Selenium and Vitamin E for Prevention of Non–Muscle-Invasive Bladder Cancer Recurrence and Progression

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Selenium and Vitamin E for Prevention of Non–Muscle-Invasive Bladder Cancer Recurrence and Progression

A Randomized Clinical Trial

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Abstract

IMPORTANCE Selenium and vitamin E have been identified as promising agents for the chemoprevention of recurrence and progression of non–muscle-invasive bladder cancer.

OBJECTIVE To determine whether selenium and/or vitamin E may prevent disease recurrence in patients with newly diagnosed NMIBC.

DESIGN, SETTING, AND PARTICIPANTS This multicenter, prospective, double-blinded, placebo-controlled, 2 × 2 factorial randomized clinical trial included patients with newly diagnosed NMIBC recruited from 10 secondary or tertiary care hospitals in the UK. A total of 755 patients were screened for inclusion; 484 did not meet the inclusion criteria, and 1 declined to participate. A total of 270 patients were randomly assigned to 4 groups (selenium plus placebo, vitamin E plus placebo, selenium plus vitamin E, and placebo plus placebo) in a double-blind fashion between July 17, 2007, and October 10, 2011. Eligibility included initial diagnosis of NMIBC (stages Ta, T1, or Tis); randomization within 12 months of first transurethral resection was required.

INTERVENTIONS Oral selenium (200 µg/d of high-selenium yeast) and matched vitamin E placebo, vitamin E (200 IU/d of D-alfa-tocopherol) and matched selenium placebo, selenium and vitamin E, or placebo and placebo.

MAIN OUTCOME AND MEASURES Recurrence-free interval (RFI) on an intention-to-treat basis (analyses completed on November 28, 2022).

RESULTS The study randomized 270 patients (mean [SD] age, 68.9 [10.4] years; median [IQR] age, 69 [63-77] years; 202 male [75%]), with 65 receiving selenium and vitamin E placebo, 71 receiving vitamin E and selenium placebo, 69 receiving selenium and vitamin E, and 65 receiving both placebos. Median overall follow-up was 5.5 years (IQR, 5.1-6.1 years); 228 patients (84%) were followed up for more than 5 years. Median treatment duration was 1.5 years (IQR, 0.9-2.5 years). The study was halted because of slow accrual. For selenium (n = 134) vs no selenium (n = 136), there was no difference in RFI (hazard ratio, 0.92; 95% CI, 0.65-1.31; *P* = .65). For vitamin E (n = 140) vs no vitamin E (n = 130), there was a statistically significant detriment to RFI (hazard ratio, 1.46; 95% CI, 1.02-2.09; *P* = .04). No significant differences were observed for progression-free interval or overall survival time with either supplement. Results were unchanged after Cox proportional hazards regression modeling to adjust for known prognostic factors. In total, 1957 adverse events were reported; 85 were serious adverse events, and all were considered unrelated to trial treatment.

(continued)

Key Points

Question Can selenium and vitamin E supplementation prevent recurrence and progression of non–muscle-invasive bladder cancer (NMIBC)?

Findings In this randomized clinical trial of 270 adults, supplementation with selenium was not associated with a decreased risk of NMIBC recurrence; vitamin E supplementation was associated with a significantly increased risk of recurrence. Neither selenium nor vitamin E was associated with progression or overall survival.

Meaning These findings suggest that vitamin E supplements may be harmful to patients with NMIBC.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Abstract (continued)

CONCLUSIONS AND RELEVANCE In this randomized clinical trial of selenium and vitamin E, selenium supplementation did not reduce the risk of recurrence in patients with NMIBC, but vitamin E supplementation was associated with an increased risk of recurrence. Neither selenium nor vitamin E influenced progression or overall survival. Vitamin E supplementation may be harmful to patients with NMIBC, and elucidation of the underlying biology is required.

