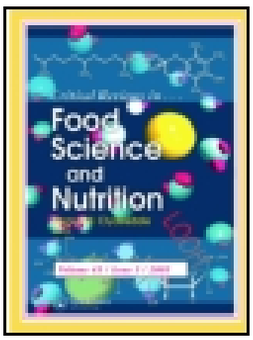

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REVIEW

Does dietary intake of selenium protect against cancer? A systematic review and meta-analysis of population-based prospective studies

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ABSTRACT

Current evidence on selenium and its effects on cancer is conflicting. This study aimed at assessing the association between dietary intake of selenium and incidence of cancers by performing systematic review and meta-analysis of population-based prospective studies. We systematically searched for articles in Medline (Ovid), Embase, Web of Science (Thomson Reuters), China National Knowledge Infrastructure, Wanfang Database and VIP Chinese Scientific Journals. Analysis was performed in Stata version 14.2. Of the 2,564 articles obtained from the databases, 39 met our inclusion criteria, 37 were included in the final analysis. Selenium at recommended daily allowance levels of $\geq$55 μg/day decreased the risk of cancer [relative risk (RR) = 0.94, 95% confidence interval (CI): 0.90–0.98]. A protective effect was found in men at levels $\geq$55 μg/day (RR = 0.97, 95% CI: 0.94–0.99). Extra selenium intake from supplements was protective at levels $\geq$55 μg/day (RR = 0.89, 95% CI: 0.82–0.97). There was an inverse relationship (p value = 0.020) between selenium intake and overall cancer risk after adjusting for age, body mass index, and smoking but there was no evidence of nonlinear relationship (p value = 0.261). The findings in this study suggest that selenium is protective against cancer however the effects vary with different cancers.

KEYWORDS

Nutrition; selenium; diet; cancer; incidence; systematic review; meta-analysis; population; prospective study

Introduction

According to the World Health Organization (WHO) report on health 2015, cancer is one of the leading causes of mortality (one in every six deaths) globally, second after cardiovascular diseases, with 70% of the deaths occurring in low-and-middle income countries (WHO 2018). With the increasing treatment costs and number of new cases expected to rise by 70% over the next two decades (WHO 2018), preventive measures are needed urgently. With proper interventions, 30–50% of cancer deaths can be prevented. Behavioural and dietary factors have been associated with a third of all cancer deaths (WHO 2018).

Antioxidants are some of the dietary factors that have been said to have protective effects against cancer and this claim is being investigated on several compounds (Meyer et al. 2005; Banim et al. 2013; Lane et al. 2017). One of the main theories that have informed research on antioxidant is free radicle theory proposed by Denham Harman in the 1950s in relation to aging. He proposed that free radicle generation results in damage to biomolecules including DNA and lipid membranes leading to aging (Pai, Shukla, and Kikkeri 2014). Antioxidants, which are mainly from the diet or supplements would neutralize these free radicles, thus preventing cellular damage. This theory was later expanded to include other diseases such as malignancies, vitiligo and Alzheimer's disease (Pai, Shukla, and Kikkeri 2014).

Selenium, a naturally occurring nonmetallic element is an essential mineral required by the body in small amounts for normal physiological processes (Boyd 2011; Vinceti et al. 2018). The recommended dietary allowance (RDA) varies with age-group, pregnancy, and breastfeeding. Children between 1–3 years require the least amount (20 μg/day) while the breastfeeding mothers require the highest amount (70 μg/day). Adults and children above 14 years require 55 μg/day (Duffield et al. 1999; Hurst et al. 2013). Although the majority of the people are said to have adequate amounts from the diet, people in regions with soil that has low level of selenium have been shown to be at an increased risk of selenium insufficiency. These regions include some parts of Europe and China (Gupta and Gupta 2000).

Although suggested for several decades (Schrauzer 1976), only recently the anticarcinogenic effects of selenium have gained increasing interest (Vinceti et al. 2018). A study conducted in Linxian, China where increased rates of esophageal

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and gastric cancers occurred established that the risk decreased by half after large supplements of selenium were administered (Mark et al. 2000). The efficacy of selenium as a cancer protective agent has continued to be tested in several studies (Duffield-Lillico et al. 2002; Lippman et al. 2009; Kristal et al. 2010). However, the results have been conflicting probably because of the relatively small number of cases (particularly of aggressive disease) identified during follow-up and/or the different baseline levels of selenium in the populations under study. Secondary analysis of data from Nutritional Prevention of Cancer Trial showed a 52–65% decreased risk of prostate cancer among those given selenium supplement (Duffield-Lillico et al. 2003) while the Selenium and Vitamin E Cancer Prevention Trial (SELECT) showed no association between selenium intake and prostate cancer (Lippman et al. 2009). Results from observational studies are also conflicting, some have reported high blood or nail selenium to be associated with a lower risk of total prostate cancer or aggressive disease (Yoshizawa et al. 1998) while others have found no statistically significant association (Ghadirian et al. 2000). In this context, the objective of the present study was to assess the association between dietary intake of selenium and risk of incidence of different cancers by conducting a systematic review and meta-analysis on population-based prospective studies.

Methods

This systematic review and meta-analysis was carried out using a protocol constructed according to the standard criteria PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) (Moher et al. 2009) and MOOSE (Meta-analysis of Observational Studies in Epidemiology) (Stroup et al. 2000). The study was registered in Prospero- international prospective register of systematic reviews (http://www.crd.york.ac.uk/PROSPERO, registration number: CRD42017057682).

