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Selenoprotein P

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Abstract. Selenoprotein P (SeP) is an extracellular, monomeric glycoprotein containing up to 10 selenocysteine residues in the polypeptide chain. It is ubiquitously expressed in mammalian tissues, and in human plasma it accounts for at least 40% of the total selenium concentration. SeP binds to heparin and cell membranes, and is associated with endothelial cells. SeP in human plasma protects against peroxynitrite-mediated oxidation and reduces phospholipid hydroperoxide in vitro, in accordance with the presumption that it has a function as an extracellular oxidant defense. Immunochemical assays have demonstrated that its concentration in plasma varies much with selenium intake, but other factors also have an influence.

Key words. Selenoprotein P; plasma; selenocysteine; heparin-binding protein; endothelial cells; oxidant defense; selenium status.

Introduction

For a long time, glutathione peroxidase was the only well-established selenoprotein known to occur in mammalian plasma. However, several early findings indicated that it was not the only selenoprotein in plasma. Several reports showed that injected ^{75}Se-selenite was specifically incorporated into a plasma protein other than glutathione peroxidase in rats [1–3], and that this protein had a strong affinity for heparin. Later, Motsenbocker and Tappel [4] discovered the same plasma protein in both rhesus monkey and rat, and called it selenoprotein P. In humans, too, early experiments indicated that plasma contained a selenoprotein other than glutathione peroxidase [5]. In later studies, gel filtration of human plasma showed that most of the selenium was located in protein peaks other than that corresponding to glutathione peroxidase activity [6]. Moreover, a major selenium-containing protein also in human plasma was shown to be reversibly bound to heparin-agarose [7].

Purification of SeP

Purification of SeP was attempted first in rat plasma [8, 4] and in monkey plasma [4], yet these efforts involving conventional chromatography failed due to the lability of the protein. Yang and co-workers [9] succeeded in purifying the protein from rat plasma by the use of immunoaffinity chromatography with monoclonal antibodies, and later purification of SeP from human plasma was performed using the same method [10].

Characterization of SeP

The deduced amino acid sequence of human SeP revealed an open reading frame of 381 amino acids. The first 19 amino acids constituted a typical signal peptide both in the rat and the human [11], which agrees with the observation that SeP is an extracellular protein. Although six typical glycosylation sites in the deduced amino acid sequence of human protein were detected, no characterization of the bound carbohydrates has been reported. SeP is the first and thus far only protein described as having more than one selenium atom per polypeptide chain, 10 selenocysteine residues being predicted by the number of UGA codons in its messenger RNA (mRNA) [11]. Nine of the selenocysteine residues are located in the C-terminal part as amino acid numbers 281–358, and one selenocysteine residue is the 40th amino acid. Moreover, SeP has a predomi-

nance of basic amino acid residues, which are concentrated in two domains, comprising in total 17 histidines and 2 lysines [12]. The presence of positively charged domains is consistent with properties of heparin-binding proteins.

SeP purified from human plasma gave two bands by SDS-polyacrylamide gel electrophoresis (PAGE) with mobilities corresponding to 55 and 61 kDa [10]. Later, five forms of the rat protein could be distinguished based on heparin-agarose affinity and SDS-PAGE migration [13], two forms migrating with an apparent mass of 45 kDa and three forms with an apparent mass of 57 kDa. Further analysis demonstrated that all five forms had the same N-terminal amino acid sequence and also contained carbohydrate. For the larger forms, all of the 10 in-frame UGA codons were read through to produce a protein with 10 selenocysteine residues. Shorter forms were truncated at the second selenocysteine residue, thus providing evidence for the existence of isoforms of SeP which differ in peptide chain length [14].

SeP in plasma and tissues

Several methods have been employed to determine the proportion of total selenium in human plasma accounted for by SeP. In a chromatographic method using heparin-agarose [7], SeP accounted for 40% of the selenium applied to the column. The SeP in the plasma of Chinese men of varying selenium status accounted for 50–60% of the selenium in their plasma [15], and using a similar chromatographic method, Harrison and co-workers [16] found that 47–59% of the total selenium was associated with SeP. In another approach based on immunoassay of SeP in intact and immunodepleted plasma, values of 40–44% were reported for healthy subjects [10, 17]. A similar value was also obtained using concanavalin affinity chromatography, a fraction probably corresponding to SeP accounting for $\sim 44\%$ of total serum selenium [18].