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Introduction

Bladder cancer is the 12th most common cancer worldwide[1]; in high-income countries, more than 90% are transitional cell carcinomas of urothelial origin, and most patients (75%-85%) present with non–muscle-invasive bladder cancer (NMIBC) (Union for International Cancer Control stages Ta, T1, and Tis).[2] Patients with NMIBC are initially treated by transurethral resection of bladder tumor and adjuvant intravesical therapy.[3] Recurrence occurs in up to 80% of patients[4]; progression to muscle-invasive bladder cancer (stages T2 or higher) occurs in up to 45% of patients diagnosed with initial stage T1 disease.[5]

Given the frequency of recurrence and progression and the chronic nature of the disease, NMIBC may be amenable to chemoprevention.[6] Selenium and vitamin E have previously been identified as promising agents[7-9]; notwithstanding, more recent clinical trials of selenium and/or vitamin E in the primary and secondary cancer prevention settings have shown no effect[10,11] or a detrimental effect.[12] Between 2005 and 2007, we established a trial protocol with the aim of providing important insights into the use of selenium and vitamin E as adjuvant therapies for NMIBC (SELENIB trial).

Methods

Study Design and Participants

From July 17, 2007, to October 10, 2011, SELENIB recruited patients with newly diagnosed NMIBC to a double-blinded, placebo-controlled, 2 × 2 factorial randomized clinical trial from 10 UK hospitals. Eligible patients were 18 years or older with newly diagnosed, pathologically confirmed urothelial NMIBC who were able to give informed consent. Ethnicity data were not collected because they were not considered to be relevant for a study of this nature. Patients were required to be randomized within 12 months of initial transurethral resection of bladder tumor. All patients provided written informed consent. SELENIB was coordinated by the Cancer Research UK Clinical Trials Unit at the University of Birmingham. The trial was conducted in accordance with the principles of the Good Clinical Practice guidelines and the Declaration of Helsinki.[13] It was approved by the UK Medicines and Healthcare Products Regulatory Agency. Research ethics approval was gained from East Midlands–Derby Research Ethics Committee, and the trial was overseen by an independent data monitoring committee. This report follows the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.[14] The trial protocol can be found in Supplement 1.

Randomization, Blinding, and Interventions

Patients were randomly assigned equally to 1 of 4 groups: oral selenium (200 µg/d of high selenium yeast, 364% recommended daily allowance[15]) and matched vitamin E placebo, vitamin E (200 IU/d D-alfa-tocopherol, 600% recommended daily allowance[16]) and matched selenium placebo, selenium and vitamin E, or placebo and placebo. Treatment allocations were blinded. Randomization was

stratified by recurrence risk group (high vs low or intermediate[17]) and treatment center. Patients took 1 tablet (selenium or placebo) and 1 capsule (vitamin E or placebo) once daily with food for up to 5 years. Patients were otherwise treated according to contemporaneous European Association of Urology guidelines.[17] Patients attended a SELENIB follow-up clinic every 6 months for up to 5 years after randomization during which treatment adherence, toxic effects, and disease status were recorded.