Data sources and search strategy

We conducted a systematic search of population-based prospective studies [cohort, nested case-control studies, randomized controlled trials (RCTs), and interventional studies] that evaluated selenium in diet and/or supplements and its association with any type of cancer. Only population-based prospective studies were included in our review to ensure that the results would be generalizable, and the retrospective studies were excluded because important confounding information was lacking. The search was conducted in Medline (Ovid), Embase, Web of Science (Thomson Reuters), China National Knowledge Infrastructure, Wanfang Database, and VIP Chinese Scientific Journals with the help of the Research Consultation Group of the University Library, Karolinska Institutet and the Department of Health Statistics, the Second Military Medical University, China. To reduce publication bias, we also used the resources of Virtual Health Library (http://bvsalud.org/en/), NARCIS (https://www.narcis.nl/), NLM gateway (https://gateway.nlm.nih.gov/gw/Cmd/), Grey literature report (http://greylit.org/), and Open gray EU (http://opengrey.eu/) for searching the gray literatures to find potential unpublished relevant studies. The key words used in the search included dietary selenium, supplementary selenium, cancer, tumor, neoplasm, incidence, epidemiological study, observational study, interventional study, population-based study, and prospective study. There was no language restriction in the search. We included all the population-based observational or interventional studies with a prospective feature, addressing selenium in diet and/or supplements and cancer incidence from the inception of the databases to March 2018 combined with manual retrieval afterwards to include the latest literatures.

Inclusion and exclusion criteria

Studies that met criteria: 1) the research was a population-based observational or interventional study with a prospective design; 2) amount of selenium intake (dietary, supplementary, and/or total) was reported; 3) the outcome of the study was the incidence of any type of cancer; 4) risk was reported as difference of incidences (DOI), relative risk (RR), odds ratio (OR), hazard ratio (HR) or incidence rate ratio (IRR) as well as the associated 95% confidence interval (CI) or other data to estimate the standard deviation or standard error; 5) the risk estimates had been adjusted for potential confounders, were considered for meta-analysis.

The studies were excluded if: 1) they were narrative reviews, editorial papers, methodological papers, retrospective studies or cross-sectional studies; 2) evaluated selenium was not in diet or supplementation; 3) there was no reliable selenium estimates; and/or 4) if the identified dietary pattern did not fit into healthy or unhealthy dietary patterns.

Data extraction and quality assessment

Two investigators (A.K. and M.L.) screened and identified potentially relevant abstracts independently. Any disagreements between the investigators regarding the eligibility of a study (or studies) were fixed through discussion or advising from an academic expert (M.L. or Y.C.). Full articles for selected abstracts were then retrieved and a standardized form in Microsoft excel was used to extract data. A.K. and M.L. extracted data independently and later compared and summarized them to have one final document on which for final analysis. The information extracted included: name of the first author, study design, year of publication, year that the study began and ended, average duration of follow up, region and country that the study was conducted in, cancer type, selenium intake type (dietary or supplementary), selenium dose levels, population size and cancer cases of each selenium dose level, how selenium was measured and cancer case confirmed, RRs and the associated 95% CIs, statistical analysis method used, and the confounders adjusted for in each study. For studies that reported several multivariable adjusted effect estimates, we selected the effect estimate that had been adjusted for all the available potential confounders.

The quality of each article included was assessed using the Newcastle-Ottawa scale (NOS) which assess the quality of non-randomized studies in meta-analysis (Wells et al. 2018). Two examiners (A.K. and X.F.) assessed the quality of the articles independently then the average of the two scores was taken to get the final quality score for each study. The last column in Supplemental Table S1 contains the average score of each study.

Statistical analysis

In the pooled meta-analysis, HR, OR and IRR were used as RR because they approximate one another when event rates are small (Zhang and Yu 1998). Different cancers with their own RRs reported in the same article were analyzed separately. If RRs for both men and women but not the overall risk were reported in a study, they were also analyzed separately. For cancer-specific analysis, the following cancer types were combined for the same clinical or pathological diagnosis: non-melanoma, melanoma, squamous and basal cell carcinoma were included in skin cancer, low and high-grade prostate cancers were analyzed as prostate cancer, esophageal squamous cell carcinoma and esophageal adenocarcinoma as esophageal cancer, and distal gastric and gastric cancer as stomach cancer.

Statistical heterogeneity was investigated using I^2 statistics (Higgins et al. 2003). $I^2 > 30\%$ was considered moderate heterogeneity while $I^2 > 50\%$ was considered substantial heterogeneity. p value of heterogeneity <0.05 was considered statistically significant (Higgins and Green 2011). Random effect model was used when heterogeneity presented among studies otherwise a fixed-effect model was used (DerSimonian and Laird 1986). The possibility of publication bias was assessed by the combination of Egger's test and visual inspection of funnel plots (Egger et al. 1997).

RRs for the highest dose of selenium compared with the lowest doses in every study were pooled to investigate the effect of highest dose of selenium and cancer incidence. We also used the RDA of selenium (55 μg/day) (Duffield et al. 1999; Hurst et al. 2013) as the cut off to assess the effect of selenium above and below the RDA on cancer incidence. Although it has been shown that different regions have different recommended daily allowance of selenium, 55 μg/day was used in this study because most of the regions uses it and there were no any recent updates in our literature review. RRs for daily selenium intake ≥55 μg/day compared to the lowest doses in every study were pooled and the same was done for daily selenium intake <55 μg/day to determine the effects on cancer incidence. Influence analysis to investigate the influence of a single study on the overall risk was also performed as sensitivity analysis.

We performed subgroup analysis for different selenium doses and cancer types to assess if selenium dosage was associated with specific individual cancer incidence. To investigate if effects of selenium on cancer incidence varied with other variables, subgroup analysis for different selenium doses and sex, study design, selenium type and region was performed. To assess potential linear and nonlinear dose-response relationship between increment in selenium intake and cancer incidence, meta-regression was performed. Restricted cubic splines with three knots were used to assess nonlinear dose-response relationship. Cancers that had been studied by only one article were excluded from the meta-regression analysis. All the analysis was performed in Stata 14 (StataCorp LLC, College Station, Texas, USA) and a two-sided p value of <0.05 was considered statistically significant unless otherwise specified.

