Selenium Exposure and Cancer Risk: an Updated Meta-analysis and Meta-regression

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The objective of this study was to investigate the associations between selenium exposure and cancer risk. We identified 69 studies and applied meta-analysis, meta-regression and dose-response analysis to obtain available evidence. The results indicated that high selenium exposure had a protective effect on cancer risk (pooled OR = 0.78; 95%CI: 0.73–0.83). The results of linear and nonlinear dose-response analysis indicated that high serum/plasma selenium and toenail selenium had the efficacy on cancer prevention. However, we did not find a protective efficacy of selenium supplement. High selenium exposure may have different effects on specific types of cancer. It decreased the risk of breast cancer, lung cancer, esophageal cancer, gastric cancer, and prostate cancer, but it was not associated with colorectal cancer, bladder cancer, and skin cancer.

Selenium (Se) is an essential trace element having considerable and particular functions for human health because it is genetically encoded for which incorporation into proteins, as the constitutive part of selenocysteine, the 21st amino acid1. Most se-proteins have been shown to have a wide range of pleiotropic effects, ranging from antioxidant to anti-inflammatory effects2, particularly the families of glutathione peroxidases (GPxs) and thioredoxin reductases (TrxRs)1, but their precise mechanism are not understood absolutely currently. Despite the scarce knowledge of mechanism, a large number of laboratory and ecologic researches focused on the associations between selenium and human health have been completed, showing that Se is associated with several human diseases including cardiovascular disease3–5, central nervous system disease 6, diabetes mellitus7–10, and cancer, but the results are inconsistent.

We can see worldwide debates on the relation between selenium and cancer risk. Observational studies and randomized controlled trials suggest different effects in human. A new meta-analysis11 published in Cochrane 2014 described the association between selenium and cancer prevention, and this article tended to analyze the effect of selenium supplement based on random controlled trials. There are other similar meta-analyses have been published, few of them established dose-response or beneficial range of selenium exposure associated with the risk reduction or determined the shape of dose-response curve to find whether it is a linear relation, saturation or U-shaped curve relation between selenium exposure level and cancer risk. On the other hand, numerous new studies have been reported in recent years, and we think it is meaningful to conduct an updated meta-analysis including different types of cancer to provide comprehensive evidence and clarify the shape of dose-response association between selenium status and cancer risk.

Methods

Search strategy. We carried out a systematic search for articles which described the relations between selenium and cancer risk in the medical and biologic databases (Medline 1980-March 2014, via Pubmed; Embase 1980-March 2014; Science Citation Index, Web of Science 1980- March 2014; CAB Health 1980- March 2014), using a comprehensive list of selenium/ selenium supplement/ serum/plasma selenium/ toenail selenium/ antioxidant/ minerals And cancer/ breast cancer/ lung cancer/ esophageal cancer/ gastric/stomach cancer/ colorectal cancer/ bladder cancer/ prostate cancer/skin cancer). We also searched references of relevant studies and reviews

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to identify works which were not found in the database search. The first two authors (Xianlei Cai and Chen Wang) conducted the search work (as shown in Fig. 1).

**Inclusion and exclusion criteria.** Inclusion criteria were as follows: (1) was a randomized controlled trial, cohort or case-control study; (2) regarded selenium as baseline exposure, and cancer event (including incidence and mortality) as outcome; (3) were original works in English language which were published and indexed from January 1980 to March 2014; (4) had key date for meta-analysis or dose-response analysis. Exclusion criteria were as follows: (1) was not involved with exposure-response associations between selenium and cancer risk; (2) cytological studies, animal studies, reviews, comments, abstracts and reviews; (3) low quality articles.

**Data extraction.** All the data were extracted independently by three reviewers (Xianlei Cai, Chen Wang and Ning Shen) with a standardized data extraction form. The characteristics of the identified works were extracted as follows: first author name, year of publication, study country, design (RCT, cohort or case-control), number of subject (we extracted number of selenium exposure group and placebo group respectively from RCT studies, number of cohort participants from cohort studies, and number of case group plus control group from case-control studies), number of cases, age (mean or ranger), participants (men, women, both gender combined or special participants described in original studies), follow-up (year), Measurements of selenium (serum/plasma selenium, toenail selenium or selenium supplement), type of cancer, outcome, and estimates (odds ratio (OR), relative risk (RR) or hazard ratio (HR) at the highest compared with the lowest selenium exposure, with 95% confidence interval (CI)); Table 1 presents the summary data of each identified work in our meta-analysis.

**Quality assessment.** We applied the Newcastle-Ottawa scale\(^{12,13}\) to assess the quality of the cohort and case-control studies. In this scale, one article was assessed on three perspectives: selection, comparability, outcome by using a “star system”. The maximum score was nine stars. We simply regarded scores of 0–3 stars as low quality, scores of 4–6 stars as moderate quality, and scores of 7–9 stars as high quality. According to RCTs, we used the Cochrane collaboration’s tool\(^{14}\) for assessing risk of bias from six domains: selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias. Results were presented as low risk of bias, unclear risk of bias or high risk of bias.