Outcomes

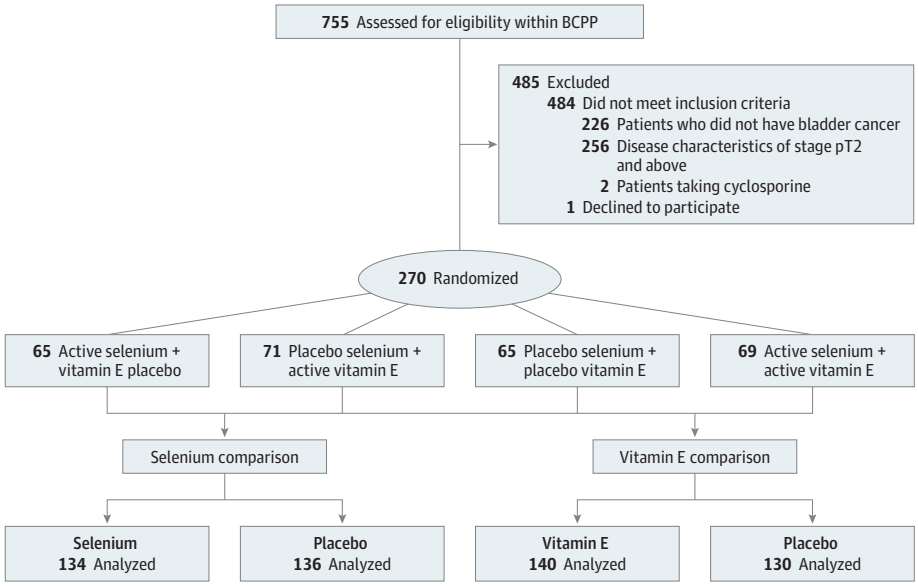
The primary outcome was recurrence-free interval (RFI), measured as the time from study entry to recurrence. For patients without recurrence at the time of analysis, the interval was censored at the date the patient was last known to be recurrence free. Recurrences at the first 3-month cystoscopy checkup were excluded. Secondary outcome measures included progression-free interval and overall survival (eMethods in Supplement 2). Quality of life was assessed at each follow-up visit.

Statistical Analysis

The primary hypothesis was addressed on an intention-to-treat basis. As a 2 × 2 factorial design, analysis consisted of 2 comparisons: (1) those patients randomized to selenium vs those randomized to the associated placebo, stratifying by vitamin E allocation; and (2) those patients randomized to vitamin E vs those randomized to the associated placebo, stratifying by selenium allocation. Interaction was not expected. Treatment groups were compared by Kaplan-Meier estimates of recurrence-free and progression-free interval; log-rank tests were used to test the hypothesis of no difference between treatments. Hazard ratios (HRs) from Cox proportional hazards regression models compared treatments, both unadjusted and adjusted for known prognostic factors. Similar methods were used for secondary outcomes. These analyses were completed on November 28, 2022.

All tests used a 2-sided $P < .05$ to indicate statistical significance, and all analysis was performed in R software, version 4.2.0 (R Foundation for Statistical Computing) using lmtest, survival, survminer and cowplot, ggplot2, and RColorBrewer for graphs.

Figure 1. SELENIB Trial Profile



Trial profile of the 4 arms and comparisons analyzed within the SELENIB trial. BCPP indicates Bladder Cancer Prognosis Programme.

Results

Participants

The study randomized 270 patients (mean [SD] age, 68.9 [10.4] years; median [IQR] age, 69 [63-77] years; 202 male [75%] and 68 female [25%]), with 65 receiving selenium and vitamin E placebo, 71 receiving vitamin E and selenium placebo, 69 receiving selenium and vitamin E, and 65 receiving both placebos (**Figure 1**). Baseline characteristics are shown in the **Table**. A total of 256 (95%) of all tumors were pure transitional cell carcinomas, and 226 (84%) had papillary morphology (eTable 1 in Supplement 2). The trial failed to recruit to its prespecified target of 515 patients and was halted because of slow accrual. Two hundred twenty-eight patients were followed up for more than 5 years. To September 26, 2018, median overall follow-up was 5.5 years (IQR, 5.1-6.1 years); with the

Table. Baseline Characteristics of the Study Participants[a]

