# Selenium and human health

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**Selenium is incorporated into selenoproteins that have a wide range of pleiotropic effects, ranging from antioxidant and anti-inflammatory effects to the production of active thyroid hormone. In the past 10 years, the discovery of disease-associated polymorphisms in selenoprotein genes has drawn attention to the relevance of selenoproteins to health. Low selenium status has been associated with increased risk of mortality, poor immune function, and cognitive decline. Higher selenium status or selenium supplementation has antiviral effects, is essential for successful male and female reproduction, and reduces the risk of autoimmune thyroid disease. Prospective studies have generally shown some benefit of higher selenium status on the risk of prostate, lung, colorectal, and bladder cancers, but findings from trials have been mixed, which probably emphasises the fact that supplementation will confer benefit only if intake of a nutrient is inadequate. Supplementation of people who already have adequate intake with additional selenium might increase their risk of type-2 diabetes. The crucial factor that needs to be emphasised with regard to the health effects of selenium is the inextricable U-shaped link with status; whereas additional selenium intake may benefit people with low status, those with adequate-to-high status might be affected adversely and should not take selenium supplements.**

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## Introduction

A decade ago, investigators believed that identification of optimal selenium status would benefit health. However, since then, excessive zeal for increasing selenium intake has at times had adverse consequences—a reminder that selenium was first known as a toxic element.[1] This Review updates an earlier one[2] and discusses present controversies, especially the effect of selenium on cancer and type-2 diabetes, with emphasis on clinically relevant studies. Appendix pp 1–4 provides additional relevant references.

## Role of selenium: selenoproteins

In human beings, the nutritional functions of selenium are achieved by 25 selenoproteins that have selenocysteine at their active centre.[3] The insertion of selenocysteine to form a selenoprotein is specified by the UGA codon in mRNA under specific conditions, but many other interacting factors are necessary.[3,4] In low selenium supply, the synthesis of some selenoproteins (eg, glutathione peroxidase, GPx4) is prioritised over that of others.[4] Many selenoproteins are important enzymes and their importance to human health is shown by the effect of single nucleotide polymorphisms (SNPs) in selenoprotein genes on disease risk or mortality (table 1).[21]

## Selenium intake

In contrast to many other micronutrients, the intake of selenium varies hugely worldwide, ranging from deficient (associated with selenium-deficiency diseases; appendix p 5) to toxic concentrations that cause garlic breath, hair and nail loss, disorders of the nervous system and skin, poor dental health, and paralysis.[22] Dietary selenium intake ranges from 7 μg per day to 4990 μg per day, with mean values of 40 μg per day in Europe and 93 μg per day (in women) to 134 μg per day (in men) in the USA.[1,23,24] Selenium-containing supplements add to these intakes, especially in the USA where 50% of the population takes dietary supplements.[24] Selenium status, as measured by plasma or serum selenium, varies by country and corresponds to intake.[2] Intakes are high in Venezuela, Canada, the USA, and Japan, and much lower in Europe, particularly in eastern Europe. China has areas of both selenium deficiency and excess. Intakes in New Zealand, which were formerly low, have improved after increased importation of high-selenium Australian wheat.[1] Recommendations for selenium intake average 60 μg per day for men and 53 μg per day for women.[25]

Reasons for the variability in intake relate not only to the selenium content of the soil on which crops and fodder are grown, but also to factors that determine the availability of selenium to the food chain (panel), including selenium

See Online for appendix

### Search strategy and selection criteria

I searched PubMed and the Cochrane Library for publications from January, 1990, to February, 2011. I used the search terms "selenium", "selenoprotein", and the names of the individual selenoproteins in combination with the terms "polymorphism", "Keshan disease", "Kashin-Beck disease", "mortality", "immune function", "immunity", "regulatory T cells", "Tregs", "virus", "antiviral-effect", "HIV", "brain", "seizures", Parkinson's disease", "cognitive decline", "dementia", "Alzheimer's disease", "fertility", "miscarriage", "preeclampsia", "preterm birth", "autoimmune thyroid disease", "cardiovascular disease", "coronary heart disease", "type 2 diabetes", "cancer", "thyroid cancer", "colorectal cancer", "prostate cancer", lung cancer", and "bladder cancer". Searches were also based on author name in their known specialist areas. Further articles were included from personal knowledge, reference lists, and review articles. Information presented at the international symposium on selenium in biology and medicine in 2010, in Kyoto, Japan, was also a useful source. Many review articles have been included because they capture a range of useful articles that cannot be cited individually, in view of the overall limitation on the number of references. Two additional papers published in May and June, 2011, were added.

