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Selenium and cancer: biomarkers of selenium status and molecular action of selenium supplements

Abstract *Background* The relationship between selenium and cancer involves many different aspects. These include the forms of selenium present in the diet and in the body, their functions and mechanisms of action, and methods employed in assessing an individual's selenium nutritional status—both in general, and in epidemiological studies of the risk of cancer in relation to diet, as well as in connection with long-term trials for investigating the disease-preventive potential of selenium supplementation. *Aim of the review* To review different aspects on selenium metabolism, the occurrence of different selenoproteins and their use as biomarkers of selenium status, the results of intervention trials of the cancer-preventive effects of selenium supplementation, the mechanisms of action involved, together with epidemiological findings on relations between the selenium status in the body and risk of cancer. *Results and conclusions* The rapid advance in the knowledge of different selenoproteins and their biological functions has opened up new possibilities for the understanding of the biological effects of selenium supplementation. A wide variety of effects of different forms and doses of selenium has been observed in a number of experimental systems, and it is at present difficult to pinpoint the mechanism that may explain the positive preventive effects of selenium supplementation observed in some human long-term trials. Moreover, additional such trials are needed to define the benefits and risks of different types and doses of selenium supplements which in the future may be implemented for public health reasons. Another necessary focus for future research is a better understanding of the mechanisms by which selenium interferes with the carcinogenesis process.

Key words selenoproteins – forms of selenium – selenium status and cancer risk – cellular actions of selenium – chemopreventive effect of selenium

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Different forms of selenium

Most of the selenium in animals, plants and microorganisms is bound within proteins, several protein-bound forms having been identified. A major part of the selenium in mammals is specifically incorporated into proteins of defined biological function, so-called selenoproteins, containing the amino acid selenocysteine (Sec; analogous to cysteine in which sulfur is replaced by selenium) (Table 1). In the diet, selenoproteins are largely found in animal foods. Another selenium-containing amino acid is selenomethionine, which is synthesized by plants and by yeast. When ingested by humans or other organisms, it is incorporated non-specifically into proteins as an analog of

Table 1 Some major inorganic and organic forms of selenium

Organic		Inorganic	
Selenocysteine (Sec)	$HSeCH_2CH(NH_2)COOH$	Selenite	SeO_3^{2-}
Selenomethionine	$CH_3Se(CH_2)_2CH(NH_2)COOH$	Selenate	SeO_4^{2-}

methionine [14]. The replacement of methionine by selenomethionine appears to be random and to be dependent on the relative concentrations of these amino acids [170]. Other proteins can also bind selenium as a ligand [13], but little is known of the role it has here.

Selenite and selenate are inorganic forms of selenium used as dietary supplements. It is uncertain whether they occur naturally in foods to any major extent. In addition to the forms of selenium mentioned, several low-molecular-weight selenium compounds have been shown to be present in different foods, some of these compounds being uncharacterized [4, 102, 159].

Metabolism of selenium

Different chemical forms of selenium are involved in metabolic pathways (Fig. 1). Selenate and selenite are reduced by glutathione to hydrogen selenide, which is either transformed into selenophosphate for incorporation into selenoproteins (see below) as Sec or is methylated to selenosugar (1-β-methylseleno-*N*-acetyl-D-galactosamine), dimethylselenide or trimethylselenonium ions for excretion. Selenomethionine and Sec can also be converted to hydrogen selenide. The major selenium metabolite excreted in urine is selenosugar, a much lesser amount being excreted as trimethylselenonium ions [152]. At toxic doses, selenium is removed as dimethylselenide via exhalation. Several studies have suggested that methylated selenium derivatives, such as Se-methylselenocysteine and selenomethionine, are the selenium compounds most effective in cancer prevention [1]. Several of these compounds can be converted to methylseleninic acid or methylselenol which have anti-carcinogenic effects in vitro [1].

Selenoproteins

A total of 25 selenoprotein genes were discovered in the human genome several years ago by sequence analysis, yet the functions of many of the proteins involved are still unknown (Table 2) [14, 97]. The distribution and concentrations of selenoproteins in different tissues are also not well known. The cellular form of glutathione peroxidase (GPx 1) was the first

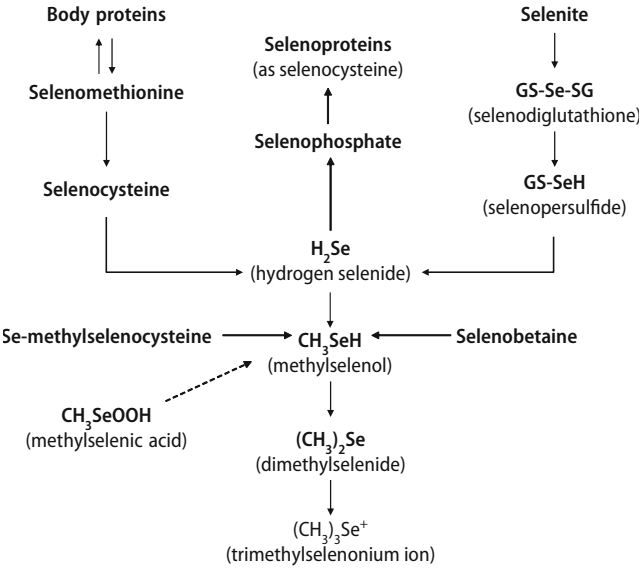

Fig. 1 Metabolic pathways of selenium. Selenomethionine, selenocysteine and selenite can be converted into the key metabolite hydrogen selenide (H_2Se), which is turn is the precursor of selenocysteine in selenoproteins and various excreted forms of selenium. Several compounds can be converted into methylselenol (from [1])

selenoprotein identified [48, 138]. It is found in almost all tissues and is believed to play a part in the body's antioxidant defence. Several other GPxs containing Sec have been found since then. The other two major groups of known selenoprotein enzymes are the iodothyronine deiodinases, that regulate thyroid hormones, and the thioredoxin reductases (TrxR), catalyzing the reduction of oxidized thioredoxin and other substrates [7, 14].

Many of the known selenoproteins catalyze redox reactions in which selenium is at the active site. Several of the selenoproteins have a homolog protein containing Cys instead of Sec, but the catalytic ability of these latter proteins is much lower. There are no selenoproteins known to be present in yeast or higher plants, these organisms tending to have homologous proteins containing Cys instead of Sec [34].

Biosynthesis of selenoproteins

Translation of the codon UGA to Sec and its insertion into proteins is a complicated process (Fig. 2). In the first step, serine is bound to $tRNA^{Sec}$ and then transformed to Sec [34]. The next major step is the interpretation of UGA as a signal to insert Sec instead of stopping the translation. This takes place when a special stem-loop structure called the Sec insertion sequence (SECIS) is present in the mRNA. This structure is located in the 3′-untranslated region of the mRNA in eukaryotes and archaea and immedi-

Table 2 Selenoproteins in the human and their putative functions

Selenoprotein	Function
15 kDa	Involved in protein folding in the ER
DI1	Thyroid hormone control
DI2	Thyroid hormone control
DI3	Thyroid hormone control
GPx 1	Peroxide reduction in the cytoplasm
GPx 2	Peroxide reduction, mainly in the gastrointestinal tract
GPx 3	Peroxide reduction in plasma and other extracellular fluids
GPx 4	Reduction of phospholipid hydroperoxides
GPx 6	Peroxide reduction, found in embryos and in the olfactory epithelium
SelH	Unknown
SelI	Unknown
SelK	Unkown, a membrane protein
SelM	Involved in protein folding in the ER
SelN	Unknown, mutations in gene associated with muscular diseases
SelO	Unknown
SeP	An antioxidant and selenium transport protein
SelR	Reduces methionine-R-sulfoxides
SelS	A membrane protein, involved in the elimination of misfolded proteins from the ER
SelT	Unknown
SelV	Unknown, only found in the testes
SelW	Can reduce peroxides using glutathione as an electron donor
SPS2	Catalyzes the formation of selenophosphate
TrxR 1	Cytoplasmic thioredoxin reductase, involved in many biological pathways
TrxR 2	Mitocondrial thioredoxin reductase, involved in many biological pathways
TrxR 3 (TGR)	Thioredoxin/glutathione reductase found mainly in testes

ately after the UGA codon in prokaryotes [98, 137]. All known eukaryotic selenoproteins have one SECIS-element, except for SeP, which has two [98]. Except for the SECIS element there are no features in the DNA sequence that selenoprotein genes are known to have in common, selenoproteins also differing markedly in the nucleotide sequence of their SECIS elements. The SECIS element consists of two helices, one or two internal loops, one apical loop, and the SECIS core, which is a short sequence of non-Watson–Crick paired nucleotides that appear to exist in all selenoprotein mRNAs. Preservation of the SECIS core and of the length of the helix between the first internal loop and the second internal loop or the apical loop are important for the functioning of SECIS [95, 98].

