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Title: The Selenium and Vitamin E Cancer Prevention Trial (SELECT): a secondary, post-intervention analysis on potential excess chronic disease incidence induced by selenium administration

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Abstract

The potential for trace amounts of selenium supplements to prevent prostate cancer and other neoplasms was studied in SELECT, a randomized trial conducted in North America for 7-12 years. 34,887 eligible men age 55 or older were assigned to take either 200 µg selenium from L-selenomethionine, 400 IU vitamin E, both selenium and vitamin E, or placebo. The trial was stopped for futility and concerns about adverse effects. Subsequently, we used incidence and mortality data from Medicare through 2019 and the National Death Index through 2024 to investigate the extent to which selenium administration was associated with increased long-term risk of cancer and neurodegenerative disease, during 341,697 person-years of follow-up. Lung cancer showed little increased risk. Associations were near null for leukemia, non-Hodgkin lymphoma and Parkinson's disease, and there was a lower risk for melanoma and colorectal cancer. In contrast, we found a higher risk for Hodgkin lymphoma, multiple myeloma and amyotrophic lateral sclerosis, which has been associated with selenium overexposure in some nonexperimental studies. Though these latter associations were based on few cases, they were consistent with findings from a range of other studies, possibly indicating long-term adverse effects of this organic selenium compound. (Registration no. NCT00006392)

Introduction

The possibility that selenium, a trace element of strong nutritional and toxicological interest, could influence chronic disease risk and particularly cancer incidence has been the object of considerable interest during the last decades (1-3). This metalloid is an essential element that is incorporated into antioxidant enzymes, such as glutathione-peroxidase and other selenoproteins (4, 5). On the other hand, no other element shows such a narrow range of safe intake (6, 7), and a potentially broad range of adverse effects following its overexposure (8-13). The upper level of safe intake is still not entirely clear, but recent advice (7) suggests a level that is not much greater than the levels recommended for consumption, ranging from 30-70 µg/day (6, 12, 14-19).

The hypothesis that selenium has a beneficial effect in counteracting both oxidative stress and chronic disease risk was bolstered by ecologic studies carried out in the 1970s and the 1980s, and the discovery that the selenium-containing glutathione peroxidase has antioxidant properties (20). Preliminary results from a randomized controlled trial (RCT) carried out in the US, published in 1996, showed a marked beneficial effect on the risk of secondary outcomes such as prostate cancer and other cancers, though not on the primary endpoint of non-melanoma skin cancer. Neither was there any indication of a beneficial effect on cardiovascular or respiratory disease (21). The finding of a reduced risk for cancer was supported by evidence from nonexperimental studies, and fueled the idea in both the scientific community and the general public that increasing selenium intake would benefit individuals who were at high risk for cancer. This hypothesis prompted additional RCTs, mostly in the US and in populations with a mixed status regarding selenium background intake (1). The results of these experimental studies have been published over the last two decades, and have also been summarized in meta-analyses (1, 22-30). These RCTs yielded results inconsistent with beneficial effects on the prevention of cancer as well as other chronic and acute diseases, while documenting occurrence of

adverse effects, ranging from alopecia and skin alterations to type 2 diabetes, high-grade prostate cancer, altered thyroid function and atrial fibrillation (6, 11, 16, 18, 31, 32).

Given these findings, further experimental studies in humans are unlikely for ethical reasons. Therefore, the already completed trials, especially the Selenium and Vitamin E Prevention Trial (SELECT), being by far the largest and having the most thorough ascertainment of exposure and outcome, continue to be the most valuable source of evidence about selenium effects in humans, including possible adverse long-term effects (27, 33, 34). Here we report the results of an extended follow-up of SELECT using the Medicare database and US National Death Index (NDI), including a post-intervention long-term phase focusing on cancer and neurodegenerative disease outcomes that have been hypothesized to be related to long-term selenium toxicity. We included neurodegenerative disease (Parkinson's disease and amyotrophic lateral sclerosis (ALS)) as well as cancer outcomes, given the growing evidence from laboratory and epidemiologic studies about both favorable and adverse effects of selenium in the central nervous system (9, 10, 12, 35, 36), and the paucity of results from trials, currently limited to incidence of Alzheimer's dementia in SELECT (37).

Methods

Data are from the Selenium and Vitamin E Cancer Prevention Trial (SELECT), a Phase III randomized placebo-controlled study that evaluated the extent to which selenium and vitamin E, alone or combined, reduced prostate cancer risk (3). The trial was conducted by United States and Canadian investigators from cooperative groups of the US National Cancer Institute and US Department of Veterans Affairs. Briefly, 35,533 men age ≥ 50 years (if African American) or ≥ 55 years (all others), with no history of prostate cancer, a serum prostate specific antigen (PSA) of ≤ 4 ng/mL, and a normal digital rectal exam (DRE) were randomized from July 2001 to October 2008 to one of 4 groups: 200 μ g/day of selenium as *L*-selenomethionine + placebo, vitamin E (400 IU/d of *all rac*- α -tocopheryl acetate) +

placebo, selenium + vitamin E, or placebo + placebo (31). In 2008, the trial's Data Safety and Monitoring Committee (DSMC) recommended that participants discontinue taking study supplements due to evidence that selenium and vitamin E were not effective in preventing prostate cancer (31, 38). In addition, the Committee had some concern over an increase in diabetes mellitus associated with selenium (RR=1.10, 95% CI, 0.99-1.22, unpublished DSMC report data) (31). Later, a further report from SELECT identified an increased risk of high-grade prostate cancer among men randomized to selenium alone (HR 1.74, 95% CI 0.81-3.72) or to 'any selenium' (HR 1.96, 95% CI 1.00-3.86) who had the highest baseline selenium status (11). Because of the potential for effects of vitamin E on chronic disease outcomes when administered alone or together with selenium, the current analysis focuses on the selenium + placebo and placebo + placebo treatment arms only, though we also carried out a secondary analysis comparing participants receiving 'any selenium' versus 'no selenium', irrespective of vitamin E administration.

The present analysis includes all 34,887 eligible and evaluable men participating in SELECT. The endpoints included in this report include two neurodegenerative diseases, amyotrophic lateral sclerosis (ALS) and Parkinson's Disease; hematopoietic cancers (including leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma, and multiple myeloma); and melanoma, colorectal cancer, and lung cancer. These endpoints were selected based on observations from a cohort exposed to selenium in drinking water. (39, 40), from the Nutritional Prevention of Cancer trial (41), from epidemiologic studies and systematic reviews (1, 39, 42-46). These outcomes were incidence of hematopoietic cancers (myeloma and Hodgkin lymphoma in particular), melanoma, ALS and Parkinson's disease. We also included in the analysis incidence of two common neoplasms, colorectal and lung cancer, pre-defined secondary endpoints for SELECT, for which the first RCTs on selenium, the Nutritional Prevention of Cancer trial, detected beneficial effects of selenium alongside prostate cancer (21, 41).

