Chapter 24
Selenium as a Cancer Preventive Agent

Matthew I. Jackson and Gerald F. Combs, Jr.

Abstract The known metabolic functions of selenium, which appear to be discharged by a fairly small number of selenoproteins, do not fully explain the anticarcinogenic effects of selenium, particularly those observed in response to selenium-supplementation of non-deficient subjects. While anticarcinogenic roles are possible for at least some selenoproteins, i.e., those involved in antioxidant protection, redox regulation and hormonal regulation of metabolism, anticarcinogenic effects of selenium have been shown in individuals with apparently full selenoenzyme expression, suggesting additional mechanisms. Seleno-compounds have been shown to alter gene expression, affect DNA damage and repair, affect cell-signaling pathways, inhibit cell proliferation, stimulate apoptosis, and inhibit metastasis and neo-angiogenesis. Underlying these effects are metabolic activities of various seleno-metabolites: redox cycling, modification of protein-thiols, and methionine mimicry. It is, therefore, likely that selenium deprivation may increase cancer risk by compromising selenoprotein expression, and that supranutritional exposures to Se reduce cancer risk in non-deficient subjects.

24.1 Evidence for a Selenium-Cancer Link

24.1.1 Emergence of Evidence

The nutritional essentiality of selenium (Se) was recognized in the late 1950s when the element was found to spare vitamin E in the diets of rats and chicks for the prevention of vascular, muscular, and/or hepatic lesions [1]. That Se may be anticarcinogenic

M.I. Jackson • G.F. Combs, Jr. (✉)
Grand Forks Human Nutrition Research Center, USDA-ARS, Grand Forks, ND 58202, USA
e-mail: gerald.combs@ars.usda.gov

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was suggested a decade later based on empirical observations of inverse relationships of cancer mortality rates and blood and forage crop Se contents in the United States [2, 3]. Subsequent evidence has shown Se status to be inversely associated with cancer risk, cancer cases tending to have lower prediagnostic serum Se levels than controls, and Se-treatment can reduce tumor yields in Se-adequate animal models [4]. Almost all have shown that supranutritional Se doses reduced the tumor yields.

24.1.2 Clinical Trial Evidence

Several clinical trials have been conducted to determine the efficacy of Se in reducing cancer risk in humans (Table 24.1). Those results [4] include reports of protection by selenite-enriched table salt against primary liver cancer [5, 6], and by Se-containing, multiagent supplements against esophageal cancer [7–12], precancerous oral lesions [13, 14], and prostate cancer [15].

The strongest evidence of anticancer efficacy of Se in humans comes from the NPC[1] Trial [16–20], a randomized, placebo-controlled clinical trial that tested the hypothesis that a daily oral dose of Se (200 μg/day as Se-enriched yeast) could reduce the rate of recurrent non-melanoma skin cancer in a high-risk group of 1,312 older Americans. The initial results [16] showed no effects on the incidences of basal or squamous cell carcinoma (BCCs or SCCs) of the skin; however, they showed significant reductions in risks to total cancer, cancer deaths and carcinomas of the prostate, lung, colon-rectum, and total non-skin. Follow-up analyses [17, 18] supported those findings and showed that, while Se-treatment did not affect BCC risk, it appeared to delay diagnosis of the first BCC [18]. The Trial showed that, for men with plasma prostate specific antigen (PSA) levels <4 ng/mL, Se-treatment caused a 65% reduction in prostate cancer risk, while for men with PSA >4 ng/mL, there was no protection [20], suggesting protection only in early stage(s) of carcinogenesis. Protection was noted mostly (86% risk reduction) among subjects with baseline plasma Se levels <106 ng/mL, i.e., in the lowest tertile of the cohort,[2] to a lesser extent (61% reduction) among those in the middle tertile (107–123 ng/mL), but not for those in the highest tertile (>123 ng/mL) [17].

The largest clinical trial of Se conducted to date, SELECT[3] [21], found no protection by Se against prostate cancer over a 5-year intervention period. That trial, while large (>32,000 subjects) used a cohort of relatively high baseline Se status (plasma Se 136 ng/mL). For this reason, those negative findings are consistent with those of NPC [20], which found Se to have no cancer-protective effect for subjects with relatively high plasma Se levels.

[1] Nutritional Prevention of Cancer.

[2] The cohort level was 114 ± 23 ng/mL; very few subjects had levels <80 ng/mL, the level Nève [20] found to be the upper limit for GPx responses to supplemental Se in healthy adults. These levels suggest an average Se intake of ≥85 μg/day, or at least 155% of the RDA [21].