| | Function or health effect | Health effects associated with polymorphisms (or haplotypes) in the selenoprotein* |
|---|---|---|
| Glutathione peroxidases (GPxs) | Family of antioxidant enzymes: remove hydrogen peroxide, lipid hydroperoxides, and (GPx4) phospholipid and cholesterol hydroperoxides[4] | .. |
| GPx1 (cytosolic) | Reduces retroviral virulence by preventing viral mutations;[5] deficiency causes cardiomyopathy[5,6] | Cardiometabolic effects: metabolic syndrome, CVD, CAD, blood pressure, restenosis, coronary-artery calcium score, intimamedia thickness, peripheral vascular disease, thoracic aortic aneurysm, intracerebral haemorrhage. Cancer: lung, prostate, bladder, primary liver; Keshan disease, *GPx1*-198Leu carriers had low blood selenium and low GPx1 activity; Kashin-Beck disease, GPx activity lower in *GPx1*-198Leu carriers; autism |
| GPx2 (gastrointestinal) | Antiapoptotic function in colon crypts; helps to maintain intestinal mucosal integrity[7] | .. |
| GPx3 (plasma) | Antioxidant in extracellular fluids; kidney is source of GPx3 in plasma;[4,8] thyroid protection from hydrogen peroxide in thyrocytes and follicular lumen[9] | Ischaemic stroke; differentiated thyroid cancer |
| GPx4 (phospholipid) | Membrane-associated; present at high concentrations in the testis, where it is essential for sperm motility and viability[10–12] | Adenomatous polyps, colorectal adenocarcinomas; colorectal cancer; breast cancer survival |
| Iodothyronine deiodinases | Production of active thyroid hormone $T_3$, and reverse $T_3$ ($rT_3$)[13] | .. |
| Dio1 (thyroid, liver, kidney, etc) | Production of $T_3$ in the thyroid and peripheral tissues[13] | Free IGF-1 concentrations, muscle strength, lean body mass |
| Dio2 (brain, pituitary, muscle, BAT, ear, heart, etc) | $T_3$ production in peripheral tissues[13] | Type-2 diabetes and insulin resistance; osteoarthritis and bone-mineral density; mental retardation (in iodine deficient areas) |
| Dio3 (cerebral cortex, skin, placenta, pregnant uterus) | Production of $rT_3$; prevents overexposure of fetus to $T_3$[13] | Osteoarthritis |
| Selenoprotein P (SEPP1) | Contains 10 selenocysteine residues; major contributor to plasma selenium and a good indicator of selenium status;[14] transports selenium from the liver via the plasma: brain, testis, and kidney have special receptors;[14] has some antioxidant function;[14] needed for brain; deficiency causes spasticity, abnormal movements, and spontaneous seizures in mice;[14,15] essential for male fertility; deficiency causes infertility with kinked and hypomotile spermatozoa in mice;[14,16] correlated with fasting plasma glucose;[17,18] may serve as heavy-metal (eg, mercury) chelator[4] | Prostate cancer; affects selenium status (plasma selenium and plasma SEPP) and expression of other selenoproteins; colorectal adenoma, colorectal cancer |
| Thioredoxin reductases (TrxR) | Redox active with a wide range of substrates, notably thioredoxin, required for DNA synthesis[4] | .. |
| TrxR1 (cytoplasmic/nuclear) | Controls activity of transcription factors, cell proliferation, apoptosis; reduction of expression leads to slower tumour-cell growth[4] | Advanced colorectal adenoma; familial amyotrophic lateral sclerosis |
| TrxR2 (mitochondrial) | Indispensable for cardiomyocyte viability[4] | Gastric cancer: an SNP in *TrxR2* interacts with *GPx1* (Pro/Leu) to affect risk |
| TrxR3 (testis-specific) | .. | .. |
| Selenoprotein S (SEPS1) | Anti-inflammatory,[19] located in the ER;[4] might protect cells from ER stress-induced apoptosis;[4] linked to glucose metabolism and insulin sensitivity[20] | Risk of pre-eclampsia; risk of CHD, ischaemic stroke; W:H ratio, BMI; gastric, colorectal, and rectal cancers |
| 15kDa selenoprotein (SEP15) | Located in the ER; may affect glycoprotein folding[4] | Prostate cancer mortality; lung cancer; rectal cancer |
| Selenoprotein N (SelN) | Located in the ER; may regulate calcium mobilisation required for early muscle development; mutations cause myopathies including multiminicore disease[4] | .. |

CVD=cardiovascular disease. CAD=coronary artery disease. IGF-1=insulin-like growth factor 1. BAT=brown adipose tissue. SNP=single nucleotide polymorphism. ER=endoplasmic reticulum. CHD=coronary heart disease. W:H=waist to hip. BMI=body-mass index. *Appendix pp 6–12 shows table with full list of references.

***Table 1:*** **A selection of selenoproteins with known functions relevant to health or with associated health effects**

speciation, soil pH and organic-matter content, and the presence of ions that can complex with selenium.[22]

## Health effects of selenium

### Mortality

In at least three prospective studies,[32–34] high selenium status has been associated with low overall mortality. A non-linear association was noted between selenium status and all-cause and cancer mortality in 13 887 adult participants followed up for up to 12 years (until the end of 2000) in the US Third National Health and Nutrition Examination Survey.[32] Figure 3 shows the updated follow-up of these participants to the end of 2006. Increasing serum selenium concentrations up to about 135 µg/L were associated with decreased mortality. In the 9-year longitudinal Epidemiology of Vascular Ageing (EVA) study[33] of 1389 elderly French individuals living independently, low plasma selenium at baseline (mean 87 µg/L) was associated with increased overall and cancer mortality. In the Baltimore Women's Health and Aging Study,[34] low serum selenium was a significant independent predictor of all-cause 5-year mortality in older women living in the community. By contrast, no association was noted between total death and baseline serum selenium

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### *Panel:* Food sources of selenium

Previous reviews have addressed food sources of selenium in detail.[1,2,24,26] Figure 1 gives an indication of the typical selenium content of common food sources.[27] The selenium content of cereals and grains, which are dietary staples, ranges from very low (mean values of 0·025–0·033 mg/kg dry weight in the UK) to as much as 30 mg/kg in high-selenium areas of the USA,[26] accounting for much of the variation in dietary intake. Although Brazil nuts are the richest selenium source, they are generally not a commonly eaten food, and in any case, the content varies greatly, ranging from 0·03 mg/kg to 512 mg/kg fresh weight.[26]

The contribution of different food groups to total dietary selenium intake in the UK is known from the Total Diet Study—a continuous market-basket survey in which foods representing the average UK diet are purchased, prepared, and combined into groups of similar foods for elemental analysis (figure 2).[28] There are no equivalent data from other countries, but estimates of dietary sources of selenium in US adults suggest that the contribution of bread and cereal sources is somewhat higher than in the UK (37% *vs* 26%).[29]

**Forms of selenium in foods[26]**

- Selenomethionine: selenium analogue of aminoacid, methionine; found in plant sources (notably cereals), selenium yeast, and other selenium supplements. It is incorporated non-specifically into body proteins in place of methionine (eg, selenomethionine in albumin contributes to selenium measured in plasma); supplements containing selenomethionine therefore seem to have more bioavailable selenium.
- Selenocysteine: selenium analogue of the aminoacid, cysteine; found in animal foods (from their selenoproteins).
- Selenoneine (2-selenyl-$N_{\alpha}$,$N_{\alpha}$,$N_{\alpha}$-trimethyl-L-histidine): newly discovered as the major selenium compound in fish such as tuna and mackerel; lower concentrations in squid, tilapia, pig, and chicken.[30] It has strong radical-scavenging activity.
- *Se*-methylselenocysteine and γ-glutamyl-*Se*-methylselenocysteine: found in plant sources such as selenium-enriched yeast, garlic, onions, and broccoli. It is metabolised to methyl selenol, which is thought to have anticancer effects.
- Sodium selenite and selenate: components of dietary supplements; selenate occasionally appears in water supplies. Some selenate is found in fish and plant sources (eg, cabbage).

