Chapter 31
The Epidemiology of Selenium and Human Health

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Abstract Few issues involving nutritional and environmental epidemiology have received as much interest as the relation between selenium (Se) intake and human health, as reflected by the large body of evidence from observational and experimental studies with reference to cancer and other clinical endpoints. Se deficiency may play a major role in favoring the onset of a human cardiomyopathy, Keshan disease. Se overexposure has been linked to skin and advanced prostate cancers in recent randomized controlled trials, in contrast with earlier hypotheses of protective effects of Se intake against cancer generally, and prostate cancer in particular. Overexposure has also been linked to higher risk for diabetes and amyotrophic lateral sclerosis. For cardiovascular disease risk, such as ischemic heart disease and stroke, little evidence of any modifying effect of Se exposure has been provided by epidemiologic studies. The results of these studies should be used in public health to set better standards for intake of organic and inorganic Se species, focusing on experimental studies with individual Se compounds more than overall exposure to the element, in order to improve reliability and reduce bias in the studies.

Keywords Cardiovascular disease • Diabetes • Epidemiology • Neoplasms • Neurological disease • Randomized controlled trials • Selenium • Thyroid disease

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31.1 Introduction

There is vast epidemiologic evidence relating selenium (Se) to major human health outcomes (Fig. 31.1). In this chapter we give emphasis to experimental studies, particularly randomized controlled trials (RCTs), as those have greater validity in human biomedical research. For more comprehensive analyses, we refer to some recent reviews on these topics [1–3] and for the outcomes not covered here, such as the relation between Se and infectious disease and AIDS (see [4] and Chap. 28), pre-eclampsia (see [5] and Chap. 30), Kashin-Beck disease osteoarthropathy [6], and critical illness [7, 8]. Also not covered are issues such as the genetic susceptibilities and mutations possibly underlying the relation between Se and human health ([9–11] and see other Chapters in Part III).

31.2 Cancer

Cancer has received more research interest in connection with Se intake than any other human disease [3, 12] with results from laboratory studies showing both carcinogenic and anticarcinogenic effects [13–15]; and more recently, the potential for Se use in cancer therapy, a fascinating issue not further taken into consideration herein [16]. Early epidemiologic research involved ecologic investigations and case-control studies carried out in the 1960s [17] and 1970s [18], and observational prospective studies in the 1980s and 1990s [19]. Most evidence supported an inverse relation between Se exposure and cancer risk, although not all studies were consistent, and in some cases, a positive association was suggested [3]. To resolve the confusing pattern of evidence, RCTs were undertaken, representing a turning point in establishing the role of Se in human cancer (and more generally in human health).

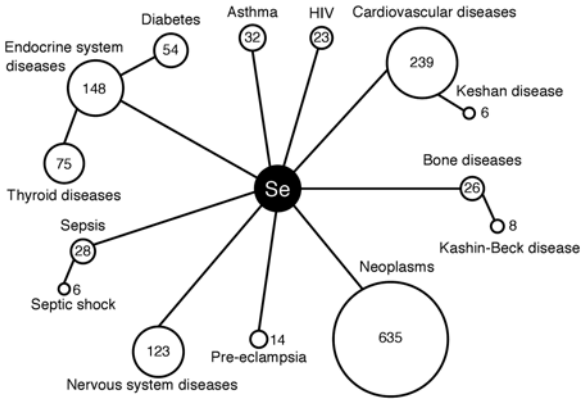

Fig. 31.1 Results of a PubMed search on the epidemiology of Se and human health. Figure shows the number of hits by January 2, 2016 based on a search strategy using the MeSH terms 'selenium' AND 'humans' AND ('epidemiology' OR 'epidemiologic methods'), plus entry terms for the various diseases

