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The effect of supplemental vitamins and minerals on the development of prostate cancer: a systematic review and meta-analysis

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Background. Vitamin supplementation is used for many purposes with mainly alleged benefits. One of these is the use of various vitamins for the prevention of prostate cancer.

Methods. We conducted a systematic review and meta-analysis on this topic. Pubmed, Embase and the Cochrane Database were searched; as well, we hand searched the references in key articles. Randomized controlled trials (RCTs), cohort studies and case–control studies were included. The review assessed the effect of supplemental vitamins on the risk of prostate cancer and on disease severity and death in men with prostate cancer.

Results. Fourteen articles were included in the final assessment. Individually, a few of these studies showed a relationship between the ingestion of supplemental vitamins or minerals and the incidence or severity of prostate cancer, especially in smokers. However, neither the use of multivitamin supplementation nor the use of individual vitamin/mineral supplementation affected the overall occurrence of prostate cancer or the occurrence of advanced/metastatic prostate cancer or death from prostate cancer when the results of the studies were combined in a meta-analysis. We also conducted several sensitivity analyses by running meta-analysis using just the higher quality studies and just the RCTs. There were still no associations found.

Conclusions. There is no convincing evidence that the use of supplemental multivitamins or any specific vitamin affects the occurrence or severity of prostate cancer. There was high heterogeneity among the studies so it is possible that unidentified subgroups may benefit or be harmed by the use of vitamins.

Keywords. Family medicine, meta-analysis, nutrition, prostate cancer, systematic review, urology, vitamin supplementation.

Introduction

In 2008, prostate cancer remained the most commonly diagnosed cancer besides non-skin epithelial malignancy in the male population.[1] Thus, defining substances that affect the risk of prostate cancer could potentially be life saving for some men. Many researchers are assessing vitamin and mineral supplementation with respect to prostate cancer risk.[2–15] In particular, multivitamins, vitamin E, vitamin C, zinc, selenium and beta-carotene have been studied in this regard. While this area is important as supplementation is becoming more popular all around the world, the literature that has been published on this subject is inconsistent. Multivitamins have been shown to be of no benefit,[9] inconlusive[4] and potentially harmful[14] in relation to their effect on risk of prostate cancer. Similarly, vitamin E has been shown to be beneficial,[5,15] harmful,[13,14] and inconclusive [3,8] in relation to risk of prostate cancer. The same inconsistencies in results are true for zinc,[6,14,15] selenium,[2,14] and beta-carotene.[5,10,14] These variations in results make the relationship between vitamins and minerals and prostate cancer difficult to interpret. In this study, we systematically reviewed the literature and performed meta-analysis in an attempt to better understand and interpret the literature. The PRISMA checklist[16] is used as a guide to the format of this article although it is not slavishly followed. As well, the PRISMA flowchart describes the systematic review process (Fig. 1).

Our PICO formulated question for this systematic review is 'Do men who take supplemental vitamins