[3] Selenium and Vitamin E Cancer Trial.

Table 24.1 Results of randomized clinical trials of Se for cancer prevention

Trial (country)	Treatment			Period (year)	Subjects	Results – RR-cancer site	References
	Dose μg Se/day	Se form	Other agents				
NPC (USA)	200	Se-yeast	None	13	1,313	0.63 – All sites 0.51 – Prostate 0.46 – Colorectal	[16, 20]
SELECT (USA)	200	SeMet	None	5	32,400	0.99 – Prostate N.S.	[21]
Qidong study (China)	200	Se-yeast	None	2	2,065 (HSA^+)	0.51 – Liver	[5, 6]
Qidong table salt study (China)	15 ppm, salt	Selenite	None	3	20,847	0.63 – Liver	[6]
Linxian general population trial (China)	50	Se-yeast	Vitamin E β-carotene	5.25	29,584	0.91 – All sites 0.87 – Cancer mort. *10 year follow-up* 0.89 – Gastric cancer mortality 0.83 – Esophageal cancer mortality	[7–9] [10]
Linxian esophogeal dysplasia trial (China)	50	Se-yeast	Vitamin E β-carotene	5.25	3,318	0.93 – All (N.S.) 0.96 – Cancer mortality (N.S.)	[7, 8]
SU.VI.MAX (France)	50	Selenite	Vitamin E Vitamin C β-carotene	8	12,749	0.51 – Prostate	[15]

RR relative risk

24.2 Mechanisms of Selenium Anticarcinogenicity

24.2.1 General Theory of Selenium-Anticarcinogenesis

That Se deficiency may increase cancer risk might be expected on the basis of the known functions of selenoenzymes in antioxidant protection, the glutathione peroxidases (GPxs) and thioredoxin reductases, (Txnrds), as mutagenic oxidative stress is thought to be a major factor in the initiation of human carcinogenesis. However, it is clear that Se intake in *excess* of the nutritional requirement can inhibit tumorigenesis: antitumorigenically effective Se-exposures in animal models (≥1.5 mg/kg diet) have often been much greater than those required to prevent Se deficiency or to support maximal expression of selenoproteins (<0.2 mg/kg diet). We proposed a theory of Se-anticarcinogenesis accommodating these various findings [22]. Our multitiered model (Fig. 24.1) links known features of Se metabolism to anticarcinogenesis through underlying actions of Se-metabolites affecting cellular mechanisms.

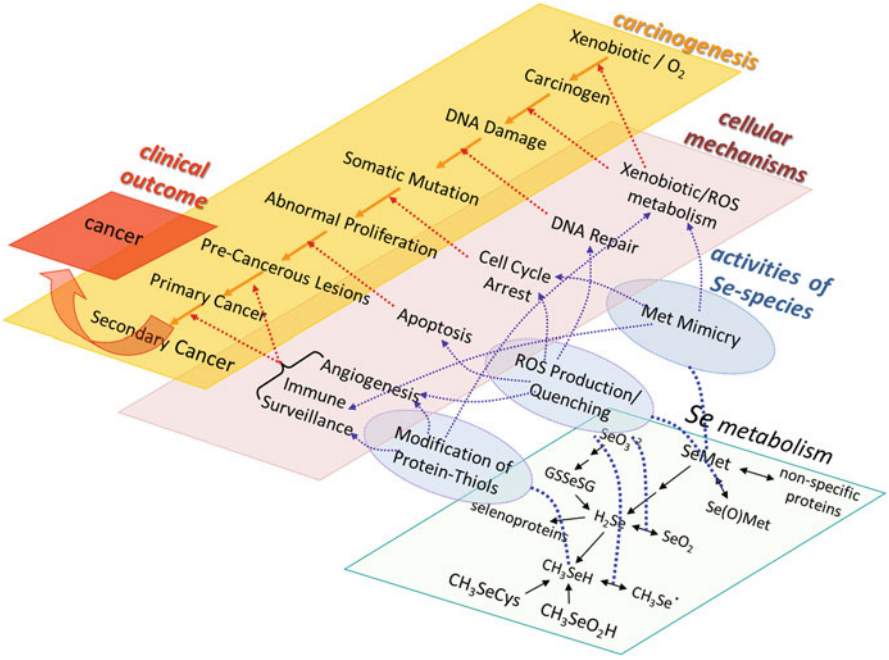

Fig. 24.1 Theory of Se-anticarcinogenesis. Figure is taken from Jackson and Combs [22] with permission. SeO_3^{-2} selenite; *SeMet* selenomethionine; *Se(O)Met* selenomethionine selenoxide; *GSSeSG* selenodiglutathione; H_2Se hydrogen selenide; SeO_2 selenium dioxide; CH_3SeH methylselenol; $(CH_3)_3Se^+$ trimethylselenonium; CH_3SeCys methylseleno-cyeteine; CH_3SeO_2H methylseleninic acid