If we exclude early Chinese trials due to potential risk of bias [3], the first RCT was the 'Nutritional Prevention of Cancer' (NPC) double-blind trial coordinated by the University of Arizona [20–23]. In this study, 200 μg Se via selenized yeast tablets, or a placebo, were randomly allocated to 1,312 subjects with a previous history of non-melanoma skin cancer (NMSC). Though the trial failed to demonstrate that Se supplementation prevented NMSC incidence (the primary endpoint), an unexpected sharp decrease of secondary endpoints such as other cancer incidence and mortality were found [20]. This led to a premature unblinding of the study, and publications of the blind phase based on 6.4 and 7.4 average years of follow-up [20–23]. The first preliminary report showed a sharp decrease in incidence of lung cancer (hazard ratio (HR) 0.56, 95 % confidence interval (CI) 0.31–1.01), prostate cancer (HR 0.35, 95 % CI 0.18–0.65), colorectal cancer (HR 0.39, 95 % CI 0.17–0.90), and total cancer (HR 0.61, 95 % CI 0.46–0.82) [20]. In the final reports based on the entire period of follow-up, beneficial but weaker effects of the intervention emerged for incidence of all cancers (HR 0.75, 95 % CI 0.58–0.97), prostate cancer (HR 0.48, 95 % CI 0.28–0.80), lung cancer (HR 0.74, 95 % CI 0.44–1.24), and colorectal cancer (HR 0.46, 95 % CI 0.21–1.02) [21]. The protective effect of Se was confined entirely to males (HR 0.67, 95 % CI 0.50–0.89) and was most evident in former smokers [21–23]. However, the authors noted an increased incidence of melanoma, bladder, breast, and head and neck cancer, as well as lymphoma and leukemia, results which 'although non-significant and based on small case numbers, may indicate potential increased risk with Se supplementation' [21]. A strong positive association between baseline plasma Se and the incidence of total cancer in the Se-supplemented subjects also emerged [21], as previously reported for prostate cancer alone [24]. Finally, increased risk for NMSC emerged with a HR 1.17 (95 % CI 1.02–1.34) [23], a finding which was replicated subsequently in a small clinical trial [25].

However, in their 2003 report, the NPC trial investigators acknowledged a serious methodological pitfall in the trial, i.e., that 35 % of men with an abnormal prostate-specific antigen in the placebo group underwent biopsies at some point during the trial, compared with only 14 % in the Se group. This detection bias may have jeopardized the trial's validity [3]. Nevertheless, this bias has been ignored subsequently by many reviewers, and the final 2002–2003 NPC trial reports themselves have received limited attention. Instead, attention has been given to the 1996 report emphasizing beneficial effects of the Se intervention [20], which generated large expectations about a cancer-preventive Se effect and contributed to the implementation of more RCTs to further elucidate the role of Se.

The most famous and widely cited among these is SELECT (Se and Vitamin E Cancer Prevention Trial), a randomized, double-blind, placebo-controlled, 2 × 2 factorial design. More than 35,000 healthy men who received daily supplemental Se as selenomethionine (200 μg/day), vitamin E, Se plus vitamin E or placebo [3, 13, 26–28] were enrolled in this trial. However, SELECT was discontinued before its planned end for three main reasons: i) its inefficacy in risk reduction, ii) concern about increased risk of prostate cancer in vitamin E-treated participants, and iii) concern about increased incidence of type 2 diabetes in the Se-treated participants [13], also taking into consideration the increased diabetes risk in the Se arm reported

in 2007 in a *post hoc* analysis of the NPC trial [29]. Overall, results of SELECT were that Se supplementation did not decrease risk of all cancers (HR 1.01, 99 % CI 0.89–1.15), prostate cancer (HR 1.04, 99 % CI 0.87–1.24), or colorectal cancer (HR 1.05, 99 % CI 0.66–1.67), while lung and bladder cancer were characterized by a HR of 1.12 (99 % CI 0.73–1.72) and 1.13 (99 % CI 0.78–1.63), respectively [26, 30]. More recently, studies on the over 1,700 prostate cancer cases diagnosed in SELECT yielded concerning results. Among Se-supplemented subjects, those with the highest baseline toenail Se showed an increased prevalence of high-grade prostate cancer [31]. A positive association between prostate cancer risk and baseline α-tocopherol plasma levels also emerged in Se-supplemented subjects, as well as an increased risk of prostate cancer (overall and low-grade) among carriers of the NKX3.1 androgen-regulated prostate tumor suppressor protein (the CC genotype at rs11781886) [32, 33]. These results are of interest given the results of a recent cohort study on 4,459 men diagnosed with non-metastatic prostate cancer, which found an increased risk of prostate cancer mortality following self-supplementation of ≥140 μg/day Se [34].

Three other carefully-conducted and low-bias trials were carried out on the role of cancer prevention by Se compounds, mainly focusing on prostate cancer [35–37]. The results show no beneficial effects of Se on primary or secondary cancer endpoints, confirming the results of SELECT, although their smaller size and shorter follow-up provide reduced precision and inability to account for long-term effects. Overall, meta-analyses of all RCTs as well as of low-bias RCTs only clearly show the lack of any beneficial effect on prostate cancer risk (Fig. 31.2) and other cancers.