Results

Characetrictics of the included articles

The intial literature search yielded 3,825 articles from all the databases, and 2,564 articles remained after filtering the duplicates. The titles and abstracts of these articles were screened, 146 abstracts were adjudged to be potentially relevant for the meta-analysis and the full articles were retrieved. One hundred and nine of the 146 articles were excluded after thourough screening by full text leaving 37 articles for the meta-analysis (Figure 1).

The included studies were conducted in different regions and addressed different cancers as shown in (Table 1). In brief, 15 studies were conducted in the USA, 11 studies in Europe, 9 studies in Asia and 2 studies in Australia, and addressed cancers in bladder, breast, colon and rectum, esophagus, hematologic, liver, lung, pancreas, prostate, skin, stomach, and other cancers. Daily selenium intake doses ranged from 0 to 400 μg/day while total number of cancer incidences were 13,484 in a total population of 579,878. A detailed summary of characteristics of the included articles is reported in Supplemental Table S1.

Association between daily selenium intake and all cancer incidences

The funnel plot of RRs for all cancer types of the included studies appears asymmetric (Figure 2), however the test of the sloping line is not statistically significant ($p = 0.564$), which indicates no publication bias. The pooled RR of all doses compared to the lowest doses of daily selenium of all cancers is barely statistically significant. The pooled RR is 0.98 and the corresponding 95% CI is 0.96–1.01 (Table 2). At the highest doses of daily selenium intake compared to the lowest doses, there is a barely statistically significant decreased risk of cancers, pooled RR is 0.96 (95% CI: 0.92–1.01; Table 2 and Figure 3). Heterogeneity was observed with $I^2 = 34.5\%$ and $p = 0.001$ (Table 2 and Figure 3). After dividing selenium doses using the RDA levels, there is a statistically significant decreased risk of cancer incidence at selenium intake ≥55 μg/day compared to the lowest dose. The pooled RR is 0.96 (95% CI: 0.92–0.99), and heterogeneity is present with $I^2 = 28.3\%$ and $p = 0.005$ (Table 2). At selenium intake below 55 μg/day, there appears to be no effect against cancer risk, and pooled RR is 1.02 (95% CI: 0.98–1.06), and no heterogeneity is present with $I^2 = 0.0\%$ and $p = 0.811$ (Table 2).

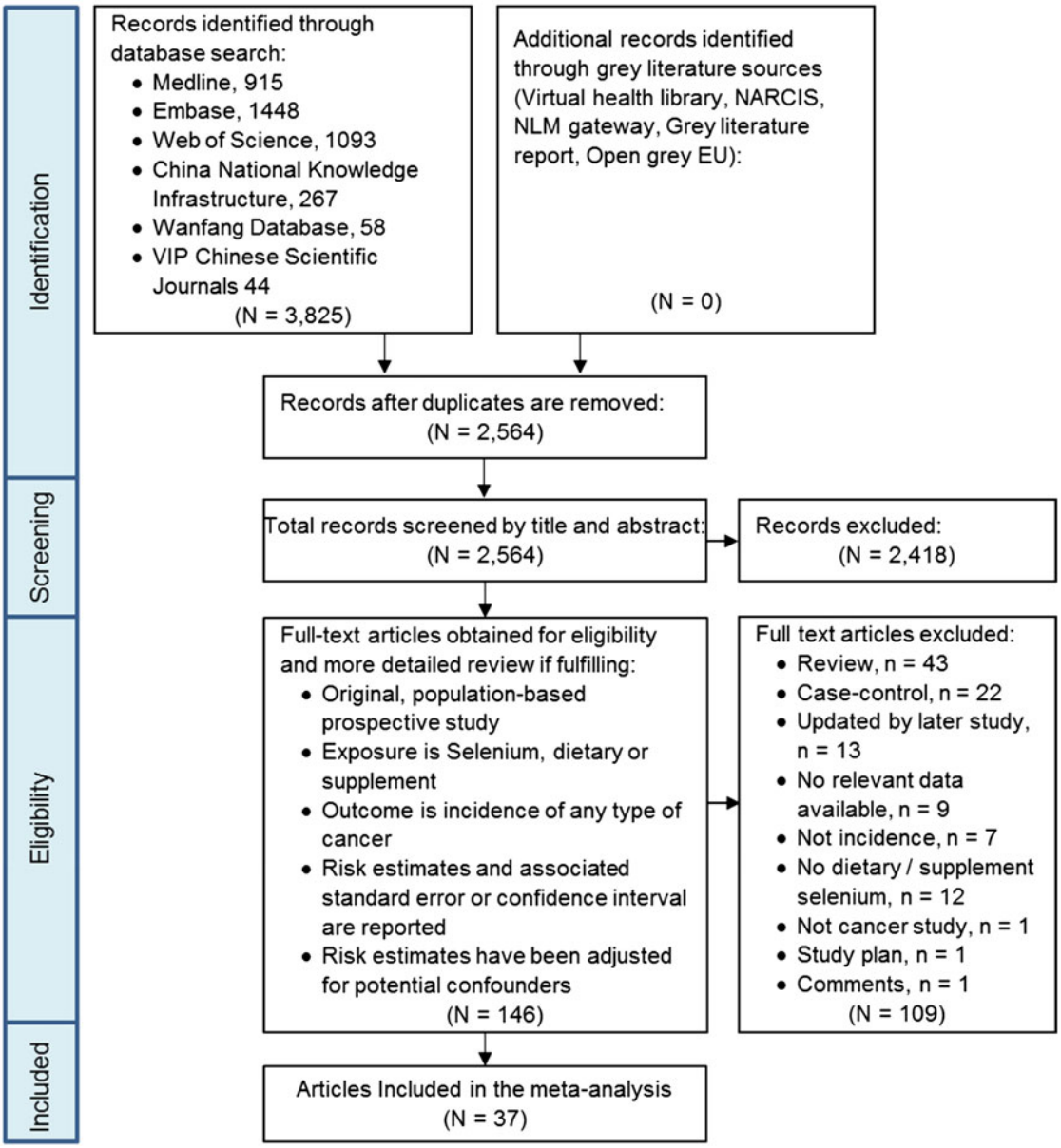

Figure 1. PRISMA flow diagram of screening and selection of articles on selenium intake and cancer incidence.