Characteristic	Selenium		Vitamin E		Overall (N = 270)
	Placebo (n = 136)	Active (n = 134)	Placebo (n = 130)	Active (n = 140)	
Age, y					
Median (IQR)	69.5 (63.0-76.2)	69.0 (62.0-77.0)	69.0 (62.2-75.8)	69.5 (63.0-78.0)	69.0 (63.0-77.0)
Mean (SD)	69.0 (10.3)	68.8 (10.6)	68.3 (10.0)	69.5 (10.9)	68.9 (10.4)
Sex					
Female	27 (20)	26 (19)	28 (22)	25 (18)	53 (20)
Male	102 (75)	100 (75)	97 (75)	105 (75)	202 (75)
Unknown	7 (5)	8 (6)	5 (4)	10 (7)	15 (6)
Baseline risk group[b]					
Low	17 (12)	21 (16)	18 (14)	20 (14)	38 (14)
Intermediate	59 (43)	55 (41)	53 (41)	61 (44)	114 (42)
High	51 (38)	53 (40)	48 (37)	56 (40)	104 (39)
Very high	9 (7)	5 (4)	11 (8)	3 (2)	14 (5)
Grade					
1	23 (17)	31 (23)	28 (22)	26 (19)	54 (20)
2	59 (43)	49 (37)	48 (37)	60 (43)	108 (40)
3	53 (39)	54 (40)	54 (42)	53 (38)	107 (40)
Unknown	1 (0.7)	0	0	1 (0.7)	1 (0.4)
Stage					
pTa	81 (60)	79 (59)	74 (57)	86 (61)	160 (59)
pTis	7 (5)	7 (5)	6 (5)	8 (6)	14 (5.2)
pT1	47 (35)	48 (36)	50 (38)	45 (32)	95 (35)
Unknown	1 (0.7)	0	0	1 (0.7)	1 (0.4)
Carcinoma in situ					
Yes	19 (14)	16 (12)	21 (16)	14 (10)	35 (13)
No	75 (55)	74 (55)	65 (50)	84 (60)	149 (55)
Unknown	42 (31)	44 (33)	44 (34)	42 (30)	86 (32)
No. of tumors					
No.	133	128	128	133	261
Median (IQR)	1.0 (1.0-2.0)	1.5 (1.0-3.0)	1.0 (1.0-3.0)	2.0 (1.0-3.0)	1.0 (1.0-3.0)
Mean (SD)	2.0 (1.9)	2.3 (1.9)	2.0 (1.8)	2.2 (2.0)	2.1 (1.9)
Unknown	3	6	2	7	9
Size of largest tumor, cm					
No.	128	124	123	129	252
Median (IQR)	2.5 (1.5-3.0)	2.0 (1.0-3.0)	2.5 (1.2-3.2)	2.0 (1.5-3.0)	2.0 (1.5-3.0)
Mean (SD)	2.9 (2.0)	2.6 (1.7)	2.8 (2.2)	2.6 (1.6)	2.7 (1.9)
Unknown	8	10	7	11	18

[a] Data are presented as number (percentage) of patients unless otherwise indicated. Baseline risk groups are not the same as those used for stratification.

[b] In calculating baseline risk group, carcinoma in situ is assumed absent if not confirmed present.

intervention of the COVID-19 pandemic, ongoing follow-up beyond this time point became unfeasible. All patients are included in the analysis.

Treatment

Across 3 approaches to assess adherence (returned tablets or capsules, diary, and patient recollection), the median percentage of days taking trial treatment was more than 95% (IQR, 90%-99%) (eTables 2 and 3 in Supplement 2). The median treatment duration was 1.5 years (IQR, 0.9-2.5 years). Of 270 participants, 264 (98%) had more than 3 years of follow-up or died within 3 years of randomization. Standard-of-care treatments received by participants are detailed in eTables 4 to 6 in Supplement 2.

Adverse Events

In total, 1957 adverse events were reported; 85 were serious adverse events, and all were considered unrelated to trial treatment. The most common adverse events were fatigue (279 [14%]), cough and/or cold (217 [11%]), and dermatitis (190 [10%]); there was no difference in adverse events between treatment arms (eResults and eTables 7-9 in Supplement 2).