Animal studies indicated that circulating SeP in plasma originates mainly in the liver, since the incorporation of intragastrically administered selenium into SeP was much diminished in rats with portacaval shunts as compared with control rats [19]. SeP is also depressed in the plasma of patients with cirrhosis, probably due to impaired protein synthesis in the diseased liver [34]. However, SeP is expressed in other organs too, such as heart muscle, kidney [11], lung, testis [12], placenta, uterus [21], brain [22], the ciliary body and epithelium of the human eye [23, 24], esophagus, stomach, small bowel and colon, and hematopoietic cells [25]. Moreover, in recent immunohistochemical studies of rat tissues, SeP was found to be associated with endothelial cells in liver, kidney and brain [20, 25].

Analysis of SeP

Yang and co-workers [9] developed a radioimmunoassay for rat SeP, using monoclonal antibodies. Later, preliminary data from a radioimmunoassay using polyclonal antibodies against human SeP was reported [10]. This assay was then further optimized [26] and employed in different studies [27–33]. The lowest level of SeP possible to detect thus far was 0.05 arbitrary units, which corresponds to approximately 3% of the normal mean value for plasma SeP. The concentration of SeP was expressed in arbitrary units (a.u.) relative to a standard of pooled plasma. The standardization of SeP levels in terms of protein amount has not yet been carried out, in part due to the appearance of at least two forms in human plasma [10], which have not been characterized for selenium content and peptide weight. Experiments with stored plasma samples showed SeP to not degrade during storage, at least not in the epitope(s) detected in the radioimmunoassay. Radioimmunoassay of SeP in human plasma has also been used in other investigations [17, 34]. The advantages of an immunoassay are that it is less tedious and time consuming than the chromatographic methods mentioned above, which are also less specific since they fail to measure pure selenoproteins.

Regulation of selenoprotein synthesis

The translation of eukaryotic selenoprotein mRNA requires the participation of a selenocysteine insertion sequence (SECIS), stem-loop structures occurring in the mRNA 3′ untranslated region (3′ UTR). Most selenoprotein mRNAs have single stem-loop structures in their 3′ UTRs, whereas SeP complementary DNAs (cDNAs) from five different species (human, cattle, mouse, rat and pig) all have two stem-loops [11, 22, 35, 36].

Some selenoproteins are maintained better than others in selenium deficiency, due to their tissue-specific regulation. For example, after injection of ^{75}Se-selenite into selenium-deficient rats, the incorporation of labeled selenite into SeP in the liver increased, and its incorporation into cellular glutathione peroxidase (cGSHPx) decreased, as compared with rats given a selenium-adequate diet [8]. The differential regulation of SeP and cGSHPx in rat liver was also investigated in rats that switched from a normal to a selenium-deficient diet for

14.5 weeks [37]. In the course of time cGSHPx decreased more rapidly and reached a lower level than did SeP. The mRNA levels for cGSHPx and SeP also decreased in a similar way to the selenoprotein levels, indicating a pretranslational regulation. Selenium deficiency not only resulted in increased degradation of the selenoprotein mRNAs, but also in lowered efficiency of the SECIS element in suppressing premature chain termination at the UGA codon [38]. Furthermore, during repletion of selenium-deficient rats, a gradual tissue-dependent shift in the distribution of the different selenocysteine $tRNA^{(Ser)Sec}$ isoacceptors was found in muscle, kidney, liver and heart tissue [39]. Thus, several mechanisms regulate the tissue levels of SeP and other selenoproteins at different selenium supplies.

Function of SeP

Although the function of SeP is not known with certainty, it has been suggested to serve as an extracellular oxidant defense [12] or as a transport protein [40]. For two reasons, the latter assumption is less plausible: first, the selenium is covalently bound in the protein, and second, its expression in tissues appears to be ubiquitous.