In addition to the SECIS element, additional factors are required for the insertion of Sec in eukaryotes such as the SECIS binding protein 2 (SBP2), the Sec-specific elongation factor (EFSec), and the recently discovered L30 protein, but the mechanisms involved have not yet been elucidated (Fig. 2). In eukaryotes the Sec codon and the SECIS element are located at some distance from each other in the mRNA. The current conception is that the mRNA and the SBP2-EFsec loops back towards the translation complex [22, 34].

The stability of selenoprotein mRNAs is affected by the amount of selenium present in the cell [173]. A special feature is that transcripts of some selenoproteins are much more stable than those of others, there being a selenoprotein hierarchy. This hierarchy is particularly noticeable in the GPx family, where the order of stability is as follows: GPx 2 ≥ GPx 4 > GPx 1 = GPx 3, but it is not yet known how this regulation operates [18, 118]. The role of the SECIS for mRNA stability was studied by combining the coding regions of GPx 2, GPx 4 and GPx 1 with the 3′UTRs (3′-untranslated regions) of each mRNA and then to study the system during selenium deficiency. It was shown that GPx 2 and GPx 4 containing each other's 3′UTRs would remain stable, but not with that from GPx 1. GPx 1 could not be stabilized by replacing its 3′UTR with those from more stable GPx mRNAs. This indicates that in the GPx 1 mRNA, at least there are factors in both the coding and the non-coding mRNA regions that influence its stability [118].

There is also a tissue selenium hierarchy that controls the retention of selenium in the tissues and organs under selenium-deficient conditions. In rats and mice fed a selenium-deficient diet, the brain and the testes retain selenium whereas the selenium concentrations in the liver and the kidneys decrease markedly [18]. Since the links between selenium and cancer probably involve different selenoproteins, an overview of the individual selenoproteins is provided.

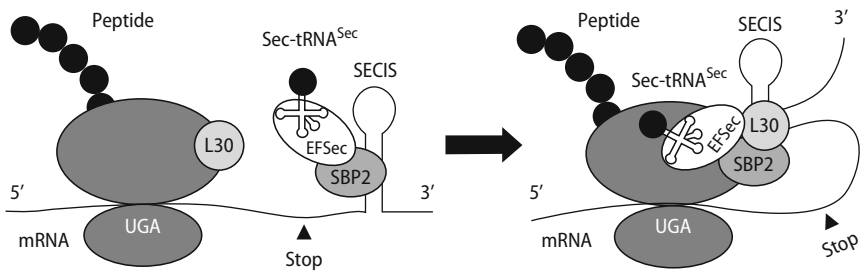

Fig. 2 Hypothesised Sec translation complex in eukaryotes. The SECIS binds to SBP2 which binds the Sec-specific elongation factor EFSec and its Sec-tRNA^{Sec}. After association with the ribosome the SBP2 and the L30 switch places, causing a conformational change which leads to the release of Sec-tRNA^{Sec}, and hydrolysis of GTP [22]

Individual selenoproteins

The glutathione peroxidase family

The GPxs generally catalyze the reduction of peroxides using mainly glutathione as the electron donor, thus contributing to the body's defence against free radicals. Five selenium-dependent GPx are known to date [97].

Cellular (or cytosolic) glutathione peroxidase (GPx 1), which is found in most tissues, catalyzes the reduction of hydrogen peroxide and organic peroxides. It consists of four identical subunits, each containing one selenium atom. Under conditions of severe selenium deficiency, the level of GPx 1 in most tissues decreases considerably, without any obvious damages to the host organism, which has led to speculations that this enzyme is a form of selenium storage to some extent [9]. GPx 1 knock-out mice have been used to explore the effects of complete loss of GPx 1 activity. These mice appear phenotypically normal but when challenged by viruses or oxidizing poisons such as paraquat they are more severely affected than mice of the wild type are. In model systems over-expressing GPx 1, protective adaptations against challenges were shown to take place, but there were also a number of negative effects such as increased obesity and insulin resistance [143].

Gastrointestinal glutathione peroxidase (GPx 2), which consists of four subunits, is mainly found in the gastrointestinal tract and also in the human liver and in mammary cells and tissue according to certain studies [24, 41]. Putative functions of this enzyme are those of protecting against ingested lipid hydroperoxides and reducing susceptibility to colon cancer [9]. GPx 2 knock-out models show no particular changes in phenotype to occur compared with the wild type, but knock-out of both GPx 1 and GPx 2 leads to colitis in mice [40].

Extracellular glutathione peroxidase, GPx 3, is a tetrameric protein produced mainly in the kidney and then secreted into the extracellular environment [11]. Other tissues such as lung, heart, thyroid, placental and mammary gland tissue produce this enzyme to a lesser extent. This GPx isoenzyme is also found in extracellular fluids such as blood plasma, milk, amniotic fluid, lung lavage and the aqueous humour [9, 12, 18, 70, 107]. This is the only selenoprotein that has been identified in milk thus far. Although the glutathione concentration in the plasma is very low GPx 3 can also use other electron donors such as the thioredoxin system [15]. The postulated roles of GPx 3 include control of peroxide transport and of the extracellular "peroxide tone" [9, 18].

Phospholipid hydroperoxide glutathione peroxidase, GPx 4, catalyzes the reduction of phospholipid hydroperoxides and is expressed in a wide range of tissues. It differs from the three GPxs just mentioned by being a monomer and having a different substrate specificity. This enzyme has been implicated in inflammation and molecular signaling. Disruption of the GPx 4 gene is lethal embryonically, unlike disruption of GPx 1 or GPx 2. GPx 4 occurs in mitochondrial, non-mitochondrial and sperm-nuclei-specific forms produced from the same gene [72, 143] and has an important role in sperm functioning [160].

The most recently discovered member of the GPx family is GPx 6, which has thus far only been found in olfactory epithelium and in embryos, and its functional significance is unclear. In mouse and rat, the Sec in this enzyme is replaced by cysteine [97].

The thioredoxin reductase family

The TrxR catalyze the reduction mainly of thioredoxin, but in mammals they can also reduce other substrates, such as vitamin C. Thioredoxin catalyzes the reduction of protein disulfides and is involved in a number of vital processes, such as DNA synthesis and the regulation of apoptosis. There are three main isoforms of TrxR, but a number of splice variants of TrxR 1 and 2 have also been reported. TrxR 1 and 2 are ubiquitous being located in the cytosol and the mitochondria, respectively [7]. The third isoform, thioredoxin/glutathione reductase (TGR), is expressed in small amounts in many tissues but is primarily found in the testis [151]. Targeted disruption of the TrxR 1 or 2 genes in mouse models is embryonically lethal [143].

The iodothyronine deiodinase family

The iodothyronine deiodinase family consists of three enzymes, iodothyronine deiodinase 1, 2 and 3 (DI1, DI2, DI3), which catalyze the removal of different iodine groups from the thyroid hormones, thus activating or deactivating them. The iodothyronine deiodinases have high priority in the selenium hierarchy, particularly DI2 and DI3, their levels remaining virtually unaltered in the case of selenium deficiency. In some tissues, DI1 decreases during selenium deficiency, but not in the thyroid. DI1 is found in the liver, kidneys and thyroid, for example, and expression of DI2 and 3 having been found in many tissues, including bovine mammary tissue [30, 100, 101].

Selenoprotein P

Selenoprotein P (SeP), the second selenoprotein to be discovered, was designated "P" because of its being

found in the blood plasma. Truncated isoforms of this protein have been found and it can contain from 1 to 17 Secs, depending on the animal species. SeP is expressed in most tissues, but is produced primarily in the liver and is secreted then into the plasma. SeP is the major form of selenium in the plasma and is involved in selenium transport [2, 21]. There are indications that it also acts as an antioxidant in the extracellular space. It is localized in the endothelium, binding to heparin and related carbohydrates [21]. It can reduce peroxynitrite and phospholipid hydroperoxides [8, 139], can also form complexes with mercury and cadmium [153], and can stimulate the survival of nerve cells in culture [177]. SeP knock-out mice exhibit low levels of selenium in the brain and testes, organs that normally are highly prioritized during selenium deficiency. These mice die after weaning of the young, unless they are rescued by a high-selenium diet [20].

