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Review

Making sense of sex and supplements: differences in the anticarcinogenic effects of selenium in men and women

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Abstract

The role of the essential trace mineral selenium in human health and disease is currently a subject of intense interest. In particular, the possible cancer preventive effects of dietary selenium supplementation are now being investigated in several large, randomized trials. The association between selenium status, genotoxic damage, and cancer risk remains enigmatic because epidemiologic studies have failed to consistently link low selenium status with increased cancer risk in men and women. In this paper, we considered the evidence that there are sex-based differences in the anticarcinogenic effects of selenium in humans. We focused our review on prospective human studies in which the relationship between selenium status and cancer risk in men and women was directly compared. Results from cohort studies conducted in seven countries (Belgium, China, Finland, Japan, Netherlands, Norway, and United States) were used to assess the strength of association between low selenium status and the incidence of all cancers, sex-specific cancers, and cancers at particular anatomic sites. In general, the available data support the hypothesis that cancer risk in men is more profoundly influenced by selenium status than cancer risk in women. Factors contributing to the apparent difference in the effects of selenium on cancer incidence in men and women may include sex-based differences in the metabolism and/or tissue distribution of selenium, as well as sex- or gender-related factors that influence tumor biology. Studies are needed to further define the dose–response relationship between selenium and cancer risk in men and women. A more complete understanding of the mechanisms by which selenium modulates cancer initiation and progression is needed to optimize dietary selenium supplementation as a practical cancer preventive strategy. Ultimately, achieving the ambitious goal of cancer prevention may require sex- and gender-specific approaches.

Keywords: Cancer incidence; Epidemiology; Cancer prevention; Dietary supplements; Micronutrients; Gender-specific risk; Cohort studies; Sex-based differences

1. Introduction

The trace mineral selenium is an essential component of several metabolically important enzymes, including the antioxidant glutathione peroxidases and thioredoxin reductases [1–3]. Because dietary selenium supplementation inhibits cancer development in

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a variety of experimental animal models [4–6], there is growing interest in the prospect that selenium status significantly influences human cancer risk.

To date, the epidemiologic evidence from prospective human studies is inconsistent—some investigations show an increased risk of cancer in individuals with lowest selenium status, whereas other studies report null results [7,8]. In a randomized, placebo-controlled study of older Americans, daily use of an oral selenium supplement substantially reduced the risk of several cancers, most notably cancer of the prostate [9]. These results suggested the exciting possibility that significant reductions in cancer risk may be realized with low, non-toxic doses of selenium that could readily be achieved by dietary supplementation. The cancer protective effects of selenium may be mediated by selenoproteins operating within enzymatic systems which are saturated at relatively low levels of selenium, or by selenium metabolites that increase substantially under conditions of supranutritional selenium intake [10].

In 1987, Kok et al. [11] in the Netherlands reported that low selenium status was associated with increased cancer risk in men, but not in women. They proposed that serum selenium may only be a useful predictor for cancer risk in men. This hypothesized sex-based difference was consistent with earlier data reported from Finland [12] and the United States [13].

In this article, we consider the evidence that there are sex-based differences[1] in the anticarcinogenic effects of selenium in humans. To accomplish this, we critically review data from prospective human studies in which the association between selenium status and subsequent cancer risk in men and women was directly compared. We also review prospective studies that were restricted to males or females as well as studies with both men and women in which sex-specific cancer risk was not reported; our discussion of these studies is limited. The purpose of this review is to provide a conceptual framework for future investigations on the underlying mechanisms and public health implications of the apparent sex-based differences in selenium anticarcinogenesis.

[1] In this article, we use the terms sex and gender to discuss the differences between men and women. These terms are used in accordance with definitions proposed by the 2001 Institute of Medicine Report, "Exploring the Biological Contributions to Human Health: Does Sex Matter?" [14]. The term sex is used when differences are primarily biological in origin and may be genetic or phenotypic; gender is used when referring to social and cultural influences based on sex [15].

2. Sex-based differences in the association between selenium status and total cancer incidence

Prospective cohort studies provide an opportunity to evaluate the association between nutrient status and the subsequent risk for cancer. In these studies, pre-diagnostic biological samples are collected from a cohort of healthy individuals who are free of cancer. After the cohort is followed longitudinally over time, samples are analyzed from all cancer cases and a matched group of controls who did not develop cancer during the observational period.

Table 1 summarizes data from six prospective cohort studies [11–13,16–18] conducted in five countries (Finland, Japan, Netherlands, Norway, and United States) in which the effect of dietary selenium intake on total cancer incidence in men and women was measured by comparing the serum selenium concentration of cancer cases versus controls without cancer. Among men, cancer cases had significantly lower selenium concentration than controls ($P < 0.05$) in four of six studies. On average, males that subsequently developed cancer at any site had an 8% (range, 5–23%) lower selenium concentration than men who did not develop cancer. In contrast, there was no significant difference between selenium concentration in female cases versus controls in any of the studies. Women with cancer had higher selenium concentration than men with cancer in four of the studies. This is consistent with the findings of Criqui et al. [19] in which mean serum selenium concentration in 74 men that subsequently had cancer mortality was 4 μg/L lower than controls ($P < 0.40$); in contrast, 62 women with cancer mortality had serum selenium concentration 11 μg/L *higher* than controls ($P = 0.03$).

In three studies [11,16,20], the relative risk of cancer in individuals with the lowest serum selenium was compared with the incidence of cancer in individuals with the highest selenium status. In Belgium, Finland, and the Netherlands, men with low selenium status had a significantly higher relative risk (2.2–2.7-fold increase) of cancer at all sites than men with high selenium. In contrast, women with low serum selenium

Table 1
Mean pre-diagnostic serum selenium concentration in cancer cases and matched controls from six prospective cohort studies

Cohort	Cases	Mean ± S.D. serum selenium concentration (μg/L)		*P*-value
		Case	Control	
Finland				
Salonen et al. [12]	16 male smokers	49.3	63.5	<0.05
	14 male non-smokers	49.9	58.4	>0.05
	21 female (all non-smokers)	59.5	60.5	>0.05
Knekt et al. [16]	597 male	59.1 ± 17.5	62.5 ± 15.4	<0.001
	499 female	63.6 ± 17.4	63.9 ± 14.3	>0.05
Japan				
Ujiie and Kikuchi [18]	35 male	105.2	112.8	0.18
	38 female	97.4	102.7	0.25
Netherlands				
Kok et al. [11]	40 male	116.7 ± 4.0	126.4 ± 3.1	0.04
	29 female	130.6 ± 6.0	129.3 ± 4.3	0.83
Norway				
Ringstad et al. [17]	26 male	124.0	130.3	0.08
	34 female	123.2	127.9	0.36
USA				
Willett et al. [13]	60 male	127.0	137.0	0.008
	51 female	132.0	134.0	0.57

had a relative risk to develop cancer that did not differ significantly from unity (Fig. 1).

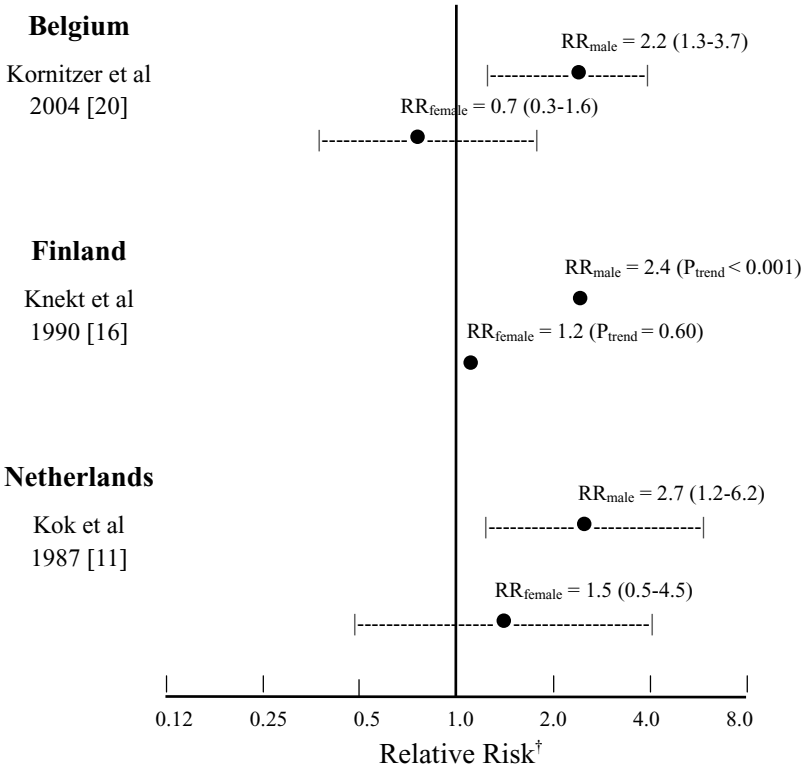
Garland et al. [21] analyzed the association between selenium and cancer risk in women (503 cancer cases and matched controls) in the Nurses Health Study. Toenail selenium concentration was not inversely associated with overall cancer risk or cancer risk at any site. The authors concluded that higher selenium intake within the range typical for US women was not protective against cancer development in women.