Association between daily selenium intake and cancer-specific incidences

Table 2 summarizes pooled RRs by cancer types and different selenium intake levels. In brief, at the highest doses of selenium intake, a statistically significant decrease in the risk of cancer incidence was observed for liver (RR = 0.61, 95% CI: 0.49–0.75) and pancreas (RR = 0.73, 95% CI: 0.55–0.97) cancers. A statistically significant increase in the risk was found in skin cancer (RR = 1.12, 95% CI: 1.04–1.21).

At daily selemium intake ≥55 μg/day, a decreased risk was observed in esophagus (RR = 0.74, 95% CI: 0.56–0.97), liver (RR = 0.66, 95% CI: 0.56–0.82), and pancreas (RR = 0.76, 95% CI: 0.64–0.90) cancers. An increased risk was still found in skin cancer (RR = 1.12, 95% CI: 1.04–1.20).

At daily selemium intake <55 μg/day, a decreased risk was found in esophagus, liver, pancreatic, and stomach cancers but the risk was not statistically significant.

Subgroup analysis by demographic characteristics and study design

Table 3 summarizes pooled results by demographic characteristics and study design. After stratifying the analysis by sex, a statistically significant protective effect of selenium was found in men at daily intake dose ≥55 μg/day (RR = 0.97, 95% CI: 0.94–0.99), and there was a similar protective effect found for women but not statistically significant (RR = 0.99, 95% CI: 0.83–1.17).

Additional selenium from supplements showed a protective effect at all doses (RR = 0.95, 95% CI: 0.90–1.00), highest doses (RR = 0.93, 95% CI: 0.87–0.99), and daily intake ≥55 μg/day (RR = 0.89, 95% CI: 0.82–0.97) doses, but not at daily intake <55 μg/day (RR = 1.00, 95% CI: 0.95–1.05). Selenium from food only showed barely statistically significant protective effect at daily intake ≥55 μg/day (RR = 0.98, 95% CI: 0.95–1.00).

Table 1. Regions and cancer types of the included studies.

Regions	Studies
USA	Duffield-Lillico et al. 2002, 2003; Reid et al. 2006; Dong et al. 2007; Wright et al. 2007; Peters et al. 2008; Reid et al. 2008; Asgari et al. 2009; Kristal et al. 2010; Klein et al. 2011; Marshall et al. 2011; Walter et al. 2011; Lotan et al. 2012; Han et al. 2013; Park et al. 2015
Europe	Hartman et al. 1998; Stolzenberg-Solomon et al. 2002; Hercberg et al. 2004; Meyer et al. 2005; Dréno et al. 2007; Ezzedine et al. 2010; Banim et al. 2013; Hansen et al. 2013; Pantavos et al. 2015; Lane et al. 2017; Muka et al. 2017
Asia	Blot et al. 1993; Li et al. 1993; Yu, Zhu, and Li1997; Li et al. 2000; Li et al. 2004; You et al. 2006; Epplein et al. 2010; Hashemian et al. 2015; Ma et al. 2017
Australia	McNaughton et al. 2005; Heinen et al. 2007
Cancer types	
Bladder	Duffield-Lillico et al. 2002; Lotan et al. 2012
Breast	Duffield-Lillico et al. 2002; Pantavos et al. 2015
Colon and rectum	Duffield-Lillico et al. 2002; Reid et al. 2006; Klein et al. 2011; Hansen et al. 2013
Esophagus	Blot et al. 1993; Li et al. 1993; Duffield-Lillico et al. 2002; Dong et al. 2007; Hashemian et al. 2015
Hematologic	Duffield-Lillico et al. 2002; Walter et al. 2011
Liver	Yu, Zhu, and Li1997; Li et al. 2000; Ma et al. 2017
Lung	Duffield-Lillico et al. 2002; Klein et al. 2011; Muka et al. 2017
Pancreas	Stolzenberg-Solomon et al. 2002; Banim et al. 2013; Han et al. 2013
Prostate	Hartman et al. 1998; Duffield-Lillico et al. 2002; Meyer et al. 2005; Wright et al. 2007; Peters et al. 2008; Kristal et al. 2010; Klein et al. 2011; Marshall et al. 2011; Park et al. 2015; Lane et al. 2017
Skin	Duffield-Lillico et al. 2003; McNaughton et al. 2005; Dréno et al. 2007; Heinen et al. 2007; Reid et al. 2008; Asgari et al. 2009; Ezzedine et al. 2010
Stomach	Blot et al. 1993; Li et al. 2004; You et al. 2006; Epplein et al. 2010
Other	Blot et al. 1993; Li et al. 1993; Duffield-Lillico et al. 2002; Hercberg et al. 2004; Reid et al. 2006; Klein et al. 2011

Stratified analysis by regions showed that no statistically significant protective effect was found in studies counducted in USA, Europe, and Australia. However, a significant protective effect of selenium was observed in Asia at highest doses compared to lowest doses (RR = 0.86, 95% CI: 0.78–0.96) and at doses ≥55 μg/day compared to the lowest doses (RR = 0.72, 95% CI: 0.63–0.82), and a barely statistically significant protective effect was also found for selenium intake <55 μg/day compared to the lowest doses (RR = 0.95, 95% CI: 0.90–1.01).