Additional selenoproteins

Selenophosphate synthetase 2 (SPS2) catalyzes the formation of selenophosphate, which is the selenium donor for the formation of Sec from serine bound in $tRNA^{Sec}$. SPS2 is a selenoprotein, this property indicating the existence of a feedback step in the production of selenoproteins. Selenophosphate synthetase 1, which is not a selenoprotein, also catalyzes the formation of selenophosphate [61]. The 15 kDa selenoprotein, located in the endoplasmic reticulum (ER), is believed to be involved in protein folding [92]. Selenoprotein M (SelM) is structurally similar to the 15 kDa protein and is supposedly also involved in protein folding in ER [44]. Selenoprotein R (SelR) reduces methionine-R-sulfoxides. This is an important step in the regulation of biological processes and the management of oxidative stress in the cell [98]. Selenoprotein N (SelN) is a 70 kDa protein located in the ER. Although its catalytic function is still unknown, mutations in the gene have been associated with various muscular diseases, such as rigid spine muscular dystrophy. To date, SelN is the only selenoprotein in which a mutation of it has been shown to cause a disease [130]. Selenoprotein S (SelS, also known as VIMP) is a membrane protein in the ER, one that has been associated with the process of eliminating misfolded proteins by transferring them to the cytosol [178] and also with inflammation [51]. The function of selenoprotein W (SelW) has not been elucidated fully but it has been implicated in white muscle disease [134]. SelW occurs mainly in muscle and brain and has been shown to act as an antioxidant, utilizing glutathione to reduce peroxides [83]. A number of other selenoproteins have been discovered in man but information regarding their function is very limited.

Indices of selenium status

The most commonly used methods for assessing the selenium status in humans involve analysis of selenium concentrations in the blood or blood fractions. In addition, the determination of selenium in the hair, nails and urine has been employed. Selenium in the plasma or serum is the best known and most accessible index, usually responding rapidly to changes in selenium status or in the dietary intake of selenium [124]. The responses to selenium intake obtained if other blood fractions are analyzed can differ. For instance, the selenium levels in whole blood or the erythrocytes appear to primarily reflect the long-term intake of selenium [103], since the turnover of erythrocyte selenium is slower.

Selenoproteins as biomarkers

In general, the measurement of selenoproteins can be expected to provide information on specific selenium functions, as compared with plasma selenium, which also includes non-specifically bound selenium. The use of selenoproteins as markers of selenium status has only been exploited thus far in a few large epidemiological studies. Another important conception is that plasma selenoproteins may not be suitable biomarkers under conditions of high selenium status, since above a certain selenium level they tend to reach saturation. When data from different cross-sectional studies was combined GPx 3 was found to approach a plateau at a plasma selenium concentration of approximately 1 μmol/l [71]. Supplementation by selenate resulted in GPx activity plateauing at a plasma selenium concentration of 1.2 μmol/l [157].

SeP, GPx and protein-bound selenomethionine are the major selenium fractions contained in plasma [19]. The activity of GPx in plasma has been used by a variety of laboratories in selenium supplementation studies, and it responds rapidly to changes in selenium status, and may thus be suitable as an indicator of short-term changes. Also the activity of GPx in whole blood, erythrocytes, platelets and leukocytes has been used as biomarkers.

Selenoprotein P as a biomarker

SeP accounts for at least 40% of the plasma selenium [2]. Immunoassays for measurement of this protein

have been developed [68, 128, 140]. In the following various results from their use in one of the authors' laboratory are summarized (Table 3). SeP levels were measured in healthy adults from 17 European Regions [111]. Considerable variation between different regions was found. There was a close correlation between SeP and plasma selenium values, with some indication of a plateau. In the Malmö Food Study [3] the relationship between the intake of different foods and selenium status was investigated. For women, significant relationships between milk intake versus SeP and urinary selenium, and also between fish intake versus serum and urinary selenium were found. In a study of Latvian fisherman [62], a highly significant positive relationship between fish intake and selenium status was obtained as well as an inverse relationship between the plasma selenium and thyroid stimulating hormone levels. Home parenteral nutrition patients with a variety of gastro-intestinal diseases showed much lower levels of GPx 3, total selenium and SeP than control subjects did [132]. Concerning the association of selenium status and exposure to toxic metals, studies of lead-exposed children in Katowice, Poland revealed an inverse relationship between the blood lead level and the level of SeP and of GPx 3 [125]. Since the direction of causality was uncertain, however, it is not possible to conclude that lead exposure produces a decrease in the selenoprotein concentration or that a poor selenium status increases susceptibility to high blood lead concentrations. Regarding the relationships between SeP, GPx 3 and plasma selenium as markers of selenium status, it was found, generally speaking, that the SeP level correlated more closely with the plasma selenium and GPx 3 level at low selenium status than at high selenium status, but that at normal selenium status SeP usually correlated more closely with plasma selenium than GPx 3 did. The levels of SeP and GPx 3 were found to vary markedly for subjects from different regions and with different diseases (Table 3) [126].

Smoking and biomarkers of selenium status

Several factors other than selenium intake may affect biomarkers of selenium status. Smokers were found to have significantly lower levels of SeP than non-smokers [129]. In other studies, lower values of plasma selenium [86, 109, 141], whole blood selenium [109, 154], erythrocyte selenium [109], and toenail selenium [142, 154, 168] were observed in smokers than in non-smokers. The factors contributing to the lower selenium status in smokers are unclear. One possible explanation to the lower SeP level in smokers could be that smoking contributes to chronic low-grade inflammation due to its irritating effect on the respiratory tract and on the vascular endothelial cells. The finding that SeP is positively correlated with albumin level and negatively correlated with α_1-antitrypsin, both being acute-phase reactants, and that these correlations are higher (more significant) in smokers, suggests that the SeP levels are reduced by inflammatory activity. This agrees with findings of Dreher et al. [33] indicating that the human SeP promoter is rendered less active by cytokine treatment, which suggests a repression of SeP expression during an acute phase reaction. Smoking may also increase oxidative stress since cigarette smoke is a rich source of reactive nitrogen species, which together with superoxide can produce peroxynitrite [8]. As reported by Sies et al. [147], selenomethionine and GPx can scavenge peroxynitrite. It has also been shown that SeP plays a role in the defence against peroxynitrite [8]. This may also explain the slightly lower SeP concentration in smokers.

Table 3 Plasma concentrations of SeP, selenium and GPx 3 in different studies (from ref. [126])

Study	*n*	SeP (a.u.)	Plasma selenium (μmol/l)	GPx 3 (mg/l)
European countries	414	1.41 (1.39, 1.44)	1.10 (1.08, 1.12)	–
Prior to LDL-apheresis	13	1.07 (0.92, 1.22)	0.73 (0.60, 0.86)	352 (306, 397)[a]
After LDL-apheresis	13	0.55 (0.44, 0.66)	0.41 (0.33, 0.51)	302 (259, 346)[a]
Finland, trial I, baseline	50	1.03 (0.98, 1.07)	0.86 (0.83, 0.88)	6.51 (6.28, 6.74)[b]
Finland, trial II, baseline	45	1.77 (1.69, 1.85)	1.38 (1.34, 1.43)	–
Cancer cases	302	1.20 (1.16, 1.24)	–	–
Controls	406	1.23 (1.21, 1.25)	–	–
Elderly subjects (Malmö Food Study)	126–205	1.47 (1.43, 1.52)	1.14 (1.11, 1.16)	4.13 (4.0, 4.27)
Patients on HPN	38	0.69 (0.56, 0.83)	0.52 (0.41, 0.64)	1.91 (1.51, 2.31)
Latvians with differing fish intake[c]	21	0.83 (0.54–1.15)	0.69 (0.30–1.14)	2.78 (1.20–4.32)
	16	1.00 (0.63–1.83)	0.91 (0.46–1.47)	3.38 (2.31–4.65)
	31	1.38 (0.75–2.21)	1.18 (0.66–1.56)	3.95 (2.69–5.73)

Values are means (95% CI)
[a]GPx activity, U/l
[b]GPx activity, mU/mg protein
[c]Data from subgroups having (top to bottom) low, medium and high fish intake, respectively. Median values (and range) are given

The natural presence of cadmium in tobacco smoke may also contribute to the lower selenium status found in smokers. It has been shown that the concentration of selenium in the blood is significantly lower in subjects smoking more than 50 g tobacco per week than in never-smokers, whereas the concentration of cadmium in the blood is significantly higher in smokers [39]. Multiple linear regression analysis of the data also suggested a depressive effect of cadmium on the concentration of selenium in the blood, whereas smoking alone did not serve as a true predictor of this effect. In another study, the blood levels of selenium and cadmium and the plasma levels of SeP were measured in children from the Katowice industrial area in Poland [125]. The cadmium blood level was found to be negatively associated both with selenium in the blood and with selenium and SeP in the plasma. Multiple regression analysis also indicated the blood cadmium to increase significantly with a decrease in the SeP level, although this association disappeared when lead was included in the model, a result that could possibly be explained by the covariance of lead and selenium in the blood [125].

It has been reported that smokers eat less selenium than non-smokers do, which could probably in part explain their lower selenium level [154]. In addition, in a meta-analysis of 51 published nutritional surveys of the relationship between smoking status and nutrient intakes, smoking was found to be significantly associated with an unhealthy pattern of nutrient intake, which could exacerbate the risk of cancer associated with smoking [31].