Taken together, these studies suggest that overall cancer incidence in men is more profoundly affected by low selenium status than is cancer incidence in women.

3. The association between selenium status and risk of breast cancer and prostate cancer

To further analyze the influence of sex or gender-related factors on the anticarcinogenic effects of selenium, we explored the association between selenium status and risk of two sex-specific cancers—breast cancer and prostate cancer. Fig. 2 summarizes data collected from the largest prospective cohort studies conducted in Finland, Netherlands, and United States. An inverse association between serum selenium concentration and prostate cancer risk was not seen in the Finnish study ($n = 61$ cases) [16]. However, two large studies from the Netherlands ($n = 540$ cases) and United States ($n = 181$ cases) showed that men with low selenium status had a significantly increased risk (RR $= 1.5$ and 2.9, respectively) of prostate cancer compared to men with high selenium status [22,23].

In a secondary cohort analysis of the Alpha Tocopherol Beta Carotene (ATBC) Cancer Prevention Study, no significant association between low selenium intake and prostate cancer risk was found in the placebo treated or α-tocopherol treated groups [24]. Similarly, low baseline selenium status was not a significant risk factor for subsequent prostate cancer in the Carotene and Retinol Efficacy Trial (CARET) [25]. Among Japanese American men in Hawaii, low selenium status was associated with a significant increased risk of prostate cancer in current smokers



† Represents the relative cancer risk for individuals with low selenium status compared to cancer risk in individuals with high selenium status. For each sex, cancer risk in individuals with high selenium status equals 1.0.

Fig. 1. Relative risk of cancer (all sites) associated with low selenium status in men and women from three prospective cohort studies.

[RR = 5.0 (1.3–10.0)] and past smokers [RR = 2.0 (0.9–5.0)], but not in never smokers [RR = 1.25 (0.5–2.5)] [26]. There was a non-significant trend toward increased prostate cancer risk with low selenium in a Washington County, MD cohort study [27]. More recently, low selenium status was associated with a four-fold increase in prostate cancer risk among participants of the Baltimore Longitudinal Study on Aging [28].

In contrast to prostate cancer, cohort studies lend little support for the hypothesis that low selenium status confers an increased risk of breast cancer [29–34]. Two large studies from the Netherlands ($n = 202$ cases; RR = 1.1) and United States ($n = 434$ cases; RR = 0.9) showed a null association between breast cancer risk and selenium status [33,34].

4. Sex-based differences in the association between selenium status and risk of particular cancer types

Next, we sought to determine whether there were sex-based differences in the association between selenium status and cancer incidence at particular anatomic sites. Figs. 3–5 summarize the data from prospective studies in which the risk of specific cancers in men and women was compared. Data from Finland (lung, colorectal, stomach, pancreatic, urinary tract, and non-melanoma skin cancer), Netherlands (lung, colorectal, and stomach cancer), and United States (lung, pancreatic cancer) are summarized below for each cancer site. With two exceptions [30,35], the cutoffs used to define low versus high selenium status in these cohorts are shown in Fig. 6. Table 2

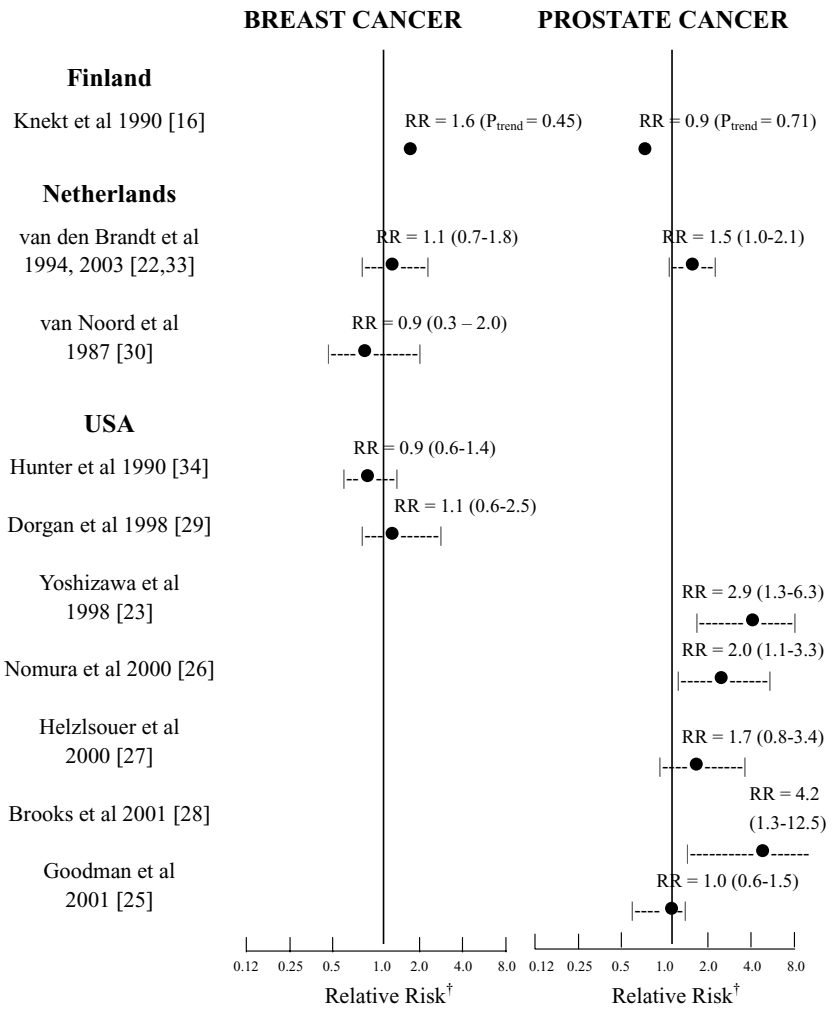


Fig. 2. Relative risk of prostate cancer and breast cancer associated with low selenium status in 11 prospective cohort studies.

shows the factors used in these prospective studies to match cases with controls and to conduct multivariate analysis of cancer risk.

4.1. Lung cancer

The risk of lung cancer in Finnish men was 3.3 times greater in men with low selenium status than in those with high selenium status (P for trend <0.001) [16] (Fig. 3). In that study, there were only nine evaluable cases of lung cancer in women, and therefore no valid conclusions could be posited regarding the association between selenium status and female lung cancer risk.

In a Netherlands cohort study [36], men with low selenium status had a statistically significant two-fold increased risk of lung cancer. Women with low selenium had a 2.5-fold increased risk of lung cancer compared to women with high selenium status, but this