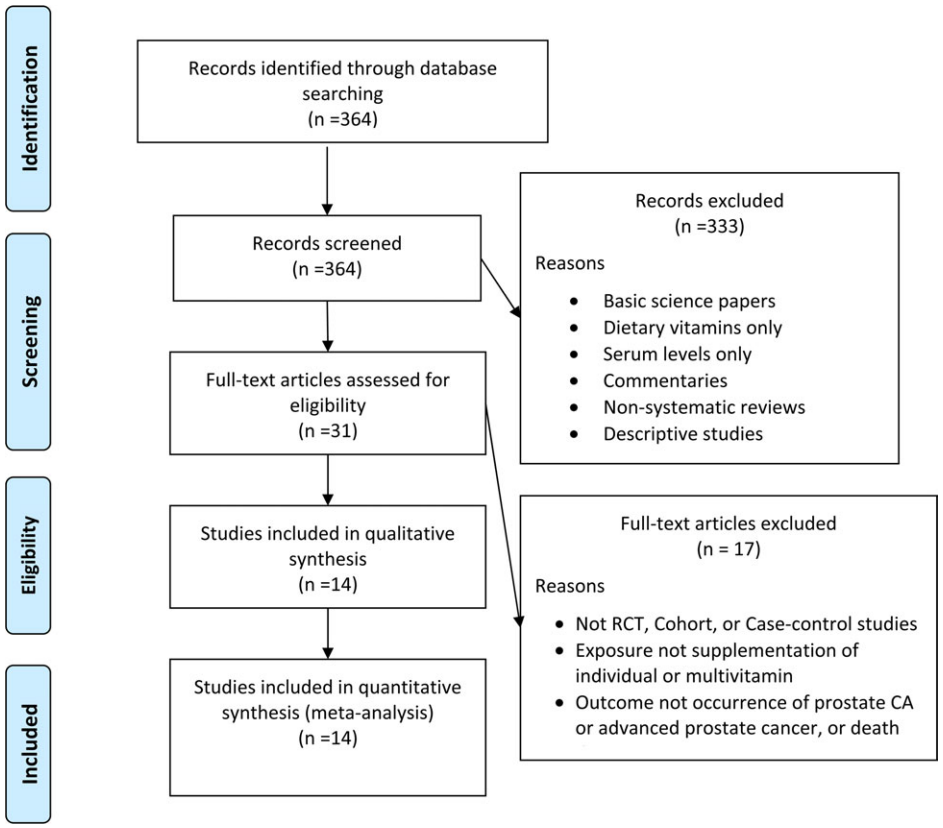


FIGURE 1 *PRISMA flow diagram.*

and minerals, specifically multivitamins, vitamin E, vitamin C, zinc, selenium, and beta-carotene, have lower risk of developing prostate cancer, or if they do, have less severe disease and lower mortality, then men who do not take these vitamins and minerals as supplements to their diet'.

Methods

Eligibility criteria

Only randomized controlled trials (RCTs), cohort studies or case–control studies were eligible for inclusion in the review. Studies had to have looked at supplementation of individual vitamins or supplementation of multivitamins as the exposure, and their primary outcome had to be either occurrence of prostate cancer, advanced/metastatic prostate cancer or death due to prostate cancer.

Information sources

We searched Pubmed, Embase and the Cochrane database with no time limitations. Last searched February 2010. We searched Pubmed first. No additional eligible articles were identified in Embase or Cochrane Database of Reviews that we did not identify in PubMed. In particular, there was no Cochrane review on the topic and the Cochrane database of RCTs did not contain papers we did not find in PubMed.

Search

Our initial search 'vitamins AND prostate' resulted in 1364 hits in Pubmed. This was far too broad and identified mostly articles that were not related to our area of interest. The search string 'Vitamins[MESH] AND prostate[MESH]' was too restrictive and resulted in just three articles. We decided to use the strategy of searching on title words that we felt would most likely detect pertinent articles without being too restrictive. The search string '(vitamin[ti] OR vitamins[ti] OR multivitamins[ti] OR multi-vitamins[ti]) AND (prostate[ti] AND cancer[ti])' resulted in 284 articles. When we limited this same search to English, Human subjects and articles with abstracts, the number was reduced to 218 articles. We subsequently realized that by not searching for certain specific vitamins that were being assessed in the literature for their effect on prostate cancer, we were potentially missing some articles. We added the search string '(selenium[ti] OR carotene[ti] or Zinc[ti] OR tocopherol[ti]) AND (prostate[ti] AND cancer[ti])' also limited to English, Human and articles with abstracts which resulted in a further 146 articles. We had identified a total of 364 articles.