The way in which these different species are metabolised is reviewed elsewhere,[26] as is their bioavailability.[31]

(mean 73 µg/L) in a cohort of 1103 Chinese people of average age 57 years, who were followed up for 15 years.[35]

Nonetheless, such studies are prone to confounding, since plasma selenium concentrations are higher in fit and well nourished elderly people than in those who are frail, poorly nourished, and unwell,[36] possibly indicating an increased concentration of inflammatory cytokines and lowering of selenium in the acute-phase response.[37,38] Selenium status could have fallen years before death owing to suboptimal kidney function (the kidney synthesises plasma GPx3) and subclinical inflammatory processes.[8,38]

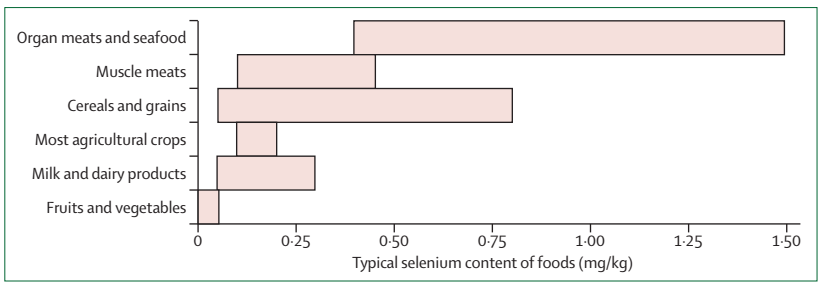


*Figure 1:* **Typical selenium content of food sources**

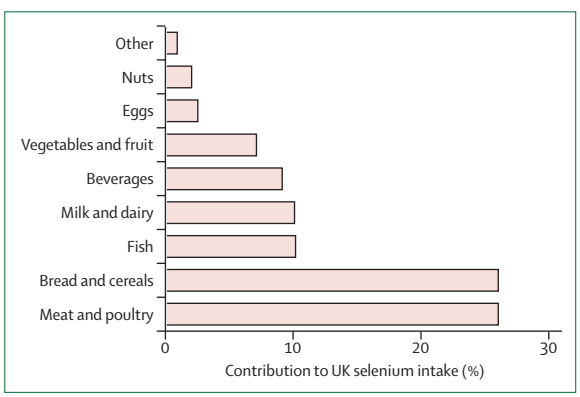


*Figure 2:* **Contribution of various food groups to UK selenium intake[28]**

### Immune function

Despite evidence from in-vitro and animal studies that selenium is important to immunity,[39–41] evidence in human beings is scarce. Selenium supplementation, even in apparently selenium-replete individuals, has pronounced immunostimulant effects, including an enhancement of proliferation of activated T cells, increased cytotoxic lymphocyte-mediated tumour cytotoxicity, and natural killer cell activity.[2,39,42–45] The immune response is often compromised in elderly people and during cancer treatment.

Selenium supplementation of elderly volunteers in Arizona with 400 µg selenium per day (as selenium yeast) significantly increased total T-cell count by 27% more than did placebo, largely because of an increase in subsets of CD4+ T cells and increased cytotoxicity of natural killer cells.[42] Supplementation with 100 µg selenium per day (as selenium yeast) for 6 months in elderly Belgian residents in an institution significantly increased the proliferative response to antigen challenge to the upper limit of the normal range for adults.[2]

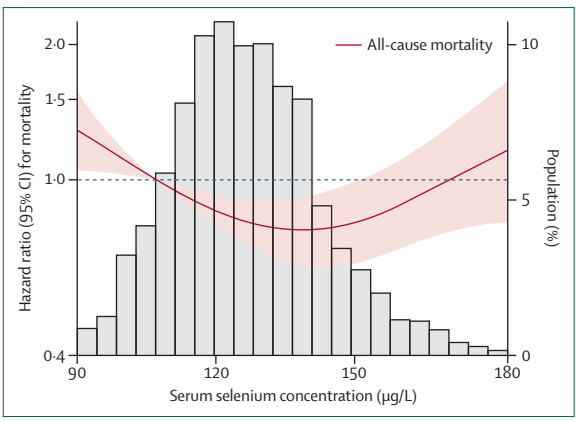


***Figure 3:*** **Adjusted hazard ratios for all-cause mortality by serum selenium concentration in adult participants of the US Third National Health and Nutrition Examination Survey followed up for up to 18 years until the end of 2006**

Shaded area shows 95% CIs. The reference value (hazard ratio 1) was set at the 10th percentile of the serum selenium distribution (105·8 µg/L). The histogram represents the frequency distribution of serum selenium concentration in the study sample. Figure constructed by Eliseo Guallar and Yiyi Zhang with updated data from the Third National Health and Nutrition Examination Survey (original follow-up to end of 2000[37]).

For the **linked mortality file of the Third National Health and Nutrition Examination Survey** see http://www.cdc.gov/nchs/data/datalinkage/nh3_mort_analytic_guidelines.pdf

Supplementation of patients with squamous-cell carcinoma of the head and neck with 200 µg per day of selenium (as sodium selenite) during surgery or radiation led to significantly enhanced cell-mediated immune responsiveness both during and after therapy.[43] By contrast, immune responsiveness decreased in patients receiving placebo.

Only one human study has shown a functional outcome of selenium supplementation on the immune system.[45] UK adults of fairly low selenium status supplemented with selenium (50 µg and 100 µg per day as sodium selenite) and challenged with an oral, live, attenuated poliovirus cleared the virus more rapidly than did those given placebo.[45]

That selenium supplementation seems to promote differentiation of CD4+ T cells into T-helper-1 (Th1) rather than T-helper-2 (Th2) effector cells is consistent with early work showing an apparent benefit of high selenium status or selenium supplementation in patients with allergic asthma.[2,39] However, in the largest randomised, double-blind, placebo-controlled trial done so far,[46] no clinical benefit of supplementation with 100 µg selenium per day (as high-selenium yeast) for 24 weeks was recorded in 197 UK adults with asthma, although most participants (75%) were taking inhaled steroids, which may have reduced any potential benefit.