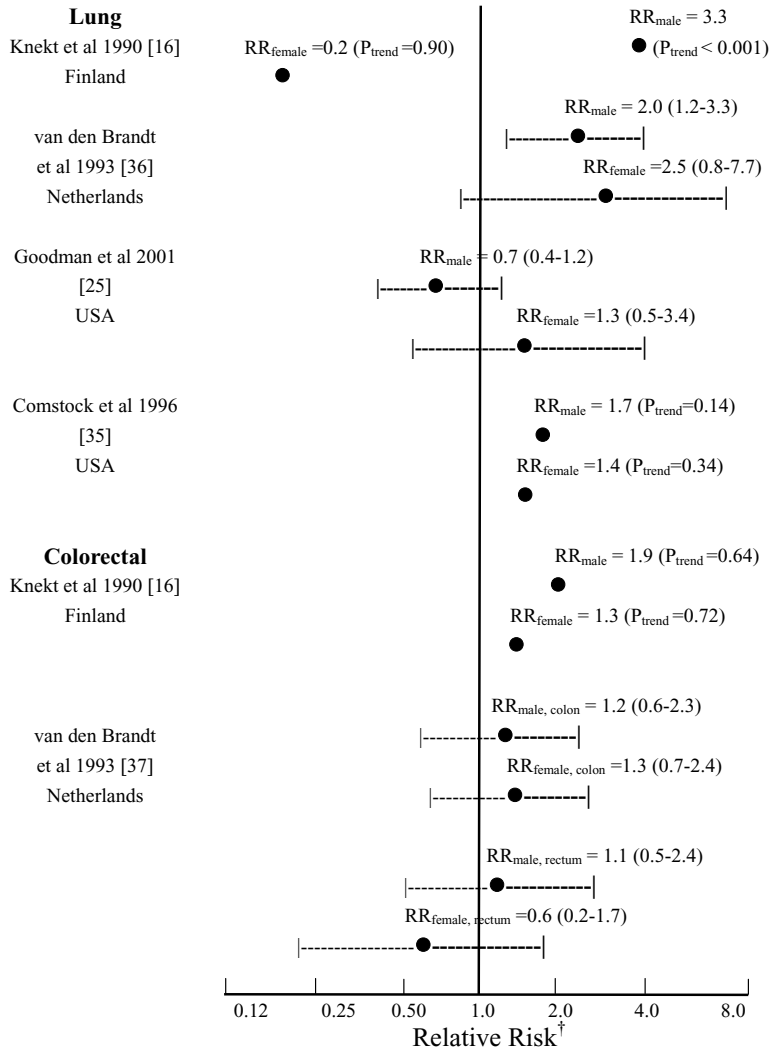
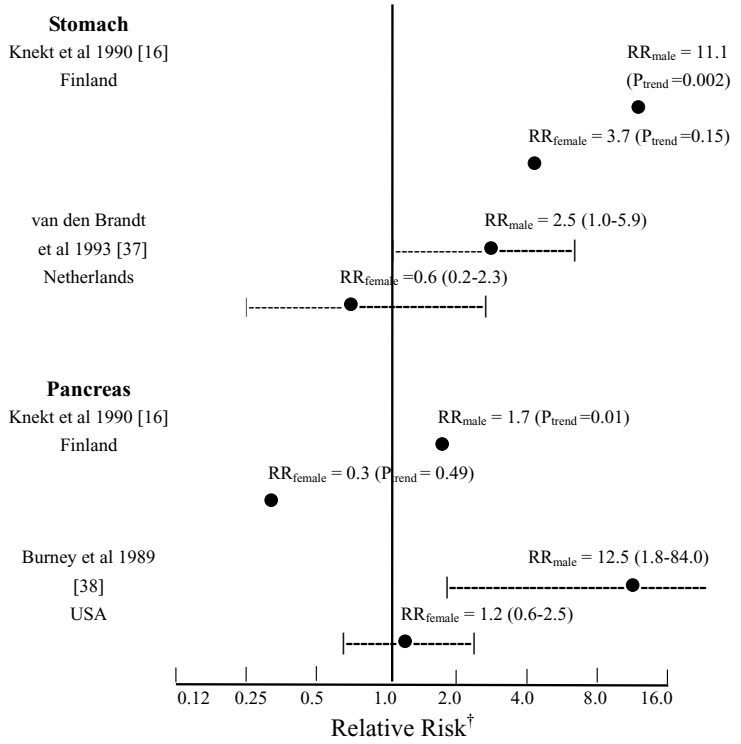


Fig. 3. Relative risk of lung and colorectal cancer associated with low selenium status in men and women from prospective cohort studies.

did not reach statistical significance perhaps due to the relatively small number of female cases ($n = 32$).

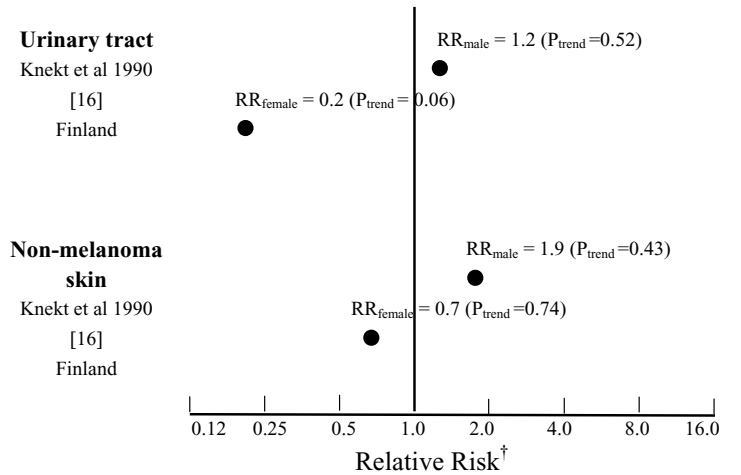
Men and women with low selenium status had similar increases in risk of lung cancer in a Washington County, MD cohort study (CLUE II) [35]. Low baseline selenium status was not a significant risk factor for lung cancer in men or women in the Carotene and Retinol Efficacy Trial [25].

It is notable that women with lung cancer in the Nurses Health Study had significantly *lower* toenail selenium concentration than matched controls ($P = 0.03$) [21]. However, selenium status had no significant influence on lung cancer risk in women after adjusting for smoking status [RR and 95% CI in the lowest versus highest tertile = 0.23 (0.03–1.85)].



† Represents the relative cancer risk for individuals with low selenium status compared to cancer risk in individuals with high selenium status.For each sex, cancer risk in individuals with high selenium status equals 1.0.

Fig. 4. Relative risk of stomach and pancreas cancer associated with low selenium status in men and women from prospective cohort studies.



† Represents the relative cancer risk for individuals with low selenium status compared to cancer risk in individuals with high selenium status. For each sex, cancer risk in individuals with high selenium status equals 1.0.

Fig. 5. Relative risk of urinary tract and non-melanoma skin cancer associated with low selenium status in men and women from prospective cohort studies.

4.2. Colorectal cancer

The association between colorectal cancer risk and selenium status was not profoundly different in men and women in two evaluable studies [16,37] (Fig. 3). Rectal cancer risk was *lowest* in Dutch women with low selenium status, but this did not reach statistical significance [36].

4.3. Stomach cancer

Data from two evaluable studies showed that risk of stomach cancer in men with low selenium status was significantly increased (RR = 2.5 Netherlands; RR = 11.1 Finland) [16,37] (Fig. 4). In contrast, low selenium status in women did not confer an increased risk of stomach cancer. In fact, the relative risk of