**Statistical analyses.** We extracted the multivariate-adjusted RRs, HRs or ORs and 95% confidence interval (CI) from original works. If some studies only provided 2×2 table data, we calculated the responding ORs. We considered these estimates as ORs when took those studies with different designs into account, for RRs and HRs were assumed to be the accurate estimates of ORs. Meta-regression analysis was conducted to figure out whether the associations between selenium exposure and cancer risk were influenced by some covariates (exposure modes, area and design), and we could recognize the influence factor with a positive meta-regression coefficient\((P \leq 0.05)\). We used Greenland and Longnecker\(^{15}\) method to conduct study-specific dose-response analyses based on the estimates of each category of plasma/serum selenium (ug/L), toenail selenium (ug/g) and selenium supplement (ug/d) respectively. We used mean or median of selenium exposure for each category when it was
| Study | Country | Design            | Subject | Case | age   | Gender | Follow-up | Measurements of selenium | Type of cancer | OR(95%CI)   | Quality score |
|-------|---------|-------------------|---------|------|-------|--------|-----------|--------------------------|----------------|------------|--------------|
| Not site specific cancer |
| Bleys J (2008) | USA | cohort | 13887 | 457  | 20–90 | M and F | 12 Y | Serum selenium | All cancer | 0.69(0.53,0.90) | 9 |
| Akbaraly NT (2005) | France | cohort | 1387 | 45  | 59–71 | M and F | 9 Y | Serum selenium | All cancer | 0.56(0.41,0.76) | 8 |
| Kornitzer M (2004) | Belgium | nested case-control | 539  | 139  | 25–74 | Men | 10 Y | Serum selenium | All cancer | 0.45(0.27,0.77) | 9 |
| Ujie S (2002) | Japan | cohort | 5019 | 2707 | N/A  | M and F | 5 Y | Serum selenium | All cancer | 0.40(0.35,0.46) | 7 |
| Persson-Moschos ME (2000) | Sweden | nested case-control | 903  | 302  | middle age | Men | 6 Y | Serum selenium | All cancer | 0.19(0.04,0.83) | 8 |
| Breast cancer |
| Harris H R (2012) | Sweden | cohort | 66651 | 3146 | mean 65 | Women | 9 Y | Diet selenium | Breast cancer | 0.69(0.52,0.92) | 9 |
| Pan S Y (2011) | Canada | case-control | 4824 | 866  | 20–76 | Premenopausal | N/A | Diet selenium | Breast cancer | 1.10(0.75,1.61) | 8 |
| Rejali L (2007) | Malaysia | matched case-control | 124  | 62   | mean 49 | Women | N/A | Serum selenium | Breast cancer | 0.89(0.84,0.94) | 8 |
| Cui Y (2007) | USA | Nested case-control | 304  | 252  | N/A | Women | N/A | Breast tissue selenium | Breast cancer | 1.06(0.70,1.62) | 9 |
| Singh P (2005) | India | case-control | 320  | 160  | mean 45 | Women | N/A | Serum selenium | Breast cancer | 0.93(0.72,1.22) | 8 |
| Mannisto S (2000) | Finland | case-control | 280  | 112  | 25–75 | Premenopausal | N/A | Serum selenium | Breast cancer | 0.90(0.30,2.70) | 9 |
| Ghadirian P (2000) | Canada | case-control | 1102 | 414  | N/A | Women | N/A | Toenail selenium | Breast cancer | 0.72(0.40,1.31) | 8 |
| Dorgan J F (1998) | USA | nested case-control | 315  | 105  | mean 58 | Women | N/A | Serum selenium | Breast cancer | 0.90(0.40,1.80) | 9 |
| Strain J J (1997) | Northern Ireland | case-control | 294  | 99   | mean 62 | Postmenopausal | N/A | Toenail selenium | Breast cancer | 0.75(0.35,1.57) | 8 |
| van T V P (1996) | Europe | case-control | 605  | 266  | 50–74 | Postmenopausal | N/A | Toenail selenium | Breast cancer | 0.96(0.63,1.47) | 8 |
| van den Brandt P A (1994) | Netherlands | cohort | 62537 | 355  | 55–69 | Postmenopausal | 3.3 Y | Toenail selenium | Breast cancer | 0.84(0.55,1.27) | 9 |
| Hardell I (1993) | Sweden | case-control | 632  | 441  | 20–84 | Women | N/A | Serum selenium | Breast cancer | 0.33(0.17,0.64) | 7 |
| van T V P (1990) | Netherlands | case-control | 371  | 133  | 25–64 | Women | N/A | Diet selenium | Breast cancer | 0.63(0.29,1.25) | 9 |
| Knekt P (1996) | Finland | cohort | N/A  | 48   | 15–99 | women | N/A | Serum selenium | Breast cancer | 1.03(0.43,2.50) | 8 |
| Lung cancer |
| Jaworska K (2013) | Poland | case-control | 172  | 86   | mean 61.6 | M and F | N/A | Serum selenium | Lung cancer | 0.10(0.03,0.34) | 8 |
| Jablonska E (2008) | Poland | case-control | 612  | 325  | 30–78 | M and F | N/A | Serum selenium | Lung cancer | 1.21(0.67,2.20) | 8 |
| Gromadzinska J (2003) | Poland | case-control | 362  | 152  | 43–78 | M and F | N/A | Serum selenium | Lung cancer | 0.33(0.18,0.60) | 8 |
| Hartman T J (2002) | Finland | Nested case-control | 500  | 250  | 50–69 | men | N/A | Toenail selenium | Lung cancer | 0.20(0.09,0.44) | 9 |
| Goodman GE (2001) | USA | case-control | 712  | 356  | 45–74 | men | N/A | Serum selenium | Lung cancer | 1.20(0.77,1.88) | 9 |
| Rattanasirnge D (2000) | China | nested case-control | 324  | 108  | 35–74 | men | 6 Y | Serum selenium | Lung cancer | 1.20(0.60,2.40) | 9 |
| Knekt P (1998) | Finland | nested case-control | 285  | 95   | mean 57 | M and F | 19 Y | Serum selenium | Lung cancer | 0.41(0.17,0.94) | 9 |
| Garland M (1995) | USA | nested case-control | 94   | 47   | 30–55 | women | 41 M | Toenail selenium | Lung cancer | 1.95(0.41,9.28) | 8 |
| Kabuto, M (1994) | Japan | case-control | 197  | 77   | 59–60 | M and F | 13 Y | Serum selenium | Lung cancer | 0.56(0.20,5.88) | 8 |
| van den Brandt P A (1993) | Netherlands | cohort | 3345 | 384  | 55–69 | M and F | 3.3 Y | Toenail selenium | Lung cancer | 0.40(0.27,0.97) | 9 |
| Knekt P (1990) | Finland | cohort | N/A  | 153  | 15–99 | men | N/A | Serum selenium | Lung cancer | 0.66(0.37,1.19) | 8 |
| Lippman SM (2009) | USA, Canada, Puerto Rico | RCT | P:8696,e:8752 | P:67,e: 75 ≥50 | men | 5.46 Y | Selenium supplement | Lung cancer | 1.12(0.73,1.72) | low risk of bias |
| Clark LC (1996) | USA | RCT | P:659, e: 653 | P:35, e: 13 mean 63 | M and F | 6.4 Y | Selenium supplement | Lung cancer | 0.56(0.31,1.01) | low risk of bias |

