**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 µg/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 databased 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 selenomethione 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.

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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/Median | %/range | N/Median | %/range | N/Median | %/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.

| | Source | | | |
|---|---|---|---|---|
| **Outcome** | **SELECT** | **Medicare[1]** | **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.

| | Any Selenium[1] | | |
|---|---|---|---|
| **Outcome** | **No, N** | **Yes, N** | **HR (95% CI)** |
| 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).

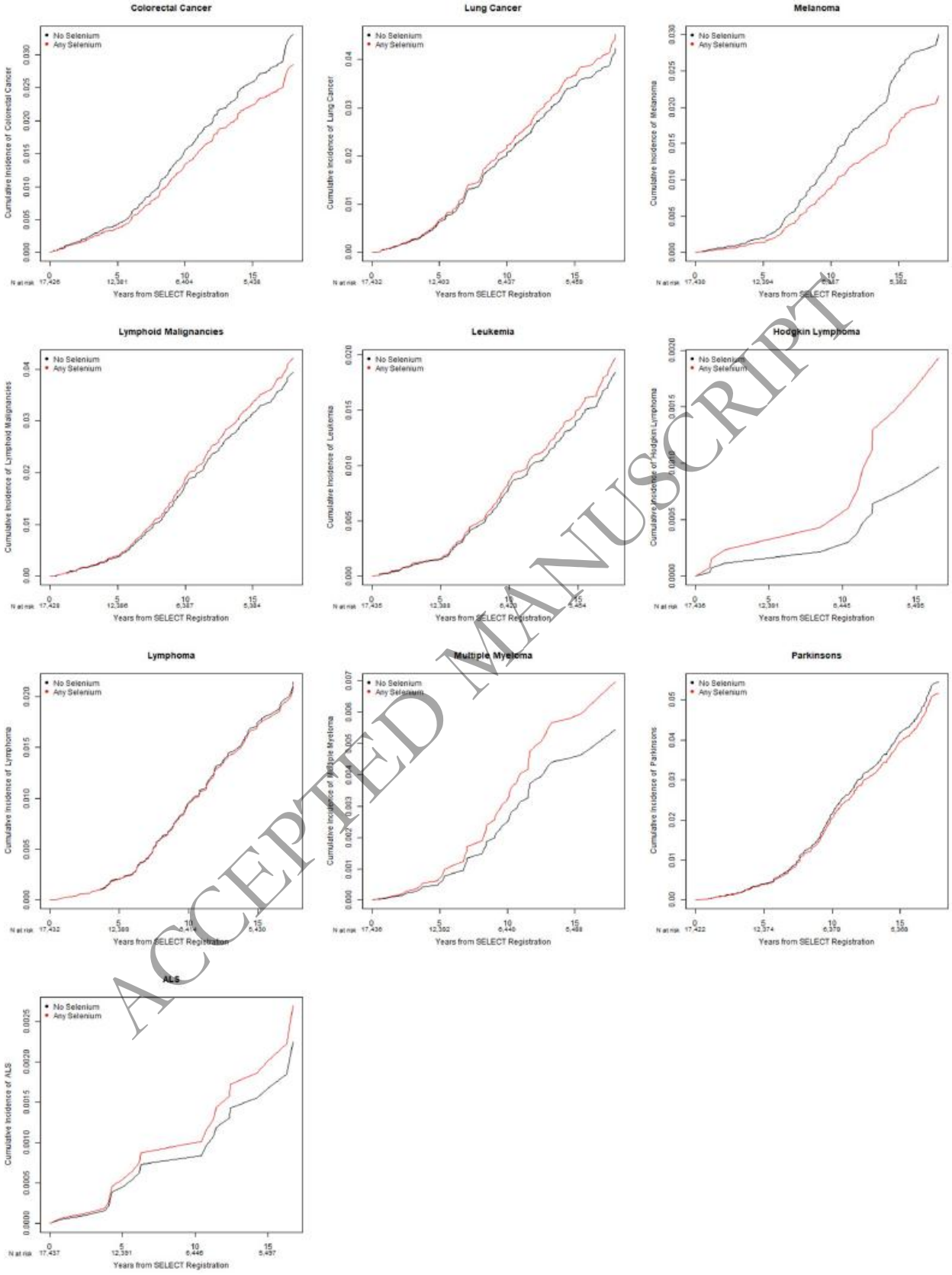

**Figure 2.** Cumulative incidence of outcomes by treatment (selenium + vitamin E and selenium + placebo versus vitamin E + placebo and placebo + placebo.