TABLE 1 *Articles included in the review*

Study description			Quality	Exposure/intervention						Outcome	
Article	Year	Study type[a]	US Preventive Task Force Quality Rating Criteria	Multi vitamins	Vitamin E	Vitamin C	Zinc	Selenium	Beta-carotene	Prostate cancer rate	Death from prostate cancer or advanced/metastatic prostate cancer
Gaziano *et al.*[3]	2009	RCT	Good		√	√				√	
Lippman *et al.*[2]	2009	RCT	Good		√			√		√	
Meyer *et al.*[4]	2005	RCT	Good	√						√	
Heinonen *et al.*[5]	1998	RCT	Fair		√				√	√	√
Gonzalez *et al.*[6]	2009	Cohort	Good				√			√	√
Peters *et al.*[7]	2008	Cohort	Good		√					√	√
Wright *et al.*[8]	2007	Cohort	Good		√					√	
Lawson *et al.*[9]	2007	Cohort	Good	√						√	√
Kirsh *et al.*[10]	2006	Cohort	Good		√	√			√	√	
Stevens *et al.*[11]	2005	Cohort	Fair	√						√	√
Rodriguez *et al.*[12]	2004	Cohort	Good		√					√	√
Chan *et al.*[13]	1999	Cohort	Good		√					√	√
Zhang *et al.*[14]	2009	Case–Control	Fair	√	√		√	√	√	√	
Kristal *et al.*[15]	1999	Case–Control	Good	√	√	√	√			√	

[a]Articles were limited to RCT, cohort and case–control studies that assess the effect of vitamin or mineral supplementation on risk of prostate cancer. (We excluded studies that look at dietary sources of these vitamins.)

We scanned the titles of the 364 articles to remove those that were obviously related to basic science work, those that looked at dietary vitamins and not supplemental vitamins and those that looked at serum vitamin levels as the independent variable rather than vitamin supplementation. We removed commentaries, non-systematic reviews and descriptive studies, and we removed others that were not directly related to supplemental vitamins (or minerals) and risk of prostate cancer or death from prostate cancer. This left 31 articles.

Study selection and quality assessment

The abstracts of the 31 identified papers were reviewed and 14 met our study design, exposure and outcomes criteria.[2–15] We hand searched the references in these 14 articles and did not find any additional papers that met the search or selection criteria.

The full content of these 14 papers were reviewed independently by each of the two authors using the US Preventive Services Task Force Quality Rating Criteria (http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=hsevidsyn&part=A52999). This quality rating system has specific features that are considered for each of the types of methodologies (RCTs, cohort and case–control) that were used in the articles. Using this system, each article is given an overall rating of good, fair or poor. After independently reviewing the 14 articles, the two authors met to discuss differences in their rating. Consensus was reached that all 14 articles were either fair or good and hence all were included in the systematic review.

There were four RCTs, eight cohort studies and two case–control studies included in the analysis. All four RCTs were blinded and placebo controlled. Concealed allocation was not specifically discussed in either of the RCTs although the process described suggests that they all used concealment. Details of the each of the studies are listed in Table 2 including dosages of the vitamins used in the RCTs. The countries in which the studies were conducted are also listed. The content of multivitamins varied from study to study but generally contained a wide range of vitamins and minerals.

Figure 1 (PRISMA diagram) outlines the literature search and article selection process. Table 1 shows the main author, publication date, exposures and outcomes assessed, for each of the 14 articles.

Meta-analysis

The Cochrane Collaboration software, Revman 5, was used for the meta-analysis[17] (http://www.cc-ims.net/revman/about-revman-5). We registered the 14 studies in Revman, entered the basic data and generated the forest plots. A Mantel–Haenzel odds ratio was calculated for each of the forest plots; a random effects model was used because of the high level of heterogeneity among the studies. This is a more conservative approach than the fixed effects model. The random