Esophageal cancer

Continued
| Study          | Country          | Design            | Subject | Case | age | Gender | Follow-up | Measurements of selenium | Type of cancer | OR (95%CI)                  | Quality score |
|---------------|------------------|-------------------|---------|------|-----|--------|-----------|--------------------------|----------------|---------------------------|---------------|
| Steevers (2010) | Netherlands      | case-cohort       | 3346    | 129  | 55–69 | M and F | 16.3 Y   | Toenail selenium          | EAC            | 0.760 (0.41,1.40)            | 9             |
|                |                  |                   | 3346    | 71   |      |         |           |                           |                | 0.370 (0.16,0.86)            |               |
| Cai, L (2006)  | China            | case-cohort       | 633     | 218  | N/A  | M and F | 10+ Y    | Selenium intake           | SCC            | 0.480 (0.25,0.89)            | 9             |
| Wei WQ (2004)  | China            | cohort            | 1103    | 75   | 40–69 | M and F | 15 Y     | Serum selenium            | ESCC death     | 0.830 (0.71,0.98)            | 9             |
| Mark SD (2000) | China            | case-cohort       | 1464    | 402  | 40–69 | M and F | 4.5 Y    | Serum selenium            | Incidence      | 0.890 (0.83,0.95)            | 9             |
|                |                  |                   |         |      |      |         |           |                           |                | 0.900 (0.83,0.97)            |               |
| Clark LC (1996)| USA              | RCT               | P:659, e: 653 | P:6, e: 2 | mean 63 | M and F | 6.4 Y    | Selenium supplement      | esophageal cancer | 0.330 (0.03,1.84) low risk of bias |               |

**Gastric cancer**

| Study          | Country          | Design            | Subject | Case | age | Gender | Follow-up | Measurements of selenium | Type of cancer | OR (95%CI)                  | Quality score |
|---------------|------------------|-------------------|---------|------|-----|--------|-----------|--------------------------|----------------|---------------------------|---------------|
| Steevers (2010) | Netherlands      | case-cohort       | 3346    | 114  | 55–69 | M and F | 16.3 Y   | Toenail selenium          | GCC            | 0.520 (0.27,1.02)            | 9             |
| Wei WQ (2004)  | China            | cohort            | 1103    | 36   | 40–69 | M and F | 15 Y     | Serum selenium            | GCC death      | 0.750 (0.59,0.95)            | 9             |
| Mark SD (2000) | China            | case-cohort       | 1479    | 87   | 40–69 | M and F | 4.5 Y    | Serum selenium            | GNC onset      | 1.020 (0.89,1.18)            | 9             |
|                |                  |                   | 1652    | 590  |      |         |           |                           |                | 0.870 (0.79,0.96)            |               |
| Kabuto, M (1994) | Japan            | case-control      | 428     | 202  | 59–60 | M and F | 13 Y     | Serum selenium            | gastric cancer | 1.000 (0.50,1.90)            | 8             |
| van den Brandt PA (1993) | Netherlands cohort | 2459 | 92 | 55–69 | M and F | 3.3 Y | Toenail selenium | gastric cancer | 0.610 (0.33,1.11) | 9 |
| Knekt P (1990) | Finland          | cohort            | N/A     | 43   | 15–99 | Men     | N/A      | Serum selenium            | gastric cancer | 0.240 (0.09,0.69)            | 8             |
|                |                  |                   |         | 30   | Women |         |           |                           |                | 0.480 (0.14,1.66)            |               |

**Colorectal cancer**

| Study          | Country          | Design            | Subject | Case | age | Gender | Follow-up | Measurements of selenium | Type of cancer | OR (95%CI)                  | Quality score |
|---------------|------------------|-------------------|---------|------|-----|--------|-----------|--------------------------|----------------|---------------------------|---------------|
| Takata Y (2011) | USA              | nested            | 1449    | 648  | 50–79 | Women   | N/A      | Serum selenium colon Ca  | 1.280 (0.91,1.79) | 9             |
|                |                  | case-control      | 950     | 149  |      |         |           |                           |                | 1.250 (0.68,2.31)            |               |
| Connelly-Frost A (2009) | USA      | case-control      | 1362    | 532  | 40–80 | M and F | N/A      | Serum selenium colon Ca  | 0.400 (0.20,0.60) | 9             |
| Ghadrian P (2000) | Canada            | case-control      | 1090    | 402  | N/A  | M and F | N/A      | Toenailselenium colorectal cancer | 0.420 (0.19,0.93) | 8             |
| Nelson RL (1995) | USA              | case-control      | 163     | 25   | 26–87 | M and F | N/A      | Serum selenium colorectal cancer | 1.700 (0.50,5.90) | 7             |
| Garland M (1995) | USA              | nested            | 178     | 89   | 30–55 | Women   | 41 M     | Toenailselenium colorectal cancer | 2.040 (0.88,4.75) | 8             |
| van den Brandt PA (1993) | Netherlands cohort | 2495 | 234 | 55–69 | M and F | 3.3 Y | Toenail colon Ca | 0.770 (0.49,1.19) | 9             |
| Knekt P (1990) | Finland          | cohort            | N/A     | 29   | 15–99 | Men     | N/A      | Serum selenium colorectal cancer | 1.010 (0.18,5.65) | 8             |
|                |                  |                   |         | 48   | Women |         |           |                           |                | 1.100 (0.42,2.92)            |               |
| Schober SE (1987) | USA              | case-control      | 215     | 72   | <75  | M and F | N/A      | Serum selenium colon cancer | 0.710 (0.29,1.67) | 7             |
| Lippman SM (2009) | US, Canada, Puerto Rico | RCT | P:6966, e: 8752 | P:60, e: 63 | ≥ 50 | men | 5.46 Y | Selenium supplement colorectal cancer | 1.090 (0.69,1.73) | low risk of bias |
| Clark LC (1996) | USA              | RCT               | P:659, e: 653 | P:19, e: 8 | mean 63 | M and F | 6.4 Y | Selenium supplement colorectal cancer | 0.420 (0.18,0.95) | low risk of bias |