A key study on the role of selenium in protecting against lipid peroxidation was published by Burk and co-workers [41]. After injection of the herbicide diquat, causing the generation of superoxide anion, selenium-deficient rats developed liver and kidney necrosis, whereas control rats did not. Selenium injection into selenium-deficient rats prior to the injection had a marked protecting effect against lipid peroxidation and mortality. No increase in glutathione peroxidase activity in liver, kidney, lung or plasma was noted, indicating that this enzyme was not responsible for the protective effect. In a later similar investigation [42], liver and plasma F2-isoprostanes were used as markers of in vivo lipid peroxidation, and once again selenium-injections protected against lipid peroxidation. After the selenium injection, SeP levels in plasma increased, whereas that of extracellular glutathione peroxidase (eGSHPx) activity did not, suggesting SeP was the mediator of the protective effect. The presence of sequences of basic amino acid residues in SeP has been associated with its binding to heparin [12, 43] and to cell membranes [44, 45]. Wilson and Tappel [45] found that SeP was bound to membranes in the following order: brain > kidney > testes > liver. In another investigation, ^{75}Se-labeled SeP was injected intravenously into selenium-deficient and selenium-adequate rats [44]. Eight hours after injection, the brain in the selenium-deficient rats had taken up 12-fold as much ^{75}Se-SeP as brain in the control rats. The authors suggested that brain has a specific uptake mechanism for SeP. The affinity of SeP for cell membranes in tissues may be important for the protection of the cell exterior against oxidant injury, perhaps through the quenching of free radicals. Immunohistochemical staining studies have indicated a location of SeP in the vicinity of vascular endothelial cells in rat liver, kidney and brain [20]. Endothelial cells constantly produce nitrogen monoxide, which together with the superoxide anion can form peroxynitrite, which is believed to be an important mediator of inflammatory toxicity. A correlation between SeP levels in human plasma and protection against peroxynitrite-mediated oxidation and nitration was observed in vitro [46]. In a study of the binding of SeP to heparin, an electrostatic interaction was suggested to facilitate the binding of SeP to proteoglycans on the vascular endothelium [47]. This may contribute to an extracellular protection in tissues against oxidants such as peroxynitrite or hydroperoxides. Moreover, it was recently demonstrated in vitro that purified SeP from human plasma has similar enzymatic activity as phospholipid hydroperoxide glutathione peroxidase, since it reduced phospholipid hydroperoxide in the presence of different thiols as reducing substances [48]. Thus, several lines of evidence suggest SeP to have antioxidant function(s).

Factors affecting the SeP level in plasma

Age and gender

Since SeP seems to have several functions, it is very important to study the factors regulating its concentration in plasma and other tissues. In a study of 414 37–70-year-old European subjects, selenium and SeP levels were investigated [27]. Men had marginally higher levels of SeP ($P = 0.007$), but plasma selenium did not vary with gender. Age was not related to SeP or to plasma selenium levels. In a study of 50–69-year-old subjects, no differences in SeP levels between men and women were found [31]. A study of SeP levels in subjects from Dechang and Mianning, China, indicated that, for Dechang county only, SeP, glutathione peroxidase acticity and plasma selenium concentration were somewhat lower in the youngest group (2–5 years) than in the older age groups [17]. In this geographical area, SeP values were also lower ($P < 0.05$) in females than in males in each of the three youngest groups (2–5, 6–12 and 13–17 years, respectively).

Cigarette smoking

In a study of 906 males [33], smokers had significantly lower levels of SeP than nonsmokers (1.20 and 1.24 a.u., respectively), but in a smaller study no relation of SeP, plasma glutathione peroxidase and selenium or

selenium intake to smoking was found [31]. In several other studies, however, lower values of plasma selenium, whole blood selenium, erythrocyte selenium and toenail selenium were observed in smokers [49–52].

The factors contributing to a lower selenium status in smokers are unclear. One possible explanation of the lower SeP level in smokers may be coupled to smoking contributing to chronic low-grade inflammation due to its irritating effect on the respiratory tract and on the vascular endothelial cells. The positive correlations between plasma levels of SeP and albumin and its negative correlation with α_1-antitrypsin, both acute phase reactants, suggest that SeP levels are decreased by inflammatory activity. This agrees with the findings of Dreher and co-workers [53], indicating that the human SeP gene contains a promoter which is rendered less active by cytokines, suggesting repression of SeP expression during the acute phase reaction. Smoking may also increase oxidative stress, since cigarette smoke is a rich source of such reactive nitrogen species as nitric oxide, which may explain the slightly lower SeP concentration in smokers.