24.2.1.1 Roles of Selenoenzymes

Etiologies of some cancers are believed to involve mutagenic oxidative stress, thus antioxidant selenoproteins are expected to have anticarcinogenic impact by removing DNA-damaging H_2O_2 and lipid hydroperoxides, blocking production of reactive oxygen species (ROS) and malonyldialdehyde, and regulating the redox signaling system critical to growth of many cancers. Partially through these actions, Se has been shown to modulate p53 activity by redox modification of cys275,277 mediated by Ref-1, enhancing repair of DNA damage [23, 24]. As p53 suppresses expression of angiogenic factor VEGF [25] and induces angiogenesis-suppressing thrombospondin-1 [26], a Se-mediated increase of p53 could play a pivotal role in switching off angiogenesis in early lesions.

The association of selenoprotein allelic variation with cancer risk responses to Se suggests the involvement of one or more selenoprotein in cancer protection. A single nucleotide polymorphism (SNP) at codon 198 of human GPx1, resulting in a leucine-for-proline substitution, has been associated with increased risks of cancers of the lung [27], breast [28], head and neck [29], bladder [30] and prostate [31]. The 198-leucine genotype may be less responsive to Se exposure than the 198-proline genotype [27], suggesting that increased cancer susceptibility of individuals with that allele may involve their reduced ability to utilize Se for selenoprotein expression.

The frequency of SNPs in the promoter of selenoprotein P (Sepp1) [32] is similar in colorectal adenoma patients and controls [33], but malignant colon tissues showed lower levels of Sepp1 than adjacent normal tissue [34, 35]. Prostate cancer cells also have low Sepp1 expression, although they express the Sepp1 transporter (ApoER2) [36]. The SNP 25191 of Sepp1 predicts increase in plasma Se level with Se-supplementation [37], most of which is associated with Sepp1. Apart from the effects of SNPs, the risk of prostate cancer decreased by 11% for every 10 μg/mL of plasma Se increase [38].

Jablonska et al. [31] found lung cancer risk related to SNPs of the 15 kDa selenoprotein (Sep15); individuals with the 1125AA genotype appeared to benefit most from higher Se status. Reduced expression of Sep15 has been observed in malignant liver and prostate [39], and malignant mesothelioma cells, which also showed resistance to Se-induced growth inhibition [40]. Reduced expression of Sep15 by mouse colon cancer cells (short hairpin RNA) decreased expression of gene pathways involved in cell growth and proliferation, [41] and reduced the cell's ability to produce metastatic tumors upon injection into surrogate mice. Lewis lung carcinoma cells were not affected by Sep15 knockdown, indicating the tissue specificity of the Sep15 effects.

The selenoprotein, methionine sulfoxide reductase A (MsrA), which reduces oxidized protein methionyl residues, is downregulated in a number of human breast cancers [42], resulting in increased tumor aggressiveness and derepression of the phosphoinositide proliferation pathway due to decreased levels of PTEN tumor suppressor protein.

Thus, one or more selenoproteins may have anticarcinogenic roles that would be limited under conditions of insufficient Se supply and by mutations affecting incorporation of selenocysteine into selenoproteins. Therefore, correction of nutritional Se deficiency can be expected to have anticarcinogenic effects; however, that hypothesis has not been extensively tested.

24.2.1.2 Roles of Se-Metabolites

Anticarcinogenic activities have been demonstrated for several intermediary metabolites of Se: selenodiglutathione (GSSeSG), the reductive metabolite of the oxidized inorganic salts (selenite, selenate); hydrogen selenide (H_2Se), the common intermediate of that reductive pathway and of the catabolism of selenoamino acids; methylated metabolites of selenide ($[CH3]_xSeH$), excretory forms; and selenomethionine (SeMet), a methionine analog and dominant food form of Se. These metabolites execute several functions that effect Se-anticarcinogenesis at underlying and intermediate levels (see Fig. 24.1).