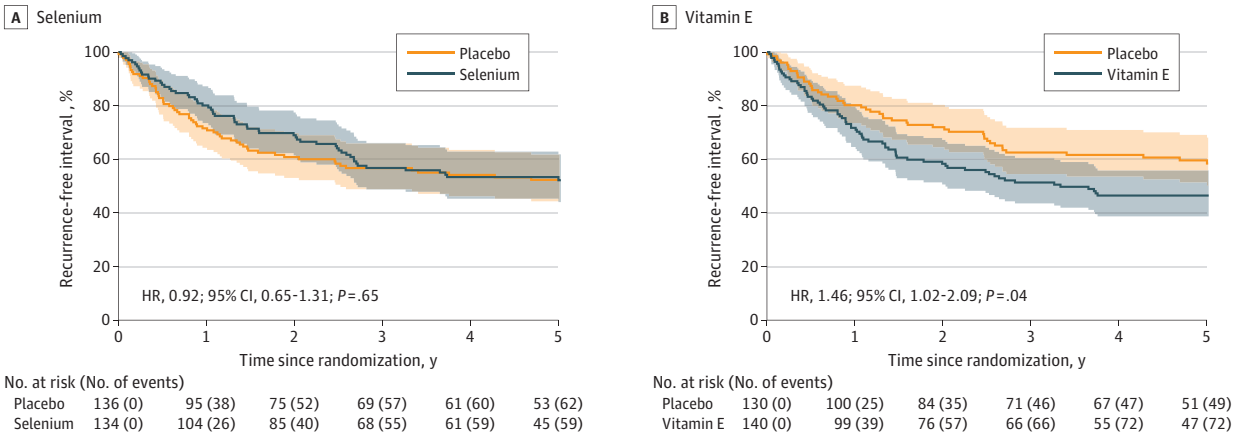
Primary Outcome

Of 122 recurrences, 60 (49%) occurred in the selenium arm and 62 (51%) in the placebo arm. For selenium, there was no statistically significant difference in RFI (HR, 0.92; 95% CI, 0.65-1.31; *P* = .65); median RFI was not reached in either arm (**Figure 2**A). Of the recurrences, 72 (59%) occurred in the vitamin E arm and 50 (41%) in the placebo arm. Vitamin E was associated with a statistically significant decrease in RFI (HR, 1.46; 95% CI, 1.02-2.09; *P* = .04); median RFI was 3.3 years (IQR, 0.89 years to not reached) for vitamin E and was not reached for the placebo arm (Figure 2B). Recurrence-free survival estimates at yearly intervals for each treatment comparison are shown in eTable 10 in Supplement 2. We observed a 13% difference in RFI at 5 years for placebo vs vitamin E (59.6% vs 46.5%), with the study originally designed for an absolute difference of 12% at 5 years. Adjusted analyses of the primary outcome were also undertaken (eTables 11 and 12 in Supplement 2).

Secondary Outcomes

Overall, 37 patients had disease progression; no significant differences in progression-free interval were observed with selenium or vitamin E (**Figure 3**). Fifty-three patients died, and no significant

Figure 2. Recurrence-Free Interval



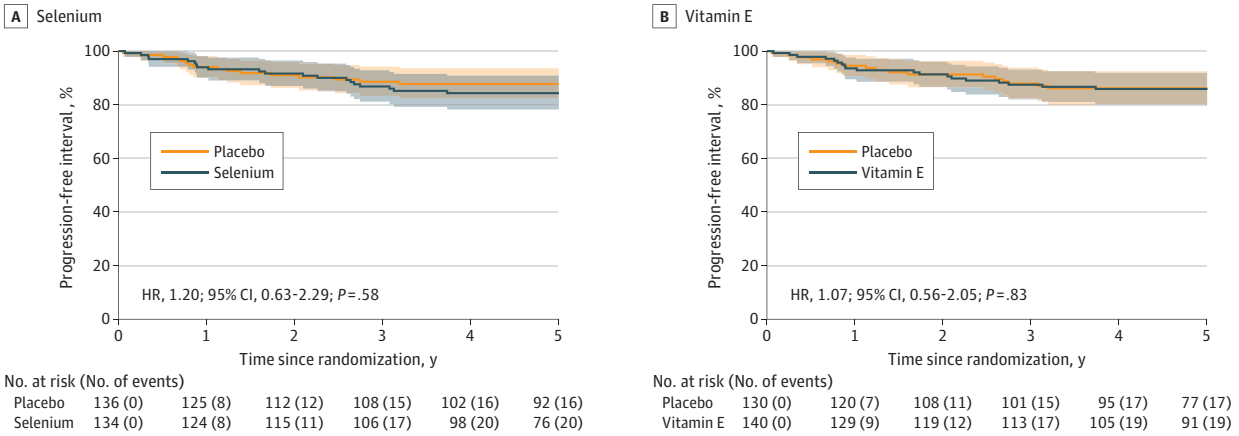
Kaplan-Meier 5-year analyses of recurrence-free intervals, defined as the time from date of study entry to date of recurrence, for selenium and vitamin E. For patients not observed to have experienced recurrence at the time of analysis, the interval was censored at the date last known to be recurrence free. HR indicates hazard ratio.