**Bladder cancer**

| Study          | Country          | Design            | Subject | Case | age | Gender | Follow-up | Measurements of selenium | Type of cancer | OR (95%CI)                  | Quality score |
|---------------|------------------|-------------------|---------|------|-----|--------|-----------|--------------------------|----------------|---------------------------|---------------|
| Hotaling JM (2011) | USA              | cohort            | 77050   | 330  | 50–76 | M and F | 6 Y      | Selenium supplement      | bladder cancer | 0.970 (0.72,1.31)            | 8             |
| Wallace K (2009) | Germany          | case-control      | 2048    | 857  | 25–74 | M and F | N/A      | Toenail selenium          | bladder cancer | 0.900 (0.68,1.19)            | 9             |
| Kellen E (2006) | Belgium          | case-control      | 540     | 362  | <50  | M and F | N/A      | Serum selenium            | bladder cancer | 0.270 (0.15,0.47)            | 9             |
| Michaud DS (2005) | US               | nested            | 446     | 222  | mean 62 | Men     | N/A      | Toenail selenium          | bladder cancer | 1.170 (0.66,2.07)            | 9             |
|                |                  |                   | 233     | 116  | Women |         |           |                           |                | 0.360 (0.14,0.91)            |               |
| Zeegers MP (2002) | Netherlands      | case-cohort       | 2890    | 431  | 55–69 | M and F | 6.3 Y    | Toenail selenium          | bladder cancer | 0.670 (0.47,0.97)            | 9             |
| Michaud DS (2002) | Finland          | nested            | 264     | 132  | 50–69 | M and F | N/A      | Toenail selenium          | bladder cancer | 0.900 (0.45,1.78)            | 8             |
| Helzlsouer K (1989) | USA              | case-control      | 95      | 35   | mean 59 | M and F | N/A      | Serum selenium            | bladder cancer | 0.490 (0.16,1.49)            | 9             |
| Lotan Y (2012)  | US, Canada, Puerto Rico | RCT | P:6966, e: 8752 | P:35, e: 63 | ≥ 50 | men | 7.1 Y | Selenium supplement bladder cancer | 1.130 (0.70,1.84) | low risk of bias |

Continued
| Study                  | Country     | Design        | Subject           | Case | age    | Gender | Follow-up | Measurements of selenium | Type of cancer          | OR (95% CI)            | Quality score |
|-----------------------|-------------|---------------|-------------------|------|--------|--------|-----------|--------------------------|------------------------|-----------------------|----------------|----------------|
| Clark LC(1996)        | USA         | RCT           | P:659, e: 653     | 6, e: 8 | Mean 63 | M and F | 6.4 Y     | Selenium supplement      | bladder cancer         | 1.27 (0.44, 3.67) | low risk of bias |

**Prostate cancer**

- Gaybels, M S(2013): Netherlands Case-cohort 2074, 898 Men 55-69, 3274, 2380 Supplement 1.50 (0.99, 2.26)
- Grundmark, B(2011): Sweden cohort 2045, 208 Men 50, 34 Y Serum selenium Prostate cancer 0.83 (0.60, 1.16)
- Steinbrecher, A(2010): European Nested case-control 734, 244 Men N/A Serum selenium Prostate cancer 0.78 (0.49, 1.22)
- Gill, J K(2009): USA Nested case-control 1403, 467 Men N/A Serum selenium Prostate cancer 0.82 (0.59, 1.14)
- Allen, N E(2008): Netherlands Case-cohort 2074, 898 Men 55–69 Men N/A Serum selenium Prostate cancer 0.37 (0.22, 0.71)
- Peters, U(2007): USA Nested case-control 1603, 724 Men 55–74 Men N/A Serum selenium Prostate cancer 0.84 (0.62, 1.14)
- Lipsky, K(2004): Austria case-control 150, 70 Men 48–95 Men N/A Serum selenium Prostate cancer 0.74 (0.22, 2.71)
- Li H(2004): USA Nested case-control 1143, 586 Men 40–84 Men 13 Y Serum selenium Prostate cancer 0.78 (0.54, 1.13)
- Allen, N E(2004): Britain case-control 600, 300 Men 44–77 Men N/A Serum selenium Prostate cancer 1.24 (0.73, 2.10)
- van den Brandt, P(2003): Netherlands Cohort 1751, 540 Men 55–69 Men N/A Serum selenium Prostate cancer 0.69 (0.48, 0.99)
- Goodman, G E(2001): USA case-control 691, 235 Men 45–75 Men N/A Serum selenium Prostate cancer 1.02 (0.65, 1.60)
- Brooks, J D(2001): USA case-control 148, 52 Men 68 Men N/A Serum selenium Prostate cancer 0.24 (0.07, 0.77)
- Ghadirian, P(2000): Canada case-control 165, 83 Men 35–84 Men N/A Serum selenium Prostate cancer 1.14 (0.46, 2.83)
- Heilzlocher, K J(2000): USA Nested case-control 350, 117 Men 70 Men N/A Serum selenium Prostate cancer 0.38 (0.17, 0.85)
- Nomura, A M(2000): USA Nested case-control 498, 289 Men 44–85 Men N/A Serum selenium Prostate cancer 0.50 (0.30, 0.90)
- Hartman, T J(1998): USA cohort 29460, 317 Men 61 Men N/A Serum selenium Prostate cancer 1.32 (0.70, 2.47)
- Yoshizawa, K(1998): USA Nested case-control 362, 181 Men 40–75 Men N/A Serum selenium Prostate cancer 0.35 (0.16, 0.78)
- Hardell, L(1995): Sweden case-control 245, 124 Men 44–87 Men N/A Serum selenium Prostate cancer 0.30 (0.10, 0.70)
- West, D W(1991): USA case-control 564, 179 Men 45–67 Men N/A Serum selenium Prostate cancer 0.80 (0.50, 1.40)
- Lippman SM(2009): USA, Canada, Puerto Rico RCT P:8696, e: 8752 P:416 ≥ 50 Men 5.46 Y Selenium supplement Prostate cancer 1.04 (0.83, 1.30)
- Duffield-Lillico, A J(2003): USA RCT P:470; E: 457 P: 42; E: 22 Supplement 0.48 (0.28, 0.80)
- Clark LC(1996): USA RCT P:659, e: 653 P:35, e: 13 Mean 63 Men and F 6.4 Y Selenium supplement Prostate cancer 0.35 (0.18, 0.65)

**Skin cancer**

- Garland M(1995): USA Nested case-control 30–55 126 63 Women 41 M Toenail selenium melanoma 1.66 (0.71, 3.85)
- Knekt P(1990): USA cohort 15–99 N/A Men N/A Serum selenium basal cell carcinoma 0.86 (0.35, 2.12)
- Reid ME(2008): USA RCT P:210, e: 213 P:108e: 98 Mean 63 Men and F 6.4 Y Selenium supplement Non-melanoma skin cancer 0.91 (0.49, 1.69)