In a case-control study of 259 HIV-1-infected drug users,[47] those with plasma selenium less than 135 µg/L had a significantly (three-fold) higher risk of developing mycobacterial disease, three-quarters of which was tuberculosis, than did those with higher plasma selenium.

Selenoproteins are essential for activated T-cell function.[2] T cells are especially sensitive to oxidative stress, and selenoprotein-deficient T cells cannot proliferate in response to T-cell-receptor stimulation because of their inability to suppress production of reactive-oxygen species.[41] In the few identified individuals with heterozygous defects in the selenocysteine (Sec) insertion sequence binding protein 2 (SBP2), the ability to synthesise most selenoproteins is lowered.[48] These individuals have reduced total lymphocyte counts and the ability of their T cells to proliferate after polyclonal stimulation is significantly reduced, emphasising the importance of selenoproteins in establishment of an effective immune response.[48]

Interactions between interleukin 2 and its receptor drive T-cell proliferation.[39] Human studies have shown a correlation between selenium supplementation and lymphocyte proliferation, preceded by enhanced expression of the high-affinity interleukin-2 receptor.[49] Mice on a high-selenium diet showed increased expression of both interleukin 2 and the high-affinity interleukin-2 receptor chain accompanied by enhanced T-cell signalling and in-vivo CD4+ T-cell responses.[39] The high selenium diet altered the Th1–Th2 balance towards Th1, leading to increased expression of interferon γ and CD40 ligand.[39] Such an effect would benefit antiviral immune or antitumour responses that depend on robust Th1 immunity.[39,40,43,45]

## Effects on HIV and other viruses

Selenium deficiency (serum or plasma selenium ≤85 µg/L) has been associated with decreased survival in HIV-infected patients.[2] However, associations between low (not necessarily deficient) serum or plasma selenium, low CD4+ cell count, and high viral load could also be attributable to the lowering of blood selenium concentration by the acute-phase response in individuals with more advanced HIV-1 infection.[50]

Two randomised controlled trials have shown apparent benefit from selenium supplementation in HIV infection.[51,52] In HIV-positive US adult drug users, selenium supplementation (200 µg per day) significantly decreased hospital admissions and the percentage of admissions due to infection.[51] In another trial in HIV-infected US adults, higher selenium concentration in serum predicted decreased viral load even after adjustment for antiretroviral-therapy regimen and adherence, HIV-disease stage and duration, and hepatitis-C virus co-infection,[52] although some have criticised the method by which the data were analysed and the relevance of the differences recorded in CD4+ cell count and viral load.[53] By contrast, supplementation with 200 µg per day selenium (selenomethionine) in a trial in 913 HIV-infected Tanzanian pregnant women (selenium status unknown) during the antenatal and post-partum periods in whom use of antiretroviral therapy was uncommon had no effect on HIV-1 viral load or CD4+ cell count, although it reduced the risk of mortality in children older than 6 weeks.[53]

Selenium deficiency has been linked to the incidence, virulence, or disease progression of other viral


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infections.[2,45] Beck and colleagues[54] have shown that selenium deficiency in mice, with its associated low or absent activity of protective GPx1, causes mutations in RNA viruses that lead to the development of virulent strains. This finding could explain the myocarditis-inducing mutations in the coxsackie virus that result in Keshan-disease cardiomyopathy.[5,6]

### Effects on the brain

Selenium is crucial to the brain; during selenium depletion, brain selenium is maintained at the expense of other tissues whereas selenium deficiency causes irreversible brain injury.[14] Selenoprotein P (SEPP1) has a special role in delivery of selenium to the brain by binding to a surface receptor, apoER2—a member of the lipoprotein-receptor family.[14] Mice that cannot synthesise SEPP1 develop spasticity, abnormal movements, and spontaneous seizures.[14,15] Evidence from studies in human beings suggests a role for selenium in seizures, coordination, Parkinson's disease, and cognitive decline.

Significantly lower serum selenium was noted in children and adults with epileptic seizures[55,56] and in children who had febrile seizures.[57,58] In a few small studies, selenium supplementation reduced intractable childhood seizures.[2]

In the InCHIANTI cohort study of 1012 participants aged 65 years or older, [59] performance-based assessments of coordination were significantly worse in participants with low plasma selenium than in those with higher concentrations. Furthermore, investigators noted a significant trend towards increased prevalence of Parkinson's disease in the lower selenium quartiles.

SEPP1 has an important neuroprotective role, enhancing neuronal survival and preventing apoptotic cell death in response to amyloid-β-induced oxidative challenge.[60] Data from human studies link the risk of Alzheimer's disease and dementia to selenium status. In the French EVA cohort of 1166 people aged 60–70 years,[61] a significantly increased risk of cognitive decline was recorded over 4 years in participants with low plasma selenium at baseline. Furthermore, cognitive decline was significantly associated with the magnitude of plasma selenium decrease over 9 years.[62] In a cross-sectional survey of 2000 rural Chinese adults aged 65 years or older, low nail selenium concentration was significantly associated with low cognitive scores in four of five tests, with a dose-response effect across selenium quintiles.[63]

However, in the context of cognitive function in elderly people, low plasma selenium could partly indicate a low production of plasma GPx3 by an inefficient kidney[8] or low selenoprotein synthesis resulting from the action of inflammatory cytokines (in the acute-phase response).[37] Failing kidneys also leak homocysteine—a known risk factor for dementia—into the bloodstream.[64] Whether nail selenium would be similarly affected is unknown.