Regarding study designs, interventional studies showed statistically significant protective effect of selenium at all doses (RR = 0.95, 95% CI: 0.90–1.00), highest doses (RR = 0.94, 95% CI: 0.88–1.00) and doses ≥55 μg/day (RR = 0.92, 95% CI: 0.86–0.99). Observational studies only showed barely statistically significant protective effect of selenium at doses ≥55 μg/day (RR = 0.97, 95% CI: 0.94–1.00).

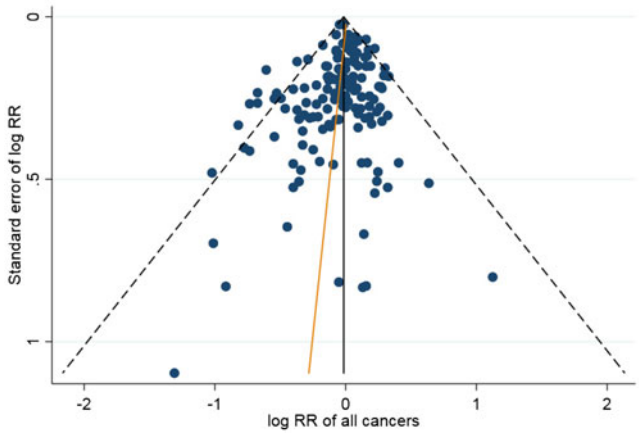

Figure 2. Funnel plot with pseudo 95% confidence limits.

Linear dose-response relationship between increased selenium intake and risk of cancer incldence

Meta-regression analysis reveals a statistically significant negative relationship between increased selenium intake and RR of cancer incidence for all cancers combined. For every 10 μg/day increase in selenium intake, the RR of cancer incidence decreases by 0.4% (95% CI: 0.001%–0.8%). After adjusting for average age and body mass index (BMI) of participants, and smoking status in the meta-regression model, the decrease in RR per 10 μg/day increase in selenium intake is even larger (RR decreased by 0.67%, 95% CI: 0.11%–1.24%).

Nonlinear dose-response relationship between increased selenium intake and risk of cancer incldence

Meta-regression analysis with restricted cubic splines shows that although it seems that the protective effect of selenium against all cancers decreases after an increment of 150 μg per day or more (Figure 4), the nonlinear relationship disappears after adjusting for age, BMI, and smoking status (Figure 5).

Discussion

Dietary selenium intake and cancer

Selenium at high levels have been suggested to prevent cancers by some studies (Hatfield et al. 2014) while others have

Table 2. Pooled RRs (compared with the lowest daily selenium intake doses) by cancer types and selenium intake levels.

Cancers	Dose level	No. of doses	Pooled RR (95% CI)	I^2	p of I^2
All cancer	All doses[†]	149	0.98 (0.96–1.01)*	19.8%	0.022
	Highest doses	88	0.96 (0.92–1.01)*	34.0%	0.001
	Doses ≥55 μg/day	106	0.96 (0.92–0.99)**	30.6%	0.003
	Doses <55 μg/day	43	1.02 (0.98–1.06)	0.0%	0.811
Bladder	All doses	2	1.16 (0.76–1.78)	0.0%	0.817
	Highest doses	2	1.16 (0.76–1.78)	0.0%	0.817
	Doses ≥55 μg/day	2	1.16 (0.76–1.78)	0.0%	0.817
	Doses <55 μg/day	None			
Breast	All doses	3	1.27 (0.99–1.62)	0.0%	0.584
	Highest doses	2	1.39 (1.00–1.95)	0.0%	0.527
	Doses ≥55 μg/day	1	1.89 (0.69–5.52)		
	Doses <55 μg/day	2	1.24 (0.96–1.59)	0.0%	0.514
Colon and Rectum	All doses	14	1.04 (0.94–1.16)	0.0%	0.562
	Highest doses	6	0.98 (0.86–1.11)	25.7%	0.242
	Doses ≥55 μg/day	9	1.00 (0.89–1.13)	3.8%	0.403
	Doses <55 μg/day	5	1.22 (0.96–1.53)	0.0%	0.889
Esophagus	All doses	8	0.93 (0.83–1.05)	28.3%	0.203
	Highest doses	5	0.99 (0.87–1.13)	0.0%	0.543
	Doses ≥55 μg/day	5	0.74 (0.56–0.97)**	3.3%	0.388
	Doses <55 μg/day	3	0.98 (0.86–1.12)	15.9%	0.305
Hematologic	All doses	4	1.00 (0.87–1.14)	0.0%	0.857
	Highest doses	2	0.96 (0.77–1.21)	0.0%	0.622
	Doses ≥55 μg/day	2	0.96 (0.77–1.21)	0.0%	0.622
	Doses <55 μg/day	2	1.02 (0.86–1.20)	0.0%	0.531
Liver	All doses	14	0.78 (0.68–0.90)**	11.2%	0.331
	Highest doses	8	0.61 (0.49–0.75)**	0.0%	0.693
	Doses ≥55 μg/day	9	0.66 (0.56–0.82)**	18.5%	0.279
	Doses <55 μg/day	5	0.91 (0.75–1.12)	0.0%	0.989
Lung	All doses	4	1.08 (0.89–1.31)	25.7%	0.257
	Highest doses	3	1.09 (0.86–1.38)	50.3%	0.134
	Doses ≥55 μg/day	2	0.91 (0.67–1.24)	0.0%	0.328
	Doses <55 μg/day	2	1.21 (0.94–1.57)	8.4%	0.296
Pancreas	All doses	11	0.76 (0.65–0.89)**	0.0%	0.574
	Highest doses	4	0.73 (0.55–0.97)**	25.3%	0.260
	Doses ≥55 μg/day	10	0.76 (0.64–0.90)**	0.0%	0.480
	Doses <55 μg/day	1	0.73 (0.40–1.32)		
Prostate	All doses	33	0.99 (0.96–1.01)	0.4%	0.460
	Highest doses	14	0.99 (0.95–1.03)	0.0%	0.453
	Doses ≥55 μg/day	25	0.97 (0.94–1.00)	0.0%	0.590
	Doses <55 μg/day	8	1.06 (0.99–1.13)	0.0%	0.709
Skin	All doses	23	1.11 (1.03–1.19)**	0.0%	0.982
	Highest doses	17	1.12 (1.04–1.21)**	0.0%	0.909
	Doses ≥55 μg/day	21	1.12 (1.04–1.20)**	0.0%	0.970
	Doses <55 μg/day	2	1.06 (0.89–1.23)	0.0%	0.669
Stomach	All doses	12	0.93(0.83–1.05)	23.4%	0.214
	Highest doses	8	0.91 (0.80–1.04)	41.7%	0.100
	Doses ≥55 μg/day	5	0.85 (0.62–1.16)	49.2%	0.096
	Doses <55 μg/day	7	0.95 (0.84–1.07)	0.9%	0.417