To examine outcomes beyond the study period, we linked SELECT clinical records to participants' cause of death data from the National Death Index (NDI) through their social security number where available, and to Medicare Parts A & B claims data through their social security number where available, as well as sex and date of birth. The linkages allowed outcomes to be identified by both SELECT clinical records and NDI and Medicare claims. Cause of death data from NDI was available through 2024. Linkage to the Medicare database required that participants had at least 12 months' continuous Medicare coverage at any time after study enrollment, to ensure sufficient opportunity to identify outcomes. Men must have had no HMO coverage concurrent with their continuous Medicare Parts A & B coverage, as Medicare claims for HMO-insurance individuals are not available for research. Medicare records included physician supplier Part B, hospital outpatient, and hospital inpatient claims from 1999 to 2019. Participants who were <65 years at study randomization were linked if they aged into the Medicare claims cohort.

Because all eligible and evaluable men were at risk of these outcomes, all participants were included in this analysis. Outcomes were identified in the SELECT database based on patient self-report in clinical records, and in the NDI database based on primary cause-of-death records. Outcomes were identified in the Medicare database as any hospital claim or two or more physician or outpatient claims ≥ 30 days apart for previously validated ICD (International Classification of Disease)-9, ICD10, and HCPCS (Healthcare Common Procedure Coding System) codes for ALS, Parkinson's Disease, lymphoid malignancies, melanoma, or colorectal or lung cancer (Appendix S1, Table S1). Date and cause of death was based on SELECT clinical records or NDI records when available, and on Medicare records when SELECT and NDI data were not available. Trial demographic factors were obtained from patient self-report.

Data Analysis

We compared participant characteristics between those on the selenium + placebo treatment arm with those on the placebo + placebo treatment arm, and between those with a Medicare linkage or cause-of-death identified through NDI linkage and those with neither. We used Cox regression to calculate the hazard ratio of developing outcomes for those on the selenium alone treatment arm compared with those receiving placebo during the intervention period, i.e., with the arms containing vitamin E excluded. We accounted for the competing risk of death by classifying deaths from any cause other than the outcome of interest as competing risk events, using the Fine and Gray method (47). For each outcome, time was indexed at SELECT study registration, and ended at the first identification of the outcome, or censored at the end of Medicare coverage, for men with an adequate Medicare link, or the end of SELECT study period, for men with no link. In some instances, gaps in observation occurred between the participant's last recorded date of SWOG contact and the start of Medicare coverage. After the start of Medicare coverage, gaps also occurred for participants who dropped out of Medicare for more than 3 months and then regained coverage (gaps <3 months were ignored to allow for minor administrative switching between plans). For men with no evidence of an outcome, participant time at risk in the Cox model included only the time under observation, and for men with evidence of an outcome, all time from SELECT study registration to first recorded date of event is included. For men with no evidence of an outcome from SELECT study records or Medicare claims data, but with a cause-of-death recorded in the NDI, we used date-of-death as a proxy for diagnosis date for that outcome. Cox regression was adjusted for age at study registration and race (Black vs non-Black). The assumption of proportional hazards was assessed by evaluating the statistical interaction of selenium treatment with the log of time. In an additional analysis, we compared the arm containing any selenium (selenium + placebo or selenium + vitamin E) to the arms not containing selenium (placebo + placebo or vitamin E + placebo). We estimated and plotted cumulative incidence of each outcome, beginning at study registration and until diagnosis or censor, with the competing risk of death by any other cause.

A number of sensitivity analyses were performed. First, we evaluated the possibility of effect modification by baseline selenium concentrations among those for whom baseline serum selenium values were available. We also conducted sensitivity analyses that restricted to Medicare-linked participants only, that included only the post-intervention period, and that excluded the first 2 years of observation.

Results

Details of the SELECT participants at baseline are presented in Table 1. There were 34,887 eligible participants, including 19,227 (55.1%) with a link to Medicare claims data, and 8,900 (25.5%) with cause of death information obtained from NDI. The main analysis includes 17,448 on the placebo + placebo (n=8,696) and selenium + placebo (n=8752) arms. Total person-years of follow-up, including SELECT observation, and Medicare and NDI information for those successfully linked, was 85,361 on the placebo + placebo arm and 85,707 on the selenium + placebo arm, while correspond figures for all participants randomized to any selenium versus those not receiving any selenium were 171,136 and 170,561, respectively. Median age at registration was 62, 13.3% of participants were Black race, and 6.6% were Hispanic ethnicity. The most common outcome was Parkinson's disease (N=899) and the least common was Hodgkin lymphoma (N=29). Overall, forty-two participants were diagnosed with ALS. For all outcomes, the majority of cases were identified through Medicare claims data (Table 2).

Participants with a Medicare link or cause-of-death identified through NDI linkage were slightly older and had slightly higher BMI and incidence of diabetes (Appendix S1, Table S2).

Men who were on the selenium + placebo arm compared with the placebo + placebo arm had a tiny increased risk of hematopoietic malignancies (HR 1.07, 95% CI 0.86-1.33 - Table 3), mainly stemming from an increased risk of myeloma (HR 1.28, 95% CI 0.73-2.26, based on 28 and 78 observed cases in the selenium intervention arm). The strongest rate ratio estimate observed was for Hodgkin lymphoma

(HR=2.01, 95% CI, 0.60-6.67), but this estimate had a wide confidence interval, being based on only 8 cases in the selenium + placebo arm and 6 in the placebo + placebo arm. No increase was seen for non-Hodgkin lymphoma (HR 0.98, 95% CI 0.73-1.33).

For more common cancers, colorectal cancer incidence in trial participants allocated to 200 µg/day selenium was lower than for placebo (HR 0.86, 95% CI 0.67-1.10). Similarly, for melanoma, HR 0.71, 95% CI 0.54-0.95, whereas for lung cancer incidence was slightly greater among those receiving selenium (HR 1.07, 95% CI 0.87-1.31).

We found no evidence of an effect on Parkinson's disease incidence (HR 0.94, 95% CI 0.78-1.14 based on 222 cases in the placebo arm and 210 in the selenium arm). There was a small and statistically unstable excess risk for ALS (HR 1.20, 95% CI 0.52-2.77), based on 10 cases in the placebo arm and 13 in the selenium arm. There was no evidence of nonproportional hazards for any of the outcomes.