Despite earlier evidence for a benefit of selenium supplementation on mood,[2] a large randomised, placebo-controlled trial in individuals aged 60–74 years showed no evidence that 6 months of selenium supplementation (100 μg, 200 μg, or 300 μg selenium per day as high-selenium yeast) benefited mood or quality of life.[65]

### Fertility and reproduction

In men, GPx4 is found in the mitochondria that make up the midpiece sheath of the sperm tail. In the early phase of spermatogenesis, GPx4, as a peroxidase, protects spermatozoa by its antioxidant function, whereas in the later phase, it forms cross-links with midpiece proteins to become a structural component of the mitochondrial sheath surrounding the flagellum, which is essential for sperm motility.[10]

In a Japanese study, 10% of infertile men and 35% of those with oligoasthenozoospermia whose spermatozoa showed extensive lipid peroxidation had GPx4-defective spermatozoa.[11] In these men, spermatozoal GPx4 expression and sperm motility were lost, and spermatozoa in the ejaculate decreased. The lower GPx4 expression was not due to selenium deficiency because selenium intake in Japan is high[1] and the level of expression in blood leucocytes did not differ from that of fertile men.[11]

Analysis of sperm samples in an Italian study showed that GPx4 protein content was significantly lower in 75 infertile men than in 37 controls (93 *vs* 188 units/mg sperm protein) and correlated with viability ($r$=0·35), morphological integrity ($r$=0·44), and forward motility ($r$=0·45).[12]

The testis has a special receptor (apoER2) to take up SEPP1, the other seleonoprotein that it requires.[14] The selenium intake required for optimal activity and concentration of GPx4 and SEPP1 is around 75 μg per day.[66] In a randomised trial, selenium supplementation (100 μg per day) of subfertile men with low selenium intake significantly increased sperm motility and enabled 11% of the men to achieve paternity, compared with none in the placebo group.[2] However, high selenium intake (about 300 μg per day) was shown to decrease sperm motility.[67]

Significantly lower selenium status has been noted in women who had either first-trimester or recurrent miscarriages than in those who did not miscarry, although this finding is not consistent.[2,68] Selenium status usually falls in pregnancy, partly because of plasma volume expansion,[68] but excessive inflammation—a probable feature of miscarriage—also decreases circulating selenium.[37,38]

Both selenium intake and status have been linked to pre-eclampsia.[68,69] Significantly lower concentrations of plasma and toenail selenium, plasma, placental GPx, and placental thioredoxin reductase have been measured in pre-eclamptic women than in matched healthy controls.[69–71]

In a UK study,[69] median selenium concentration in toenail clippings (which are largely laid down before pregnancy) from women with pre-eclampsia of mean gestational age 34 weeks was significantly lower than in the controls ($p<0·001$). Women in the lowest tertile of toenail

selenium were significantly (4·4 times) more likely to have pre-eclampsia than were those in the higher tertiles.[69]

Selenoproteins could counteract features of pre-eclampsia by reducing oxidative stress, endoplasmic-reticulum stress, and inflammation, protecting the endothelium, controlling eicosanoid production, and regulating vascular tone.[68] Since systemic inflammation is a major feature of pre-eclampsia, selenoprotein S (SEPS1), which is involved in management of the stress response in the endoplasmic reticulum and in inflammation control,[72] may be crucial. A retrospective study in a large Norwegian case-control cohort[72] showed that women with pre-eclampsia (n=1139) were significantly more likely than were controls (n=2269) to carry the A allele of the *SEPS1* g.-105G>A polymorphism, implicating SEPS1 in the risk of pre-eclampsia.

A cross-sectional study in the Netherlands of 1129 pregnant women showed that those who delivered preterm had significantly lower serum selenium at 12 weeks' gestation than did those who delivered at term.[73] Even after adjustment for the occurrence of pre-eclampsia, which is associated both with selenium status[69] and with preterm birth, women in the lowest quartile of serum selenium had a significantly (two-fold) greater risk of preterm birth did than the rest. However, whether low selenium status was a cause or an outcome (eg, of the associated increased inflammation) is unknown.[73]

### Thyroid function and autoimmune thyroid disease

The thyroid gland has the highest selenium concentration of all tissues.[13] Selenium has various roles in the thyroid: the selenium-dependent iodothyronine deiodinases produce active thyroid hormone, triiodothyronine (T3), from its inactive precursor, thyroxine (T4).[13] Nonetheless, no evidence of an effect on thyroid function or on the ratio of free or total T4 to T3 was shown in a randomised controlled trial of selenium supplementation in 368 apparently euthyroid, UK elderly adults with low-to-moderate selenium status.[74]

Selenium, in the form of GPx3, protects thyroid cells from the hydrogen peroxide that is generated there to be used by thyroid peroxidase in the synthesis of $T_3$ and $T_4$ from iodide and thyroglobulin.[13] This function is consistent with the inverse association detected between selenium status and thyroid volume, thyroid tissue damage, and goitre in French women,[75] and the positive association between the incidence of thyroid cancer and low prediagnostic serum-selenium concentration in Norway.[76] Moreover, several studies have shown that selenium supplementation (80 μg or 200 μg per day as sodium selenite or selenomethionine) is effective against Hashimoto's thyroiditis, the most common form of autoimmune thyroid disease, characterised by the presence of complement-fixing autoantibodies to thyroid peroxidase.[77,78] A systematic review and meta-analysis showed that selenium supplementation significantly lowered thyroid peroxidase autoantibody titre at 3 months.[77]

Pregnant women with autoimmune thyroiditis (thyroid-peroxidase-antibody positive) are prone to develop post-partum thyroid dysfunction and permanent hypothyroidism. When women were given 200 μg per day selenomethionine, thyroid inflammatory activity fell, and post-partum thyroid disease and permanent hypothyroidism were significantly reduced.[79]

Selenium is also effective in autoimmune hyperthyroidism—ie, Graves' disease. In a randomised controlled trial of 100 μg sodium selenite twice daily, or pentoxifylline (600 mg), or placebo for 6 months, selenium treatment alone was significantly associated with an improved quality of life, less eye involvement, and slower progression of Graves' orbitopathy.[80]

### Critical illness

Selenium administration has been associated with benefit in systemic inflammatory response syndrome and sepsis.[81] Patients with systemic inflammatory response syndrome or septic shock had a 40% decrease in plasma selenium and a 70% decrease in plasma SEPP1 (important because SEPP1 is thought to provide endothelial protection).[82,83] Two meta-analyses have shown that mortality tended to decrease when such patients were infused with high-dose sodium selenite.[82] However, treatment needs to be initiated by bolus (1 mg), since studies in which continuous administration was used have shown no effect on mortality.[82]