differences in overall survival were observed with either selenium or vitamin E (**Figure 4**). No significant differences in quality of life were observed between the arms (eFigure in Supplement 2).

Discussion

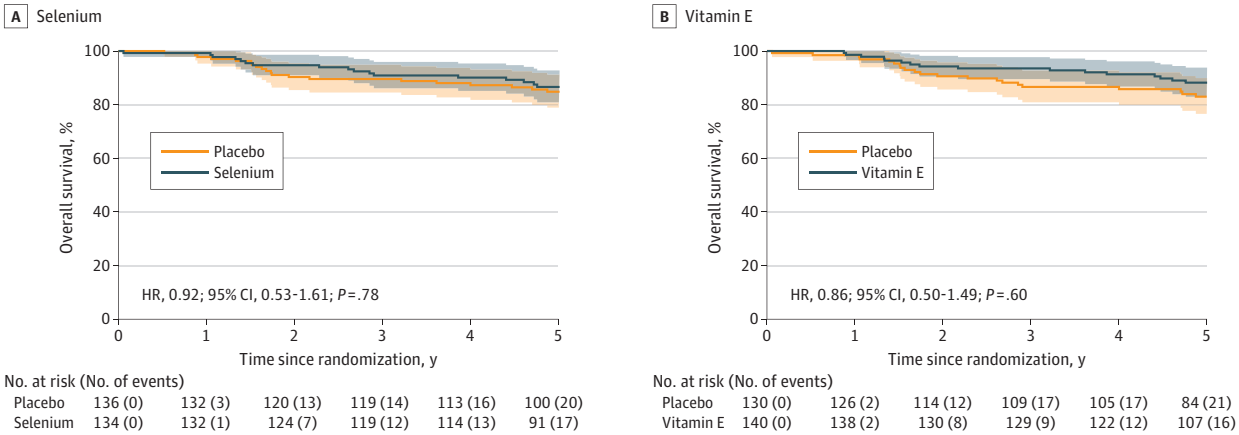
We observed no benefit of selenium for recurrence, progression, or overall survival in patients with NMIBC. We observed an association between vitamin E supplementation and an increased risk of recurrence but no association with progression or overall survival. The assumptions of the factorial trial design were demonstrated to be correct. The randomization used contemporary risk categorization as a stratification factor; over time, risk categorization has changed.[3,17] For enabling

Figure 3. Progression-Free Interval



Kaplan-Meier 5-year analyses of progression-free intervals as time from date of study entry to date of progression, for selenium and vitamin E. Progression was defined as recurrence with an increase in grade from grade 1 or grade 2 to grade 3 or an increase in T stage (determined by histopathologic analysis) or the new occurrence of carcinoma in situ (CIS) in a bladder previously free from CIS or the new occurrence of multiple urothelial tumors following the initial diagnosis of a solitary urothelial tumor. Progression was also reported if there was the need for a cystectomy because of refractory disease or the new development of nodal and/or distant metastases (determined by imaging). For those patients not observed to have experienced progression by the time of analysis, the interval was censored at the date last known to be progression free. HR indicates hazard ratio.