Therefore, the most recent RCTs, all with a low risk of bias, have demonstrated that Se supplementation in populations with no evidence of deficiency, has no beneficial effect on cancer risk, while supplementation might increase risk of some

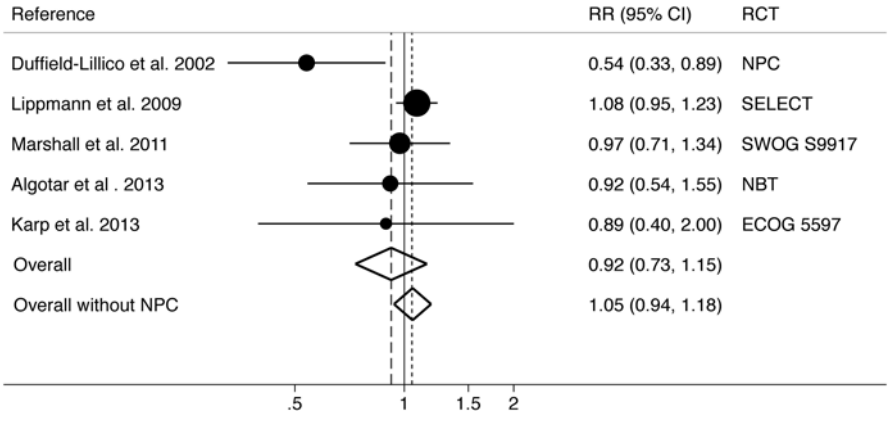

Fig. 31.2 Summary relative risk of prostate cancer following selenium supplementation in RCTs. Figure shows the forest plot of random-effect meta-analysis summary RRs of prostate cancer (95 % CI) from RCTs [21, 26, 35–37]. The vertical dashed lines show the effect of Se on prostate cancer risk for all studies (Overall) and for those with low risk of bias only (Overall without NPC trial)

site-specific cancers. Thus, a question arises about some results of the NPC trial. While detection bias may at least partially explain the results at least for prostate cancer, it has been suggested that two other trial characteristics, i.e., the specific Se species used for supplementation (200 μg/day Se as selenized yeast in NPC trial and selenomethionine in SELECT), and the different baseline Se levels, may explain these discrepancies. However, both hypotheses are unlikely. First, Se is mainly present in selenized yeast as organic Se forms, the major part of which is selenomethionine [12, 38], though we cannot entirely rule out an effect of the other Se forms or metabolites present in yeast despite their smaller amounts. Second, different baseline Se exposure is also unlikely to explain the results [3, 12], as the difference in intakes represented only about 15 μg/day Se [39] with a large overlap between the two populations (Fig. 31.3). In addition, the recent dose-response analyses in SELECT ruled out a beneficial effect of Se even at the lowest levels of exposure [31]. Finally, the specific study population in the NPC trial (subjects with NMSC history) may at least partially explain the different results of that trial [22].

Of interest may also be the results of a 'natural experiment' concerning an Italian municipality, wherein a cohort of 2,065 residents accidentally consumed drinking water with unusually high Se content (~8 μg/L) in its inorganic hexavalent form for several years. Notwithstanding the potential effects of unmeasured lifestyle confounders, such exposure was associated with increased cancer mortality, mainly due to melanoma and colorectal cancer, kidney cancer in males, and lymphoid