In Figure 1, we report the cumulative incidence of outcomes by treatment status (selenium + placebo versus placebo + placebo). There was a clear trend with an increasing risk difference for melanoma between the two arms (selenium + placebo versus placebo + placebo), with the selenium group having a lower risk. For multiple myeloma and Hodgkin lymphoma the risk difference increased over time and became evident only ten and more years after the start of the intervention period, with an indication of an excess risk in the selenium + placebo arm. For the other outcomes, no important risk differences accumulated during the follow-up.

When arms containing vitamin E were included, comparing the selenium + placebo and selenium + vitamin E treatment arms ('Any selenium') to the vitamin E + placebo and placebo + placebo arms ('No selenium') (Appendix S1, Table S3), results were similar (Table 4, Figure 2), indicating no major effect-measure modification by co-administration of vitamin E. In an exploratory secondary analysis, we evaluated effect measure modification by baseline serum selenium concentration by including an interaction term between selenium treatment assignment and baseline serum selenium concentrations,

among the subset of participants with available baseline serum measures (1286 on the selenium + placebo arm and 1249 on the placebo + placebo arm). We found little evidence for interaction, indicating that any effect of the selenium intervention on outcomes did not depend on pre-supplementation selenium concentrations. In secondary analyses limited to participants with a Medicare linkage, to post-intervention time, or to observation time after the first two years, results were similar (Appendix S1, Tables S4-S6).

Discussion

This study investigated a few potential chronic toxicity endpoints of selenium administration in a long term follow-up of SELECT trial participants, despite the study being discontinued because preliminary results indicated that the interventions were ineffective, and because of concern about excess diabetes incidence in the selenium-supplemented arm and prostate cancer in the vitamin E supplemented arm (31). Overall, the rationale for evaluating adverse effects on the outcomes investigated in this study is driven by *a priori* epidemiologic and toxicological findings about endpoints possibly related to selenium overexposure, and the recent recognition of its unexpected toxicity at low-doses, with its designated safe upper level having been recently lowered below that assigned to SELECT participants (7).

We found some evidence of adverse effects, namely an increased incidence of two hematopoietic malignancies, Hodgkin lymphoma and multiple myeloma, and possibly ALS. Conversely, we found a decreased risk of melanoma, an outcome hypothesized to be a risk of selenium supplementation. We also found a decreased risk of colorectal cancer, a small increase in lung cancer risk, and equivocal findings for Parkinson's disease. However, for most of these outcomes the magnitude

of association was small, with the exception of the increased risk for Hodgkin lymphoma and myeloma, and to a lesser extent the decreased risk for melanoma and increased risk for ALS.

An excess risk for hematopoietic cancer, mainly due to excess incidence of Hodgkin lymphoma and multiple myeloma, has been reported in the natural experiment linked to the distribution of high-selenium drinking water in Rivalta, Northern Italy (39, 40). Approximately 2000 residents consumed roughly 20 µg/day of inorganic hexavalent selenium over several years. This form of selenium is a much more toxic form than the organic selenium, selenomethionine, used in SELECT (6, 48). The first selenium trial, NPC, also reported an excess incidence of cancers grouped as 'Lymphoma and leukemia' (alongside four other cancer types) though based on few cases (no.=8, HR 1.25, 95% CI 0.43-3.61) (41). The authors stated that "These results, although nonsignificant and based on small case numbers, may indicate potential increased risk with selenium supplementation" (41). NPC was based on dietary supplementation with selenized yeast, largely expected to be composed of organic selenium and selenomethionine in particular (49, 50), as in SELECT. Overall, the present results from SELECT appear to indicate an increased risk of multiple myeloma for those with high levels of exposure to selenium. This could also be the case for Hodgkin lymphoma, though the small number of cases makes this inference much more tentative.

The lung cancer results are difficult to interpret and nearly null, since the excess incidence in the selenium arm was small (+7%). Meta-analysis of the only two RCTs rated at low risk of bias (including SELECT) yields a summary risk ratio estimate of 1.16 (95% CI 0.89 to 1.50) (1), slightly greater than the value reported here.

Results for the other two cancer types, colorectal cancer and melanoma, unexpectedly indicated a possible inverse relation with selenium administration, though there were fewer cases than for lung cancer. There is little evidence linking selenium supplementation with any effects on colorectal cancer based on the RCTs (summary RR in experimental studies at low risk of bias 0.99, 95% CI 0.69-1.43). For

melanoma there was a slight indication of a potentially increased risk from the Italian natural experiment (39) and from RCTs (summary risk ratio 1.24, 95% CI 0.57-2.68 (26)). Thus, the extended follow-up of the SELECT cohort does not appear to support a detrimental effect of selenium on melanoma; if anything, there is an indication of a beneficial effect. The same was true for colorectal cancer. However, the decreased risk for these two diseases is inconsistent with the results of a previous meta-analysis that pooled the results of RCTs for many cancer outcomes, including melanoma and colorectal cancer.

For the two neurological outcomes, Parkinson's disease and ALS, we found somewhat inconsistent findings despite emerging evidence of selenium neurotoxicity as a driver of neurodegeneration (9, 10). Parkinson's disease has rarely been investigated in relation to selenium exposure, with no data made available by trials and an indication of excess mortality from the Italian natural experiment (39) and other evidence (42). Our findings provide little evidence that organic selenium in the form of selenomethionine and at the amounts supplemented in this study raises the risk of this disease. Conversely, for ALS, we found a 20% excess incidence in selenium-supplemented participants, though based on few cases and therefore difficult to interpret. There is epidemiologic evidence linking selenium overexposure to ALS (51), based on nonexperimental studies (43, 44, 46, 52), some of which used central nervous system exposure biomarkers (53, 54). The link between excess selenium exposure and ALS is also supported by biological plausibility, such as the observation of a selective toxicity of selenium species on motor neurons in animal studies (55-58), and the capacity to disrupt intracellular microtubules and induce in laboratory studies other adverse biochemical effects characteristic of the human disease (59-62).

With specific reference to cancer, selenium is genotoxic and immunotoxic at levels slightly exceeding the recommended dietary allowance (23, 63-66), and at surprisingly low doses in human (23).

Selenium species, including selenomethionine, may have pro-oxidant and other toxic properties (67-71), all these mechanisms being potentially related to increased cancer risk.

Our follow-up was extended several years after the end of the trial, and the differences in mortality rates widened over time, suggesting the need for lengthy follow-up to detect delayed effects. This limitation, coupled with the anticipated difficulty in replicating any selenium trial, make the observations from long-term SELECT follow-up uniquely valuable.