TABLE 2 *Details of included articles*

Article	Study type	Population	Exposure or intervention	Outcomes assessed	Results and conclusion
Gaziano *et al.*[3]	RCT	Physicians Health Study II. 14 641 male physicians aged 50 years and over. Country: USA	● Vitamin E 400 IU every other day (n = 3659) ● Vitamin C 500 mg daily (n = 3673 ● Placebo (n = 3653) ● Vitamin E and vitamin C arm. Not used in our analysis	Occurrence of prostate cancer. Mean follow-up 8 years.	Vitamin E: 9.1 cases of prostate cancer per 1000 person-years versus 9.5 cases per 1000 person-years in placebo (HR, 0.97; 95% CI, 0.85 to 1.09; P = 0.58) Vitamin C: 17.6 versus 17.5 cases per 1000 person-years (HR, 1.01; 95% CI, 0.92 to 1.10; P = 0.86)No impact of Vitamin E or Vitamin C on prostate cancer.
Lippman *et al.*[2]	RCT	Selenium and Vitamin E Cancer Prevention Trial [SELECT]. 35 533 men aged 50+, with PSA <4.0 ng/dl and normal rectal examination. Countries: USA, Canada, Puerto Rico	● Selenium 200 μg/day (n = 8752) ● Vitamin E 400 IU/day (n = 8737) ● Placebo (n = 8696) ● Selenium and vitamin E	Occurrence of prostate Cancer. Mean follow-up 5.46 years.	Neither vitamin E nor selenium, alone or in combination, prevented prostate cancer. Compared to placebo, the HRs (99% CIs) for prostate cancer were 1.13 (99% CI, 0.95 to 1.35; n = 473) for vitamin E, 1.04 (99% CI, 0.87 to 1.24; n = 432) for selenium and 1.05 (99% CI, 0.88 to 1.25; n = 437) for selenium + vitamin E.
Meyer *et al.*[4]	RCT	5034 men from the SU.VI.Max trail randomized to multivitamin and placebo groups. Mean age 51.3 years Country: France	● Multivitamins (n = 2522) ● Placebo (n = 2512)	Occurrence of prostate cancer. Mean follow-up 8.8 years.	Overall multivitamin supplementation did not affect prostate cancer rate (HR, 0.88; 95% CI, 0.60 to 1.29). However, in patients with a normal PSA at baseline, there was a reduction in prostate cancer incidence (HR, 0.52; 95% CI, 0.29 to 0.92) in men taking multivitamins.
Heinonen *et al.*[5]	RCT	29 133 male smokers aged 50–69 years from south-western Finland. Country: Finland	● Vitamin E (alpha-tocopherol) 50 mg (n = 7286) ● Beta-carotene 20 mg) (n = 7282) ● Both agents (n = 7278) ● Placebo (n = 7287)	Occurrence of prostate cancer. Death from prostate cancer. Follow-up 5–8 years.	A 32% decrease (95% CI, –47% to –12%) in the incidence of prostate cancer was observed among the subjects receiving alpha-tocopherol compared with those not receiving it. Mortality from prostate cancer was 41% lower (95% CI, –65% to –1%) among men receiving alpha-tocopherol.This study concluded that vitamin E 50 mg/day reduced prostate cancer incidence and death.
Gonzalez *et al.*[6]	Cohort	From the Vitamin and Lifestyle Cohort (VITAL) study. Age range 50–77 years Country: USA	No zinc supplementation (n = 13472) Any zinc supplementation (n = 20 775)	Occurrence of prostate cancer. Advanced/metastatic prostate cancer.	No effect on incidence of prostate cancer (HR, 0.82; 95% CI, 0.58 to 1.14) Decreased risk of advanced/metastatic prostate cancer (HR, 0.34; 95% CI, 0.13 to 1.09). They concluded that long-term supplemental zinc intake was associated with reduced risk of clinically relevant advanced disease.