The natural presence of cadmium in tobacco smoke may also contribute to the lower selenium status in smokers. Blood selenium was significantly lower, and blood cadmium was significantly higher in subjects smoking more than 50 g of tobacco per week than in complete nonsmokers [54]. Moreover, multiple linear regression analysis of the data suggested there to be 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. Very recently, blood levels of selenium and cadmium and plasma levels of SeP were measured in children from the Katowice industrial area in Poland [55]. Blood cadmium was found to be negatively associated with both selenium in the blood and selenium and SeP in the plasma. Moreover, multiple regression analysis indicated that blood cadmium increased significantly with a decrease in SeP, but that association disappeared when blood lead was included in the model. It is clear that several possible mechanims may explain the lower SeP level among smokers.

Geographic location

In plasma samples from subjects living in 17 European regions, the variation between regions was significant for both SeP and selenium ($P < 0.001$) [27]. When the highest concentration of SeP, encountered in samples from Maldegem (Belgium), was set to 100%, the mean concentration for other regions was: Barcelona, 92%; Ipswich and London, 91%; Malmö and Vosselaan, 89%; Lisbon, 86%; Netherlands, 85%; Umeå, 83%; Uppsala, 82%; Paris, 80%; Heidelberg, 79%; Gothenburg and Grenoble, 78%; Giessen, 74%; Ioannina, 71% and Epirus, 69%. The variation across regions was approximately one-fifth of the total variation in SeP and approximately half of the variation in plasma selenium. Moreover, the ratio of SeP to selenium used as a measure of the proportion of plasma selenium that could be accounted for by SeP varied significantly ac-

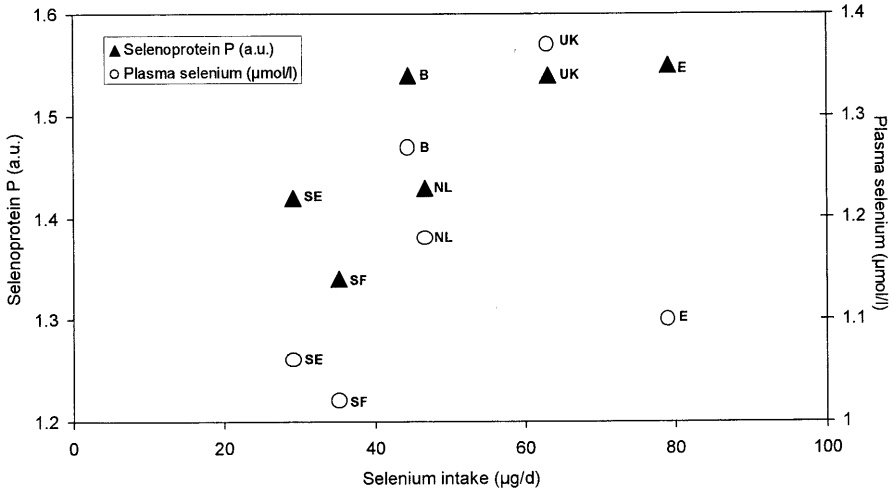

Figure 1. The association of selenium intake with plasma levels of selenium and selenoprotein P in different European countries. The linear correlation of selenium intake with SeP and plasma selenium was 0.84 ($P < 0.05$) and 0.5 ($P = 0.3$), respectively. B, Belgium; E, Spain; NL, Netherlands; SE, Sweden; SF, Finland; UK, United Kingdom. Data on plasma selenium, selenium intake and selenoprotein P from [56], [57] and [27], respectively.