Continued
Table 1. Characteristics of studies included in meta-analysis of studies on selenium and cancer.

| Study         | Country | Design     | Subject | Case | age | Gender | Follow-up | Measurements of selenium | Type of cancer | OR(95%CI) | Quality sore |
|---------------|---------|------------|---------|------|-----|--------|-----------|--------------------------|----------------|-----------|--------------|
| Garland M(1995) | USA     | RCT        | P:659, e:635 | P:190e:218 | mean 63 | M and F | 6.4 Y | Selenium supplement | squamous cell carcinoma | 1.140(0.93,1.39) | low risk of bias |
| Knekt P(1990)  | USA     | cohort     | 15–99   | N/A  | 26 | Men     | N/A       | Serum selenium         | Urinary tract cancer | 0.340(0.06,0.06) | 8           |
| Knekt P(1990)  | USA     | cohort     | 15–99   | N/A  | 22 | Women   | N/A       | Serum selenium         | Pancreas cancer | 0.860(0.21,3.52) | 8           |
| Clark LC(1996) | USA     | RCT        | P:659, e:653 | P:5, e:8 | mean 63 | M and F | 6.4 Y | Selenium supplement | leukemia/lymphomas | 1.500(0.49,6.40) | low risk of bias |
| Clark LC(1996) | USA     | RCT        | P:659, e:653 | P:5, e:8 | mean 63 | M and F | 6.4 Y | Selenium supplement | leukemia/lymphomas | 1.500(0.49,6.40) | low risk of bias |
| Garland M(1995) | USA     | nested-case-control | 182 | 91 | 30–55 | women | 41 M | Toenail selenium | Uterine cancer | 1.380(0.62,3.08) | 8           |
| Garland M(1995) | USA     | nested-case-control | 182 | 91 | 30–55 | women | 41 M | Toenail selenium | Uterine cancer | 1.380(0.62,3.08) | 8           |

Abbreviation: M and F: Male and Female; p: placebo; e: exposure; RCT: randomized controlled trials; N/A: not available; EAC: esophageal adenocarcinoma; ESCC: esophageal squamous cell carcinoma; GCC: gastric cardia cancer; GNC: gastric noncardia cancer; M: months; Y: years.

Results

Characteristics of the study. The meta-analysis included 69 studies (26 case-control studies, 14 cohort studies, 19 nested case-control studies, 5 case-cohort studies, 5 randomized controlled trials) reporting 114 independent estimates (as shown in Table 1) from Asia (4 studies from China, 2 from Japan, and 1 from Malaysia, Iran, and India, respectively), Europe (8 from Netherlands, 5 studies from Sweden, 5 from Finland, 3 from Poland, 2 from Belgium, 1 from Northern Ireland, Britain, Germany and France, respectively, and 3 studies from European countries) and America (27 studies from the United States, 2 from Canada and 1 from Austria). There were more than 36,474 participants with 26,138 cancer events. 5 studies used all types of cancer as outcome, 14 studies used breast cancer as outcome, 13 studies used lung cancer as outcome, 5 studies used esophageal cancer as outcome, 6 studies used gastric cancer as outcome, 10 studies used colorectal cancer as outcome, 9 studies used bladder cancer as outcome, 25 studies used prostate cancer as outcome, 4 studies used skin cancer as outcome, 1 study regarded urinary tract cancer, pancreas cancer, leukemia/lymphoma, uterine and ovarian cancer as outcome respectively. 11 studies mentioned above reported more than one cancer as an outcome, and several studies reported more than one estimate (as shown in Table 1). 56 studies assessed biochemical selenium status: 37 used plasma/serum specimens and 19 used toenail specimens as exposure. 11 studies investigated selenium supplement or intake as exposure, using interviews or validated food frequency questionnaires. One study used breast tissue selenium as exposure, and the last one reported selenium intake, plasma selenium and toenail selenium as exposure respectively.

Selenium exposure and all cancer. The relation between selenium exposure and all cancer risk, represented 114 independent estimates from 69 studies (as shown in Table 1). Meta-regression was done to detect the possible influencing factors, and we found that exposure mode (plasma/serum selenium, toenail selenium or selenium supplement), area (Asia, Europe and America) and design (case-control, cohort or RCT) were not influencing factors (exposure mode: P = 0.388; area: P = 0.523; design: P = 0.715). Therefore, we took the 114 estimates into meta-analysis. The result of the pooled analysis showed that high selenium exposure had a protective efficacy on cancer at the highest compared with the lowest category (pooled OR = 0.78; 95%CI: 0.73–0.83), with obvious heterogeneity (Q = 423.52; I² = 73.3%) and publication bias (Begger’s test z = 2.55, P = 0.011; Egger’s test t = −2.61, P = 0.010). Sensitivity analysis showed that the result was robust (as shown in Supplementary Table S1). The heterogeneity was due to a large amount of included estimates and different types of cancer.
The pooled result from 58 independent estimates showed that high serum/plasma selenium had an effect on cancer prevention at the highest compared with the lowest category (pooled OR = 0.75, 95%CI: 0.69–0.82, Fig. 2), with obvious heterogeneity (Q = 268.57; P = 0.000; I²% = 78.8) and publication bias (Beggar’s test zc = 2.54, P = 0.025; Egger’s test t = -2.43, P = 0.018). But the funnel plot was symmetry (supplementary Fig. S1). The heterogeneity could be due to a large amount of included estimates and publication bias. 17 groups of data were incorporated into dose-response analysis. The pooled OR was 0.95 (95%CI: 0.94–0.98) with 10 μg/L increase of plasma/serum selenium. Otherwise, we found obvious downward trends in the plots between plasma/serum selenium and total cancer risk in nonlinear dose-response analysis (P = 0.67 for non-linearity, Fig. 3).