Biomarkers of selenium status in relation to selenium supplementation

Many studies on efforts to improve selenium status through selenium supplementation have been performed and a review of different modes of selenium supplementation has been assembled [85]. Considerable attention has been directed at two studies conducted in Finland regarding the use of different forms of selenium [5, 104]. The scientists there compared the responses to oral supplementation of 200 μg selenium per day in healthy subjects on two occasions. In the first study, in which the subjects were low in selenium status, the SeP values increased after selenium supplementation, plateauing within 2 weeks [127] (Fig. 3). In the second study, performed after the introduction of selenium-enriched fertilizers in Finland, the selenium status of the subjects thus being higher, no significant increase in SeP levels was observed after selenium supplementation and no differences were found between groups given different forms of selenium [127]. A summary of the responses shown by the different selenium indices in the first of these two studies is provided in Fig. 3. In a recent study of Chinese subjects of low selenium status given different doses of selenite and selenomethionine, full expression of GPx was achieved with use of 37 μg Se day^{-1} in the form of selenomethionine and with 66 μg Se day^{-1} in the form of selenite. Full expression of SeP was not achieved at the highest dose of either form (66 μg/day). This suggested that SeP is a better indicator of selenium nutritional status than GPx is [176].

Generally speaking, in view of the many regulatory mechanisms that exist for the incorporation of selenium into selenoproteins and the varying effects of different forms of dietary selenium on indices of the selenium status, it appears that a more adequate assessment of the selenium status would be obtained through the use of several biomarkers being employed concurrently than through analysis of only total selenium or of a single selenoprotein.

Intervention trials on the effect of selenium supplementation on cancer

No definite proof of a protective effect of selenium in connection with cancer has been presented as yet in human investigations but there has been increasing interest in the cancer preventive action of selenium supplementation, several intervention studies having indicated beneficial effects [17, 25]. In the Linxian trial involving supplementation of β-carotene, α-tocopherol and selenium given for a 5.25-year period, a small but significant reduction in total cancer mortality was obtained (RR = 0.91), in particular mortality due to stomach cancer [17]. Patients with a history of skin carcinomas who were treated with 200 μg selenium per day showed significant reduc-

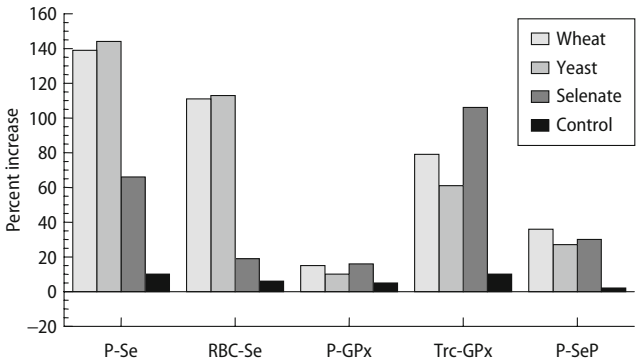

Fig. 3 Percentual changes in selenium status variables after supplementation of Finnish subjects of low selenium status with 200 μg/day of selenium in different forms (from ref. [104, 127]). *Trc* thrombocytes (platelets), *P* plasma, *RBC* red blood cells

tions in total cancer mortality (RR = 0.50) and in incidence of lung (RR = 0.54), colorectal (RR = 0.42) and prostate (RR = 0.37) cancer [25], whereas later results showed selenium supplementation to be ineffective in preventing basal cell carcinoma and that it increased the risk of squamous cell carcinoma and of total non-melanoma skin cancer [35]. Experimental findings also indicate that in some experimental systems selenium can both promote and inhibit cancer [123]. Recent results of the SUVIMAX study showed supplementation with vitamin C, vitamin E, β-carotene, selenium and zinc to reduce the rate of prostate cancer in men having normal levels of prostate-specific antigen in their plasma [117]. In another Chinese investigation, selenomethionine supplementation of subjects with mild to moderate esophageal squamous dysplasia showed there to be a non-significant trend toward an increased regression and decreased progression of dysplasia as well as a significant beneficial effect in the subgroup showing mild esophageal squamous dysplasia [106]. A summary of results of the first generation of nutritional intervention studies to prevent cancer have been presented [156] and future directions and criteria for evaluating the efficacy of such interventions have been proposed [47, 156]. In addition, evaluation of health claims by the FDA in the U.S. concerning the purportedly positive effects of selenium in connection with the prevention of cancer provided certain evidence for permitting a qualified health claim regarding selenium and cancer [158].

Selenium and cancer risk: epidemiological results

Several studies have shown the development of cancer in humans to be inversely related to the intake of specific dietary components, including nutrients, micronutrients and phytochemicals [32, 58]. Research over the last decade points to a significant protective role of selenium in preventing the development of malignant neoplasms. Low plasma selenium concentrations are thought to be associated with increased morbidity and mortality from cancer. In a Chinese study, a statistically significant increase in morbidity from oesophagus and stomach cancer was noted in a population with low levels of selenium, but no such relationship was found for lung cancer [23]. An inverse association between selenium and risk of cancer has been reported both in case–control studies and in follow-up cohort studies. Prospective cohort studies appear to show in a more distinct manner the possible association found between the prediagnostic selenium concentration level and risk of cancer. Case–control studies tend to reflect the short-term selenium concentrations in the organism, such as the selenium level associated with the dietary pattern at the time of sampling in cases and controls. In spite of the positive findings, however, the results of epidemiologic studies have been somewhat inconsistent. Some authors have reported there to be an association between cancer risk and selenium status, whereas others have obtained null results [167, 172]. The findings for three major forms of cancer are summarized below.

Lung cancer

Studies to test the hypothesis that low selenium concentrations contribute to the development of lung cancer have been conducted in many countries (Table 4). The significant, dose-dependent protective activity of selenium was documented in Finnish and Dutch studies [91, 161] in which selenium in both serum and toenail samples was analyzed, whereas no association between selenium level and risk of lung cancer was found in two studies of non-European populations [56, 133]. It is notable that of the women investigated within the Nurses Health Study, those with high toenail selenium levels were found to have a particularly high relative risk of lung cancer (RR: 4.33, 95% CI: 0.54–34.60) after adjustments for smoking status were made [52].

A review of epidemiologic studies of lung cancer and of the selenium concentration found in biological material, undertaken by Zhuo et al. [183], indicated selenium to have a certain protective effect, but only in populations with a low mean selenium level. In a meta-analysis of 14 epidemiologic studies, 11 of which had a prospective design, the risk of lung cancer at high selenium concentrations was found to be RR = 0.74 (95% CI: 0.57–0.97) (Table 4). Interestingly, when the study population was divided up according to selenium level, the mean value obtained for groups showing a high basic concentration of selenium was RR = 0.86 (95% CI: 0.61–1.22), whereas the value for groups with a low basic level of selenium was RR = 0.72 (95% CI: 0.45–1.16). In the control group of non-cancer patients the mean serum selenium concentration was 100 ng/ml blood serum, representing a daily selenium intake of 55 µg. Of the studies considered in the meta-analysis, only the findings for the two Finnish populations (RR = 0.41; 95% CI: 0.17–0.94 and RR = 0.20; 95% CI: 0.09–0.44) and for the Dutch population (RR = 0.50; 95% CI: 0.30–0.81) revealed a statistically significant protective effect of high selenium concentrations. In most of the reports, the protective activity of selenium could be clearly discerned when the reference group con-

Table 4 Epidemiological studies of the selenium level in the body and risk of lung cancer (according to Zhuo et al. [183])

Author	Study	Se index	Gender	Population	Years of follow up	No. cases (mean Se level)	No. controls (mean Se level)	RR (95% CI) (high vs. low Se)	*P* for dose-response trend
Comstock et al. [29]	NCC[a]	Serum	All	USA	15–18	258 (0.108 ppm)	515 (0.110 ppm)	0.65 (0.41–1.02)	0.08
Goodman et al. [56]	NCC	Serum	All	USA	5–14	356 (119.1 (19.6) μg/l)	356 (117.7 (18.5) μg/l)	1.20 (0.77–1.88)	0.49
Kabuto et al. [86]	NCC	Serum	All	Japan	11–13	77 (113.0 μg/l)	120 (119.1 (2.0) μg/l M; 112.2 (2.3)μg/l F)	0.56 (0.20–1.43)	NA
Knekt et al. [90]	NCC	Serum	Male	Finland	8–12	153 (57.0 (16.7) μg/l)[b]	153 (61.0 (13.5) μg/l)[b]	0.66 (0.37–1.19)	0.001
Knekt et al. [91]	NCC	Serum	All	Finland	16–19	77 (53.2 (24.3) μg/l)[c]	145 (57.8 (16.9) μg/l)[d]	0.41 (0.17–0.94)	0.46
Ratnasinghe et al. [133]	NCC	Serum	Male	China	4–5	108 (46.5 μg/l)	216 (45 μg/l)	1.20 (0.60–2.40)	0.52
Garland et al. [52]	NCC	Toenail	Female	USA	3.5	47 (0.811 (0.166) μg/g)	47 (0.897 (0.308) μg/g)	4.33 (0.54–34.60)	0.17
Hartman et al. [65]	NCC	Toenail	Male	Finland	5–8	250 (0.537 (0.134) mg/kg)	250 (0.550 (0.129) mg/kg)	0.20 (0.09–0.44)[e] 0.61 (0.27–1.41)[f]	NA
Van den Brandt et al. [161]	Cohort	Toenail	All	The Netherlands	3.3	317 (0.529 (0.206) μg/g male; 0.537 (0.080) μg/g female)[g]	2,459 (0.547 (0.126) μg/g male; 0.575 (0.109) μg/g female)	0.50 (0.30–0.81)	0.006
Hu et al. [69]	CC	Diet	All	China	–	227 (33.12) μg/day	227 (33.07 μg/day)	1.30 (0.70–2.20)	0.48
Kromhout [96]	Cohort	Diet	Male	The Netherlands	25	63 (NA)	870 (64.6 (15.2) μg/day)	0.98 (0.41–2.36)	>0.01
Zhou et al. [182]	CC	Diet	Female	China	–	290 (36.10 (16.0) μg/day)	290 (39.80 (33.0) μg/day)	0.76 (0.47–1.15)	0.11