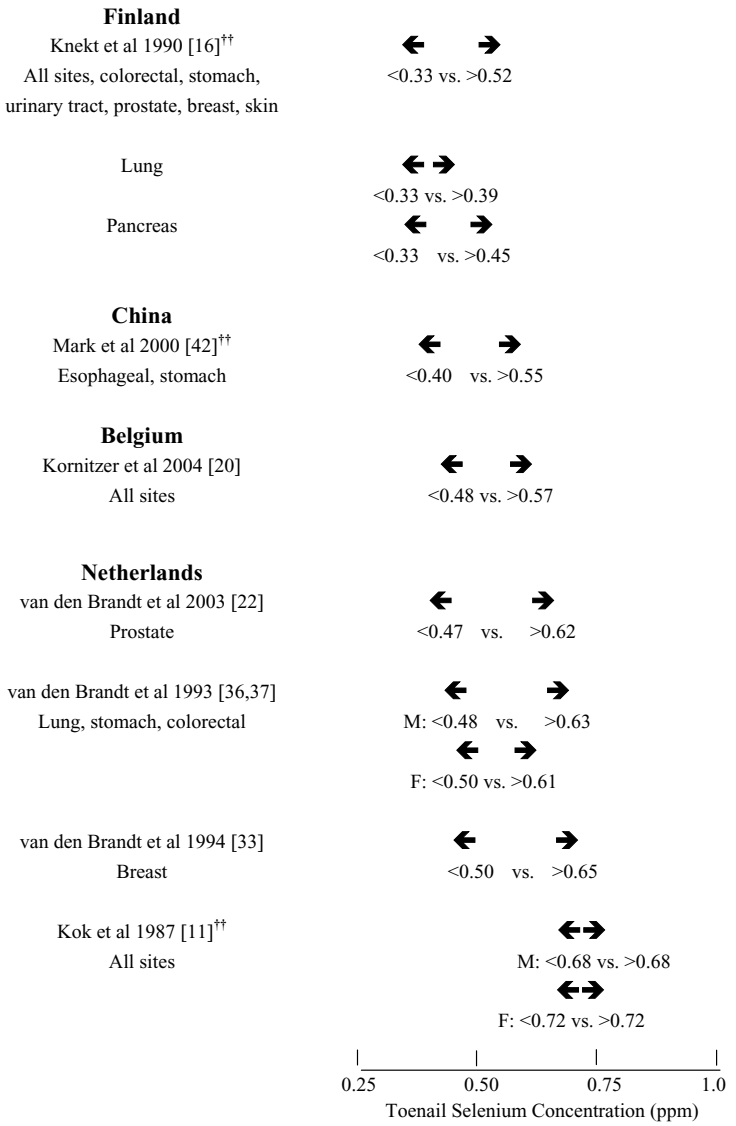
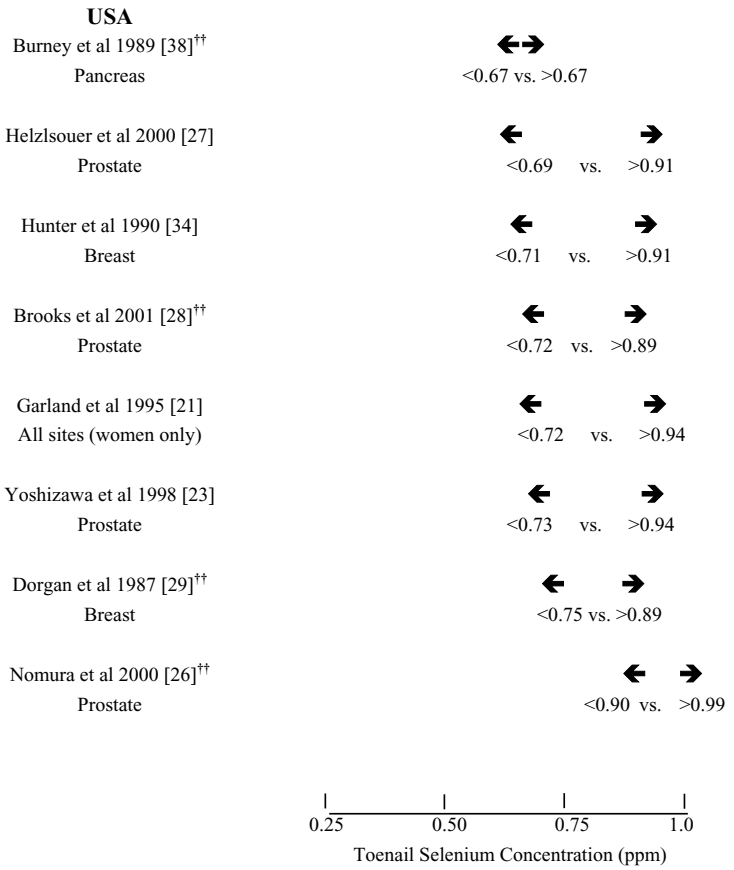


Fig. 6. Cutoffs used to define low vs. high selenium groups† within study cohorts from Finland, China, Belgium, Netherlands, and United States.



†Arrows represent the selenium concentration cutoffs for the low and high selenium groups that were used to estimate the relative risk of cancer associated with low selenium status. Relative risks are shown in Figures 1-5.

†† For the purpose of comparing studies in which selenium status was measured by either serum or toenail selenium levels, the serum selenium concentration reported in these six studies are expressed as toenail selenium equivalents here. The toenail and plasma selenium concentration in 12 healthy human volunteers were simultaneously measured to generate a ratio (6.7 ± 0.7) that could be used to convert plasma selenium concentration to predicted toenail values [J.S. Morris, unpublished data]. In this figure, toenail selenium equivalents (ppm) = serum selenium concentration (μg/L) x 0.0067.

Fig. 6. (*Continued*)

stomach cancer was *lower* in Dutch women with low selenium compared to those with high selenium status [37].

4.4. Pancreatic cancer

Data from both Finland [16] and the United States [38] showed statistically significant sex-based differences in the association between selenium status and risk of pancreatic cancer (Fig. 4).

4.5. Urinary tract cancer

The relationship between selenium and risk of urinary tract cancer in Finnish men and women supported the hypothesis that there are sex-based differences in

Table 2
Factors used in prospective studies for matching cases with controls and for multivariate analysis of the association between cancer risk and selenium status

Cohort	Factors				Other
	Sex	Age	Smoking status	Sample collection	
Belgium					
Kornitzer et al. [20]	✓	✓			Body mass index; intake of alcohol, total energy, total fat, saturated fat, dietary fiber, retinol, and Vitamin C
China					
Mark et al. [42]	✓	✓			
Finland					
Salonen et al. [12]	✓	✓	✓		
Knekt et al. [16]	✓	✓	✓		Residence
Japan					
Ujiie and Kikuchi [18]	✓	✓			Residence
Netherlands					
Kok et al. [11]	✓	✓	✓		
van Noord et al. [30]	✓	✓		✓	Residence, premenopausal status
van den Brandt et al. [22,33,36,37]	✓	✓	✓	✓	Education level; intake of alcohol and energy [33], beta-carotene and Vitamin C [37]
Norway					
Ringstad et al. [17]	✓	✓	✓	✓	Residence
USA					
Willett et al. [13]	✓	✓	✓	✓	Initial blood pressure, antihypertensive medication, randomization, parity and menopausal status (women)
Burney et al. [38]	✓			✓	Race
Hunter et al. [34]	✓	✓		✓	Intake of alcohol
Garland et al. [21]	✓	✓	✓		Toenail weight, laboratory batch
Comstock et al. [35]	✓	✓	✓	✓	
Yoshizawa et al. [23]	✓	✓	✓	✓	Body mass index, residence; intake of lycopene, saturated fat and calcium
Dorgan et al. [29]	✓	✓	✓	✓	Body mass index, time of diagnosis, total serum cholesterol
Nomura et al. [26]	✓	✓	✓	✓	Subgroups
Helzlsouer et al. [27]	✓	✓		✓	Race
Brooks et al. [28]	✓	✓	✓	✓	Body mass index, intake of alcohol
Goodman et al. [25]	✓	✓	✓	✓	Year of randomization, intervention arm, exposure population

the anticarcinogenic effects of selenium [16] (Fig. 5). Males with low serum selenium had a non-significant *increased* relative risk of 1.2 compared to males with high selenium status. However, females with low serum selenium had an 80% *decreased* urinary tract cancer risk ($P = 0.06$) compared to females with high selenium status.

4.6. Non-melanoma skin cancer

Men in the Finnish cohort [16] who had the lowest serum selenium had a non-significant two-fold *increased* skin cancer risk. In contrast, females with low serum selenium had a non-significant 40% *decreased* risk of skin cancer (Fig. 5).

5. Results of the Nutritional Cancer Prevention Trial

In 1983, Clark et al. [9] launched the Nutritional Cancer Prevention Trial (NCPT) to determine whether daily selenium supplementation with selenium would significantly decrease the incidence of cancer in patients with non-melanoma skin cancer. In the NCPT, 1312 participants (980 men, 332 women) were randomized to treatment groups that received placebo or 200 μg selenium daily in the form of high selenium yeast.[2] When data from the entire blinded treatment period were analyzed [39], men receiving selenium supplementation had a 33% reduction in overall cancer incidence [hazard ratio (95% CI) = 0.67 (0.50–0.89; $P = 0.005$]. In contrast, women who received supplementation had a non-significant *increase* in total cancer incidence [hazard ratio = 1.20 (0.66–2.20; $P = 0.55$]. The apparent cancer protective effect of selenium supplementation was limited to males, even after adjusting for age and smoking status. Selenium supplementation was associated with a 26% reduction in risk of lung cancer and a 54% reduction in risk of colorectal cancer, but these results were not statistically significant after a mean of 7.4 years follow-up. However, the significant reduction in prostate cancer that was originally reported remained highly significant (52% reduction; $P = 0.005$) [40]. Low baseline selenium status prior to supplementation was an important predictor of the prostate cancer protective effects of dietary selenium supplementation [39,40]. It is interesting to note that selenium supplementation was associated with a non-significant *increase* in the incidence of five cancer types: melanoma, bladder, breast, head and neck, and lymphoma/leukemia [39].