There were 32 independent estimates describing the relation between toenail selenium and cancer risk. The result showed that high toenail selenium decreased cancer risk (pooled OR = 0.74, 95%CI: 0.62–0.87, as shown in Fig. 4), with obvious heterogeneity (Q = 70.95, P = 0.000; I²% = 56.3). There was no publication bias (Beggar’s test zc = 0.05; P = 0.961; Egger’s test t = 0.52, P = 0.605), and the funnel plot did not show asymmetry (Fig. S2). 15 groups of data were incorporated into dose-response analysis. The pooled OR was 0.94 (95%CI: 0.92–0.97) with per 0.1 μg/g increase of toenail selenium. An downward trends was found in the plots of nonlinear dose-response analysis between toenail selenium and cancer risk (P = 0.500 for non-linearity, Fig. 5).

There were 23 independent estimates describing the relation between selenium supplement and cancer risk. The result showed that selenium supplement was not associated with cancer risk (pooled OR = 0.91; 95%CI: 0.80–1.03, Fig. 6), with obvious heterogeneity (Q = 49.35, P = 0.001; I²% = 55.4). There was no publication bias (Beggar’s test zc = 1.98; P = 0.05; Egger’s test t = 0.06, P = 0.21), and the funnel plot did not show...
asymmetry (Fig. S3). However, we just extracted two relevant data for selenium supplement and all cancer risk, the linear or nonlinear dose-response analysis was not conducted.

**Selenium exposure and breast cancer.** 18 estimates from 14 studies were incorporated in the pooled analysis. We found that exposure mode, area and design were not influencing factor (exposure mode: \(P = 0.417\);
area: \( P = 0.705 \); design: \( P = 0.095 \) after Meta-regression. The pooled result showed that high selenium exposure decreased risk of breast cancer (pooled OR = 0.88; 95% CI: 0.84–0.93, Fig. 7), with no heterogeneity (Q = 20.83, \( P = 0.234 \); \( I^2 \% = 18.4 \)) and publication bias (Begger's test \( z_c = 1.74; P = 0.081 \); Egger's test \( t = -1.21, P = 0.245 \)). Sensitivity analysis showed the result was robust (as shown in Supplemental Table S1). We lacked sufficient data to conduct the linear or nonlinear dose-response analysis.

**Selenium exposure and lung cancer.** 13 estimates from 13 studies were incorporated into the pooled analysis. We found that exposure mode, area and design were not influencing factor (exposure mode: \( P = 0.706 \); area: \( P = 0.581 \); design: \( P = 0.705 \)). Therefore, we took the 13 estimates into meta-analysis. The result showed that high selenium exposure presented a protective effect on lung cancer (pooled OR = 0.60, 95% CI: 0.41–0.88, Fig. 8), with moderate heterogeneity (Q = 52.34, \( P = 0.000 \); \( I^2 \% = 77.1 \)), but without publication bias (Begger's test \( z_c = 1.16; P = 0.246 \); Egger's test \( t = -0.79, P = 0.448 \)). Sensitivity analysis showed the result was robust (Supplemental Table S1). 5 groups of data were incorporated into dose-response analysis between plasma/serum selenium and lung cancer risk. The result of linear dose-response analysis presented that plasma/serum selenium
was not associated with cancer risk per 10 µg/L increases of plasma/serum selenium (pooled OR, 0.92; 95%CI: 0.83–1.01, \( P = 0.0001 \)). Otherwise, we did not find a threshold effect in the plot between plasma/serum selenium and lung cancer risk in nonlinear dose-response analysis (\( P = 0.182 \) for non-linearity; Fig. S4).

**Selenium exposure and esophageal cancer.** 7 estimates from 5 studies were incorporated into the pooled analysis. The pooled OR was 0.88 (95%CI: 0.84–0.93, Fig. 9) with no heterogeneity (\( Q = 9.60, P = 0.142; \) \( I^2 \% = 37.5 \)) and publication bias (Begger's test \( z_c = 1.80; P = 0.072; \) Egger's test \( t = -4.57, P = 0.006 \)). Sensitivity
analysis showed that the result was robust (Supplemental Table S1). We lacked sufficient data to conduct the linear or nonlinear dose-response analysis.

Selenium exposure and gastric cancer. 10 estimates from 6 studies were incorporated into the pooled analysis. We found that exposure mode, area and design were not influencing factor (exposure mode: \( P = 0.288 \); area: \( P = 0.077 \); design: \( P = 0.769 \)). Therefore, we took the 10 estimates into meta-analysis. The pooled OR was 0.86 (95%CI: 0.77–0.96, as shown in Fig. 10) with moderate heterogeneity (\( Q = 22.63, P = 0.007; I^2 \% = 60.2 \)). There was no publication bias (Begger’s test \( z_c = 0.54; P = 0.592 \); Egger’s test \( t = -1.29, P = 0.235 \)). Sensitivity analysis showed that the result was robust (as shown in Supplemental Table S1). We lacked sufficient data to conduct the linear or nonlinear dose-response analysis.

Selenium exposure and colorectal cancer. 13 estimates from 10 studies were incorporated into the pooled analysis. We found that exposure mode, area and design were not influencing factor (exposure mode: \( P = 0.671 \); area: \( P = 0.871 \); design: \( P = 0.963 \)). Therefore, we took the 13 estimates into meta-analysis. The result
showed that high selenium exposure was not associated with colorectal cancer (pooled OR = 0.89, 95%CI: 0.67–1.17, Fig. 11), with moderate heterogeneity (Q = 26.71, P = 0.009; I² = 55.1), but without publication bias (Begger's test zc = 0.06; P = 0.951; Egger's test t = −0.49, P = 0.634). Sensitivity analysis showed that the result was robust (Supplemental Table S1).

**Selenium exposure and bladder cancer.** 10 estimates from 9 studies were incorporated in the pooled analysis. We found that exposure mode, area and design were not influencing factor (exposure mode: P = 0.05; area: P = 0.708; design: P = 0.601). Therefore, we took the 10 estimates into meta-analysis. The result showed that high selenium exposure was not associated with bladder cancer (pooled OR = 0.76, 95%CI: 0.58–1.01, as shown in Fig. 12) with moderate heterogeneity (Q = 25.06, P = 0.003; I² = 64.1), but without publication bias (Begger's test zc = 0.72; P = 0.474; Egger's test t = −0.90, P = 0.395). 3 groups of data were incorporated into dose-response...
analysis between toenail selenium and bladder cancer risk. The consequence of linear dose-response analysis presented that toenail selenium was not associated with bladder cancer risk per 0.1 ug/g increase of toenail selenium (pooled OR = 0.95, 95%CI: 0.90–1.01). Otherwise, we did not find a threshold effect in the plot between toenail selenium and bladder cancer risk in nonlinear dose-response analysis (P = 0.413 for non-linearity; Fig. S5).