TABLE 2 *Continued*

Article	Study type	Population	Exposure or intervention	Outcomes assessed	Results and conclusion
Peters *et al.*[7]	Cohort	From the Vitamin and Lifestyle Cohort (VITAL) study. 35 242 men recruited between 2000 and 2002 from western Washington state. Median age ~60 years. Country: USA	Vitamin E >30 IU/day (n = 16 660) Non-users (n = 11 425) Selenium>20 μg/day (n = 8028) Non-users (n = 14 061)	Occurrence of prostate cancer. Advanced prostate cancer. Follow-up 4 years.	Long-term supplemental intake of vitamin E and selenium were not associated with prostate cancer risk overall. There was a trend for Vitamin E to decrease risk of advanced prostate cancer.
Wright *et al.*[8]	Cohort	Survey responses from 567 169 people aged 51–70 years in the 3.5 million NIH-AARP Diet and Health Study. Country: USA	Any vitamin E supplementation (n = 179 556) No vitamin E supplementation (n = 115 788)	Occurrence of prostate cancer. Advanced prostate cancer. 5-year follow-up.	No convincing effect of vitamin E on incidence of prostate cancer or advanced prostate cancer Any supplementation 6218 cases of prostate cancer; 912 advanced cancer No supplementation 4023 cases of prostate cancer; 564 advanced cancer
Lawson *et al.*[9]	Cohort	NIH-AARP Diet and Health Study, n = 295 344 Men aged 50–71 years. Country: USA	Any multivitamins (n = 152 710) No multivitamins (n = 142 634)	Occurrence of prostate cancer. Advanced prostate cancer. 5-year follow-up.	Multivitamins does not affect risk of prostate cancer. High doses of multivitamins might slightly increase risk Any supplementation 5310 cases of prostate cancer 865 advanced cancer or death No supplementation 4931 case of prostate cancer 790 advanced cancer or death
Kirsh *et al.*[10]	Cohort	Data from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. 29 361 men aged 55–74 years Supplement use assessed by questionnaire. Country: USA	Vitamin E supplementation (n = 15 155) Vitamin C and E supplementation (n =15 080) Beta- carotene supplementation (n = 12 203) No vitamin supplementation (n = 12 813)	Occurrence of prostate cancer. 4.2 years average follow-up.	In general, no effect found. However some effect in subgroups. Vitamin E supplementation in male smokers and beta-carotene supplementation in men with low dietary beta-carotene intakes were associated with reduced risk of this disease. Vitamin E: 675 cases in non-users; 663 cases in users Vitamin C: 666 cases in non-users; 672 in cases in users Beta-carotene: 801 cases in non-users; 537 cases in users
Stevens *et al.*[11]	Cohort	475 726 men aged 47–70 years had multivitamin supplementation assessed by questionnaire. Country: USA	Regular multivitamin use (n = 86 089) No multivitamin use (n = 338 055)	Death from prostate cancer. 18-year follow-up.	No convincing evidence for an effect of multivitamin use on prostate cancer deaths Regular multivitamin use 1065 deaths from prostate cancer No multivitamin use 3949 deaths from prostate cancer

TABLE 2 *Continued*

Article	Study type	Population	Exposure or intervention	Outcomes assessed	Results and conclusion
Rodriguez *et al.*[12]	Cohort	Participants in the Cancer Prevention Study II Nutrition Cohort. Data on vitamin supplementation assessed by questionnaire. 72 704 men aged 50–74 years. Country: USA	Any vitamin E supplementation (n = 27 736) No vitamin E supplementation (n = 44 968)	Occurrence of prostate cancer. Advanced prostate cancer. 7-year follow-up	No relationship found between vitamin E supplementation and prostate cancer Any vitamin E supplementation 1693 cases of prostate cancer 255 cases of advanced prostate cancer No vitamin E supplementation 2588 cases of prostate cancer 413 cases of advanced prostate cancer
Chan *et al.*[13]	Cohort	Health Professionals Follow-up Study (HPFS) 47 780 men aged 40–75 years. Country: USA	Vitamin E supplementation (n = 20 828) No vitamin E supplementation (n = 26 952)	Occurrence of prostate cancer Metastatic prostate cancer or death	Vitamin E was not associated with prostate cancer risk, in general. There was a small inverse effect in smokers, where vitamin E supplementation was associated with increased risk of metastatic prostate CA. Any vitamin E supplementation 926 cases of prostate cancer 110 cases of advanced prostate cancer No vitamin E supplementation 970 cases of prostate cancer 122 cases of advanced prostate cancer
Zhang *et al.*[14]	Case–control	Total of 3110 participants: 1706 cases and 2404 controls. Mean age ~60 years. About 80% white race. Country: USA	Looked at exposure to multivitamins, vitamin E, zinc, selenium and beta-carotene	Cases were men aged 40–79 years admitted to hospital with a diagnosis of prostate cancer.Controls were selected from men of the same age group admitted to the same hospitals for non-cancer reasons.	Cases were more likely to have used zinc. No other convincing associations (OR, 1.9; 95% CI, 1.0 to 3.6)
Kristal *et al.*[15]	Case–control	Total of 1363 participants. 697 cases and 666 controls. Age 40–64 years. Population based. Country: USA	Looked at exposures to multivitamins, vitamin E, vitamin C and zinc	697 incident prostate cancer cases identified from a registry in Washington state.Controls recruited from the same overall population using random-digit dialling sampling	Cases were not more or less likely to have consumed any of the vitamin supplements studied compared to controls.