In this analysis, we used Medicare and the National Death Index as data sources, a methodology that will have low sensitivity in detecting cases of disease with low lethality or morbidity. Additionally, as participants entered Medicare coverage at different times, with some experiencing a large gap between the initiation of selenium supplementation and identification of outcomes through Medicare claims data, there could be bias in outcome detection and follow-up. However, any underascertainment or outcome detection by Medicare enrollment time is the same for those receiving selenium or placebo, and would not be expected to bias ratio measures of effect (72).

We focused in our analysis on the 'selenium only' and placebo arms of the trial, given the evidence suggesting that selenium biologically interacts with many other dietary factors of nutritional and toxicological importance (). However, we also looked at the treatment arms containing 'any Selenium' and compared them with those containing 'No Selenium', despite the potential for effect-measure modification by vitamin E supplementation. We found substantially similar results, with statistically more stable risk ratio estimates.

This trial used only one chemical form of organic selenium, selenomethionine, the most common form in foods (73). Given the markedly different nutritional and toxicological properties of organic and inorganic selenium species (6, 74, 75), we are reluctant to draw inferences about other forms of selenium. Similarly, our findings should not be extrapolated to populations exposed to extremely high or extremely low amounts of selenium, though the blood selenium distribution in SELECT

overlapped that observed in other trials and in many Western countries (6, 7). In addition, this trial was restricted to males, and the applicability of the findings to females is unknown. Sex differences in the effects of selenium have been reported (39-41). Moreover, the study didn't allow a dose-response analysis, given that only one dosage of selenium supplements (200 µg/day) was used in the trial. Finally, compliance to the intervention was imperfect, as expected, but was still good even in the medium term (84% in the selenium arm and 85% in the placebo arm at year 1, and 69% in both arms at year 5 based on pill count (31)), implying little bias from differential decreasing adherence to the study protocol over time.

Data Availability: The data used for the current study are not publicly available due to privacy concerns.

References

1. Vinceti M, Filippini T, Del Giovane C, et al. Selenium for preventing cancer. *Cochrane Database Syst Rev*. 2018;1:CD005195. <https://doi.org/10.1002/14651858.CD005195.pub4>.
2. Vinceti M, Crespi CM, Malagoli C, et al. Friend or foe? The current epidemiologic evidence on selenium and human cancer risk. *J Environ Sci Health C Environ Carcinog Ecotoxicol Rev*. 2013;31(4):305-341. <https://doi.org/10.1080/10590501.2013.844757>.
3. Lippman SM, Goodman PJ, Klein EA, et al. Designing the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *J Natl Cancer Inst*. 2005;97(2):94-102. <https://doi.org/10.1093/jnci/dji009>.
4. Hatfield DL, Tsuji PA, Carlson BA, et al. Selenium and selenocysteine: roles in cancer, health, and development. *Trends Biochem Sci*. 2014;39:112-120. <https://doi.org/10.1016/j.tibs.2013.12.007>.
5. Labunskyy VM, Hatfield DL, Gladyshev VN. Selenoproteins: Molecular pathways and physiological roles. *Physiol Rev*. 2014;94(3):739-777. <https://doi.org/10.1152/physrev.00039.2013>.
6. Vinceti M, Filippini T, Wise LA. Environmental selenium and human health: an update. *Curr Environ Health Rep*. 2018;5(4):464-485. <https://doi.org/10.1007/s40572-018-0213-0>.
7. EFSA Panel on Nutrition Novel Foods Food and Allergens, Turck D, Bohn T, et al. Scientific opinion on the tolerable upper intake level for selenium. *EFSA J*. 2023;21(1):e07704. <https://doi.org/10.2903/j.efsa.2023.7704>.
8. Vinceti M, Filippini T, Cilloni S, et al. Health risk assessment of environmental selenium: emerging evidence and challenges. *Mol Med Rep*. 2017;15(5):3323-3335. <https://doi.org/10.3892/mmr.2017.6377>.
9. Vinceti M, Mandrioli J, Borella P, et al. Selenium neurotoxicity in humans: bridging laboratory and epidemiologic studies. *Toxicol Lett*. 2014;230(2):295-303. <https://doi.org/10.1016/j.toxlet.2013.11.016>.

10. Naderi M, Puar P, Zonouzi-Marand M, et al. A comprehensive review on the neuropathophysiology of selenium. *Sci Total Environ*. 2021;767:144329. <https://doi.org/10.1016/j.scitotenv.2020.144329>.
11. Kristal AR, Darke AK, Morris JS, et al. Baseline selenium status and effects of selenium and vitamin e supplementation on prostate cancer risk. *J Natl Cancer Inst*. 2014;106(3):djt456. <https://doi.org/10.1093/jnci/djt456>.
12. Williams SC, Navas-Acien A, Goessler W, et al. Urinary selenium, cranial MRI, and cognitive function in American Indians: the Strong Heart Study. *Environ Res*. 2025;269:120913. <https://doi.org/10.1016/j.envres.2025.120913>.
13. Makino K, Iwata H, Yamaguchi T, et al. Toxic metals and trace elements in maternal blood and urinary tract infection during the first 2 years of life: the Japan Environment and Children's Study. *Sci Total Environ*. 2025;1006:180895. <https://doi.org/10.1016/j.scitotenv.2025.180895>.
14. Chen J, Jiang H, Fang X. The association between non-alcoholic fatty liver disease with blood selenium level based on the NHANES 2017-2020. *Clin Exp Med*. 2026;26(1):98. <https://doi.org/10.1007/s10238-025-01984-6>.
15. Zhao D, Domingo-Rellos A, Tellez-Plaza M, et al. High level of selenium exposure in the Strong Heart Study: a cause for incident cardiovascular disease? *Antioxid Redox Signal*. 2022;37(13-15):990-997. <https://doi.org/10.1089/ars.2022.0029>.
16. Vinceti M, Filippini T, Wise LA, et al. A systematic review and dose-response meta-analysis of exposure to environmental selenium and the risk of type 2 diabetes in nonexperimental studies. *Environ Res*. 2021;197:111210. <https://doi.org/10.1016/j.envres.2021.111210>.
17. Cheng L, Zeng Z, Quan H. Association of selenium with type 2 diabetes and obesity: a univariate and multivariate Mendelian randomization study. *Medicine (Baltimore)*. 2025;104(42):e45338. <https://doi.org/10.1097/MD.00000000000045338>.
18. Winther KH, Bonnema SJ, Cold F, et al. Does selenium supplementation affect thyroid function? Results from a randomized, controlled, double-blinded trial in a Danish population. *Eur J Endocrinol*. 2015;172(6):657-667. <https://doi.org/10.1530/EJE-15-0069>.
19. Rayman MP, Winther KH, Pastor-Barriuso R, et al. Effect of long-term selenium supplementation on mortality: results from a multiple-dose, randomised controlled trial. *Free Radic Biol Med*. 2018;127:46-54. <https://doi.org/10.1016/j.freeradbiomed.2018.02.015>.
20. Vinceti M, Rovesti S, Bergomi M, et al. The epidemiology of selenium and human cancer. *Tumori*. 2000;86:105-118. <https://doi.org/10.1177/030089160008600201>.
21. Clark LC, Combs GF, Turnbull BW, et al. Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized controlled trial. Nutritional Prevention of Cancer Study Group. *JAMA*. 1996;276(24):1957-1963. <https://doi.org/10.1001/jama.1996.03540240035027>.
22. Urbano T, Wise LA, Fiore G, et al. Effects of selenium administration on blood lipids: a systematic review and dose-response meta-analysis of experimental human studies. *Nutr Rev*. 2026;84(3):551-570. <https://doi.org/10.1093/nutrit/nuaf049>.
23. Filippini T, Fairweather-Tait S, Vinceti M. Selenium and immune function: a systematic review and meta-analysis of experimental human studies. *Am J Clin Nutr*. 2023;117(1):93-110. <https://doi.org/10.1016/j.ajcnut.2022.11.007>.
24. Vinceti M, Filippini T, Rothman KJ. Selenium exposure and the risk of type 2 diabetes: a systematic review and meta-analysis. *Eur J Epidemiol*. 2018;33(9):789-810. <https://doi.org/10.1007/s10654-018-0422-8>.
25. Khodadadi H, Ebrahimi A, Jalali F, et al. Dose-response association between circulating selenium and blood pressure: a systematic review and meta-analysis. *BMC Public Health*. 2025;25(1):3986. <https://doi.org/10.1186/s12889-025-24205-x>.