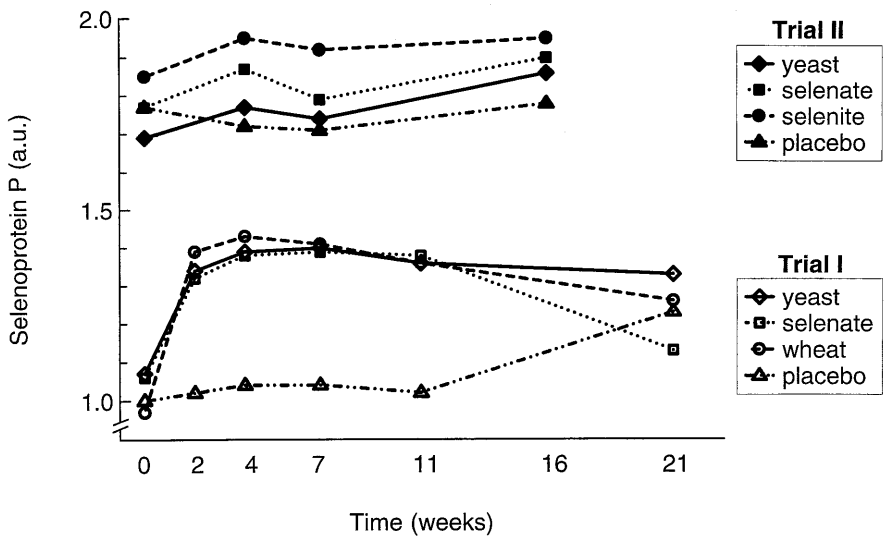

Figure 2. Changes in selenoprotein P levels in the plasma of healthy Finnish men receiving different forms of selenium supplements (200 μg selenium/day) in two studies, trial I [58] and trial II [59]. In trial II the subjects had acquired a higher selenium status through a nationwide selenium supplementation of fertilizers that started in 1984. Supplementation was started at week 0 and stopped either at week 11 (trial I) or at week 16 (trial II). Figure from [32].

cording to region ($\sim 1/3$ of the total variation). Thus, both the concentration of SeP and its proportion of the total plasma selenium in adult subjects varied between different regions of Europe. The different plasma levels of selenium and SeP can be expected to reflect differences in selenium intake to a large extent. In figure 1, data on plasma selenium [56] and SeP levels [27] in healthy subjects living in some European countries are shown together with data on the selenium intake collected in another study [57].

Dietary selenium

The concentration of selenium and SeP in plasma can be influenced by the dietary intake of selenium [17, 32]; however, data on dietary selenium intake are scarce [57]. The relation of different major food groups to indices of selenium status in plasma and in urine was studied in 206 50–69-year-old Swedish men and women [31]. During the course of 1 year the subjects performed six weighed 3-day dietary records, and the selenium intake was calculated from national food tables. After correction for energy intake, the mean selenium intake and urinary selenium was positively correlated with the plasma selenium concentration in men and the SeP level in women. Furthermore, significant correlations were found between the intake of selenium or protein (E%) and SeP in women, which can be explained by the preferential occurrence of selenium in protein-rich foods such as meat, milk, fish and egg. In multiple regression analysis, the intake of fish, egg and cereals plus grains had weak, positive associations to the SeP levels in plasma for all subjects.

In another study [30], the relationship between fish intake and selenium status was investigated in 68 Latvian men (age 24–79 years). Each subject's average consumption of different species of fish was estimated by using a food frequency method, and the subjects were divided into three groups depending on their intake of fish (0–3, 4–20 and 21–50 meals per month). The number of fish meals per month was significantly correlated with plasma selenium, SeP ($r = 0.62$) and extracellular glutatione peroxidase. The mean plasma selenium level of the subjects was rather low, 0.66 μmol/l, which may be an important factor contributing to the marked impact of fish intake on selenium status in this study group.

Intake of different forms of selenium

Many studies on the bioavailability of different forms of selenium in animals have been carried out, but only few studies of humans have been performed. In a Finnish supplementation study [58, 32], the results indicated that three selenium forms (wheat, yeast and selenate) were equally efficient in increasing the SeP level in plasma (fig. 2). A plateau was approached after only 2 weeks of supplementation, and at 4 weeks the maximum levels of SeP were reached, with plasma selenium levels in the range of 1.2–1.7 μmol/l. However, in a

later similar trial performed when the selenium status in Finland had increased due to nationwide supplementation [59], no increase in SeP levels was observed in any supplemented group. Probably SeP had already reached a maximum level at baseline due to the high selenium status of the subjects. On the other hand, when Chinese men who were low in initial plasma selenium level (0.5 μmol/l) were supplemented by 200 μg of selenium per day (as selenate) for 2 weeks, SeP levels tended to reach a plateau after 2 weeks with a plasma selenium concentration of only 0.9 μmol/l [17]. Several factors can influence the plasma selenium level at which SeP reaches a plateau, as discussed elsewhere [32].