24.2.2 Underlying Mechanisms

24.2.2.1 Redox Cycling

Redox cycling and covalent protein-thiol modification appear to constitute competing pathways available to Se. The disposition of Se-metabolites through these pathways would appear to determine their biological effects. Selenite, diselenides, and the oxidation product of H_2Se, selenium dioxide (SeO_2), are reduced by GSH producing selenolate ion (RSe^-) and oxidized glutathione (GSSG) [43]; in the presence of molecular oxygen $(O_2)^-$, they can redox cycle to deplete GSH and produce the ROS, superoxide (O_2^-) and hydrogen peroxide (H_2O_2) [44]. Selenite elicits biological effects through cell damage responses initiated by such ROS, leading to DNA damage and thiol modification [45, 46]. This appears to be the basis of: (i) caspase-independent apoptosis in selenite-treated cervical cancer cells, suppressible by antioxidants and exacerbated by prior GSH depletion [47]; (ii) DNA damage by chronic selenite feeding [48]; and (iii) increased Txnrd associated with hepatotoxic selenite doses [49]. MeSeH can also redox cycle; but the anticarcinogenic effects of MeSeH-precursors are qualitatively different from H_2Se-precursors, indicating different mechanisms.

Free and peptide-bound forms of SeMet scavenge ROS and are regenerated nonenzymically by GSH; the SeMet/Se(O)Met couple may, thus, serve as a cellular defense mechanism. Met(O) formation can alter protein activity; calmodulin kinase is activated by ROS from angiotensin signaling [50]. SeMet is more readily oxidized than Met [51], thus Met → SeMet substitution may sensitize regulatory proteins to ROS.

24.2.2.2 Modification of Protein-Thiols

Application of Se compounds alters protein-thiol redox status, driving cell-signaling mechanisms [52]; products derived from both H_2Se and MeSeH react with protein-thiols, resulting in covalent adduction, altering protein activity. Similarly, thiols in cell surface proteins may react with oxidized Se to become crosslinked [53]. The dominant species of both intracellular H_2Se and MeSeH is likely to be a mixed selenosulfide of GSH, i.e., GSSeSG for H_2Se and MeSeSG for MeSeH. Se-species can act through protein-thiol modification; for example SeMet-treatment affected the expression of redox-sensitive proteins of prostate cancer cells (and see reference [54]).

Se-induced inhibition, presumably by such reactions, has been demonstrated for several relevant enzymes: ribonuclease [55], Na^+, K^+-ATPase [56], and PKC [57]. Inhibition of PKC would be expected to trigger a number of downstream effects including cell cycle arrest, apoptosis, and angiogenic switch regulation. Some of these effects have been reported after treatment with MeSeH-precursors, including decreased cdk2 kinase activity [58] and inhibition of vascular endothelial MMPs and VEGF expression [59]. These effects target certain factors, rather than affecting the far-reaching perturbations in cellular redox control exerted by Se-proteins, as Se-metabolites are present at much lower levels and are not always catalytic in action.

24.2.2.3 Methionine Mimicry

SeMet competes with Met in general metabolism including protein synthesis. It can charge $tRNA^{Met}$, resulting in substitution of SeMet for Met in proteins [60], trapping Se and limiting its conversion to anticarcinogenic H_2Se and MeSeH. Li et al. [61] showed that SeMet raised tumor Se levels eight-fold more than MeSeH-precursors did, but failed to affect tumor burden. This may be relevant to cancer management under circumstances of restricted Met intake [62]. SeMet is converted to analogues of Met-metabolites, and as such is more effective than Met as a substrate for Met-adenosyl transferase [63], forming Se-adenosylselenomethionine (SeSAM). Further, SeSAM is a better substrate for methyltransferases than *S*-adenosylmethionine [64]; these apects of Se metabolism may be relevant to anticarcinogenesis, as methyltransferases play roles in gene silencing, repair of damaged proteins, and activation of oncogenes.

24.2.3 Intermediate Mechanisms

24.2.3.1 DNA Damage and Repair

Selenite can cause DNA damage in both malignant and normal tissues [48, 65]. Letavayová et al. [66] found selenite to induce DNA double-strand breaks and frame-shift deletions in yeast, effects not seen for SeMet or a MeSeH-precursor.

Se has been shown to induce the ATM mismatch repair pathway by facilitating an interaction with hMLH1 in colorectal cancer cells, allowing cells to respond to and correct nascent DNA mutations [67]. The findings of Hu et al. [68] suggest that DNA repair secondary to damage can impair carcinogenesis: a high-Se milk protein enhanced the removal of carcinogen-induced DNA lesions in mice. That Se-yeast failed to produce comparable effects suggests an active principle other than SeMet.