CI, confidence interval; HR, hazard ratio; PSA, prostate-specific antigen; OR, odds ratio.

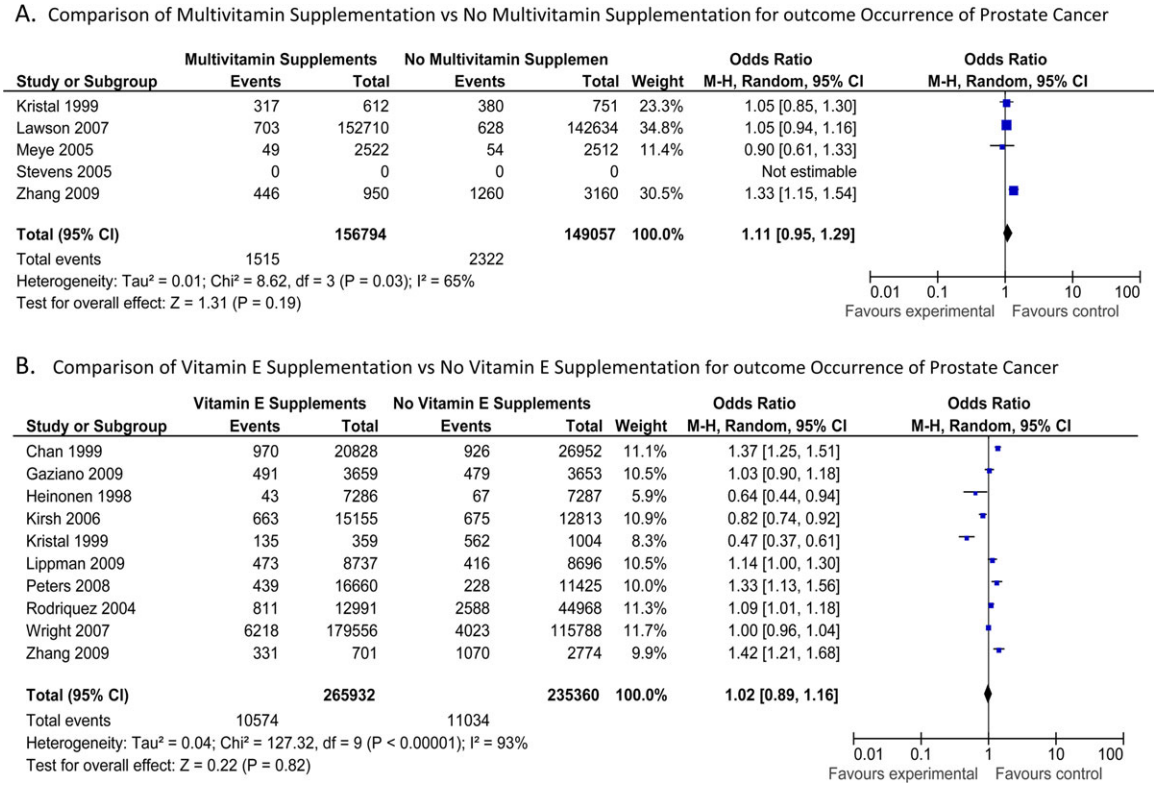


FIGURE 2 *Forest plots for outcome Occurrence of Prostate Cancer. (A) Comparison of multivitamin supplementation versus no multivitamin supplementation for outcome Occurrence of Prostate Cancer. (B) Comparison of vitamin E supplementation versus no vitamin E supplementation for outcome Occurrence of Prostate Cancer. (C) Comparison of zinc supplementation versus no zinc supplementation for outcome Occurrence of Prostate Cancer. (D) Comparison of selenium supplementation versus no selenium supplementation for outcome Occurrence of Prostate Cancer. (E) Comparison of beta-carotene supplementation versus no beta-carotene supplementation for outcome Occurrence of Prostate Cancer.*

effects model accounts for between-study as well as within-study variation.