Taken together, the results of this interventional trial support the hypothesis that overall cancer incidence in men may be more responsive to changes in selenium status than in women. However, a balanced interpretation of the NCPT results must consider that neither overall cancer mortality nor site-specific cancer incidence (with the exception of non-melanoma skin cancer) were primary endpoints of the study. Moreover, this trial was not adequately powered to detect a cancer protective effect in women because 75% of the participants were men.

6. Results of the General Population Trial (Linxian, China)

From 1986 to 1991, the General Population Trial was conducted in Linxian, China to determine if nutritional supplementation could significantly reduce cancer incidence, cancer mortality, or overall mortality [41]. Twenty-nine thousand five hundred and eighty-four adults were randomized to receive placebo or one of seven different combinations of nutrient supplements. Compared with the placebo group, a significant 13% reduction in overall cancer mortality was observed in the group receiving Factor D, a supplement containing selenium (50 μg) in the form of selenized yeast, β-carotene (15 mg), and α-tocopherol (30 mg). However, no information was provided on whether men and women receiving this selenium-containing supplement experienced equivalent cancer protective effects.

Recently, Mark et al. [42] analyzed the relationship between pre-trial (baseline) serum selenium concentration and subsequent risk of developing esophageal and gastric cancer in the participants of the General Population Trial. Low baseline selenium status was associated with a significant increase in risk of esophageal cancer [RR = 1.8 (1.4–2.3)] and cancer of the gastric cardia [RR = 2.1 (1.5–3.0)], but not cancers affecting the non-cardiac region of the stomach [RR = 0.9 (0.5–1.8)]. Relative risk estimates for cancers at these three sites were nearly identical in men and women. Interestingly, among individuals with low baseline selenium status, the high risk of esophageal and gastric cardia cancers was not significantly influenced by selenium treatment, i.e. the development of incident cancers was similar in the selenium supplemented and non-supplemented groups. Apparently, the high risk of cancer associated with low selenium status could not be reduced by daily supplementation with 50 μg of selenium.[3]

[2] High selenium yeast contains a cocktail of different organic selenium compounds; selenomethionine is the most abundant form of selenium in this supplement.

[3] This level of supplementation resulted in a more than two-fold increase in total daily selenium intake because the estimated selenium intake in residents of Linxian was 36–42 μg selenium/day [43].

The results of the General Population Trial do not support the hypothesis that there are differences between men and women in the association between low selenium status and subsequent cancer risk. However, the epidemic rate of esophageal and gastric cancer (these sites accounted for 87% of all cancer deaths) and consistently low concentration of several micronutrients in the inhabitants of Linxian make it difficult to generalize these findings to Western populations [44].

7. Other studies

To determine whether the overarching hypothesis—that low selenium status has a stronger association with cancer risk in men than in women—was refuted by other prospective studies, we also reviewed studies that were restricted to males or females as well as those that included both men and women in which analysis of sex-specific cancer risk was not reported. These included 24 reports relating pre-diagnostic selenium concentration in blood or toenails to subsequent cancer incidence at the following anatomic sites: stomach, colon, rectum, or gastrointestinal; lung or respiratory; lymphoma, leukemia, or hematologic; urinary bladder and other urogenital; skin (squamous cell or basal cell carcinoma, melanoma); oropharyngeal; hepatocellular carcinoma; cervical and ovarian; all sites [19,45–66]. Nine of these studies had exclusively or predominately males [45–53] and three studies had exclusively females [54–56]. In the remaining studies, sex-based analysis was not reported [57–64] or was incomplete [19,65–67].

Although the results of these studies varied, none persuasively argued against the hypothesis. However, conclusions based upon a survey of the literature may overestimate real differences in the relationship between selenium and cancer risk in men and women. There may have been no significant differences in the association between selenium status and cancer risk in men and women in studies in which results of sex-based analysis were not reported. We also recognize that there is inherent bias which favors publication of significant rather than non-significant results.

8. Potential underlying explanations for the apparent sex-based differences in the anticarcinogenic effects of selenium

8.1. Sex-specific cancers affecting men and women may differ in their response to selenium

Differences in the association between selenium status and total cancer incidence in men and women may reflect that certain sex-specific cancers of men (e.g. prostate cancer) are selenium responsive, whereas those affecting women (e.g. breast cancer) are insensitive to changes in selenium status. However, Garland et al. [21] showed a null association between selenium status and the incidence of 503 non-breast cancers in women of the Nurses Health Study. This suggests that breast cancer cannot solely account for the weak association observed between selenium status and overall cancer incidence in women.

8.2. Sex-based differences in tumor biology

Growing evidence suggests there are sex-based differences in the biology of particular types of cancer that affect both men and women [68]. For example, the frequency of G to T transversions in the p53 tumor suppressor gene are higher in the lung cancers of female smokers than in male smokers [69]. After adjusting for smoking exposure, non-tumorous lung tissue of women had higher levels of DNA adducts than lung tissue from men [70]. It has been speculated that some of the sex-based differences in tumor biology might reflect a diminished DNA repair capacity in women [71]. It is plausible that sex-based differences in selenium's effects on cancer incidence are the consequence of differences in certain tumor cell or host factors that favor cancer progression in men and women. A more complete understanding of the molecular and cellular biological differences between the cancers of men and women could help to elucidate the specific mechanisms by which selenium exerts its anticancer effects.

8.3. Sex-based differences in the dose–response relationship between selenium and cancer prevention

The dose–response for the anticarcinogenic effect of selenium may be significantly modified by sex or

gender-related factors. If this hypothesis is correct, the level of selenium that minimizes cancer risk would be different in men and women. Indeed, in some studies [16,37], women with the lowest selenium levels had the *lowest* risk for colorectal, stomach, urinary tract, and non-melanoma skin cancers. Analysis of data collected from four Canadian provinces suggested that men and women have non-linear dose–response relationships that are not superimposable [72]. In the Canadian study, the slope of the regression between estimated age-adjusted cancer death rates (all sites) and toenail selenium concentration was steeper for males, indicating that estimated cancer mortality in men was more strongly influenced by incremental changes in selenium status [72]. Sizeable international differences in selenium status (i.e. toenail selenium levels in the low selenium status group within cohorts from Finland, Netherlands, and United States were <0.33, <0.50, and <0.91 ppm, respectively; Fig. 6) provide an opportunity to determine whether selenium's influence on cancer incidence is strengthened or abrogated within populations that have relatively low selenium intake.

8.4. Sex-based differences in metabolism or tissue distribution of selenium

From animal studies, it is apparent that there are sex-based differences in the metabolism and tissue concentrations of selenium [73]. The vulnerability of dogs and rodents to the toxicity of selenium compounds is influenced by sex; males were more sensitive than females to the toxic effects of intragastric or oral doses of L-selenomethionine [74]. Interestingly, in some rat studies, sex-based differences in toxicity were observed despite equivalent plasma concentrations in males and females [74].

Population-based studies reveal differences in the toenail selenium concentration of men and women, suggesting that the biodistribution of dietary selenium in humans is influenced by sex-based factors. Mean toenail selenium level in men was lower than in women in the Netherlands [75], Canada [72], and United States [76]. It is unclear whether high concentrations of selenium harbored within "priority tissues" of the male reproductive tract contribute to the lower toenail selenium concentrations seen in men. It is unlikely that the sex-based differences in selenium status can be explained by higher dietary selenium intake in women. Whole body residence time of selenium has been estimated by Patterson et al. [77] to be greater in men than in women. Also, urinary excretion of selenium per kilogram of body weight in females may be higher than in males [78]. However, in contradiction to the aforementioned studies, analysis of 7102 male and 7517 female participants in NHANES III showed that mean serum selenium concentration was slightly higher in men (men = 124 μg/L versus women = 122 μg/L; $P < 0.0001$) [79].

Although unproven, men and women may differ in the rate of formation or tissue distribution of certain anticarcinogenic metabolites [6] of selenium. This raises an important methodologic issue because measurement of total selenium concentration within nails or blood may be an insensitive means of detecting individual differences in the concentration of cancer fighting selenium metabolites.

8.5. Sex-based differences in the interaction between selenium and other factors

There may be differences between men and women in the extent to which selenium status is influenced by confounding variables, such as health-related behaviors or dietary intake of other nutrients. For example, alcohol consumption was positively associated with serum selenium in women, but not in the men of NHANES III [79]. Also, the inverse association between toenail selenium concentration and smoking was reported to be stronger in men than in women [75].