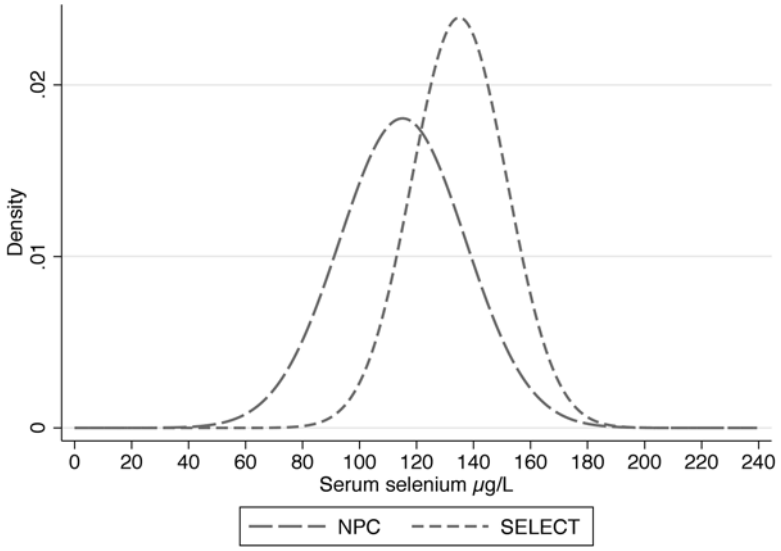

Fig. 31.3 Estimated distribution of plasma/serum selenium in the NPC trial and SELECT. Data extracted for the NPC trial from Duffield-Lillico et al. 2003 [22] (mean (SD) plasma Se 115.1 μg/L (22.05)), and for SELECT from Lippmann et al. 2009 [26] (Table 2, mean (SD) serum Se computed as 136.3 (18.66) μg/L from median and interquartile values using the equation found in http://handbook.cochrane.org/chapter_7/7_7_3_5_mediansand_interquartile_ranges.htm [101])

malignancies in females [40]. These results are of interest being the only data so far available for inorganic hexavalent Se exposure, and also for some similarities with increased risks noted in the NPC trial [21]. The excess melanoma risk, validated by an incidence study [41], finds support from an observational cohort study [42], a case-control study [43], and from time trends of the excess melanoma incidence detected in a French trial after administration of Se and other substances [44].

31.3 Cardiovascular Disease

While some support for a beneficial effect on cardiovascular health from a higher Se status originally came from observational cohort studies, the RCTs have demonstrated that no effect is induced by Se supplementation independently of baseline Se status [1, 45]. In SELECT, the relative risk (RR) for any cardiovascular events (including death) was 1.02 (99% CI 0.92–1.13) based on 1,080 cases in the Se group and 1050 in the placebo group [26], while corresponding estimates in the intermediate NPC trial report were 0.96 (95% CI 0.64–1.44) on the basis of 47 and 46 events in the Se and placebo groups, respectively [20]. Conversely, no other trial, nor the final NPC report itself, has investigated this issue. The above mentioned natural experiment reported in an Italian community was also unable to show any beneficial effect on cardiovascular mortality since standardized mortality ratio among residents exposed versus unexposed was 1.06 (95% CI 0.81–1.38) in males and 1.04 (95% CI 0.80–1.34) in females [40].

Furthermore, two recent RCTs have investigated the possible effect of Se administration as selenized yeast on a putative cardiovascular risk factor, i.e., serum cholesterol levels. In the first of these trials, administration of 100 μg/day Se for 6 months in 501 elderly UK subjects decreased total cholesterol levels compared with placebo. However, no dose-response relationship was found with higher doses, leading to the authors' statement that 'Se supplementation seemed to have modestly beneficial effects on plasma lipid levels in this sample of persons with relatively low Se status' [46]. More recently, a RCT carried out in 491 Danish elderly individuals with a considerably longer period of follow-up, also using Se doses of 100, 200 and 300 μg/day, was unable to find relevant and dose-response related changes in total cholesterol in the Se-supplemented group compared with placebo [47].

In addition to overall cardiovascular disease, Keshan disease, an endemic and severe childhood cardiomyopathy occurring in some Chinese areas, has been frequently related to Se status. Two main lines of epidemiologic evidence suggest that low Se intake may represent a risk factor for Keshan Disease: its increased prevalence in low-Se areas of China, and the ability of Se administration as sodium selenite to lower its incidence [48–51]. However, Chinese investigators noted some peculiar characteristics of this disease, such as its seasonal trend in incidence, which cannot be explained by nutritional deficiency [48, 49], suggesting an infectious etiology like a Coxsackie virus [52]. Furthermore, background levels of intake as low as 16 μg/day appear to be enough to prevent this disease [52]. In addition, the effectiveness of Se in reducing disease incidence does not *per se* imply that Se deficiency was a cause, due to the absence of reports of Keshan disease in other areas of the world with very low Se status. The possibility

that Se had a beneficial effect in the Chinese trial due to its pharmacological effects, considering its high doses (500–1000 μg/week sodium selenite), should also be considered. Selenite has the ability to inhibit Coxsackie virus replication even at low concentrations [53, 54] as well as other microorganisms [12]. Thus, the etiology of Keshan disease, including the possible role of Se, is still a matter of debate [51, 55].