**Selenium exposure and prostate cancer.** 26 estimates from 25 studies described the association between selenium and risk of prostate cancer. We found that exposure mode, area and design were not influencing factor (exposure mode: P = 0.682; area: P = 0.362; design: P = 0.478). Therefore, we took the 26 estimates into meta-analysis. The result showed that high selenium exposure decreased risk of prostate cancer (pooled OR = 0.72, 95%CI: 0.61–0.86, Fig. 13), with moderate heterogeneity (Q = 81.6, P = 0.000; I²% = 69.4). There was no publication bias (Begger's test zc = 1.92; P = 0.055; Egger's test t = −1.90, P = 0.070). Sensitivity analysis showed that the result was robust (Supplemental Table S1).

7 groups of data were incorporated into dose-response analysis between plasma/serum selenium and prostate cancer and 5 groups of data were included between toenail selenium and prostate cancer. The result of linear dose-response analysis presented that plasma/serum selenium was associated with prostate cancer risk per 10 ug/L increases (pooled OR = 0.97, 95%CI: 0.95–0.99; Q = 19.5, P = 0.003). The result presented that toenail selenium was associated with prostate cancer risk per 0.1 ug/g increases (pooled OR = 0.94, 95%CI: 0.89–0.99; Q = 20.27, P = 0.000). We did not find threshold effects in the plots between plasma/serum and toenail selenium and prostate cancer risk in nonlinear dose-response analyses (P = 0.739, P = 0.886 for non-linearity, respectively; Fig. S6,S7).

**Selenium exposure and risk of skin cancer.** 6 estimates from 4 studies were incorporated into the pooled analysis. We found that exposure mode and area were not influencing factor (exposure mode: P = 0.395; area: P = 0.454). Therefore, we took the 6 estimates into meta-analysis. The result of the pooled analysis showed that high selenium exposure was not associated with skin cancer (pooled OR = 1.09, 95%CI: 0.98–1.21, Fig. 14), with no heterogeneity (Q = 3.65, P = 0.601; I²% = 0.0) and publication bias (Begger's test zc = 0.00; P = 1.000; Egger's test t = 0.42, P = 0.697). Sensitivity analysis showed that the result was robust (Supplemental Table S1).

**Other subgroup analysis.** The further stratified analysis were conducted by gender and study design. The results indicated that the protective effect of high selenium exposure had no gender difference (as shown in Table 2). When stratified by design, we found the results from observational studies presented the protective effect of selenium on cancer while the results from RCTs indicated null effect (as shown in Table 2).
Discussion
Debating on Se-Cancer association is persistent. Selenium has been hypothesized to be a cancer preventive agent, a cancer therapeutic agent, or be a carcinogen. Several studies presented results that blood selenium was associated with cancer. According to breast cancer, results from Harris H R et al., Rejali et al., and Hardell, L et al. studies presented a protective effect of selenium, while other observational studies showed null associations between selenium and breast cancer. For lung cancer, findings from Jaworska K et al., Gromadzinska, J et al., Hartman, T. J et al. Knekt, P. et al. et al. studies showed that high selenium exposure decreased lung cancer risk, but other observational studies described the relation between digest system cancer, but the results were also inconsistent. Stevens, J et al. study presented that toenail selenium was associated with esophageal squamous cell carcinoma, but not with gastric cardia cancer. Wei WQ et al. study in China showed that serum selenium was associated with mortality of esophageal squamous cell carcinoma and gastric cardia cancer. Several studies presented null relation between serum selenium and colon cancer, rectal cancer. However, Clark LC et al. randomized controlled trial showed selenium supplement decreased risk of colorectal cancer in people with skin carcinoma. According to bladder cancer, different studies showed different results. Hotaling JM et al. study presented that long-term use of supplemental selenium could not decrease bladder cancer risk after 6 years' follow-up. Lotan Y et al. randomized controlled trial presented a similar result. Michaud, D. S et al. study showed a gender-specific relation between toenail selenium and bladder cancer that high toenail selenium had a protective effect on female bladder cancer. According to prostate cancer, the US Selenium and Vitamin E Cancer Prevention Trial showed that a long term oral supplement of selenomethionin did not prevent prostate cancer. And numerous observational studies also presented inconsistent results. Hurst, R et al. meta-analysis which included twelve studies showed that prostate cancer risk reduced with the increase of plasma/serum and toenail selenium. The Nutritional Prevention of Cancer Trial (NPCT) investigated the effect of selenium supplement on the development of skin cancer, and found no protective efficacy, Reid, M. E et al. study which was a sub-study of NPCT showed a similar result.

The results of meta-analysis suggest an inverse relation between selenium exposure and the total cancer risk (including breast cancer, lung cancer, esophageal cancer, gastric cancer, colorectal cancer, bladder cancer, prostate cancer, skin cancer, not site-specific cancer and other cancer). What is more, the results of dose-response analysis show a downward trend between plasma/serum selenium, toenail selenium and total cancer risk. The biomarker of selenium (serum/plasma and toenail selenium) was associated with cancer risk and could be easily measured and monitored to evaluate people health status. However, our results find that selenium supplement is not associated with cancer risk. Selenium supplement contains either inorganic or organic species or a mixture of both. The SELECT trial uses L-selenomethionine as an oral supplement, while the NPCT trial uses selenium yeast tablets. The different types of selenium supplement may present different effects on human health. On the other hand, first-pass elimination and bioavailability of different participants should be considered. Burk et al. study presents the results that the full expression of selenoprotein P requires more Se intake than that required by the full expression of GPxs, indicating that the Se intakes of the current studies are probably inadequate for optimizing the protective effects. We also cannot exclude the possibility that it is what associated with higher biochemical selenium level presents the shielding effect other than selenium exposure itself. We know that RCTs should research the association between selenium supplement and cancer risk, while observational
Analyses. However, two randomized controlled trials (the NPCT trial\textsuperscript{28} and the SELECT trial\textsuperscript{27}) focusing on selenium and prostate cancer support the result, and downward trends are shown in nonlinear dose-response effects on bladder cancer risk. According to prostate cancer, we find a protective effect of high selenium exposure. These results are supported by the findings of seven epidemiologic studies presenting that plasma/serum selenium and toenail selenium have protective effects. We also conduct linear dose-response analyses which are stricter than high-versus-low analysis and the results of these analyses show dose-response trends in plots which are visual and accessible.