9. Knowledge gaps and summary

In a recent review of the epidemiology of selenium and human cancer, Vinceti et al. [7] stated that "the relationship between the trace element selenium and the etiology of human cancer in humans remains elusive and intriguing". In order to understand the role that selenium plays in cancer protection, the biological factors and methodological issues contributing to the inconsistency of the epidemiological evidence linking low selenium status and increased cancer risk must be identified. In this survey, we evaluated the strength of evidence supporting the hypothesis that there are sex-based differences in the anticarcinogenic effects of

selenium. We conclude that, in general, the data support the hypothesis that cancer risk in men is more profoundly influenced by selenium status than in women. However, our analysis revealed relatively few informative prospective studies that directly compared the association between selenium and cancer risk in men and women. This was particularly true for men and women living in the United States. The most consistent sex-based difference within Western populations was the association between low selenium status and cancer incidence at all sites, and in particular, the cancers of the stomach and pancreas. Data supporting a difference in men and women was weakest for colorectal cancer. The influence of sex on the anticancer effects of selenium has not been extensively evaluated in animal tumor models. Relevant hypotheses could be formally tested using the most appropriate animal models and selenium doses relevant to human populations [80].

In several published studies [57–64], the results from sex-specific analysis of cancer incidence were not reported. Future studies should report the results of these analyses, even if no differences between men and women are found. All analyses should appropriately consider potential confounding variables, such as age and smoking status. Clearly, a more complete understanding of the extent to which sex modifies the influence of nutritional status (and other factors) on cancer risk is needed to establish sound health recommendations.

Finally, the anticarcinogenic dose–response of most cancer-fighting nutrients is unknown. It is doubtful that observational data from cohort studies can reliably predict the cancer risk reduction achievable with high doses of nutrient supplements, because the expected nutrient levels in supplement users are likely to exceed the range seen in the general population [25]. As scientists and clinicians seek to identify the dietary intake of selenium that minimizes cancer risk, it will be important to determine whether the dose–response relationship between selenium and anticarcinogenesis is non-linear [81,82]. A non-linear dose–response predicts that not all persons will benefit from increasing their selenium intake through daily supplementation. The possibility that the anticarcinogenic effects of selenium may differ significantly between men and women contributes further to the complexity of this already challenging area of inquiry.

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References

[1] M.P. Rayman, The importance of selenium to human health, Lancet 356 (2000) 233–241.
[2] J.T. Rotruck, A.L. Pope, H.E. Ganther, A.B. Swanson, D.G. Hafeman, W.G. Hoekstra, Selenium: biochemical role as a component of glutathione peroxidase, Science 179 (1973) 588–590.
[3] H.E. Ganther, Selenium metabolism, selenoproteins, and mechanisms of cancer prevention: complexities with thioredoxin reductase, Carcinogenesis 20 (1999) 1657–1666.
[4] G.F. Combs Jr., W.P. Gray, Chemopreventive agents: selenium, Pharmacol. Ther. 79 (1998) 179–192.
[5] C. Ip, H.J. Thompson, H.E. Ganther, Selenium modulation of cell proliferation and cell cycle biomarkers in normal and premalignant cells of the rat mammary gland, Cancer Epidemiol. Biomarkers Prev. 9 (2000) 49–54.
[6] C. Ip, C. Hayes, R.M. Budnick, H.E. Ganther, Chemical form of selenium, critical metabolites, and cancer prevention, Cancer Res. 51 (1991) 595–600.
[7] M. Vinceti, S. Rovesti, M. Bergomi, G. Vivoli, The epidemiology of selenium and human cancer, Tumori 86 (2000) 105–118.
[8] M. Garland, M.J. Stampfer, W.C. Willett, D.J. Hunter, The epidemiology of selenium and human cancer, in: B. Frei (Ed.), Natural Antioxidants in Human Health and Disease, Academic Press, 1994, pp. 263–286.
[9] L.C. Clark, G.F. Combs Jr., B.W. Turnbull, E.H. Slate, D.K. Chalker, J. Chow, L.S. Davis, R.A. Glover, G.F. Graham, E.G. Gross, A. Krongrad, J.L. Lesher Jr., H.K. Park, B.B. Sanders Jr., C.L. Smith, J.R. Taylor, The nutritional prevention of cancer with selenium 1983–1993: a randomized clinical trial, J. Am. Med. Assoc. 276 (1996) 1957–1963.
[10] G.F. Combs Jr., J. Lu, Selenium as a cancer prevention agent, in: D.L. Hatfield (Ed.), Selenium, Its Molecular Biology and Role in Human Health, Kluwer Academic Publishers, Norwell, MA, 02061, 2001, pp. 205–217.
[11] F.J. Kok, A.M. deBruijn, A. Hofman, R. Vermeeren, H.A. Valkenburg, Is serum selenium a risk factor for cancer in men only? Am. J. Epidemiol. 125 (1987) 12–16.
[12] J.T. Salonen, R. Salonen, R. Lappetelainen, P.H. Maenpaa, G. Alfthan, P. Puska, Risk of cancer in relation to serum concentrations of selenium and vitamins A and E: matched case-control analysis of prospective data, Br. Med. J. 290 (1985) 417–420.