[a]Nested case–control
[b]Data from 189 sets
[c]Data from 91 individuals
[d]Data from 177 individuals
[e]Male subjects randomized in the earliest phase of the trial
[f]Male subjects randomized in the fifth year
[g]Data from 370 individuals

Table 5 Epidemiological studies of the selenium level in the body and risk of prostate cancer

Author	Study	Se indicator	Population	Years of follow up	No. cases (mean Se level)	No. controls (mean Se level)	RR (95% CI) (high vs. low Se)	*P* for dose-response trend
Knekt et al. [90]	NCC[a]	Serum	Finland	8–12	46 (59.6 (19.4) μg/l)[b]	46 (58.3 (14.8) μg/l)[b]	1.00 (0.42–2.40)	0.707
Goodman et al. [56]	NCC	Serum	USA	5–14	235 (114.8 (19.6) μg/l)	456 (114.3 (20.4) μg/l)	1.02 (0.65–1.60)	0.69
Yoshizawa et al. [179]	NCC	Toenail	USA	5	181 (0.82 μg/g)	181 (0.96 μg/g)	0.39 (0.18–0.84)	0.05
Helzlsouer et al. [67]	NCC	Toenail	USA	1–6	117 (0.77 μg/g)	233 (0.79 μg/g)	0.38 (0.17–0.85)	0.12
Van den Brandt et al. [164]	Cohort	Toenail	The Netherlands	6.3	540 (0.530 (0.090) μg/g)	1,211 (0.547 (0.126) μg/g)	0.69 (0.48–0.99)	0.008
Nomura et al. [121]	Case–control	Serum	USA (Japanese–Americans)	–	249 (128.0 μg/l)	249 (131.6 μg/l)	0.5 (0.3–0.9)	0.02
Li et al. [105]	NCC	plasma	USA	13	586 (0.106 (0.018) μg/g)	577 (0.108 (0.018) μg/g)	0.78 (0.54–1.13)	0.16
Allen et al. [6]	Case–control	Nails	UK	–	300 (0.622 μg/g)	300 (0.611 μg/g)	1.24 (0.73–2.10)	0.581

[a]Nested case–control
[b]Data from 51 sets

sisted of subjects showing the lowest level of this trace element. The protective effect of selenium in connection with lung cancer could also be noted in studies examining selenium concentration in the toenails. The total RR values for lung cancer in patients showing high selenium levels ranged from 0.46 (95% CI: 0.24–0.87) when toenail selenium was used as a marker of the concentration of selenium in the body, to 0.80 (95% CI: 0.58–1.10) for the serum selenium level, to 1.00 (95% CI: 0.77–1.30) in studies of selenium intake based on use of a questionnaire. These findings confirm the assumption that the selenium level in the toenails can be used as a marker of long-term selenium concentration [183].

Prostate cancer

A majority of prospective and case–control studies show high levels of selenium intake to have a protective role in preventing the development of prostate cancer (Table 5). Several studies have shown that selenium can be of specific help in combating prostate cancer [25]. In the Health Professionals Follow-Up Study, in which the selenium concentration in the toenails served as a measure of long-term selenium intake, the odds ratio (OR) for the development of cancer that was associated with a high level of selenium intake was 0.49 (95% CI: 0.25–0.96) [179]. In the Netherlands Cohort Study, which involved a 6.3 years' follow-up period, high selenium concentration in the toenails was associated with an appreciably lower risk of prostate cancer [164]. In two large case–control studies of male populations in Great Britain and Canada, however, the selenium level in the toenails was not found to be associated to any marked degree with the level of risk of prostate cancer [6, 54]. Similar results were obtained in a 6-year follow-up nested case–control study in which the mean toenail selenium concentration in prostate cancer cases and in matching controls were not found to differ significantly, although a protective effect of a high selenium level (fifth quintile) was found (OR = 0.38, 95% CI: 0.17–0.85). In addition, the protective effect of high selenium levels and high α-tocopherol concentrations in the plasma was only particularly strong when the γ-tocopherol level was high [67]. A nested case–cohort study conducted on Japanese–American men (at a >20-year follow-up) also confirmed the association between a high selenium level in the plasma and a decreased risk of prostate cancer (OR = 0.5; 95% CI: 0.3–0.9) [121]. A high prediagnostic selenium level was found, in the Physicians' Health Study, to be associated (at a 13-year follow up) with a significantly reduced risk of prostate cancer, especially men who had a PSA concentration equal to or higher than 4 ng/ml [105]. The lack of a protective effect of selenium in connection with risk of prostate cancer risk was observed in the men participating in the carotene and retinol efficacy trial (CARET) [56]. A systematic review of 16 studies (11 cohort studies and 5 case–control studies) was conducted recently to investigate the association between selenium level and risk of prostate cancer. The findings of this review showed that the pooled RR of prostate cancer for a particular selenium intake, defined as the average of the first and fourth quintiles or the first and third quartiles, was 0.72 (95% CI: 0.61–0.84) in cohort studies and 0.74 (95% CI: 0.61–1.39) in case–control studies, indicating that the intake of selenium was able to reduce the risk of prostate cancer [42].

Colorectal cancer

Results of prospective and case–control studies of the risk of colorectal cancer in relation to the selenium level in the body are summarized in Table 6. In a US case–control study of the relation between the risk of colonic malignant or benign tumor and the serum selenium level, no protective effect of higher selenium levels was found in either of the groups investigated [120]. A lower selenium concentration in the serum was found to be associated with a stronger tendency to be afflicted with a colorectal tumor. Also, colorectal cancer patients with low selenium concentrations were found to have a significantly lower survival time and a lower cumulative cancer-related survival rate than such patients with higher selenium concentrations did [131]. However, in a recent study no differences between healthy individuals and individuals with adenomatous colon polyps or colorectal cancer were found in terms of selenium level, SeP concentration or GPx activity in the plasma [36]. Colorectal cancer risk was also analyzed in a 41-month follow-up of the Nurses' Health Study [52], no significant association being found between risk of cancer and toenail selenium status. A similar result was obtained in a 3.3-year follow-up study of a Dutch cohort in which toenail selenium level was used as an indicator [162]. In a Canadian case–control study, however, a significant inverse association was obtained between toenail selenium level and risk of colon cancer (OR = 0.42; 95% CI: 0.19–0.93) [54]. Two studies in which the serum selenium status was measured did not indicate there to be a clear association between serum selenium levels and risk of colorectal cancer [90, 169].

To gain further insight into the anti-carcinogenic potential of selenium, a pooled analysis of data

Table 6 Epidemiological studies of the selenium level in the body and risk of and colorectal cancer

Author	Study	Se indicator	Gender	Population	Years of follow up	No. cases (mean Se level)	No. controls (mean Se level)	RR (95% CI) (high vs. low Se)	*P* for dose-response trend
Knekt et al. [90]	NCC[a]	Serum	Male	Finland	8–12	29 (63.3 (18.9) μg/l)[b]	29 (64.0 (18.2) μg/l)[b]	1.01 (0.18–5.65)	0.643
Knekt et al. [90]	NCC	Serum	Female	Finland	8–12	48 (64.0 (18.7) μg/l)[c]	48 (65.3 (15.3) μg/l)[c]	1.10 (0.42–2.92)	0.724
Wallace et al. [169]	NCC	Serum	All	USA	1–4	276 (131.5 (19.7) μg/l)	276 (130.3 (17.8) μg/l)	0.76 (0.44–1.30)	0.50
Nelson et al. [120]	Case–control	Serum	All	USA	–	25 (138 μg/l)	138 (134 μg/l)	1.7 (0.5–5.9)	NA
Garland et al. [52]	NCC	Toenail	Female	USA	3.5	89 (0.863 (0.146) μg/g)	47 (0.843 (0.186) μg/g)	2.04 (0.88–4.75)	0.12
Van den Brandt et al. [162]	Cohort	Toenail	Male	The Netherlands	3.3	Colon 121 (0.535 (0.092) μg/g) Rectal 76 (0.593 (0.411) μg/g)	1,209 (0.547 (0.123) μg/g)	0.82 (0.43–1.58) 0.91 (0.41–2.00)	0.326 0.131
Van den Brandt et al. [162]	Cohort	Toenail	Female	The Netherlands	3.3	Colon 112 (0.560 (0.106)) Rectal 36 (0.578 (0.091))	1,246 (0.575 (0.108))	0.77 (0.41–1.45) 1.58 (0.59–4.22)	0.733 0.273

[a]Nested case–control
[b]Data from 32 sets
[c]Data from 59 sets

from three clinical trials of colorectal adenoma was conducted: the Wheat Bran Fiber Trial, the Polyp Prevention Trial, and the Polyp Prevention Study. The selenium level was measured in blood specimens of 1,763 trial participants. After adjustment for age, gender, smoking status and study site, there was found for each of the three studies to be a lower risk of recurrence of an adenoma in patients with blood selenium levels in the highest quartile than in those in the lowest quartile, although this result was only statistically significant in the case of the Polyp Prevention Study (OR: 0.57, 95% CI: 0.34–0.95) [82].

