. (1990) Selenium and immune cell functions. II. Effect on lymphocyte-mediated cytotoxicity. Proc. Soc. Exp. Biol. Med. **193:** 143–148

121 Roy M., Kiremidjian-Schumacher L., Wishe H. I., Cohen M. W. and Stotzky G. (1993) Supplementation with selenium and human immune cell functions. I. Effect on lymphocyte proliferation and interleukin 2 receptor expression. Biol. Trace Elem. Res. **41:** 113–114

122 Roy M., Kiremidjian-Schumacher L., Wishe H. I., Cohen M. W. and Stotzky G. (1994) Supplementation with selenium and human immune cell functions. II. Effect on cytotoxic lymphocytes and natural killer cells. Biol. Trace Elem. Res. **41:** 115–127

123 Kiremidjian-Schumacher L., Roy M., Wishe H. I., Cohen M. W. and Stotzky G. (1996) Supplementation with selenium augments the functions of natural killer and lymphokine-activated killer cells. Biol. Trace Elem. Res. **52:** 227–239