*$p < 0.10$.
**$p < 0.05$.
[†]All doses do not include the lowest doses in the individual studies because they were used as reference group.

suggested that it can be toxic leading to diabetes and dermatological conditions (Jablonska and Vinceti 2015). Since it is required by the body in small amounts for other physiological roles (Kornhauser and Timmer 1995), it is necessary to study the efficacy of selenium in diet against cancer risk to inform on the need to take high amounts. Previous meta-analysis done on this topic have used peripheral biomarkers such as toenails, plasma and tissue to assess selenium intake (Dennert et al. 2011; Cai et al. 2016; Vinceti et al. 2018) These biomarkers show long term intake of selenium while diet indicates short term intake of selenium (Shils et al. 1999). Selenium in the diet has been shown to correlate with selenium in the biomarkers (Pestitschek et al. 2013).

The results from our meta-analysis suggest that at the highest daily intake levels of the included studies, selenium decreases the risk of cancer. This finding is consistent with previous two other studies (Dennert et al. 2011; Cai et al. 2016) that demonstrated protective effect of selenium at high doses compared to low doses. A recent meta-analysis by Vinceti et al (2018) showed a null association between selenium at high doses compared to low doses. Our findings could be different from this meta-analysis because of the different methods used in exposure assessment. Although a correlation has been identified between selenium in diet and selenium in peripheral biomarkers (Pestitschek et al. 2013), selenium levels in peripheral biomarkers is affected by other factors including smoking. Smoking exposes individuals to cadmium which increases excretion of selenium from the body, leading to low levels of selenium in peripheral biomarkers (Vinceti et al. 2017).