26. Filippini T, Mazzoli R, Wise LA, et al. Selenium exposure and risk of skin cancer: a systematic review and dose-response meta-analysis of epidemiologic evidence. *J Trace Elem Med Biol*. 2025;90:127693. <https://doi.org/10.1016/j.jtemb.2025.127693>.
27. Cramon PK, Winther KH, Boesen VB, et al. Selenium supplementation in individuals with newly diagnosed Graves' hyperthyroidism: a double-blind, multi-centre RCT. *Eur Thyroid J*. 2026;15(1):ETJ250264. <https://doi.org/10.1530/ETJ-25-0264>.
28. Kostadinov N, Kirovakov Z, Penchev P. Efficacy of selenium supplementation in Graves' orbitopathy: a systematic review and meta-analysis of randomized controlled trials with trial sequential analysis. *J Clin Med*. 2026;15(12):4710. <https://doi.org/10.3390/jcm15124710>.
29. Ahn HY, Lee MJ, Jung KY, et al. Selenium vs control for Graves ophthalmopathy in a selenium-sufficient area: a randomized clinical trial. *JAMA Ophthalmol*. 2025;143(4):287-294. <https://doi.org/10.1001/jamaophthalmol.2024.6337>.
30. Stoppe C, McDonald B, Meybohm P, et al. Effect of high-dose selenium on postoperative organ dysfunction and mortality in cardiac surgery patients: the SUSTAIN CSX randomized clinical trial. *JAMA Surg*. 2023;158(3):235-244. <https://doi.org/10.1001/jamasurg.2022.6855>.
31. Lippman SM, Klein EA, Goodman PJ, et al. Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA*. 2009;301(1):39-51. <https://doi.org/10.1001/jama.2008.864>.
32. Catena D, Stoppe C, Mohsen G, et al. Perioperative high-dose selenium supplementation in open thoracic aortic surgery: a post hoc subgroup analysis of the SUSTAIN CSX trial. *J Thorac Dis*. 2026;18(2):72. <https://doi.org/10.21037/jtd-2025-1-2471>.
33. Kryscio RJ, Abner EL, Schmitt FA, et al. A randomized controlled Alzheimer's disease prevention trial's evolution into an exposure trial: the PREADViSE trial. *J Nutr Health Aging*. 2013;17(1):72-75. <https://doi.org/10.1007/s12603-012-0083-3>.
34. Goodman PJ, Hartline JA, Tangen CM, et al. Moving a randomized clinical trial into an observational cohort. *Clin Trials*. 2013;10(1):131-142. <https://doi.org/10.1177/1740774512460345>.
35. Schweizer U, Fabiano M. Selenoproteins in brain development and function. *Free Radic Biol Med*. 2022;190:105-115. <https://doi.org/10.1016/j.freeradbiomed.2022.07.022>.
36. Vinceti M, Urbano T, Chiari A, et al. Selenoprotein P concentrations and risk of progression from mild cognitive impairment to dementia. *Sci Rep*. 2023;13(1):8792. <https://doi.org/10.1038/s41598-023-36084-6>.
37. Kryscio RJ, Abner EL, Caban-Holt A, et al. Association of antioxidant supplement use and dementia in the Prevention of Alzheimer's Disease by Vitamin E and Selenium Trial (PREADViSE). *JAMA Neurol*. 2017;74(5):567-573. <https://doi.org/10.1001/jamaneurol.2016.5778>.
38. Klein EA, Thompson IM, Jr., Tangen CM, et al. Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA*. 2011;306(14):1549-1556. <https://doi.org/10.1001/jama.2011.1437>.
39. Vinceti M, Ballotari P, Steinmaus C, et al. Long-term mortality patterns in a residential cohort exposed to inorganic selenium in drinking water. *Environ Res*. 2016;150:348-356. <https://doi.org/10.1016/j.envres.2016.06.009>.
40. Vinceti M, Vicentini M, Wise LA, et al. Cancer incidence following long-term consumption of drinking water with high inorganic selenium content. *Sci Total Environ*. 2018;635C:390-396. <https://doi.org/10.1016/j.scitotenv.2018.04.097>.
41. Duffield-Lillico AJ, Reid ME, Turnbull BW, et al. 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*. 2002;11(7):630-639.