Relation between the selenoprotein P level and risk of cancer

In most studies of the association between selenium status and risk of cancer, plasma selenium has been used as a marker of selenium status. More recently the premorbid level of SeP in the plasma of subjects who had developed cancer at different sites was studied in a nested case–control study [129]. When cases were divided into subgroups according to cancer site, the SeP levels for cancer of the respiratory tract were found to be significantly lower than in matched healthy control subjects. The association between the relative risk of getting cancer and the SeP concentration found was also estimated from quintiles of the SeP level. For increasing quintiles, the ORs (adjusted for smoking) were 5.2, 2.3, 2.9, 2.0 and 1.0, respectively (P for trend = 0.01). In addition, the ORs in tertiles of the SeP level were calculated for the respiratory, digestive and urinary tract and for cancer of other sites. These were 6.0, 3.4, 0.2, and 0.6, respectively, in the lowest tertile as compared with the cases in the highest tertile. The previously reported association of plasma selenium levels with cancer risk can very likely be explained by the corresponding association of SeP levels. This is probably due to SeP constituting at least 40% of the total selenium in human plasma [2]. In a recent study no differences between healthy individuals and individuals with adenomatous colon polyps or colorectal cancer were found in terms of selenium level, SeP concentration or GPx activity in the plasma [36].

To sum up, a number of epidemiologic studies show a low selenium level, especially in males, to be associated with an elevated risk of lung and prostate cancer. No inverse association of selenium level and cancer risk was found for lung cancer in females, possibly due in part to the rather low proportion of women in the study population [90]. In contrast to prostate cancer, breast cancer was not found to be

influenced by the selenium level [163, 165, 171]. The majority of studies on relations between selenium level and occurrence of colorectal cancer have yielded null results for both males and females. However, there are some reports of a significant inverse relationship between blood selenium levels and the prevalence of adenomatous polyps [26, 45]. The potential role of dietary selenium in the early prevention of colorectal neoplasms would need to be confirmed, and the preventive role of selenium regarding cancer of this type, as found in the Polyp Prevention Study [82], would need further verification as well.

Mechanisms responsible for the link between selenium and cancer prevention

Early experiments

The anti-carcinogenic effect of selenium in animals was first reported in 1911, when Wassermann et al. (cf. [166]) managed to inhibit the development of placental tumors in mice by use of selenium compounds. Another early observation of such an effect was that of Clayton and Baumann [27], who reported that in rats a diet enriched with 5 ppm selenium decreased the incidence of liver tumors brought on by 3′-methyl-1,4-dimethylaminobenzene (3′-MeDAB). These findings were confirmed in a study showing that the number of liver tumors induced in male Spraque-Dawley rats by 3′MeDAB decreased from 92% in rats fed simply a control diet to 46 and 67%, respectively, in rats to which either of two different forms of selenium were administered [59]. Supplementing a standard diet with administration of sodium selenite was also found to reduce the number of tumors that developed in rats that were given 2-acetylaminofluorene (2-AAF) as a carcinogenic agent [63].

Ip and Sinha [78] investigated the effect of various concentrations of selenium on the development of breast cancer induced in rats by 7,12-dimethylbenzantracene (DMBA). Two groups of animals received a diet containing maize oil. The incidence of cancer was found to decrease with increasing level of selenium in the diet. At the same time, the selenium concentration influenced neither the level of malondialdehyde (a final product of lipid peroxidation) in the breast carcinoma cells nor the level of GPx activity there. The authors concluded that the protective role of selenium was not due to its being able to inhibit lipid peroxidation or to its having any antioxidative function in fat metabolism [78]. Ip [73] also studied the effect of selenium on different stages of cancer development in rats given 5 ppm selenium at different time intervals after the administration of 10 mg DMBA. Supplying selenium was found to decrease the number of tumors induced (from 97 to 46%), particularly when it was provided at both the initiation and the promotion stage of chemical carcinogenesis. Selenium supplied during only one of these two phases had a much weaker effect [73]. Harr et al. [63] showed that adding 0.1–0.5 ppm selenium to the diet of rats given a carcinogenic substance led to a decrease in the occurrence of tumors from 80% (in the non-supplemented group) to 10% (in the group receiving Se). Providing selenium at a still higher level (2.5 ppm) reduced the incidence of cancer even more, to 3%. The anti-carcinogenic effect of selenium has been found to depend on the chemical form in which the element is administered, its dose and the agent that induces the development of cancer [37].

Overview of experiments performed in animals

About 200 experiments have been performed aimed at assessing the effects of selenium given to laboratory animals in doses higher than those usually employed in standard diets used to counteract the development of cancer induced by chemicals, viruses or transplanted tumors [28]. Two-thirds of these experiments provided evidence for high doses of selenium reducing cancer development to a moderate extent (15–35% in relation to controls), in the majority of cases the reduction being quite significant. Experiments in which no effect of selenium was observed were rather rare. The anti-carcinogenic effect of selenium has been found to reach an optimum if it is given prior to the onset of the disease or in an early phase of its development. Cells adequately supplied with selenium have been shown to be less sensitive to effects of both endogenous and exogenous carcinogens. The experiments as a whole strongly suggest that consumption of selenium in doses higher than those customarily given in such cases appreciably reduces the development of neoplastic tumors. At the same time, one should bear in mind that the results of animal studies cannot be directly extrapolated to humans.

Experimental studies have thus shown that adding high levels of selenium to the diet of animals treated with carcinogenic chemicals has a carcinostatic effect [74]. Regarding the mechanisms involved, it has been postulated that the chemopreventive effect is related to the toxicity of selenium and the oxidative stress it induces, since reactive oxygen species (ROS) can promote apoptosis in vitro [149]. It has also been shown, however, that selenium compounds can induce cell death through a mechanism distinct from oxidant toxicity [135, 175]. In addition, high levels of selenium compounds in the diet can reduce both the extent to which DNA adducts are formed and the

extent to which DNA damage by carcinogens occurs. In several studies, the activity of xenobiotic-metabolizing enzymes in vivo has been reported to increase when selenium compounds are given, resulting in more efficient carcinogen detoxification [64, 77]. It is also possible that selenium in the form of GPxs, and perhaps SeP and other selenoproteins as well, can prevent mutations by serving as free radical scavengers [8, 50, 147].

Thus a number of mechanisms for the anti-carcinogenic effects of selenium and of many selenocompounds have been proposed, including their providing protection against oxidative damage, altering the metabolism of carcinogens, enhancing immune responses, affecting the cell cycle, and inhibiting angiogenesis [38, 181] (Tables 7, 8). Some reports suggest that the action of selenium toward cells that have been transformed earlier and toward normal cells differ [80]. The anti-carcinogenic effects of selenium depend upon the chemical form of the compound involved and the nature and dosage of the carcinogen. The effects can occur at a systemic, cellular or nuclear level. The activity of many cellular targets, in which the metabolism, proliferation and differentiation of the cells can be affected, depends on the cellular GSH/GSSG ratio. GPxs and TrxRs are involved in the scavenging of ROS. This suggests that selenoproteins participate in the regulation of intracellular signal transduction [57]. Yet non-protein selenium metabolites may also be important in the regulation of intracellular communication and metabolism. Selenium and the selenoproteins play a regulatory role in the following processes, for example:

- ROS-activation of protein kinases in the cytoplasm and nucleus;
- ROS-activated modification of the thiol and hydroxyl groups in the Cys and Tyr;
- Controlling changes in the cell redox potential through inducing activation of the transcriptional factors and initiating de novo gene expression;
- Regulating the expression of membrane and nuclear receptors responsible for cell maintenance, intercellular communication, and changes in cell growth;
- Affecting apoptosis, necrosis and cell survival processes [114].