[13] W.C. Willett, B.F. Polk, J.S. Morris, M.J. Stampfer, S. Pressel, B. Rosner, J.O. Taylor, K. Schneider, C.G. Hames, Prediagnostic serum selenium and risk of cancer, Lancet 2 (1983) 130–134.
[14] T.M. Wizermann, M.L. Pardue (Eds.), Exploring the Biological Contributions to Human Health: Does Sex Matter? National Academy Press, 2001.
[15] V.W. Pinn, Sex and gender factors in medical studies, J. Am. Med. Assoc. 289 (2003) 397–400.
[16] P. Knekt, A. Aromaa, J. Maatela, G. Alfthan, R.K. Aaran, M. Hakama, T. Hakulinen, R. Peto, L. Teppo, Serum selenium and subsequent risk of cancer among Finnish men and women, J. Natl. Cancer Inst. 82 (1990) 864–868.
[17] J. Ringstad, B.K. Jacobsen, S. Tretli, Y. Thomassen, Serum selenium concentration associated with risk of cancer, Clin. Pathol. 41 (1988) 454–457.
[18] S. Ujiie, H. Kikuchi, The relation between serum selenium value and cancer in Miyagi, Japan: 5-year follow up study, Tohoku J. Exp. Med. 196 (2002) 99–109.
[19] M.H. Criqui, S. Bangdiwala, D.S. Goodman, W.S. Blaner, J.S. Morris, S. Kritchevsky, K. Lippel, I. Mebane, H.A. Tyroler, Selenium, retinol, retinol-binding protein, and uric acid. Associations with cancer mortality in a population-based prospective case-control study, Ann. Epidemiol. 1 (1991) 385–393.
[20] M. Kornitzer, F. Valente, D. De Bacquer, J. Neve, G. De Backer, Serum selenium and cancer mortality: a nested case-control study within an age- and sex-stratified sample of the Belgian adult population, Eur. J. Clin. Nutr. 58 (2004) 98–104.
[21] M. Garland, J.S. Morris, M.H. Stampfer, G.A. Colditz, V.L. Spate, C.K. Baskett, B. Rosner, F.E. Speizer, W.C. Willett, D.J. Hunter, Prospective study of toenail selenium levels and cancer among women, J. Natl. Cancer Inst. 87 (1995) 497–505.
[22] P.A. van den Brandt, M.P.A. Zeegers, P. Bode, R.A. Goldbohm, Toenail selenium levels and the subsequent risk of prostate cancer: a prospective cohort study, Cancer Epidemiol. Biomarkers Prev. 12 (2003) 866–871.
[23] K. Yoshizawa, W.C. Willett, J.S. Morris, M.J. Stampfer, D. Spiegelman, E.B. Rimm, E.J. Giovannucci, Study of prediagnostic selenium level in toenails and the risk of advanced prostate cancer, J. Natl. Cancer Inst. 90 (1998) 1219–1224.
[24] T.J. Hartman, D. Albanes, P. Pietinen, A.M. Hartman, M. Rautalahti, J.A. Tangrea, P.R. Taylor, The association between baseline vitamin E, selenium, and prostate cancer in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, Cancer Epidemiol. Biomarkers Prev. 7 (1998) 335–340.
[25] G.E. Goodman, S. Schaffer, D.D. Bankson, M.P. Hughes, G.S. Omenn,. The Carotene Retinol Efficacy Trial (CARET) Co-Investigators Predictors of serum selenium in cigarette smokers and the lack of association with lung and prostate cancer risk, Cancer Epidemiol. Biomarkers Prev. 10 (2001) 1069–1076.
[26] A.M.Y. Nomura, J. Lee, G.N. Stemmermann, G.F. Combs, Serum selenium and subsequent risk of prostate cancer, Cancer Epidemiol. Biomarkers Prev. 9 (2000) 883–887.
[27] K.J. Helzlsouer, H.Y. Huang, A.J. Alberg, S. Hoffman, A. Burke, E.P. Norkus, J.S. Morris, G.W. Comstock, Association between alpha-tocopherol, gamma-tocopherol, selenium, and subsequent prostate cancer, J. Natl. Cancer Inst. 92 (2000) 2018–2023.
[28] J.D. Brooks, E.J. Metter, D.W. Chan, L.J. Sokoll, P. Landis, W.G. Nelson, D. Muller, R. Anres, H.B. Carter, Plasma selenium level before diagnosis and the risk of prostate cancer development, J. Urol. 166 (2001) 2034–2038.
[29] J.F. Dorgan, A. Sowell, C.A. Swanson, N. Potischman, R. Miller, N. Schussler, H.E. Stephenson, Relationships of serum carotenoids, retinal, alpha-tocopherol, and selenium with breast caner risk: results from a prospective study in Columbia, Missouri (United States), Cancer Causes Control 9 (1998) 89–97.
[30] P.A.H. van Noord, H.J.A. Collette, M.J. Maas, F. De Waard, Selenium levels in nails of premenopausal breast cancer patients assessed prediagnostically in a cohort-nested case-referent study among women screened in the DOM project, Int. J. Epidemiol. 16 (1987) 318–322.
[31] P.A.H. van Noord, M.J. Maas, I. Van der Tweel, C. Collette, Selenium and the risk of postmenopausal breast cancer in the DOM cohort, Breast Cancer Res. Treat. 25 (1993) 11–19.
[32] K. Overvad, D.Y. Wang, J. Olsen, D.S. Allen, E.B. Thorling, R.D. Bulbrook, J.L. Hayward, Selenium in human mammary carcinogenesis: a case-cohort study, Eur. J. Cancer 27 (1991) 900–902.
[33] P.A. van den Brandt, R.A. Goldbohm, P. van't Veer, P. Bode, E. Dorant, R.J.J. Hermus, F. Sturmans, Toenail selenium levels and the risk of breast cancer, Am. J. Epidemiol. 140 (1994) 20–26.
[34] D.J. Hunter, J.S. Morris, M.J. Stampfer, G.A. Colditz, F.E. Speizer, W.C. Willett, A prospective study of selenium status and breast cancer risk, J. Am. Med. Assoc. 264 (1990) 1128–1131.
[35] G.W. Comstock, A.J. Alberg, H.Y. Huang, K. Wu, A.E. Burke, S.C. Hoffman, E.P. Norkus, M. Gross, R.G. Cutler, J.S. Morris, V.L. Spate, K.J. Helzlsouer, The risk of developing lung cancer associated with antioxidants in the blood: ascorbic acid, carotenoids, alpha-tocopherol, selenium, and total peroxyl radical absorbing capacity, Cancer Epidemiol. Biomarkers Prev. 6 (1997) 907–916.
[36] P.A. van den Brandt, R.A. Goldbohm, P. van't Veer, P. Bode, E. Dorant, R.J. Hermus, F. Sturmans, A prospective cohort study on selenium status and the risk of lung cancer, Cancer Res. 53 (1993) 4860–4865.
[37] P.A. van den Brandt, R.A. Goldbohm, P. van't Veer, P. Bode, E. Dorant, R.J.J. Hermus, F. Sturmans, A prospective cohort study on toenail selenium levels and risk of gastrointestinal cancer, J. Natl. Cancer Inst. 85 (1993) 224–229.
[38] P.G.J. Burney, G.W. Comstock, J.S. Morris, Serologic precursors of cancer: serum micronutrients and the subsequent risk of pancreatic cancer, Am. J. Clin. Nutr. 49 (1989) 895–900.
[39] A.J. Duffield-Lillico, M.E. Reid, B.W. Turnbull, G.F. Combs Jr., E.H. Slate, L.A. Fischbach, J.R. Marshall, L.C. Clark, Baseline characteristics and the effect of selenium

supplementation on cancer incidence in a randomized clinical trial: a summary report of the Nutritional Prevention of Cancer Trial, Cancer Epidemiol. Biomarkers Prev. 11 (2002) 630–639.

[40] A.J. Duffield-Lillico, B.L. Dalkin, M.E. Reid, B.W. Turnbull, E.H. Slate, E.T. Jacobs, J.R. Marshall, L.C. Clark,. Nutritional Prevention of Cancer Study Group Selenium supplementation, baseline plasma selenium status and incidence of prostate cancer: an analysis of the complete treatment period of the Nutritional Prevention of Cancer Trial, BJU Int. 91 (2003) 608–612.

[41] W.J. Blot, J.Y. Li, P.R. Taylor, W. Guo, S. Dawsey, G.Q. Wang, C.S. Yang, S.F. Zheng, M. Gail, G.Y. Li, Y. Yu, B.Q. Liu, J. Tangrea, Y.H. Sun, F. Liu, J.F. Fraumeni, Y.H. Zhang, B. Li, Nutrition intervention trials in Linxian, China: supplementation with specific vitamin/mineral combinations, cancer incidence, and disease-specific mortality in the general population, J. Natl. Cancer Inst. 85 (1993) 1483–1492.

[42] S.D. Mark, Y.L. Qiao, S.M. Dawsey, Y.P. Wu, H. Katki, E.W. Gunter, J.F. Fraumeni, W.J. Blot, Z.W. Dong, P.R. Taylor, Prospective study of serum selenium levels and incident esophageal and gastric cancers, J. Natl. Cancer Inst. 92 (2000) 1753–1763.

[43] X.N. Zou, P.R. Taylor, S.D. Mark, A. Chao, W. Wang, S.M. Dawsey, Y.P. Wu, Y.L. Qiao, S.F. Zheng, Seasonal variation of food consumption and selected nutrient intake in Linxian, a high risk area for esophageal cancer in China, Int. J. Vitam. Nutr. Res. 72 (2002) 375–382.

[44] S.E. Benner, W.K. Hong, Clinical chemoprevention: developing a cancer prevention strategy, J. Natl. Cancer Inst. 85 (1993) 1446–1447.

[45] P. Knekt, J. Marniemi, L. Teppo, M. Hellovaara, A. Aromaa, Is low selenium status a risk factor for lung cancer? Am J. Epidemiol. 148 (1998) 975–982.

[46] D. Ratnashinghe, J.A. Tangrea, M.R. Forman, T. Hartman, E.W. Gunter, Y.L. Qiao, S.X. Yao, M.J. Barett, C.A. Giffen, Y. Erozan, M.S. Tockman, P.R. Taylor, Serum tocopherols, selenium and lung cancer risk among tin miners in China, Cancer Causes Control 11 (2000) 129–135.

[47] T.J. Hartman, P.R. Taylor, G. Alfthan, R. Fagerstrom, J. Virtamo, S.D. Mark, M. Virtanen, M.J. Barrett, D. Albanes, Toenail selenium concentration and lung cancer in male smokers (Finland), Cancer Causes Control 13 (2002) 923–928.

[48] J. Virtamo, E. Valkeila, G. Alfthan, S. Punsar, J.K. Huttunen, M.J. Karvonen, Serum selenium and risk of cancer: a prospective follow-up of nine years, Cancer 60 (1987) 145–148.

[49] G. Fex, B. Pettersson, B. Akesson, Low plasma selenium as a risk factor for cancer death in middle-aged men, Nutr. Cancer 10 (1987) 221–229.

[50] A. Nomura, L.K. Heilbrun, J.S. Morris, G.N. Stemmermann, Serum selenium and the risk of cancer, by specific sites: case-control analysis of prospective data, J. Natl. Cancer Inst. 79 (1987) 103–108.

[51] M.R. Karagas, E.R. Greenberg, D. Nierenberg, T.A. Stukel, J.S. Morris, M.M. Stevens, J.A. Baron, Risk of squamous cell carcinoma of the skin in relation to plasma selenium, alpha-tocopherol, beta-carotene, and retinol: a nested case-control study, Cancer Epidemiol. Biomarkers Prev. 6 (1997) 25–29.