42. Adani G, Filippini T, Michalke B, et al. Selenium and other trace elements in the etiology of Parkinson's disease: a systematic review and meta-analysis of case-control studies. *Neuroepidemiology*. 2020;54(1):1-23. <https://doi.org/10.1159/000502357>.
43. Vinceti M, Filippini T, Malagoli C, et al. Amyotrophic lateral sclerosis incidence following exposure to inorganic selenium in drinking water: a long-term follow-up. *Environ Res*. 2019;179:108742. <https://doi.org/10.1016/j.envres.2019.108742>.
44. Benatar M, Heiman-Patterson TD, Cooper-Knock J, et al. Guidance for clinical management of pathogenic variant carriers at elevated genetic risk for ALS/FTD. *J Neurol Neurosurg Psychiatry*. 2025;96(3):209-218. <https://doi.org/10.1136/jnnp-2024-334339>.
45. Chen Q, Hu X, Zhang T, et al. Association between Parkinson disease and selenium levels in the body: a systematic review and meta-analysis. *Medicine (Baltimore)*. 2024;103(17):e37919. <https://doi.org/10.1097/MD.00000000000037919>.
46. Jang DG, Dou JF, Koubek EJ, et al. Multiple metal exposures associate with higher amyotrophic lateral sclerosis risk and mortality independent of genetic risk and correlate to self-reported exposures: a case-control study. *J Neurol Neurosurg Psychiatry*. 2025;96(4):329-339. <https://doi.org/10.1136/jnnp-2024-333978>.
47. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94(446):496-509. <https://doi.org/10.1080/01621459.1999.10474144>.
48. Vinceti M, Filippini T, Jablonska E, et al. Safety of selenium exposure and limitations of selenoprotein maximization: molecular and epidemiologic perspectives. *Environ Res*. 2022;211:113092. <https://doi.org/10.1016/j.envres.2022.113092>.
49. Yoshida M, Sugihara S, Suenaga T, et al. Digestibility and chemical species of selenium contained in high-selenium yeast. *J Nutr Sci Vitaminol (Tokyo)*. 2002;48(5):401-404. <https://doi.org/10.3177/jnsv.48.401>.
50. McSheehy S, Yang L, Sturgeon R, et al. Determination of methionine and selenomethionine in selenium-enriched yeast by species-specific isotope dilution with liquid chromatography-mass spectrometry and inductively coupled plasma mass spectrometry detection. *Anal Chem*. 2005;77(1):344-349. <https://doi.org/10.1021/ac048637e>.
51. Filippini T, Michalke B, Mandrioli J, et al. Selenium neurotoxicity and amyotrophic lateral sclerosis: An epidemiologic perspective. In: Michalke B, ed. *Selenium Molecular and Integrative Toxicology*: Springer, Cham, 2018:231-248. https://doi.org/10.1007/978-3-319-95390-8_12.
52. Vinceti M, Guidetti D, Pinotti M, et al. Amyotrophic lateral sclerosis after long-term exposure to drinking water with high selenium content. *Epidemiology*. 1996;7(5):529-532.
53. Mandrioli J, Michalke B, Solovyev N, et al. Elevated levels of selenium species in cerebrospinal fluid of amyotrophic lateral sclerosis patients with disease-associated gene mutations. *Neurodegener Dis*. 2017;17(4-5):171-180. <https://doi.org/10.1159/000460253>.
54. Vinceti M, Solovyev N, Mandrioli J, et al. Cerebrospinal fluid of newly diagnosed amyotrophic lateral sclerosis patients exhibits abnormal levels of selenium species including elevated selenite. *Neurotoxicology*. 2013;38:25-32. <https://doi.org/10.1016/j.neuro.2013.05.016>.
55. SAC Consulting Veterinary Services. Selenium toxicity causes paralysis in Scottish pigs. *Vet Rec*. 2010;166(9):255-258. <https://doi.org/10.1136/vr.c883>.
56. Raber M, Sydler T, Wolfisberg U, et al. Feed-related selenium poisoning in swine. *Schweiz Arch Tierheilkd*. 2010;152(5):245-252. <https://doi.org/10.1024/0036-7281/a000056>.
57. Casteignau A, Fontan A, Morillo A, et al. Clinical, pathological and toxicological findings of a iatrogenic selenium toxicosis case in feeder pigs. *J Vet Med A Physiol Pathol Clin Med*. 2006;53(6):323-326. <https://doi.org/10.1111/j.1439-0442.2006.00830.x>.

58. Panter KE, Hartley WJ, James LF, et al. Comparative toxicity of selenium from seleno-DL-methionine, sodium selenate, and *Astragalus bisulcatus* in pigs. *Fundam Appl Toxicol*. 1996;32(2):217-223. <https://doi.org/10.1093/toxsci/32.2.217>.
59. Maraldi T, Beretti F, Anselmi L, et al. Influence of selenium on the emergence of neuro tubule defects in a neuron-like cell line and its implications for amyotrophic lateral sclerosis. *NeuroToxicology*. 2019;75:209-220. <https://doi.org/10.1016/j.neuro.2019.09.015>.
60. Maraldi T, Riccio M, Zamboni L, et al. Low levels of selenium compounds are selectively toxic for a human neuron cell line through ROS/RNS increase and apoptotic process activation. *Neurotoxicology*. 2011;32(2):180-187. <https://doi.org/10.1016/j.neuro.2010.10.008>.
61. Ren H, Shen X. Multi-omics reveals the hepatic metabolic mechanism of neurological symptoms caused by selenium exposure in Przewalski's gazelle (*Procapra przewalskii*). *Environ Pollut*. 2025;375:126341. <https://doi.org/10.1016/j.envpol.2025.126341>.
62. Estevez AO, Mueller CL, Morgan KL, et al. Selenium induces cholinergic motor neuron degeneration in *Caenorhabditis elegans*. *Neurotoxicology*. 2012;33(5):1021-1032. <https://doi.org/10.1016/j.neuro.2012.04.019>.
63. Urbano T, Filippini T, Wise LA, et al. Selenium exposure and urinary 8-oxo-7,8-dihydro-2'-deoxyguanosine: major effects of chemical species and sex. *Sci Total Environ*. 2023;870:161584. <https://doi.org/10.1016/j.scitotenv.2023.161584>.
64. Zwolak I, Zaporowska H. Selenium interactions and toxicity: a review. *Cell Biol Toxicol*. 2012;28:31-46. <https://doi.org/10.1007/s10565-011-9203-9>.
65. Santos DB, Schiar VP, Ribeiro MC, et al. Genotoxicity of organoselenium compounds in human leukocytes in vitro. *Mutat Res*. 2009;676(1-2):21-26. <https://doi.org/10.1016/j.mrgentox.2009.03.006>.
66. Cemeli E, Marcos R, Anderson D. Genotoxic and antigenotoxic properties of selenium compounds in the in vitro micronucleus assay with human whole blood lymphocytes and TK6 lymphoblastoid cells. *ScientificWorldJournal*. 2006;6:1202-1210. <https://doi.org/10.1100/tsw.2006.204>.
67. Lazard M, Dauplais M, Blanquet S, et al. Recent advances in the mechanism of selenoamino acids toxicity in eukaryotic cells. *Biomol Concepts*. 2017;8(2):93-104. <https://doi.org/10.1515/bmc-2017-0007>.
68. Uddin MH, Salvador C, Ritu JR, et al. Selenomethionine-induced neurotoxicity and behavioural alterations in larval zebrafish (*Danio rerio*). *Ecotoxicol Environ Saf*. 2025;303:118788. <https://doi.org/10.1016/j.ecoenv.2025.118788>.
69. Stolwijk JM, Garje R, Sieren JC, et al. Understanding the redox biology of selenium in the search of targeted cancer therapies. *Antioxidants (Basel)*. 2020;9(5):420. <https://doi.org/10.3390/antiox9050420>.
70. Malheiros RSP, Goncalves FCM, Brito FAL, et al. Selenomethionine induces oxidative stress and modifies growth in rice (*Oryza sativa* L.) seedlings through effects on hormone biosynthesis and primary metabolism. *Ecotoxicol Environ Saf*. 2020;189:109942. <https://doi.org/10.1016/j.ecoenv.2019.109942>.
71. Dauplais M, Romero S, Lazard M. Exposure to selenomethionine and selenocystine induces redox-mediated ER stress in normal breast epithelial MCF-10A cells. *Biol Trace Elem Res*. 2025;203(3):1453-1464. <https://doi.org/10.1007/s12011-024-04244-y>.
72. Yland JJ, Wesselink AK, Lash TL, et al. Misconceptions about the direction of bias from nondifferential misclassification. *Am J Epidemiol*. 2022;191(8):1485-1495. <https://doi.org/10.1093/aje/kwac035>.
73. Tinggi U. Selenium: its role as antioxidant in human health. *Environ Health Prev Med*. 2008;13(2):102-108. <https://doi.org/10.1007/s12199-007-0019-4>.