31.4 Diabetes

A relationship between Se (specifically its overexposure) and risk of type 2 diabetes represents a new issue in Se research. The link was established unexpectedly following a secondary analysis of the NPC trial results [29], and then adding this outcome to the safety endpoints of the subsequent RCTs [56]. The possibility that Se may modify diabetes risk had long been suspected [57], but it was the NPC trial report which raised the possibility of a strong diabetogenic effect of Se. After SELECT, the RCTs have systematically confirmed an increased diabetes risk in Se-supplemented subjects [58], although mostly statistically imprecise due to the low number of observed cases in these smaller intervention studies [26, 27, 36, 37]. A diabetogenic effects of Se finds support from most, but not all, observational studies and from several laboratory studies [57, 59]. Currently, an excess risk of diabetes represents one of the most concerning adverse effects which might be attributed to Se overexposure [12], calling for further research to carefully assess the association (see also Chap. 49).

31.5 Thyroid Disease

Se is an essential component of the iodothyronine deiodinases and therefore is required for normal thyroid function [60, 61]. However, even low dose administration has been unexpectedly suggested or demonstrated to alter thyroid function in case reports, ecological and clinical intervention studies [62], including RCTs [63–65]. On the other hand, recent RCTs have shown a potential efficacy of Se compounds in the treatment of Hashimoto thyroiditis and other autoimmune thyroid diseases, and Graves' disease, which is clearly worth further investigation, though the exact pharmacological activity and safety of Se in these diseases still need to be defined [2, 66, 67].

31.6 Neurological Disease

Several recent studies suggest that Se and selenoproteins have key roles in brain and, more generally, in nervous system functions [68–70]. This is generating speculation for a beneficial role of this element in both prevention and treatment of central nervous system (CNS) diseases [69, 71]. Conversely, epidemiologic studies have suggested a broad spectrum of neurotoxic effects of environmental Se [72].

The original epidemiologic evidence for Se neurotoxicity came from studies among occupationally-exposed subjects, subjects consuming misformulated Se-supplements and populations from seleniferous areas of China [72]. However, most of these studies cannot be properly considered as epidemiologic studies, since they were frequently case reports of acute Se intoxication with neurological symptoms in workers exposed to high levels of Se compounds or attempting to use Se for suicide [72]. In addition, most investigations were flawed methodologically, e.g., inadequate Se exposure assessment, or lack of adequate control groups. Nevertheless, these studies provided evidence linking Se overexposure with neurological endpoints such as confusion, memory loss, depression, tremors and ataxia, lethargy, dizziness, sleep disturbances and paresthesias, weakness and fatigue [72]. In the seleniferous areas of China, selenium exposure has been associated with acroparesthesia and dysesthesia, hyperreflexia, convulsions, motor weakness, paralysis and even hemiplegia [72–74]. However, the exact clinical nature of this broad spectrum of neurological alterations, the specific signs and symptoms due to Se overexposure, the exposure levels, and the possible role of modifying factors, would require a comprehensive, in-depth epidemiologic investigation [72].

The most specific CNS disease associated with Se exposure is amyotrophic lateral sclerosis (ALS), first associated with Se overexposure among farmers in a seleniferous South Dakota area in 1977 [75]. More recently, investigation of the small Italian cohort exposed to hexavalent inorganic Se showed an excess ALS incidence [76, 77]. Case-control studies have also supported this association, despite their inherent methodological limitations, including a recent study analyzing Se species in a key CNS biomarker, cerebrospinal fluid [78]. In that study, the various Se species showed profound and inconsistent differences between cases and controls: higher levels of selenite and lower levels of organic Se forms in ALS patients [78]. This suggests an involvement of the most neurotoxic Se compounds in disease etiology, and also the potential for exposure misclassification when Se speciation is not used [79]. An association of Se overexposure with ALS risk is also strongly supported by animal [80] and in vitro studies [81, 82], showing a selective toxicity of Se species on neural cells, particularly motor neurons.