### Cardiovascular disease

Potential cardiovascular benefits of selenium are supported by evidence that selenoproteins prevent oxidative modification of lipids, inhibit platelet aggregation, and reduce inflammation[2,68,84] in addition to the many cardiometabolic effects that have been linked to polymorphisms in GPx1, GPx3, Dio2, and SEPS1 (table 1). However, randomised trials of selenium-containing supplements have not shown a significant protective effect on cardiovascular disease or mortality endpoints,[85–87] although a meta-analysis of 25 observational studies showed a significant inverse association between selenium status and risk of coronary heart disease, particularly in populations with low selenium intake or status.[85] By contrast, no associations were recorded between toenail-selenium concentration and measures of subclinical atherosclerosis—carotid intimamedia thickness and coronary-artery calcium score—in a study of 3112 young American adults.[88]

Several cross-sectional studies have shown an association between high selenium status and raised plasma cholesterol.[84] In the UK PRECISE Pilot randomised trial of 501 elderly people with low selenium status,[84] total serum cholesterol and non-HDL cholesterol were significantly lowered after 6 months supplementation with 100 μg and 200 μg selenium per day (as high-selenium yeast) but not with 300 μg selenium per day, even though this dose raised HDL cholesterol


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significantly. With increasing selenium dose, the ratio of total cholesterol to HDL cholesterol significantly decreased, suggesting a potentially beneficial effect of supplementation on cardiovascular risk, at least in that population. In two other small trials, no significant difference between treatment groups was reported.[89,90]

Selenium status of the populations studied might account for differences in results. Beyond a specific plasma selenium concentration (at which relevant selenoproteins might be optimised), there may be no further advantage of high selenium status in reduction of cardiovascular mortality, and there is some evidence of a U-shaped association.[32] For example, at the baseline selenium status of participants in the UK PRECISE trial, GPx1 activity would only have been optimised in half the volunteers, so that potential benefits of selenium supplementation could be detected.[84] By contrast, the negative results reported in American trials[86,87] were in populations in whom most selenoproteins would already have been optimised at baseline[66,91,92] so that if the beneficial effect of selenium is dependent on raising selenoprotein concentrations, no effect of supplementation would have been apparent. In support of a potentially beneficial effect of GPx1 activity on cardiovascular risk, baseline erythrocyte GPx1 activity was a strong predictor of the risk of a subsequent cardiovascular event during 4·7 years of follow-up in a cohort of 636 patients with suspected coronary artery disease whose selenium status was low (mean plasma selenium 74 µg/L).[93]

## Cancer

Prospective studies have provided some evidence for a beneficial effect of selenium on the risk of lung,[94] bladder,[95] colorectal,[96] liver,[97] oesophageal,[35] gastric-cardia,[35] thyroid,[76] and prostate cancers.[21,96,98–100] Table 2 summarises results of meta-analyses of selenium supplementation for lung, bladder, and prostate cancers.

Two subsequent studies did not show significant associations between selenium intake[101] or status[102] and lung cancer risk, despite a significant inverse trend in men in an earlier large case-control study based on dietary-selenium intake.[103] No subsequent study has shown a significant beneficial or detrimental effect on prostate cancer risk,[104–107] except for African-American men of the US Multiethnic Cohort whose risk was 41% lower in the top rather than the bottom tertile of serum selenium.[108] However, in the EPIC-Heidelberg cohort, a significantly decreased risk, especially of high-grade disease, was noted in the third (although not the fourth, ≥95·0 µg/L) quartile of serum selenium concentration compared with the first quartile.[107]

A review[96] of all but the three most recent prostate cancer studies[106–108] shows that more significant protective associations are consistently detected between selenium and risk of advanced, rather than localised or low-grade, prostate cancer, and that the strongest associations are in smokers.

| | RR/OR (95% CI) | Type of study included | Comparison | Authors |
|---|---|---|---|---|
| **Lung** | | | | |
| 16 studies | 0·74 (0·57 to 0·97)* | Cohort, case-control | Higher *vs* lower selenium exposure (serum, toenails, intake) | Zhuo et al (2004)[94] |
| **Bladder** | | | | |
| 7 studies | 0·61 (0·42 to 0·87)* | Cohort, nested case-control, case-control | Highest *vs* lowest selenium status (serum, toenails) | Amaral et al (2010)[95] |
| **Prostate** | | | | |
| 5 studies | 0·74 (0·61 to 1·39) | Case-control | Any *vs* lowest selenium exposure† | Etminan et al (2005)[98] |
| 5 studies | 0·74 (0·39 to 1·39) | Case-control | Moderate *vs* lowest selenium exposure† | Etminan et al (2005)[98] |
| 11 studies | 0·72 (0·61 to 0·84)* | Cohort | Any *vs* lowest selenium exposure† | Etminan et al (2005)[98] |
| 11 studies | 0·74 (0·61 to 0·90)* | Cohort | Moderate *vs* lowest selenium exposure† | Etminan et al (2005)[98] |
| 20 studies | –0·23 (–0·40 to –0·05)* | Cohort, nested case-control, case-control | Overall pooled standardised mean difference (serum, plasma, toenail selenium) | Brinkman et al (2006)[99] |

RR=relative risk. OR=odds ratio. *Significant finding. †Any intake: average between the first and fourth quintile (plasma, serum, toenail concentrations, or intake) or the first and third quartile. Moderate intake: average between the second and fourth quintile or the second and third quartile. The lowest level (first quartile) was used as the reference group.

*Table 2:* **Meta-analyses of prospective studies of selenium and cancer risk, by tissue type**

Interventions with selenium as a single nutrient are scarce. A systematic review and meta-analysis[109] of antioxidant supplements for the prevention of gastrointestinal cancers pooled data from three trials in Qidong, China, where 15% of the population is hepatitis B positive; although supplementation significantly reduced the incidence of hepatocellular carcinoma by 50%, the quality of reporting of the trials has been criticised.

The Nutritional Prevention of Cancer (NPC) trial recruited 1312 volunteers with a previous history of non-melanoma skin cancer from southeastern USA.[110] Treatment with 200 µg selenium per day (as selenium yeast) for a mean of 4·5 years had no effect on the primary outcome of non-melanoma skin cancer but led to a significant reduction in cancer mortality (50%) and in the incidence of total (37%), prostate (67%), colorectal (58%), and lung (46%) cancers after a follow-up of 6·4 years. However, in later analyses, only the reduction in incidence of total (25%) and prostate (52%) cancers remained significant,[111] except for those in the bottom tertile of plasma selenium (<106 µg/L) at baseline.[112] Those in the highest tertile (>122–123 µg/L) had non-significant increases in the risk of total (20%) and prostate cancers (14%). Furthermore, a significantly increased risk of squamous-cell carcinoma was recorded in participants with baseline plasma selenium in the top two tertiles, although the risk was non-significantly decreased in the bottom tertile (plasma selenium >106 µg/L).[111,113,114] Clearly there is no protective effect of

supplementation, and indeed the possibility of increased risk, in participants with baseline plasma selenium greater than 122 µg/L.