The relation of SeP to other biomarkers of selenium status in plasma

Correlations with selenium and glutathione peroxidase in plasma

Table 1 summarizes the concentrations of SeP and other markers of selenium status measured in the different studies in our laboratory. The relation between SeP levels and plasma selenium concentrations in different studies were combined in figure 3. The linear correlation between SeP and plasma selenium was in most cases high, in the range of 0.68–0.82 [26–28], but in some cases it was lower (0.30–0.34 at baseline prior to selenium supplementation, [32]). Correlations between SeP and eGSHPx in different studies are discussed in detail elsewhere [60].

In Chinese men with widely varying selenium status, Hill and coworkers [17] found that the correlation between SeP and selenium was also high ($r = 0.91$). For subjects in different European regions, the correlation between SeP and plasma selenium was generally more marked in areas with low plasma selenium [27]. In patients with malabsorption due to intestinal disease with a mean plasma selenium concentration of only 0.5 μmol/l, the SeP level was likewise highly correlated with plasma selenium ($r = 0.91$) [29]. The lower correlations at higher plasma selenium concentrations may largely be due to the SeP level approaching a plateau at selenium concentrations in the range of 1.2–1.5 μmol/l.

SeP during depletion of selenium status

Markers of selenium status in plasma can be influenced by altered dietary intake of selenium, by medical treatment or by decreased absorption related to disorders of the digestive tract. In a group of Swedish adults switching from their usual mixed diet to a lactovegetarian diet for a year, selenium intake decreased by approximately 50%. SeP did not change significantly over time, but the selenium concentration in the plasma decreased by 11%, and eGSHPx decreased by 17% during the period from 0 to 3 months, suggesting that if selenium intake decreases, eGSHPx decreases before SeP does [26]. This result is in agreement with observations made in rats [8], in which dietary selenium was restricted, resulting in injected ^{75}Se being preferentially incorporated into SeP rather than eGSHPx.

Table 1. Plasma concentrations of SeP, selenium and eGSHPx in different studies performed in the authors' laboratory. Values are means (95% CI).

Study	*n*	SeP (a.u.)	Plasma selenium (μmol/l)	eGSHPx (mg/l)	Ref. no.
Varberg inhabitants baseline	18–20	1.16 (1.03, 1.29)	1.01 (0.93, 1.09)	4.08 (3.41, 4.76)	[26]
European countries	414	1.41 (1.39, 1.44)	1.10 (1.08, 1.12)	–	[27]
Before LDL-apheresis	13	1.07 (0.92, 1.22)	0.73 (0.60, 0.86)	352 (306, 397)*	[28]
After LDL-apheresis	13	0.55 (0.44, 0.66)	0.41 (0.33, 0.51)	302 (259, 346)*	[28]
Finland, trial I baseline	50	1.03 (0.98, 1.07)	0.86 (0,83, 0.88)	6.51 (6.28,6.74)†	[32]
Finland, trial II baseline	45	1.77 (1.69, 1.85)	1.38 (1.34, 1.43)	–	[32]
Cancer cases	302	1.20 (1.16, 1.24)	–	–	[33]
Controls	406	1.23 (1.21, 1.25)	–	–	[33]
Elderly subjects	126–205	1.47 (1.43, 1.52)	1.14 (1.11, 1.16)	4.13 (4.0, 4.27)	[31]
Patients on HPN	38	0.69 (0.56, 0.83)	0.52 (0.41, 0.64)	1.91 (1.51, 2.31)	[29]
Latvians with different fish intake‡	21	0.83 (0.54–1.15)	0.69 (0.30–1.14)	2.78 (1.20–4.32)	[30]
	16	1.00 (0.63–1.83)	0.91 (0.46–1.47)	3.38 (2.31–4.65)	[30]
	31	1.38 (0.75–2.21)	1.18 (0.66–1.56)	3.95 (2.69–5.73)	[30]

* GSHPx activity, U/l.
† GSHPx activity, mU/mg protein.
‡ Data from subgroups with from above low, medium and high fish intake. Data are expressed as median (range).