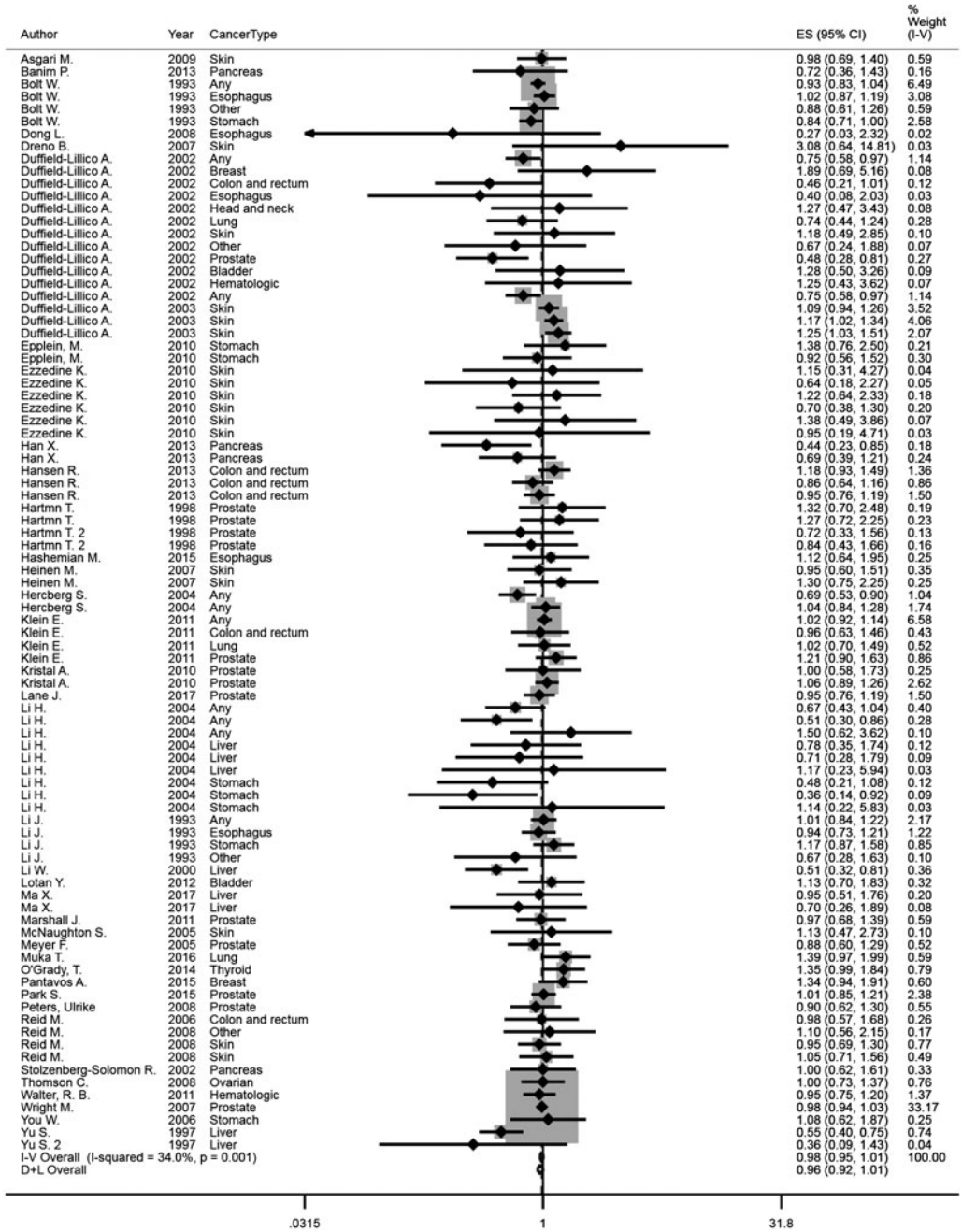

Figure 3. Study-specific and pooled RRs of all cancer types associated with highest doses compared to lowest doses of daily selenium intake. Studies appear multiple times in the plot because the subtype-specific or sex-specific RRs were used. Any cancer indicates the cancers that were not specified in a study, which did not duplicate with the cancers specified.

It is necessary to investigate the effects of selenium at recommended daily allowance (RDA) because majority of the people follow guidelines to inform them on their nutritional intake. Health care professionals and policy makers will also rely on the guidelines in their evidence-based medicine practice or policy formulations (Gray 2009). We find that selenium is associated with decreased risk of all cancers at doses $\geq$55μg/day but the effects on specific cancers vary. While some cancers show a decreased risk (esophagus, liver, and pancreas), others show an increased risk (skin, bladder, and breast). The statistically nonsignificant increased risk for bladder and breast cancer due to few dose levels should however be interpreted carefully. The increased risk for skin cancer that was observed in our study disappeared after controlling for age, BMI and smoking. Although our study used diet as exposure measurement, there is a consistent finding with other meta-analysis (Dennert et al. 2011; Cai et al. 2016; Vinceti et al. 2018) that selenium effects varies with specific cancers. There has been suggestions that the observed differences could be due to pathophysiology of the different cancers (Connolly et al. 2000). Generally, there was no association between selenium below the RDA and cancer risk, however, different cancers showed different effects. Most of the cancers showed an increased risk, however, cancers of esophagus, liver, pancreatic and stomach showed a protective effect. This finding

Table 3. Pooled RRs (compared with the lowest daily selenium intake doses) by demographic characteristics and study design.

Subgroup	Dose level	No. of doses	Pooled RR (95% CI)	I^2	p of I^2
Males	All doses	48	0.98 (0.96–1.01)*	0.0%	0.549
	Highest dose	21	0.98(0.94–1.02)*	14.9%	0.265
	Doses ≥55 μg/day	36	0.97 (0.94–0.99)	0.0%	0.602
	Doses <55 μg/day	12	1.06 (0.99–1.12)	0.0%	0.846
Females	All doses	18	1.03 (0.93–1.14)	0.0%	0.952
	Highest dose	11	1.04 (0.90–1.19)	0.0%	0.839
	Doses ≥55 μg/day	9	0.99 (0.83–1.17)	0.0%	0.910
	Doses <55 μg/day	9	1.05 (0.93–1.19)	0.0%	0.765
Supplements	All doses	72	0.95 (0.90–1.00)**	37.5%	0.001
	Highest dose	62	0.93 (0.87–0.99)**	41.4%	0.000
	Doses ≥55 μg/day	51	0.89 (0.82–0.97)**	48.2%	0.00
	Doses <55 μg/day	21	1.00 (0.95–1.05)	0.0%	0.686
Diet	All doses	52	0.99(0.96–1.02)	9.5%	0.282
	Highest dose	17	1.00 (0.96–1.05)	28.4%	0.133
	Doses ≥55 μg/day	35	0.98 (0.95–1.00)*	12.6%	0.258
	Doses <55 μg/day	17	1.08 (1.01–1.16)	0.0%	0.807
North America	All doses	56	1.01 (0.97–1.05)	31.7%	0.014
	Highest dose	37	1.00 (0.94–1.06)	33.7%	0.026
	Doses ≥55 μg/day	41	0.99 (0.94–1.04)	40.2%	0.005
	Doses <55 μg/day	15	1.05 (1.00–1.11)	0.0%	0.849
Europe	All doses	48	1.00 (0.95–1.06)	0.0%	0.696
	Highest dose	22	0.99 (0.92–1.08)	14.8%	0.262
	Doses ≥55 μg/day	38	0.97 (0.91–1.03)	0.0%	0.811
	Doses <55 μg/day	10	1.19 (1.03–1.36)	0.0%	0.799
Asia	All doses	38	0.91 (0.86–0.96)	25.6%	0.078
	Highest dose	26	0.86 (0.78–0.96)**	41.6%	0.015
	Doses ≥55 μg/day	20	0.72 (0.63–0.82)**	28.1%	0.118
	Doses <55 μg/day	18	0.95 (0.90–1.01)*	0.0%	0.951
Australia	All doses	7	1.08 (0.86–1.36)	0.0%	0.962
	Highest dose	3	1.09 (0.78–1.52)	0.0%	0.691
	Doses ≥55 μg/day	7	1.08 (0.86–1.36)	0.0%	0.962
	Doses <55 μg/day	None			
Interventional study	All doses	81	0.95 (0.90–1.00)*	31.7%	0.004
	Highest dose	65	0.94 (0.88–1.00)*	39.5%	0.001
	Doses ≥55 μg/day	66	0.92 (0.86–0.99)**	37.4%	0.002
	Doses <55 μg/day	15	0.99 (0.94–1.05)	0.0%	0.532
Observational study	All doses	58	0.99 (0.96–1.02)	6.0%	0.347
	Highest dose	20	0.99 (0.95–1.04)	22.5%	0.177
	Doses ≥55 μg/day	30	0.97 (0.94–1.00)*	18.7%	0.180
	Doses <55 μg/day	28	1.06 (1.00–1.13)	0.0%	0.911

*$p < 0.10$.
**$p < 0.05$.
†All doses do not include the lowest doses in the individual studies because they were used as reference group.

strengthens the above theory of pathophysiology of the different cancers.