The Selenium and Vitamin E Cancer Trial (SELECT), which investigated the effect of selenium and vitamin E on prostate cancer risk in 35 533 American men, showed that administration of 200 µg selenium per day (as selenomethionine) to men of median baseline serum selenium 136 µg/L did not reduce the risk of localised prostate cancer after a median follow-up of 5·5 years.[87] However, the trial included almost no participants within the range of selenium status (<106 µg/L in plasma) that had previously shown benefit from selenium supplementation on prostate cancer risk.[111,113] In men in SELECT, the IQR of baseline serum selenium was 122·4–151·8 µg/L, which, according to the NPC trial, put them into the category of non-significant increased risk from selenium supplementation. Indeed, the investigators recorded some potential indications of toxic effects in terms of alopecia and dermatitis in the selenium group.[87] Additionally, participants in SELECT were given selenium as selenomethionine rather than selenium yeast, in which 30–40% of the selenium is not selenomethionine.[25]

Results of SELECT do not explain the effect of selenium on: (1) risk of advanced disease, for which various studies have suggested a greater effect,[96,100,115] since only 1% of cases were non-localised; (2) prostate cancer mortality, since only one participant died from prostate cancer;[87] (3) current smokers, for whom the strongest protective effects have been detected,[96] since they represented only 7·5% of the SELECT population; or (4) men of low selenium status, since very few were included in the study.[116] Clearly, whereas at least a third of men in the NPC trial did not have optimal SEPP1 or even GPx concentration or activity before supplementation, this is unlikely to be true of men in SELECT, since most would have had maximal selenoprotein activities or concentrations at baseline.[116]

Various factors could explain the disparate findings between studies and especially between the trials. First, selenium might be more important in prevention of prostate cancer progression, hence its stronger effect against advanced than primary disease.[23,96] Second, selenium might show an effect on risk only over a particular range of status, neither too low nor too high—eg, when the selenium concentrations in the group under investigation range from below, to above, the concentration needed to optimise the activity of selenoenzymes such as GPx and SEPP1. This scenario would not have been the case in SELECT (too high) nor probably in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort (too low).[21,87,106,117] Indeed for selenium, as for many nutrients, several human studies have provided evidence of a U-shaped relationship between intake or status and protection from cancer.[1,96,111] Third, the interaction between selenium intake or status and genetic background could be important. SNPs in selenoprotein genes can affect the efficiency with which a selenoprotein is synthesised, its activity and concentration in plasma, and risk of disease.[21] Examples include a *GPx1* SNP that affects the risk of prostate, lung, breast, and bladder cancers; SNPs in *SEPP1, GPx4*, and *SEPS1* that affect the risk of colorectal cancer; a SNP in *GPx3* linked with thyroid cancer; variants in *SEP15* that affect the risk of lung and rectal cancers and survival from prostate cancer; and a *GPx4* SNP that affects breast cancer survival (table 1). Moreover, these selenoprotein SNPs (and SNPs in related pathways) can interact with selenium status such that individuals with specific genetic variants might benefit more from additional selenium than might others.[115,118]

## Type-2 diabetes

Evidence linking selenium to glucose metabolism is conflicting.[119] High selenium status was associated with reduced diabetes prevalence in three case-control studies,[120–122] while in the prospective EVA study,[123] high plasma selenium correlated with a decreased risk of onset of hyperglycaemia during a 9-year follow-up period in male participants.

By contrast, high serum selenium concentration was associated with an increased prevalence of diabetes in the large US National Health and Nutrition Examination Surveys.[124,125] Similarly, in the French SUVIMAX trial population,[126] investigators recorded positive correlations between plasma selenium and fasting plasma glucose both at baseline and follow-up.

Results from randomised trials in which type-2 diabetes was a secondary outcome also vary. In SELECT, supplementation of 35 533 American men with 200 µg selenium per day as selenomethionine had no effect on risk of type-2 diabetes after a median follow-up of 5·5 years.[87] By contrast, a post-hoc analysis of the NPC trial in 1312 participants in southeastern USA showed a significantly increased risk of type-2 diabetes in those supplemented with selenium (200 µg per day as selenium yeast) and followed up for a mean of 7·7 years.[127] An exposure-response gradient was noted across tertiles of baseline plasma selenium concentration, and the increased risk was driven by those in the highest tertile (>121·6 µg/L) whose risk was significantly increased with supplementation.[127]

How might these discrepant findings be interpreted? The lower selenium status measured in men with type-2 diabetes in the case-control studies might be an effect of the disease, or its associated inflammation, on selenium status. For example, a systemic inflammatory response produces cytokines that inhibit the expression of SEPP1 and will reduce plasma selenium.[37,38,83] Similar effects associated with preclinical disease are unlikely to explain fully the decreased risk of onset of hyperglycaemia in male participants of the EVA study.[123] Insulin resistance can be triggered by oxidative stress and ameliorated by antioxidant treatment.[128] The plasma

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selenium of men in the EVA cohort ranged from below to above the concentration needed for optimum antioxidant GPx activity, suggesting that participants in the top tertile were better protected from oxidative stress, and hence the development of insulin resistance, than were those in the bottom tertile (median plasma selenium 104 µg/L *vs* 71 µg/L).[123] Why the same effect was not noted in women is unclear.