24.2.3.2 Cell Cycle and Apoptosis

SeMet or MSA increases expression of genes associated with apoptosis in transformed cell lines, and androgen-regulated genes in prostate cells[69]. High Se intakes can arrest the cell cycle in different ways: selenite in S-phase leading to caspase-independent apoptosis; methylated Se in G1-phase leading to caspase-mediated apoptosis [65]. In contrast, SeMet transiently activates Akt before inactivating it in a PTEN-dependent fashion resulting in its degradation through caspase and proteosome pathways [70]. Rudolf et al. [47] showed that selenite can activate a p53-dependent pathway, increasing p21 and phosphorylated p53, as well as a p38 pathway leading to accumulation of Bax. The product of the thiol-dependent reduction of selenite, GSSeSG, has been shown to inhibit the DNA-binding of AP-1 [71], inhibit cell proliferation [72], and enhance apoptosis [73]. Wang et al. [74] showed that methylated Se produced transient upregulation of p21/CIP1 and p27/KIP1 in G1-arrested endothelial cells, with a modest increase in p16/INK4a, indicating a link between cell cycle and Se-antiangiogenesis. Differential sensitivity has been found for cell types to apoptosis induced by methylated Se, on the order of: breast carcinoma cells > hepatoma and neuroblastoma cells > colon cancer cells and nonmalignant mammary epithelial cells [75]. Hu et al. [76] showed the response to methylated Se involves downregulated expression of two anti-apoptosis proteins, Bcl-XL, and survivin. The MeSeH-precursor, CH_3SeCys, can inhibit mammary cell growth, arresting cells in the G_1 or early S-phase and inducing apoptosis in a caspase-dependent manner involving mitochondrial cytochrome C release, poly (ADP-ribose) cleavage, and nucleosomal DNA fragmentation [77, 78]. In cell lines that lack functional p53, the pro-apoptotic action of methyl-Se is caspase-dependent [79, 80]. In addition to apoptotic mechanisms, subapoptotic levels of methyl-Se have been shown to reduce androgen receptor protein expression [81], reduce PSA expression, and cause rapid PSA degradation [82] and inhibit androgen-stimulated PSA promoter transcription [83–85], suggesting a unique basis for the apparent sensitivity of the prostate to Se-anticarcinogenesis.

24.2.3.3 Metastasis and Angiogenesis

Both selenite and SeMet can inhibit the growth of secondary tumors in animal models [83, 84]. Hurst et al. [85] showed that this involves altered collagen gene expression preferentially affected by methylated Se. Kim et al. [86] showed SeMet decreased

tumor cell invasion by decreasing ROS and blunting Akt-dependent matrix metalloproteinase secretion. In a murine model of melanoma invasiveness, Se application did not reduce primary tumor size, but did reduce tumor metastasis and in vitro cell culture growth, suggesting a role in periods of adaptation during metastasis [87]. The MeSeH-precursor MSA reduced NFKb protein expression, resulting in decreased IL-6, MCP-1, COX-2, and iNOS expression in osteoblasts challenged with conditioned media from breast cancer cells. This implies that osteoblast/osteoclast-induced bone demineralization, which occurs with cancer metastasis to bone, may be ameliorated by Se-treatment [88].

MeSeH-precursors inhibit expression of matrix matalloproteinase-2 in vascular endothelial cells and of vascular endothelial growth factor in cancer cells [77, 78, 89, 90]. This suggests that methyl-Se inhibits cellular proliferation and survival of activated endothelial cells by inhibiting neo-angiogenesis. Jiang et al. [65] found Se-treatment to impair microvascular development of tumors. They also found methyl-Se to reduce microvessel density in tumors developing from prostate cancer cell xenografts by inducing cell cycle arrest in microvascular endothelial cells [76]. Li et al. [61] found methylated Se more effective than selenite in this regard, an effect that Bhattcharya et al. [91] showed can provide therapeutic synergy with anticancer drugs, finding CH_3SeCys to reduce vascular permeability of carcinoma xenografts and consequent tumor uptake of doxorubicin.

24.3 Conclusions

Se compounds, including those in foods, can inhibit and/or delay carcinogenesis. These effects may involve the protective, nutritional functions of Se as an essential constituent of metabolically important selenoenzymes; such functions may be compromised in Se-deficient individuals and those with allelic variants of certain selenoproteins. In addition, certain Se-metabolites appear to inhibit carcinogenesis through mechanisms unrelated to the nutritional functions of Se. These appear to involve ROS production, protein-thiol modification and replacing Met in critical proteins, resulting in alterations of DNA damage/repair, cell cycle/apoptosis and metastasis/angiogenesis. Because most ingested forms of Se can be metabolized to one or more of these species, competing metabolic pathways would appear to underlie differences in their relative anticarcinogenic activities. Understanding the interplay of these processes with individual metabolic differences will be necessary to determine who will likely benefit from increased Se intake.

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