Fibronectin is an extracellular component that plays an important role in intercellular communication. Inorganic selenium compounds such as selenite reduce the number of fibronectin receptors at the cell surface. Since this is an immediate action, it cannot come about through activity of the selenoproteins. Selenite activates the protein kinases involved in the pathways of cellular response to stimulation by inflammatory agents, whereas these processes can be inhibited by selenate [114]. Oxidation of the thiol groups in the transductional proteins results in their being modified structurally, which can lead to their becoming activated. This process in turn results in the activation of AP-1 and of such transductional proteins as ras/rac, fos, myc and c-Jun N kinase [110, 116]. In human hepatoma cells, selenite inactivates the c-myc oncogene and activates the c-fos genes that lead to the growth of normal cells [180]. In human colon cancer cells, selenium inhibits the expression of one of the activating zinc finger proteins that regulates the activation of the c-myc oncogene [119].

Mechanisms involving redox regulation

The redox potential is an important factor in regulating the nuclear factor κB (NF-κB) and the activation of AP-1 [99]. NF-κB is a crucial target in the pathogenesis of various chronic inflammatory, degenerative and neoplastic diseases. It regulates the effector genes in the promoter regions and can thus activate or repress gene expression. The up- or down-regulation of the effector genes can modulate many different cell pathways, such as those of proliferation, growth suppression, differentiation and senescence. NF-κB is also an important factor in regulating activation of the genes involved in the control of cell necrosis and apoptosis, the cell cycle, the immune response, and repair processes [99]. NF-κB activation involves changes in protein conformation and in the binding of numerous genes, such as cytokines, for example, to the promoter regions. ROS activates the phosphorylation of one of the NF-κB subunits, I-κB, directly. GPx overexpression inhibits the translocation of another NF-κB subunit and reduces the phosphorylation of I-κB [93, 94, 112]. This process has been found to be inhibited in cells cultured in a selenium-supplemented medium and to be intensified in the case of selenium deficiency [87]. The process the translocation of NF-κB and its binding to DNA is multiphasic and highly complex. The phosphorylation of mitogen-activated protein kinases (MAPK) represents one of these phases. The activation of individual kinases of the MAPK family triggers the transcription factors involved in changes in chromatin conformation and in the expression of numerous genes of proinflammatory and antioxidative proteins, as well as the genes involved in apoptosis activation, and in cellular proliferation or differentiation [110]. MAPK inactivation inhibits the cellular proliferation occurring in the course of the carcinogenic process.

Table 7 The effects of selenium compounds on cell growth and on the molecular targets of cancerogenesis (ref. [37])

Form of selenium	Parameter	Outcome
Selenite	Growth of Ehrlich ascites tumor cells in mice	I
Selenite	Growth of L1210 leukemic cells	I
Selenodiglutathione	Growth of L1210 leukemic cells	I
Selenite, selenodiglutathione	Cell growth (in vitro)	I
p-XSC, BSC, selenite	DNA, RNA, protein synthesis	I
	Apoptosis	E
Selenite	DNA synthesis (in vitro)	I
Selenite	RNA and protein synthesis	I
	Cell death (necrosis SSB)	E
Selenite	Cell growth	I
Selenite	Cell cycle	Block S/G2-M
Selenite	p53	E
	AP-1	I
	NF-κB	I
CH_3SeCN, p-XSC, Se-methylselenocysteine	DNA synthesis (in vitro)	I
	Cell cycle	Block G1
	Apoptosis	E
BSC and its glutathione conjugates	ACF	I
	COX-2	I
p-XSC, BSC	PKC, PKA	I
Selenite	PKC	I
p-XSC	TK	I
Selenite, selenium dioxide, selenic acid	Phospholipid/Ca^{+2} dependent PKC	I
Ebselen	PKC	I
p-XSC, BSC	JNK	Dose dependent E/I
p-XSC, BSC, selenite	DNA cytosine methyltransferase	I
Se-methylselenocysteine	PKC (in vitro)	I
Se-methylselenocysteine, triphenylselenium chloride	Cell proliferation and cell cycle biomarkers (in vitro)	I/E/NE
p-XSC	PKC and isoprostane (in vivo)	I

I inhibition, *E* enhancement, *W* weak, *NE* no effect, *AP-1* activator protein 1, *NF-κB* nuclear factor κB, *ACF* aberrant crypt foci, *COX-2* cyclooxygenase, *PKA, PKC* protein kinase A and C, *TK* thymidine kinase, *JNK* Jun-N-kinase, *p-XSC* 1,4-phenylenebis(methylene)selenocyanate, *BSC* benzyl selenocyanate

GPx and SeP are considered to have a particular role in MAPK inactivation [146]. GPx in particular can act as a suppressor of protein kinases. The breakdown of hydroperoxides by GPx and the resulting decrease in the cellular hydroperoxide level inhibit the selenium-activated kinase p38 [114].

The strength of the binding of NF-κB to DNA is influenced by selenium, which modifies the structure of Cys in the regulatory subunit of NF-κB so as to prevent oxidation of the thiol group located within this factor [114]. The reduced thiol group in Cys is essential for maintaining the activity of numerous transcription factors [113]. Trx plays a key role in this process. Oxidative stress induced by chemical or physical factors translocates Trx to the nucleus, intensifying the binding of NF-κB and AP-1 to the DNA. This process is made possible by intracellular reduction in the disulfide bridges (–S–S–), mainly in regions in which DNA binding to nuclear factors occurs [122]. Through acting as a protein disulfide reductase, TrxR thus affects the redox regulation of a variety of enzymes and receptors, as well as such transcriptional and nuclear factors as NF-κB and AP1 [53]. Trx inhibits certain kinases of the MAPK family (e.g. ASK1) directly. Selenium is also known to arrest several kinase pathways important in signal transduction, such as protein kinase A, Ca^{+2}-dependent and -independent kinase C (PKC), diacylglycerol kinase and thymidyl kinase [55].

It has been shown that selenium creates a dose-dependent increase in TrxR activity and in the expression and stability of TrxR mRNA in different cancer-cell lines [99]. Trx limits DNA synthesis, whereas Trx/TrxR activates ribonucleotide reductase, a key enzyme in the deoxyribose formation needed for DNA synthesis. TrxR also regulates gene expres-

Table 8 In vitro effects of selenite and methylated selenocompounds [75]

Endpoints	Selenite	Methylselenocyanate or Se-methylselenocysteine
Cell morphology	Extensive cytoplasmic vacuolization, cell detachment	Normal
Membrane damage	Yes	No
Cell growth inhibition	++++	++
DNA synthesis inhibition	++++	++
Cell cycle block	S/G2-M	G1
DNA single strand breaks	++++	None
Cell death	Necrosis	Apoptosis
Gadd gene induction	Late	Early

sion by affecting the cellular redox status and activating numerous DNA-binding transcription factors: NF-κB, AP-1, ref-1, p53, and the glucocorticoid receptors [114, 144]. At the same time, not only the Sec incorporated into the protein structure, but also its metabolites, affect cellular metabolism. The various chemical forms of selenium have been shown to differ widely in their anticancer properties. Some low molecular weight selenium compounds have been shown to influence the regulation of gene expression, reduction in the oxidative DNA damage that occurs, the bioactivation of carcinogens, modulation of tumor angiogenesis, cellular growth, etc. [84, 150]. It is important to note that different selenocompounds are essential for the growth and differentiation of both normal and neoplastic cells [79].

Effects of selenium on apoptosis and necrosis

In 1992 it was shown that Se(IV) compounds can induce the necrotic death of a cell by damaging a single DNA strand [174]. It was also observed that methylated selenium derivatives can induce apoptosis [55]. The anti-carcinogenic activities of various selenium compounds are summarized in Table 7 [37]. It has been found that both sodium selenite and selenomethionine suppress tumor growth in many animal models involving a dose-dependent response [76, 115, 149]. Selenite has been shown to be more effective than selenomethionine in the inhibition of cancer cell growth during chemically induced carcinogenesis [75, 76], the concentration of selenium in the tissues also being found to be higher after the administration of selenomethionine than after selenite supplementation. From this it can be concluded that a high concentration of selenium is not crucial for the inhibition of carcinogenesis, but it is likely that one of selenium metabolites is essential to this process.

Effect of different selenium compounds in cancer prevention

The chemoprevention of cancer by selenium can involve the action of different selenometabolites. Selenite, selenodiglutathione, selenomethionine and Se-methylselenocysteine can be transformed into selenides. In cells with a high selenium level, high concentrations of selenides tend to also be generated. When selenides are generated in sizeable amounts, they react with oxygen to produce superoxide and hydrogen peroxide [88]. It is believed that the role of selenium in the inhibition of carcinogenic processes is associated with oxidative damages caused by the redox cycle of selenides. When selenium is supplied in high concentrations, however, any surplus of it is excreted from the body. Over 90% of the circulating selenium is incorporated into the structure of the selenoproteins, only about 5% of it being found in other metabolites. It appears then that the anti-carcinogenic action of selenium is due to the combined effect of selenium and selenoproteins [57].