We also find that selenium has diverse effects on specific types of cancer. According to breast cancer, we find an inverse relation when taking all relevant estimates into account. Nonetheless, we lack sufficient data to conduct dose-response analyses. According to lung cancer, we find that high selenium exposure presents a protective efficacy. Though a downward trend is seen in the nonlinear dose-response analysis, there is no statistical significance between plasma/serum selenium and lung cancer risk in linear dose-response analysis. The association between lung cancer and selenium exposure needs more discussion. According to esophageal cancer and gastric cancer, we find an obvious inverse relation. The quantity of estimates included in meta-analyses is not as many as other types of cancer, and we lack sufficient data to conduct dose-response analyses. According to colorectal cancer, we find no association between selenium exposure and cancer risk. Nevertheless, Ou Y et al.\textsuperscript{25} found an inverse relation when taking all relevant estimates into account. Nonetheless, we lack sufficient data to conduct dose-response analyses. According to colorectal cancer, we find no association between selenium exposure and cancer risk. Nevertheless, Ou Y et al.\textsuperscript{25} presented that high selenium exposure presents a protective role in colorectal adenomas (OR = 0.67; 95%CI: 0.55–0.81). Selenium exposure probably plays a protective role in colorectal benign tumor rather than cancer, and the results need more researches. According to bladder cancer, we find no statistical significance between selenium exposure and bladder cancer. However, Amalar A F et al.\textsuperscript{36} presented that plasma/serum selenium and toenail selenium have protective effects on bladder cancer risk. According to prostate cancer, we find a protective effect of high selenium exposure for prostate cancer. The results of linear dose-response analyses between plasma/serum selenium, toenail selenium and prostate cancer support the result, and downward trends are shown in nonlinear dose-response analyses. However, two randomized controlled trials (the NPCT trial\textsuperscript{28} and the SELECT trial\textsuperscript{27}) focusing on selenium supplement present the consequence that selenium supplement is not associated with prostate cancer risk. According to skin cancer, we find selenium is not associated with skin cancer risk.

There are numerous hypotheses about the potential anticarcinogenic mechanisms of selenium. The major positive effect may be contributed by the antioxidant function of GPxs and selenoprotein P\textsuperscript{94}. Selenium is associated with the regulation of protein folding via the function of the endoplasmic reticulum to influence the process of necrosis and apoptosis of malignant cells\textsuperscript{95,96}. Selenium also has the effect on DNA stability\textsuperscript{96}. However, different malignant cells have their special biological characteristics and microenvironment for progress and invasion. They probably have disparate abilities of utilizing selenium. Hence, selenium probably has no effect on some types of cancer. The exact mechanism has yet to be investigated. On the other hand, the adverse effects of selenium supplement: mainly diabetes\textsuperscript{27,99}, glaucoma\textsuperscript{28}, and dermatologic alterations\textsuperscript{27} could not be ignored. So we should try to clarify what level of selenium supplement is needed for adequate nutrition and at what level dose is "unsafe".

Our meta-analysis has several limitations clearly. Measurement errors in the assessment of selenium exposure may bias the effect estimates. Even among those studies regarding the same biochemical selenium as exposure, different measurement methods, different facilities and different staffs are all easy to produce measurement errors, and it is hard to make corrections. As showed in our inclusion criteria, we select case-control studies, cohort studies and RCTs into our meta-analysis. Selenium exposure may be linked to other behaviors like age, income, race, smoking status, alcohol consumption, body mass index, physical activity. These controlled confounding factors differ among sixty-nine studies and may influence the association between selenium exposure and cancer risk. Because of the insufficient number of relevant estimates, we have limited power to conduct subgroup analysis of pathological types of different cancer, and other controlled confounding factors.

Our study also has a few strength. We bring in a large number of studies and have largely avoided some main influencing factors by meta-regression analyses. And the robust outcomes of sensitivity analysis suggest that there is no distinct date making particularly contribution to the results. We detect the association between selenium exposure and different types of cancer to find a comprehensive understanding from global effects to local effects. We also conduct linear dose-response analyses which are stricter than high-versus-low analysis and the results of nonlinear dose-response analyses show dose-response trends in plots which are visual and accessible.

### Table 2. The stratified analysis by gender and study design.

| Subgroup | Type of subgroup | No of estimates | OR(95%CI) | Homogeneity test | P | F(%) |
|----------|-----------------|----------------|-----------|-----------------|---|------|
| Design   | cohort          | 40             | 0.75(0.68,0.82) | 209.01 | 0.000 | 81.8 |
|          | Case-control    | 61             | 0.77(0.69,0.86) | 162.63 | 0.000 | 63.7 |
|          | RCT             | 13             | 0.89(0.74,1.08) | 31.32  | 0.002 | 61.7 |
| Gender   | Men             | 39             | 0.74(0.64,0.86) | 111.94 | 0.000 | 66.1 |
|          | Women           | 31             | 0.90(0.86,0.95) | 42.01  | 0.071 | 28.6 |
|          | Both combined   | 44             | 0.73(0.66,0.80) | 260.02 | 0.000 | 83.5 |

### Conclusions

High selenium exposure could decrease cancer risk, especially high plasma/serum selenium and toenail selenium. High selenium exposure may have dissimilar effects on specific types of cancer. Future epidemiological studies should pay more attention to the procedure from selenium supplement to biochemical selenium status to figure out the reasons for the inconsistent effects of selenium supplement and biochemical selenium for preventing cancer. And future epidemiological studies and intervention trials should try to research selenium supplement, plasma/serum selenium and toenail selenium at the same time to reduce the potential bias.
and intervention trials should try to research selenium supplement, plasma/serum selenium and toenail selenium at the same time to reduce the potential bias. The exact mechanism needs to be further investigated.

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Author Contributions

X.C. and C.W. conducted the search work and all the data were extracted independently by X.C., C.W. and N.S. X.C. and C.W. wrote the main manuscript text and prepared the tables. N.S., W.Y., W.F., S.W. and P.W. prepared figures. X.L. reviewed and corrected the manuscript. F.W. reviewed the manuscript.

Additional Information

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