74. Michalke B, Willkomm D, Drobyshev E, et al. The importance of speciation analysis in neurodegeneration research. *Trends Analyt Chem.* 2018;104:160-170.
<https://doi.org/10.1016/j.trac.2017.08.008>.
75. Weekley CM, Harris HH. Which form is that? The importance of selenium speciation and metabolism in the prevention and treatment of disease. *Chem Soc Rev.* 2013;42(23):8870-8894.
<https://doi.org/10.1039/c3cs60272a>.

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Table 1. Baseline characteristics by selenium treatment

	All SELECT		Placebo + Placebo Treatment Arm		Selenium + Placebo Treatment Arm	
	(N=34,887)		(N=8696)		(N=8752)	
	N/M edia n	%/r ang e	N/Medi an	%/rang e	N/Medi an	%/range
Age, median (range)	62	50.0 - 93.0	62	50.0- 91.0	62	50.0- 90.0
<65 years	21828	62.6 %	5434	62.5%	5412	61.8%
≥65 years	13059	37.4 %	3262	37.5%	3340	38.2%
Race						
Black	4642	13.3 %	1148	13.2%	1138	13.0%
Other	1478	4.2%	378	4.3%	365	4.2%
White	28767	82.5 %	7170	82.5%	7249	82.8%
Ethnicity						
Non-Hispanic	32586	93.4 %	8124	93.4%	8182	93.5%
Hispanic	2301	6.6%	572	6.6%	570	6.5%
Smoking Status						
Current	2682	7.7%	674	7.8%	648	7.4%
Former	17157	49.2 %	4287	49.3%	4288	49.0%
Never	14881	42.7 %	3682	42.3%	3780	43.2%
Unknown/Missing	167	0.5%	53	0.6%	36	0.4%
BMI, median (range)	28.0	15.0 - 77.6	28.0	15.0- 62.1	28.0	15.0- 77.6
<25	6967	20.1 %	1732	20.0%	1776	20.4%
25 to <30	16751	48.3 %	4178	48.3%	4203	48.3%
≥30	10970	31.6 %	2734	31.6%	2720	31.3%
Unknown/Missing	199	--	52	--	53	--
Diabetes						
No	27084	77.6 %	6742	77.5%	6802	77.7%

Yes	7798	22.4 %	1953	22.5%	1948	22.3%
Unknown/Missing	5	--	1	--	2	--
Selenium concentration from toenails						
N (% of total) available	4819	13.8 %	1173	13.5%	1187	13.6%
Median (range)	0.87	0.5-12.9	0.87	0.5-9.0	0.87	0.6-12.9
Selenium concentration from serum						
N (% of total) available at baseline	5170	14.8 %	1249	14.4%	1286	14.7%
Median (range)	0.14	0.1-0.5	0.14	0.1-0.2	0.14	0.1-0.2
N (% of total) available at year 1	325	0.9%	75	0.9%	74	0.8%
Median (range)	0.18	0.1-0.4	0.14	0.1-0.3	0.24	0.1-0.4
Outcomes						
Colorectal Cancer	521	1.5%	144	1.7%	124	1.4%
Lung Cancer	728	2.1%	176	2.0%	191	2.2%
Melanoma	446	1.3%	118	1.4%	88	1.0%
All Lymphoid Malignancies	682	2.0%	160	1.8%	171	2.0%
Leukemia	295	0.8%	72	0.8%	78	0.9%
Hodgkin lymphoma	29	0.1%	6	0.1%	8	0.1%
(Non-Hodgkin) lymphoma	353	1.0%	87	1.0%	86	1.0%
Myeloma	109	0.3%	22	0.3%	28	0.3%
Parkinson's disease	899	2.6%	222	2.6%	210	2.4%
ALS	42	0.1%	10	0.1%	13	0.1%
External Data Linkages						
Linked to Medicare	19227	55.1 %	4774	54.9%	4813	55.0%
Cause of death provided by NDI	8900	25.5 %	2219	25.5%	2224	25.4%
Total person-years of follow-up, including SELECT and Medicare/NDI observation	341,697		85,361		85,707	

Table 2. Outcomes by data source.

Outcome	Source			
	SELECT	Medicare¹	NDI ²	Total
Colorectal Cancer	71	389	61	521
Lung Cancer	248	480		728
Melanoma	15	410	21	446
Leukemia	41	254	0	295
Hodgkin lymphoma	0	29	0	29
(non-Hodgkin) lymphoma	21	328	4	353
Myeloma	11	98	0	109
Parkinsons	20	793	86	899
ALS	15	27	0	42

¹ Additional outcomes identified by Medicare, not already identified by SELECT

² Additional outcomes identified by NDI, not already identified by SELECT or Medicare

Table 3. Association between selenium treatment and outcomes, including the selenium alone + placebo as compared with the placebo + placebo arms.