Figure 4. Overall Survival Analysis



Kaplan-Meier 5-year analyses of overall survival time defined as time from the date of randomization to the date of death from any cause, for selenium and vitamin E. Patients alive at the time of analysis were censored at the date last known to be alive. For patients not observed to have experienced recurrence at the time of analysis, the interval was censored at the date last known to be recurrence free. HR indicates hazard ratio.

up-to-date risk categorization and applicability to current practice, data were collected on each of the contributory factors.

SELENIB is, to our knowledge, the first trial to investigate the use of selenium and vitamin E for preventing recurrence and progression in patients newly diagnosed with NMIBC. In 2011, the Selenium and Vitamin E Cancer Prevention Trial (SELECT) concluded that dietary supplementation with vitamin E (400 IU/d all-rac-α-tocopheryl acetate) significantly increased the risk of prostate cancer among healthy men[12]; a secondary analysis in 2012 investigated bladder cancer incidence, demonstrating no preventive effect of selenium or vitamin E alone or combined on bladder cancer incidence within the SELECT population.[10]

Trials of dietary supplements in cancer prevention are important, as demonstrated here. Our data show no evidence of benefit from selenium and evidence of harm from vitamin E—a compound readily available over the counter. Future micronutrient and/or vitamin chemoprevention studies in NMIBC should carefully consider choice of compound, underlying biology, preclinical evidence, and study design.[18,19]

Limitations

This study has some limitations, including the fact that patient accrual fell below the intended 515 due to an unexpectedly high proportion of ineligible patients, the elderly age of the patient population with accompanying comorbidities and medication, and the proposed trial duration. Furthermore, trial funding was withdrawn in 2010, resulting in the decision to end recruitment and treatment in 2011. Consequently, study participants received considerably less selenium and vitamin E than intended, and 245 fewer patients than required were recruited; thus, these analyses are underpowered.

Conclusions

In this randomized clinical trial of selenium and vitamin E in patients with newly diagnosed NMIBC, selenium supplementation did not reduce the risk of disease recurrence, whereas vitamin E supplementation was associated with an increased risk of recurrence. Neither selenium nor vitamin E influenced progression or overall survival. These findings suggest that vitamin E supplementation may be harmful to patients with NMIBC, and elucidation of the underlying biology is required.

ARTICLE INFORMATION

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Author Contributions: Dr Bryan had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Zeegers and Cheng contributed equally.

Concept and design: Bryan, Lewis, Wallace, James, Billingham, Zeegers, Cheng.

Acquisition, analysis, or interpretation of data: Bryan, Pirrie, Abbotts, Maycock, During, Lewis, Grant, Bird, Devall, James, Billingham, Zeegers, Cheng.

Drafting of the manuscript: Bryan, Pirrie, Abbotts, Maycock, James, Cheng.

Critical review of the manuscript for important intellectual content: Bryan, Pirrie, During, Lewis, Grant, Bird, Devall, Wallace, James, Billingham, Zeegers, Cheng.

Statistical analysis: Pirrie, Maycock.

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Administrative, technical, or material support: Bryan, Abbotts, Lewis, Grant, Bird, Devall, Wallace, Zeegers.

Supervision: Bryan, Pirrie, Wallace, James, Billingham, Zeegers, Cheng.

Conflict of Interest Disclosures: Dr Bryan reported receiving grants from Cancer Research UK and nonfinancial support from Pharma Nord during the conduct of the study, receiving personal fees from Cystotech ApS outside the submitted work, and serving as an unpaid charity trustee for Action Bladder Cancer UK. Dr Pirrie reported receiving grants from Cancer Research UK during the conduct of the study. Dr Billingham reported receiving grants from Cancer Research UK during the conduct of the study. No other disclosures were reported.

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Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Group Information: The SELENIB Investigators appear in Supplement 3.

Data Sharing Statement: See Supplement 4.

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SUPPLEMENT 1.
Trial Protocol

SUPPLEMENT 2.
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