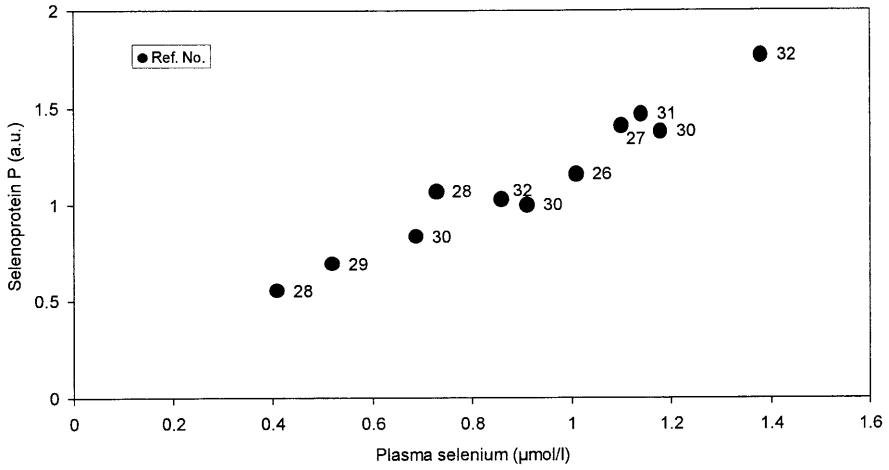

Figure 3. The association of selenoprotein P levels with plasma selenium concentrations. Data are mean values obtained from various studies. The linear correlation was 0.94 ($P < 0.001$). The series numbers refers to table 1.

Medical treatment can also influence the selenium status. For example, patients with severe hypercholesterolemia on therapy with low-density lipoprotein (LDL)-apheresis have lower plasma selenium concentrations than control subjects (0.73 vs. 1.10 µmol/l) [28]. During one LDL-apheresis, the SeP level decreased significantly from 1.11 to 0.51 a.u., plasma selenium also decreasing significantly to 0.42 µmol/l. The decrease in SeP and selenium was presumably due to SeP being bound to the dextran sulfate cellulose columns. Consequently, the treatment of hypercholesterolemic patients by LDL-apheresis resulted in a selenium depletion of the plasma. Assuming the plasma volume to be 3.5 l, this would correspond to a total depletion of the plasma by 0.09 mg of selenium, which is approximately 1% of a total body selenium content.

A number of studies have shown that the concentration of selenium in body fluids in patients on parenteral nutrition depends on the amount of selenium supplied. Thirty-eight patients who had been on parenteral nutrition with no addition of selenium for 3–216 months had a mean plasma concentration about half of that measured in healthy subjects [29]. Eighty-nine percent of the patients had SeP values lower than mean – 2 SD of the reference material, and the lowest value observed was only 3% of the reference value.

The relation of SeP level to cancer risk

In several studies on the association between cancer risk and selenium status, plasma selenium has been used as a marker of selenium status. Very recently, the premorbid level of SeP in the plasma of subjects with cancer at different sites was studied in a nested case-control study [33]. In the cases divided into subgroups according to cancer site, the SeP levels were significantly lower than in the respective controls for the respiratory tract cancer group (1.20 and 1.30 a.u., respectively). The association between the relative risk of getting cancer and SeP concentration was also estimated from quintiles of the SeP level. For increasing quintiles, the odds ratios (ORs) (adjusted for smoking) were 5.2, 2.3, 2.9, 2.0 and 1.0, respectively (p for trend = 0.01). Moreover, the ORs (adjusted for smoking) in tertiles of SeP level were calculated for the respiratory tract, digestive tract, urinary tract and remaining cancer groups (fig. 4). 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. In figure 5, case-control differences of plasma selenium and SeP are compared for major cancer sites in several study populations. The previously reported association of plasma selenium levels with cancer risk can probably be explained by the corresponding association of SeP levels. This is likely due to SeP constituting at least 40% of the total selenium in human plasma [10].