Outcome	Placebo, N	Selenium, N	HR (95% CI)
Colorectal Cancer	144	124	0.86 (0.67-1.10)
Lung Cancer	176	191	1.07 (0.87-1.31)
Melanoma	118	88	0.71 (0.54-0.95)
Hematopoietic malignancies ¹	160	171	1.07 (0.86-1.33)
Leukemia	72	78	1.06 (0.77-1.47)
Hodgkin lymphoma	6	8	2.01 (0.60-6.70)
(Non-Hodgkin) lymphoma	87	86	0.98 (0.73-1.33)
Multiple myeloma	22	28	1.28 (0.73-2.26)
Parkinson's disease	222	210	0.94 (0.78-1.14)
Amyotrophic lateral sclerosis	10	13	1.20 (0.52-2.77)

¹ Includes leukemia, Hodgkin lymphoma, lymphoma, and myeloma. Because some participants were diagnosed with more than one of these malignancies, the counts of each malignancy don't sum to the lymphoid total.

Table 4. Association between selenium treatment and outcomes.

Outcome	Any Selenium ¹		HR (95% CI)
	No, N	Yes, N	
Colorectal Cancer	277	244	0.88 (0.74-1.05)
Lung Cancer	364	364	0.99 (0.86-1.14)
Melanoma	238	208	0.84 (0.70-1.02)
Hematopoietic malignancies ²	328	354	1.07 (0.92-1.25)
Leukemia	144	151	1.03 (0.82-1.29)
Hodgkin lymphoma	11	18	1.77 (0.78-4.02)
(Non-Hodgkin) lymphoma	172	181	1.05 (0.85-1.29)
Multiple Myeloma	49	60	1.22 (0.84-1.79)
Parkinson's disease	456	443	0.97 (0.85-1.10)
Amyotrophic lateral sclerosis	19	23	1.15 (0.62-2.13)

¹ Any Selenium No includes Vitamin E + Placebo and Placebo + Placebo arms, Any Selenium Yes includes Selenium + Vitamin E and Selenium + Placebo arms.

² Includes leukemia, Hodgkin lymphoma, lymphoma, and myeloma. Because some participants were diagnosed with more than one of these malignancies, the counts of each malignancy don't sum to the lymphoid total.

Figure 1. Cumulative incidence of outcomes by treatment (selenium + placebo versus placebo + placebo).

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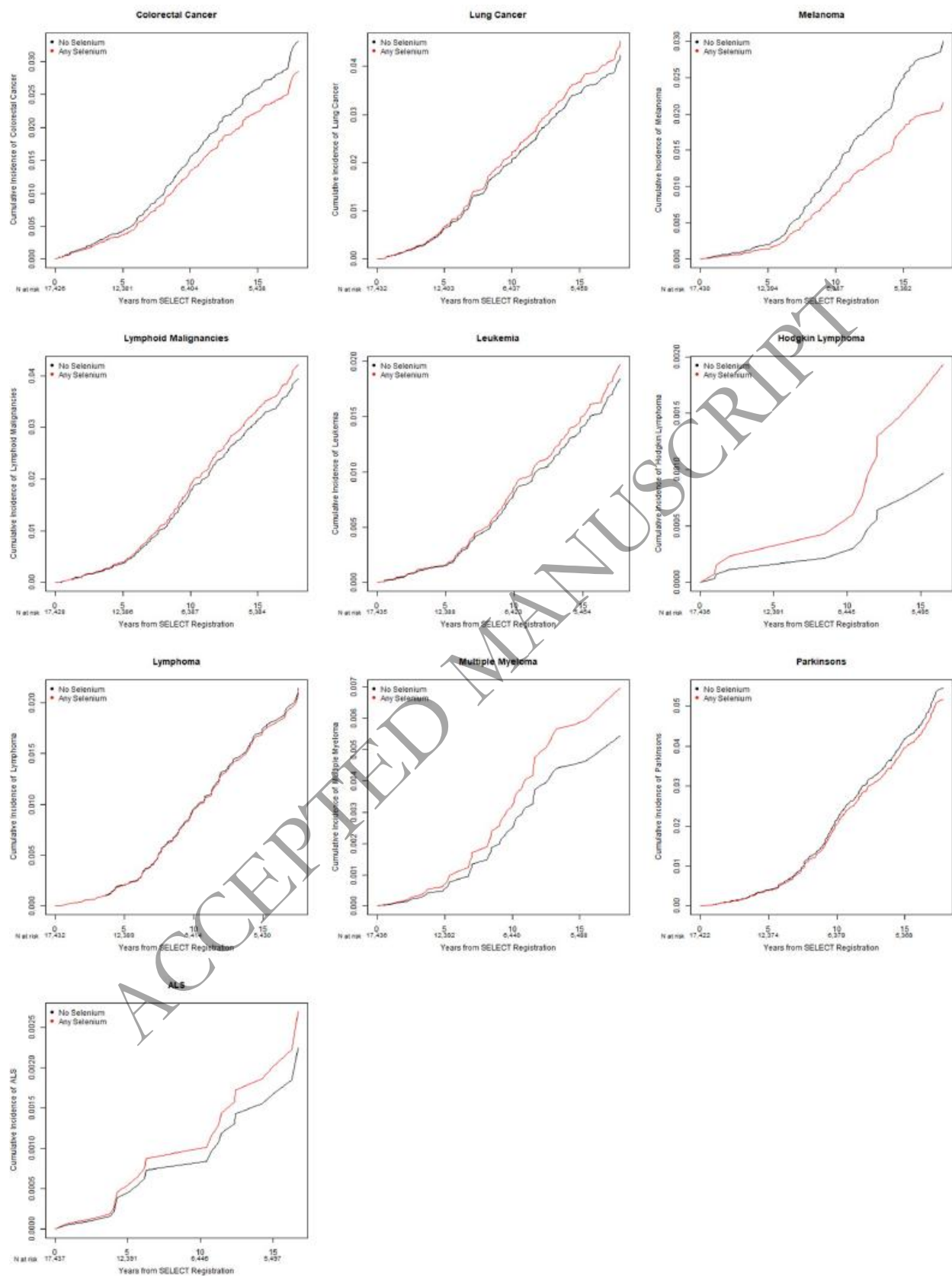


Figure 2. Cumulative incidence of outcomes by treatment (selenium + vitamin E and selenium + placebo versus vitamin E + placebo and placebo + placebo).

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