Regarding the selenocompounds, it is the actions of sodium selenite, responsible for single and double DNA strand breaks, and of selenomethionine, which is not a DNA-damaging agent, that have been investigated most frequently [144]. Inorganic selenium compounds added to cell cultures at a concentration of 5–10 μM can induce 8-OHdG lesions or DNA single-strand breaks and cell death by necrosis. Experimental studies have shown that the organic selenium compounds induce apoptosis without DNA damage, even at rather high concentrations (10–50 μM) [38]. Based on results from studies of selenium metabolism, it has been suggested that methylated selenium derivatives are the most effective selenium compounds for cancer prevention [1, 49]. Such methylated selenium compounds as methylselenocysteine and selenomethionine show powerful anti-carcinogenic activity and also lack some of the toxic effects produced by other selenium forms, DNA strand breaks after selenite treatment being an example. The metabolic pathways of Se-methylselenocysteine and selenobetaine involve the release of methylselenol or methylseleninic acid derivatives, which have been shown in in vitro experiments to affect apoptosis or to arrest the cell cycle (see Fig. 1). The results of in vitro experiments on cells treated with selenite and methylated selenocompounds are summarized in Table 8 [75]. Methylselenocysteine is one of the most important selenocompounds for chemopreventive activity. It is twice as active as selenomethionine in suppressing mammary carcinogenesis in rodents [80].

Selenium compounds can also affect activation of the p53 gene since the main dietary selenium compound, selenomethionine, modulates p53 activity. In normal cells, p53 regulates the activity of genes involved in DNA repair processes. In human cancer cells, p53 is often mutated and its functional activity suppressed. Selenomethionine has been shown to act together with the p53 tumor suppressor protein in affecting the redox status. It oxidizes the thiols of the p53 molecules at 275 and 277 cysteine residues. Seo et al. [144] demonstrated that the selenium concentration is a determinant of basal p53 activity, p53-dependent DNA repair being activated within the concentration range of 10–20μM. Fiala et al. [46] showed that the selenium compounds selenite, 1,4-phenylenebis-(methylene)selenocyanate and benzyl selenocyanate inhibit the activity of DNA cytosine

methyltransferase, an enzyme involved in DNA repair processes. They suggested that this pathway may be the major mechanism involved in the chemoprevention that selenium compounds provide after the initiation of carcinogenesis. Two other selenium compounds, sodium selenite and methylseleninic acid, were found to cause phosphorylation of the serines and threonines contained in the p53 molecule. This modulation of the p53 molecule may be a specific mechanism of p53 activation. Methylseleninic acid in a range of concentration of 0.5–1 μM was found to promote DNA repair processes by increasing the expression of two proteins associated with the p53 gene, and to be involved in the pathway connected with the p53-dependent activation of DNA repair processes [148]. There is a need of explaining how triggering of the p53-dependent DNA repair process by two different selenium compounds can be achieved when a 10–20-fold higher selenium concentration is employed. One possibility is that a small fraction of the selenomethionine is metabolized to a low-molecular-weight compound [80]. Seo et al. [144] showed that in normal human fibroblasts, selenomethionine protects the cells from DNA damage through the induction of DNA repair. Limitations in the DNA repair capacity appear to be a key determinant of predisposition to cancer [60, 144]. Enhanced formation of the DNA repair complex in cells treated with selenomethionine has been considered to be a possible mechanism for the inducible capacity for repair of DNA [144, 145]. Blessing et al. [16] described the incorporation of selenium into the factors involved in DNA repair regulation. Reducible selenium compounds (phenylseleninic acid, ebselen, Sec, and 2-nitrophenylselenocyanate) were found to cause a dose-dependent decrease in the activity of formamidopyrimidine-DNA glycosylase (Fpg), one of the enzymes involved in DNA repair processes. These selenocompounds affect the DNA repair processes through oxidation of the zinc finger structures and the release of zinc from DNA, as well as damaging the integrity of the genes of the DNA repair enzymes [16, 66]. They also affect the integrity of the XPA protein (xeroderma pigmentosum group A protein), which has an essential role in recognizing DNA lesions in the nucleotides and in the excision of damaged nucleotides in mammalian cells.

Studies conducted in cell cultures suggest that selenocompounds may exert their chemopreventive effects via induction of apoptosis and cell growth inhibition in the transformed cells. It has been found that selenium derivatives can activate the p53 gene, but that the induction of apoptosis is not a simple result of the regulation of p53 by selenium [37]. In investigating the ability of inorganic selenium compounds to induce apoptosis, it was found that the human oral squamous cell carcinoma line (HSC-3) lost >80% of its GSH after treatment by 10 μM selenite or 100 μM selenodioxide for 72 h. This decreased GSH concentration in the cells induced apoptosis, which is a dominant mechanism of the cell death these compounds bring about [155].

Selenium can also affect DNA methylation, an important epigenetic mechanism that exerts control over gene expression. The postsynthetic methylation of DNA is catalyzed by the family of S-adenosylmethionine-dependent DNA methyltransferases [136]. The methylation of selenium compounds results in a decrease in methyl donation, this preventing DNA methylation from occurring. DNA methylation is one of the first steps in the carcinogenesis induced by certain chemicals, such as benzo(a)pyrene and arsenic [181].

Selenium can also act as an inductor of the enzymes participating in phase II detoxification and it modulates expression of the enzymes involved in phase I detoxification. In vitro studies of a mammary cell line exposed to DMBA showed 1,4-phenylene-bis(methylene)selenocyanate and its putative glutathione conjugate to inhibit the expression of various CYP450 isoenzymes and to induce the expression of various enzymes involved in phase II or DMBA detoxication [108].

Effects of selenium on immune functions

Certain anticancer properties of the selenocompounds may be associated with their effects on cellular immunity. Selenium compounds can activate cytotoxic cells, stimulate the expression of cytokine receptors and the proliferation of lymphocytes [89]. Low selenium concentrations in the tissues and in human body fluids also appear to be associated with numerous changes in the immune system, such as suppression of the host immune response to bacterial and viral infections, the inhibition of prostaglandin and immunoglobulin synthesis, reduction in the activity of T lymphocytes, NK cells and macrophages, and impairment of the body's ability to reject implants and to destroy neoplastic tumors [10, 81]. Cellular membranes of the T lymphocytes are particularly sensitive to selenium deficiency, due to the large amounts of unsaturated fatty acids present in their structure. The decrease in the number and the activity of cytotoxic T lymphocytes (CTL) is accompanied by the reduced excretion of lymphotoxins and the inhibition of both leukocyte and macrophage migration. CTL activity has been found to be significantly increased in selenium (SeIV) supplemented patients with cancer located in the head and neck region that were given standard anti-carcinogenic

therapy. Insufficient dietary intake of selenium results in many types of defects of the immune processes, such as in connection with antibody production and specific cell immunity [10]. Selenium regulates the immune response by stimulating natural killer cells and activating antigens of various types to destroy the tumor cells [43]. Selenium can stimulate the expression of IL-2 receptors found on activated T lymphocytes and on NK cells [43]. The anti-carcinogenic effect of selenium is also partly based on its ability to produce antitumor metabolites (e.g. methylselenol). These metabolites that are synthetized in the cell can be involved in the cell's metabolic pathways and destroy the integrity of tumor cells or induce apoptosis in these cells [84].

Concluding comments

Results of epidemiologic and laboratory studies have indicated selenium to have a protective role in counteracting or preventing the development of cancer. A low level of selenium concentration in the body was shown to be associated with a higher risk of lung, prostate or colorectal cancer. However, a variety of confounding factors such as geographical location, gender, age, environmental exposure, genetic susceptibility, and the like need to be taken into account. There is a need of clarifying the role of selenium in the aetiology of certain types of cancer through further epidemiologic investigation. We now have evidence from laboratory studies of selenium compounds affecting cell growth, the cell cycle, DNA repair, gene expression, and signal transduction. In the experiments involved, the effects of both organic forms of selenium (selenomethionine and methylated selenocompounds) and inorganic forms of it (selenites and selenates) were evaluated. The metabolic pathways of the action of the two forms differ and depend on the basic levels of the compounds in question. Various hypotheses endeavor to explain the connection between the metabolic pathways in which selenium is involved and the effects these can have on chemically induced cancerogenesis, such as in connection with the regulation of cell signaling and of the redox status, the modulation of transcriptional factors, and the activation of DNA repair. Results of animal and in vitro studies have shown that the form of the selenium compound (methylated selenocompound) in question may be of critical importance to the chemoprotective actions it can perform. It is also apparent from this review that selenium can play an important role in cancer prevention, but additional human studies are needed to determine whether there is also an increased risk of some forms of cancer after selenium supplementation. The type of selenium supplements best employed is also in need of further investigations. A better understanding of the mechanisms by which selenium interferes with the carcinogenesis process is a necessary focus for future research also for the evaluation of selenium related biomarkers.

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