Definite evidence of a protective effect of selenium in human investigations has not yet been shown; however, there has been increasing interest in the cancer-preventive action of selenium supplementation since recent intervention studies have indicated beneficial effects [61, 62]. Several mechanisms may explain a protective action of SeP on some forms of cancer [63, 64]. One possible mechanism for this protection is that glutathione peroxidases, SeP and some other selenoproteins can prevent

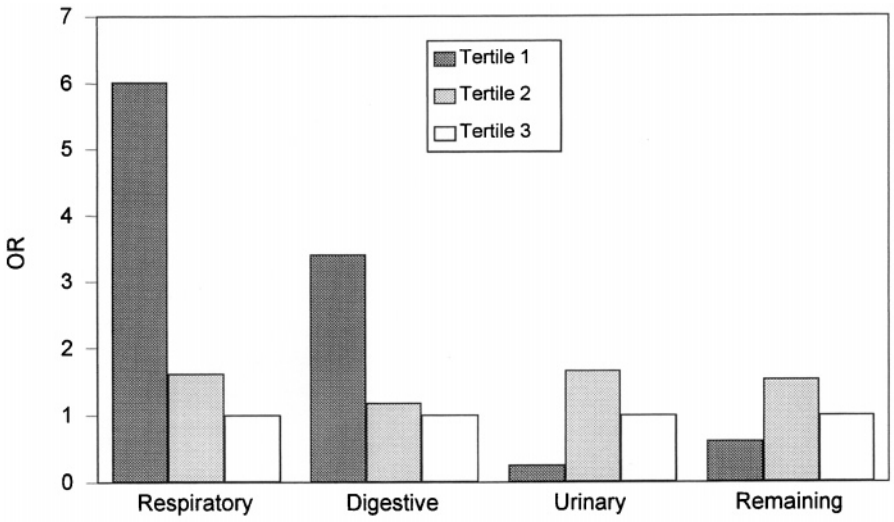

Figure 4. Odds ratios (ORs) for cancer risks of different sites associated with tertiles of SeP concentrations. The data were adjusted for smoking. The ORs of the third tertile were set to 1 for all cancer groups. *P* values for trends were 0.004, 0.002, 0.2 and 0.5 for respiratory, digestive, urinary and remaining cancer groups. Figure from [33].

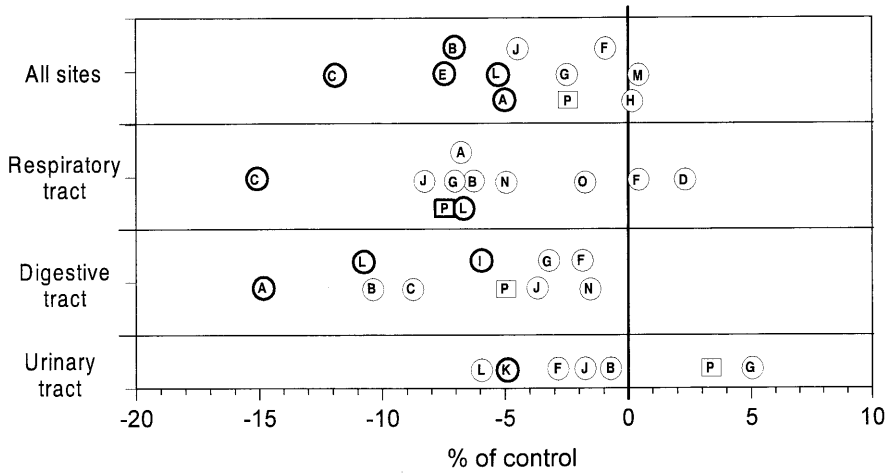

Figure 5. Percentage differences of prediagnostic selenium and SeP plasma levels between cancer cases and controls for cancer of different sites. Circles represent selenium and squares represent SeP. Bold contour, $P < 0.05$, normal contour, $P \geq 0.05$. The individual references are cited in [64].

mutations by acting as free-radical scavengers [46, 47, 65].

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