[52] D.S. Michaud, T.J. Hartman, P.R. Taylor, P. Pietinen, G. Alfthan, J. Virtamo, D. Albanes, No association between toenail selenium levels and bladder cancer risk, Cancer Epidemiol. Biomarkers Prev. 11 (2002) 1505–1506.

[53] M.W. Yu, I.S. Horng, K.H. Hsu, Y.C. Chiang, Y.F. Liaw, C.J. Chen, Plasma selenium levels and risk of hepatocellular carcinoma among men with chronic hepatitis virus infection, Am. J. Epidemiol. 150 (1999) 367–374.

[54] K.J. Helzlsouer, A.J. Alberg, E.P. Norkus, J.S. Morris, S.C. Hoffman, G.W. Comstock, Prospective study of serum micronutrients and ovarian cancer, J. Natl. Cancer Inst. 88 (1996) 32–37.

[55] R.M. Bostick, J.D. Potter, D.R. McKenzie, T.A. Sellers, L.H. Kushi, K.A. Steinmetz, A.R. Folsom, Reduced risk of colon cancer with high intake of vitamin E: the Iowa women's health study, Cancer Res. 53 (1993) 4230–4237.

[56] A.M. Batieha, H.K. Armenian, E.P. Norkus, J.S. Morris, V.E. Spate, G.W. Comstock, Serum micronutrients and the subsequent risk of cervical cancer in a population-based nested case-control study, Cancer Epidemiol. Biomarkers Prev. 2 (1993) 335–339.

[57] S.E. Schober, G.W. Comstock, K.J. Helsing, R.M. Salkeld, J.S. Morris, A.A. Rider, R. Brookmeyer, Serologic precursors of cancer. I. Prediagnostic serum nutrients and colon cancer risk, Am. J. Epidemiol. 126 (1987) 1033–1041.

[58] R.J. Coates, N.S. Weiss, J.R. Daling, J.S. Morris, R.F. Labbe, Serum levels of selenium and retinol and the subsequent risk of cancer, Am. J. Epidemiol. 128 (1988) 515–523.

[59] M.S. Menkes, G.W. Comstock, J.P. Vuilleumier, K.J. Helsing, A.A. Rider, R. Brookmeyer, Serum beta-carotene, vitamins A and E, selenium, and the risk of lung cancer, N. Engl. J. Med. 315 (1986) 1250–1254.

[60] K.J. Helzlsouer, G.W. Comstock, J.S. Morris, Selenium, lycopene, alpha-tocopherol, beta-carotene, retinol, and subsequent bladder cancer, Cancer Res. 49 (1989) 6144–6148.

[61] W. Zheng, W.J. Blot, E.L. Diamond, E.P. Norkus, V. Spate, J.S. Morris, G.W. Comstock, Serum micronutrients and the subsequent risk of oral and pharyngeal cancer, Cancer Res. 53 (1993) 795–798.

[62] R.A. Breslow, A.J. Alberg, K.J. Helzlsouer, T.L. Bush, E.P. Norkus, J.S. Morris, V.E. Spate, G.W. Comstock, Serological precursors of cancer: malignant melanoma, basal and squamous cell skin cancer, and prediagnostic levels of retinol, beta-carotene, lycopene, alpha-tocopherol, and selenium, Cancer Epidemiol. Biomarkers Prev. 4 (1995) 837–842.

[63] J.T. Salonen, G. Alfthan, J.K. Huttunen, P. Puska, Association between serum selenium and the risk of cancer, Am. J. Epidemiol. 120 (1984) 342–349.

[64] K. Wallace, T. Byers, J.S. Morris, B.F. Cole, E.R. Greenberg, J.A. Baron, A. Gudino, V. Spate, M.R. Karagas, Prediagnostic serum selenium concentration and the risk of recurrent colorectal adenoma: a nested case-control study, Cancer Epidemiol. Biomarkers Prev. 12 (2003) 464–467.

[65] M. Kabuto, H. Imai, C. Yonezawa, K. Neriisi, S. Akiba, H. Kato, T. Suzuki, C.E. Land, W.J. Blot, Prediagnostic serum selenium and zinc levels and subsequent risk of lung and stomach cancer in Japan, Cancer Epidemiol. Biomarkers Prev. 3 (1994) 465–469.
[66] I. Peleg, S. Morris, C.G. Hames, Is serum selenium a risk factor for cancer? Med. Oncol. Tumor Pharmacother. 2 (1985) 157–163.
[67] M.P.A. Zeegers, R.A. Goldbohm, P. Bode, P.A. van den Brandt, Prediagnostic toenail selenium and risk of bladder cancer, Cancer Epidemiol. Biomarkers Prev. 11 (2002) 1292–1297.
[68] E.A. Zang, E.L. Wynder, Differences in lung cancer risk between men and women: examination of the evidence, J. Natl. Cancer Inst. 88 (1996) 183–192.
[69] D.G. Guinee Jr., W.D. Travis, G.E. Trivers, et al., Gender comparisons in human lung cancer: analysis of p53 mutations, anti-p53 antibodies and C-*erb*B-2 expression, Carcinogenesis 16 (1995) 993–1002.
[70] S. Mollerup, D. Ryberg, A. Hewer, D.H. Phillips, A. Haugen, Sex differences in lung CYP1A1 expression and DNA adduct levels among lung cancer patients, Cancer Res. 59 (1999) 3317–3320.
[71] Q. Wei, L. Cheng, C.I. Amos, L.-E. Wang, Z. Guo, W.K. Hong, M.R. Spitz, Repair of tobacco carcinogen-induced DNA adducts and lung cancer risk: a molecular epidemiologic study, J. Natl. Cancer Inst. 92 (2000) 1764–1772.
[72] J.S. Morris, T. Rohan, C.L. Soskolne, M. Jain, T.L. Horsman, V.L. Spate, C.K. Baskett, M.M. Mason, T.A. Nichols, Selenium status and cancer mortality in subjects residing in four Canadian provinces, J. Radioanal. Nuclear Chem. 249 (2001) 421–427.
[73] J.W. Finley, R.L. Kincaid, Effect of sex and time of sampling on selenium and glutathione peroxidase activity in tissues of mature rats, Biol. Trace Elem. Res. 29 (1991) 181–191.
[74] NCI, DCPC Chemoprevention Branch and Agent Development Committee, Clinical development plan: *l*-selenomethionine, J. Cell Biochem. 26S (1996) 202–218.
[75] P.A. van den Brandt, R.A. Goldbohm, P. van't Veer, P. Bode, R.J.J. Hermus, F. Sturmans, Predictors of toenail selenium levels in men and women, Cancer Epidemiol. Biomarkers Prev. 2 (1993) 107–112.
[76] C.A. Swanson, M.P. Longnecker, C. Veillon, S.M. Howe, O.A. Levander, P.R. Taylor, P.A. McAdam, C.C. Brown, M.J. Stampfer, W.C. Willett, Selenium intake, age, gender, and smoking in relation to indices of selenium status of adults residing in a seleniferous area, Am. J. Clin. Nutr. 52 (1990) 858–862.
[77] B. Patterson, C.C. Veillon, P. Taylor, K. Patterson, O.A. Levander, Selenium metabolism in humans differs by gender: results from a stable isotope tracer study, FASEB J. 15 (2001) A969.
[78] E.M. Rodrigue Zrodriguez, M.T. San Zalaejos, C. Dia Zromero, Urinary selenium status of healthy people, Eur. J. Clin. Chem. Clin. Biochem. 33 (1995) 127–133.
[79] M.R. Kafai, V. Ganji, Sex, age, geographical location, smoking, and alcohol consumption influence serum selenium concentrations in the USA: third National Health and Nutrition Examination Survey, 1988–1994, J. Trace Elem. Med. Biol. 17 (2003) 13–18.
[80] D.J. Waters, S. Shen, D.M. Cooley, D.G. Bostwick, J. Qian, G.F. Combs Jr., L.T. Glickman, C. Oteham, D.L. Schlittler, J.S. Morris, Effects of dietary selenium supplementation on DNA damage and apoptosis in canine prostate, J. Natl. Cancer Inst. 95 (2003) 237–241.
[81] W. Mertz, The essential trace elements, Science 213 (1981) 1332–1338.
[82] W.C. Willett, M.J. Stampfer, Selenium and human cancer: epidemiological aspects and implications for clinical trials, J. Am. Coll. Toxicol. 5 (1986) 29–36.