The increased risk of type-2 diabetes with high selenium intake or supplementation might be explained by the effect of high selenium on insulin signalling. Binding of insulin to its receptor initiates the insulin-signalling cascade, which is accompanied by a burst of hydrogen peroxide that acts as a second messenger.[119] High activity of GPx1, which removes hydrogen peroxide, might thus interfere with insulin signalling. For example, transgenic mice overexpressing GPx1 developed insulin resistance, hyperglycaemia, hyperinsulinaemia, and obesity,[129] and a strong correlation was noted between increased erythrocyte GPx1 activity and mild insulin resistance in pregnant women.[130] By contrast, knockout of GPx1 improved insulin-induced glucose uptake and insulin resistance in mice.[119] However, GPx1 cannot be the only relevant selenoprotein because plasma GPx activity is maximised well below the selenium doses associated with increased risk of type-2 diabetes, while a polymorphism in Dio2 is known to affect the risk of insulin resistance and type-2 diabetes (table 1). Indeed, individuals with a reduced ability to synthesise many selenoproteins (owing to heterozygous defects in SBP2) had enhanced systemic and cellular insulin sensitivity.[48]

Another selenoprotein implicated in diabetes risk is SEPP1, which requires a higher selenium intake than does GPx1 to achieve maximum plasma concentration.[66] SEPP1 functions as a negative insulin modulator: it inhibits the insulin-induced burst of reactive oxygen species in vitro and further contributes to insulin resistance by inactivating AMP-activated protein kinase—a positive regulator of insulin synthesis and secretion in pancreatic islet β cells.[17] Clinical studies in Japanese adults have shown that serum SEPP1 concentration is significantly correlated with glycated haemoglobin $A_{1c}$ and fasting plasma glucose, and is raised in people with type-2 diabetes.[17] Furthermore, serum SEPP1 concentrations were significantly higher in Korean patients with type-2 diabetes or pre-diabetes than in those with normal glucose tolerance and decreased in a stepwise manner.[18] SEPP1 was higher in overweight and obese participants than in lean participants,[18] indicating that dysregulated carbohydrate metabolism could be driving the increase in SEPP1 through the action of PGC1α—a transcription factor co-activator that is a key regulator of both hepatic gluconeogenesis and SEPP1 biosynthesis.[119]

Why did selenium supplementation cause an increased risk of type-2 diabetes in participants in the NPC trial but not in SELECT? The small NPC trial was at much

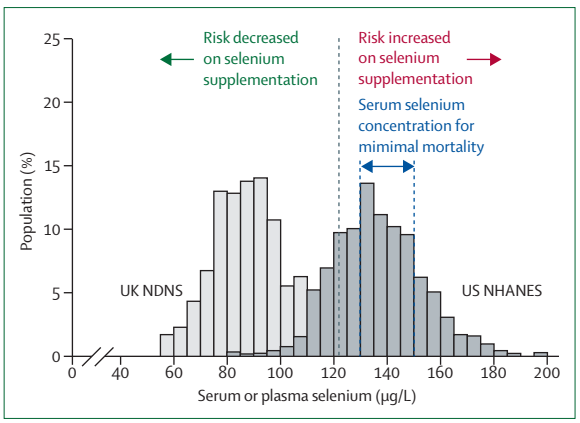


***Figure 4:*** **Distribution of serum or plasma selenium in adults aged 40–64 years in the UK 2001 NDNS population[132] (representing status in Europe), and the US 2003–04 NHANES population[133] (representing status in North America)**

The height of the histogram bars represents the weighted percentage of the population having the corresponding range of serum or plasma selenium. The dotted black vertical line at 122 µg/L represents the concentration of baseline plasma selenium that delineates a change in risk of cancer, non-melanoma skin cancer, and type-2 diabetes from lower to higher on supplementation with 200 µg selenium per day in the Nutritional Prevention of Cancer trial.[110,111,114,127] The blue dotted lines show the range of serum selenium concentration associated with minimum mortality in the third NHANES population.[32] Histograms constructed by Eliseo Guallar and Yiyi Zhang. NDNS=National Diet and Nutrition Survey. NHANES=National Health and Nutrition Examination Survey.

greater risk of chance findings than was the much larger SELECT. Alternatively, the higher baseline selenium status of men in SELECT (median serum selenium 136 µg/L *vs* mean plasma selenium 114 µg/L[87,127]) had already caused selenoprotein expression or activity to plateau or pass a threshold of risk before supplementation. In support of this assertion, the number of cases in the placebo group per 1000 person-years in SELECT was higher than in the NPC trial (14·1 *vs* 8·4).

In animal models, low levels of expression of GPx1 and other stress-related (regulated by the amount of selenium in the diet) selenoproteins are as damaging as high levels of expression with respect to insulin resistance and hyperglycaemia.[131] Hence a U-shaped association between selenoproteins and type-2 diabetes risk might explain some of the apparently contradictory findings.

## Selenium status in relation to health effects

Selenium status varies widely in different parts of the world, in line with selenium intakes.[1,2] The distribution of plasma selenium in the UK[132] and that in the USA[133] (figure 4) shows the difference in status between Europe (represented by UK data) and North America (represented by US data). The dotted vertical line on figure 4 (at 122 µg/L) represents the concentration of baseline plasma selenium that marked a change from negative to positive in the risk of cancer, non-melanoma skin cancer, and type-2 diabetes with selenium supplementation in the NPC trial.[110,111,114,127] The implications are clear: people whose serum or plasma selenium

concentration is already 122 µg/L or higher—a large proportion of the US population—should not supplement with selenium.

The converse, however, is also true: there are various health benefits, and more importantly, no extra risk, for people with serum or plasma selenium concentrations less than 122 µg/L associated with raising their selenium status, perhaps to 130–150 µg/L—a concentration associated with minimal mortality (figure 3).[32]

## Conclusions and suggestions for future research

The effects of selenium on human health are multiple and complex,[1] necessitating further research to optimise the benefits and reduce the risks of this potent trace mineral. Trials should be undertaken only in populations of low or relatively low selenium status. Furthermore, since polymorphisms in selenoproteins affect both selenium status and disease risk or prognosis (table 1), future studies must genotype participants. Further work aimed at understanding the potential links between selenoproteins and the highly prevalent condition of type-2 diabetes should also be a priority.

The crucial factor that needs to be emphasised is the inextricable U-shaped link with selenium status: additional selenium intake (eg, from food fortification or supplements) may well benefit people with low status. However, people of adequate or high status could be affected adversely and should not take selenium supplements. This observation is a particular case of the general principle recognised by Paracelsus as long ago as 1567.

**Conflicts of interest**

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