The Italian cohort study of subjects overexposed to inorganic Se through drinking water has also shown an excess mortality from Parkinson's disease, but epidemiologic studies on this issue are lacking, with the exception of three case-control studies, all of which found higher blood Se levels in patients compared to controls [72]. Few studies exploring potential etiologic or therapeutic roles of Se in Alzheimer's disease show little evidence of association [72]. The influence of Se on cognitive performance has also been investigated in a cross-sectional and two prospective studies, finding in two cases a positive association [83, 84] and no relation in the remaining study [85]. However, well-known limitations in nutritional epidemiology, mainly inadequate long-term exposure assessments and potential for unmeasured confounding variables, limits the reliability of these findings. Depression has been investigated in relation to Se status in six prospective studies with observational [86, 87] and experimental design [88–91]. A small Australian cohort-nested case-control study based on 18 major depression events showed a

triplicated risk in the lowest Se intake category at baseline (Odds Ratio (OR) 2.95, 95 % CI 1.00–8.72) compared with the highest category [86]. Conversely, a large prospective study, based on 25 years of follow-up and a total of 407 depression cases, found a positive dose-response association between baseline toenail Se content and disease risk [87]. Multivariate OR of depression was 4.25 (95 % CI 1.79–10.14) in the highest category of toenail Se (1.61–1.98 μg/g) versus the lowest one (0.51–0.88 μg/g), and a doubling of Se levels was associated with 56 % higher odds of having depressive symptoms at an exam. Concerning RCTs, their findings have been inconsistent in that the two small case-crossover studies yielded conflicting results and only weak evidence supporting a beneficial Se effect on mood [88, 89]. Furthermore, Se administration had no effect on mood and quality of life in a trial with 501 UK participants aged 60–74 randomly allocated to 100, 200 or 300 μg/day Se [90]. A slightly lower score of a postpartum depression was associated with 100 μg/day Se administration in a small Iranian trial on 85 women [91], though the study suffered from a high risk of bias for several reasons, including high attrition rate [92]. Finally, no beneficial effect on depression and anxiety scores was induced by 200 μg/day Se administration in patients with initially untreated thyrotoxicosis [67]. Overall, a link between Se and depression risk remains thus far unclear, though it warrants further investigation.

Finally, three recent studies raised the possibility that Se may affect neurological functions in children. A case-control investigation in Inuit children found a positive association between blood Se and longer visually evoked potentials latencies, and thus with possible optic nerve demyelination, even after adjusting for methylmercury toxicity in multivariate analysis [93]. A cohort study in Chinese neonates showed a U-shaped relation between Se umbilical cord and the Neonatal Behavioral Neurological Assessment score [94], that apparently supported a very narrow safe range of Se intake in neonatal life. A second cohort study in Sweden showed little evidence of any association between Se (and manganese) levels in umbilical cord serum and diagnosis of Attention-Deficit/Hyperactivity Disorder (ADHD) in childhood, with the exception of a high OR (2.6, 95 % CI 1.2–5.5) for Se levels above the 90th percentile compared with the 10th–90th category, suggesting the need to further assess a possible association between Se and ADHD [95].

31.7 Concluding Remarks

Why have results of observational studies been so inconsistent with each other, and with those of RCTs? Indicators commonly used in observational studies to assess Se exposure include biomarkers such as blood (serum, plasma and erythrocyte), toenail, hair and urine content, as well as dietary intake assessments (24 h recalls, food frequency questionnaires). Each method has its own characteristics, strengths and limitations for epidemiologic research, as reviewed elsewhere [13, 96]. Correlation between dietary Se intake and Se biomarkers has been found to be weak in some studies [13], due for instance to a high variability in actual food Se content

compared to average values reported in food composition databases. However, caution should be used when favoring biomarkers of Se intake over dietary assessment methods. The various Se species are distributed and excreted to different extents [79], and organic species have higher retentions as well as lower toxicological activity, compared with inorganic forms [79]. Moreover, the various Se species (both organic and inorganic) have markedly different and sometimes even opposite biological effects [79, 97], thus emphasizing the need to consider individual Se species levels when assessing Se exposure. Unfortunately, food composition data on Se species, and elemental speciation generally, are rarely available [98]. Finally, a major limitation of epidemiologic studies is the use of circulating biomarkers of Se exposure and not Se levels found in target tissues, an important issue when assessing health outcomes such as neurological disease [78].

Discrepancies between observational and experimental studies, and among observational studies themselves, may also be due to unmeasured confounding variables, thus confirming the key role of RCTs to understand Se health effects. However, due to the null results or unforeseen risks arising in some RCTs, replication of Se trials appears unfeasible for ethical reasons. Thus, we must rely on secondary analyses for additional outcomes from the most recent and powerful low-bias trials, which have greatly clarified the major controversial relationships between Se and cancer. In addition, the exact nature of the relation between Se and Keshan disease needs to be further investigated through well-conducted epidemiologic studies. These studies, along with a newly emerging body of research, will better define the still-debated safe range of intake of this metalloid [12, 99, 100].

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