An inverse linear association was found between increased selenium intake and risk of all cancers. As selenium dose increased, the overall risk of cancer incidence decreased. Previous studies (Dennert et al. 2011; Cai et al. 2016) have had similar findings. These findings of the inverse association should be interpreted carefully because selenium beyond the

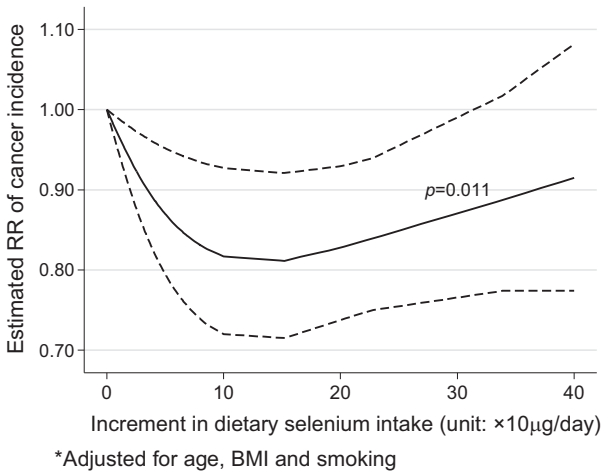

Figure 4. Nonlinear dose-response relationship between RR of incidence for all cancers and selenium intake, unadjusted model.

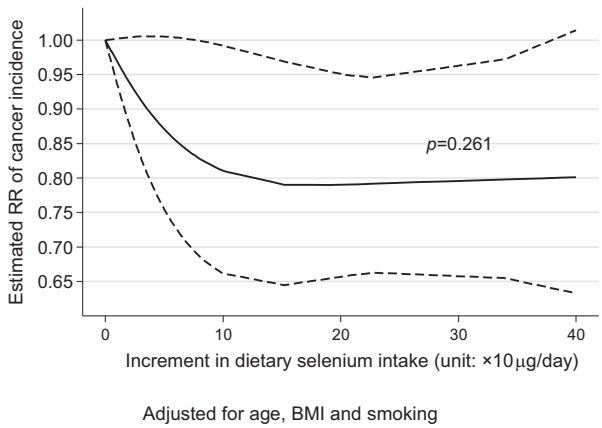

Figure 5. Nonlinear dose-response relationship between RR of incidence for all cancers and selenium intake, adjusted model.

safe upper limit level of 400 μg/day has been shown to be toxic leading to conditions like diabetes and dermatological conditions (Vinceti et al. 2017). There was no evidence of non-linear relationship between increased selenium intake and cancer risk after adjusting for age, BMI and smoking. A previous study (Cai et al. 2016) did not have sufficient data to conduct linear/nonlinear dose response for specific cancers.

Men appeared to be more protected by selenium compared to women, this could probably be due to the fact that most studies had men as their study population but this findings are similar to other studies (Dennert et al. 2011; Vinceti et al. 2018) that studied the effects of selenium on men and women. A study by Seale et al (Seale, Ogawa-Wong, and Berry 2018) suggests that there could be a difference on how selenium is metabolized in men as compared to women. However, this claim is still premature and further research is required. Additional selenium from supplements showed a significant protective effect unlike selenium from food only. This indicates that extra intake of selenium other than food might be essential for cancer prevention. Asiatic regions showed a protective effect from use of extra selenium unlike other regions. This protective effect could be attributed to the interventions of selenium supplementation such as in Linxian, China where an increased rate of esophageal and gastric cancers was observed compared to other regions in China. After supplementation, the risk of cancers decreased by half (Mark et al. 2000). Most Asian studies included in this meta-analysis were conducted in this region.

Strengths and limitations

The strengths of this study include use of a large sample to ensure the estimates obtained were precise. To our knowledge, this is the first meta-analysis that investigates dietary selenium with a cut off at the RDA and the risk of cancer incidence. Both linear and nonlinear relationships of selenium and cancer risk were investigated in our study, and the results obtained will be informative in human nutrition. Use of prospective studies especially the prospective follow up of interventional studies (mainly RCTs) adds to the strength of our study due to minimized biases in RCTs.

The major limitation of our study was heterogeneity which was present but the issue was addressed by use of random effects analysis. The relative short duration of follow up (8 years ±3 years) in the studies involved could have underestimated the effects of selenium since cancer develops over a long time. Some cancers such as breast and bladder cancers did not have sufficient doses hence the results for them should be interpreted carefully. Our study focused on selenium in the diet and supplements that implies short term intake, the results may therefore underestimate long term effects of selenium.

Conclusion

This study suggests that selenium above the RDA of selenium (≥55 μg/day) is protective against cancer, this is consistent with current evidence. Selenium has different effects on specific cancers with majority of the cancers showing an inverse relationship to selenium dosage. There is insufficient evidence so far to conclude on the association between dietary selenium intake and breast and bladder cancers. There is need for further research on selenium and these specific cancers because of the inconsistent findings.

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Conflicts of interest

The authors declare no conflict of interest.

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Author contributions

Y.C. and J.A. designed the research; Y.C. and A.K. provided study oversight and took primary responsibility for the final content of the manuscript; A.K., X.F. and M.L. undertook literature screening, data extraction and study quality assessment; X.F. and A.K. performed statistical analysis; A.K. drafted the manuscript; and all the authors contributed to the manuscript writing, made critical revision, read and approved the final manuscript.

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