Results

The meta-analyses did not show any benefit of any of the individual vitamin or multivitamin supplementation included in this review. Some individual studies showed a beneficial effect for some supplements but in general, there was a wide range of results. For instance, in the studies looking at vitamin E supplementation, three studies suggested a beneficial effect, three suggested a potential harmful effect and four suggested no effect whatsoever. This wide range of effects led to a high statistical heterogeneity with I^2 results in the range of 65%–95%. However, it also suggests that publication bias is low. Also, there were interesting subgroup results in some studies: Heinonen showed a decrease in incidence and mortality from prostate cancer in smokers who used vitamin E supplementation. However, Chan's study suggested increased risk of metastases from prostate cancer in men using vitamin E. As discussed in the introduction, these kinds of discrepancies indicate the need for a meta-analysis.

Results are presented in two ways. Qualitatively each of the 14 studies and their results are presented in Table 2. Quantitatively, meta-analysis was used to combine the results of the studies. Mantel–Haenzel odds ratios and 95% confidence intervals were determined for each study and combined into an overall effect for each exposure and outcome measured in the studies.

Figure 2 shows the results of meta-analysis for the outcome: occurrence of prostate cancer. Neither the use of multivitamin supplementation nor the use of individual vitamin/mineral supplementation affected the occurrence of prostate cancer when the results of the studies were combined in a meta-analysis.

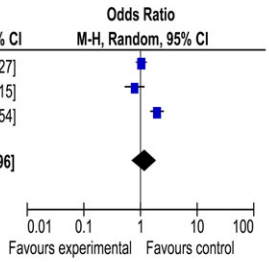
Figure 3 shows the results of meta-analysis for the outcome: advanced/metastatic prostate cancer or death from prostate cancer. Neither the use of multivitamin supplementation nor the use of individual vitamin/mineral supplementation affected the occurrence of advanced/metastatic prostate cancer or death from prostate cancer when the results of the studies were combined in a meta-analysis.

We also conducted several sensitivity analyses by running meta-analysis using just the higher quality studies and just the RCTs. There were still no associations found.

C. Comparison of Zinc Supplementation vs No Zinc Supplementation for outcome Occurrence of Prostate

Study or Subgroup	Zinc Supplements Events	Total	No Zinc Supplements Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Gonzalez 2009	103	4243	729	31001	35.1%	1.03 [0.84, 1.27]
Kristal 1999	53	116	644	1247	30.8%	0.79 [0.54, 1.15]
Zhang 2009	141	253	1260	3222	34.1%	1.96 [1.51, 2.54]
Total (95% CI)		**4612**		**35470**	**100.0%**	**1.18 [0.71, 1.96]**
Total events	297		2633			

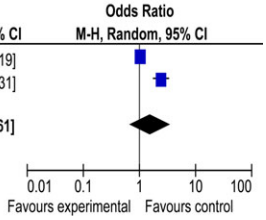
Heterogeneity: Tau² = 0.18; Chi² = 20.45, df = 2 (P < 0.0001); I² = 90%
Test for overall effect: Z = 0.65 (P = 0.52)



D. Comparison of Selenium Supplementation vs No Selenium Supplementation for outcome Occurrence of Prostate

Study or Subgroup	Selenium Supplementation Events	Total	No Selenium Supplementati Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Lippman 2009	432	8752	416	8696	51.4%	1.03 [0.90, 1.19]
Zhang 2009	108	177	1293	3298	48.6%	2.43 [1.78, 3.31]
Total (95% CI)		**8929**		**11994**	**100.0%**	**1.57 [0.68, 3.61]**
Total events	540		1709			

Heterogeneity: Tau² = 0.35; Chi² = 24.31, df = 1 (P < 0.00001); I² = 96%
Test for overall effect: Z = 1.05 (P = 0.29)



E. Comparison of Beta-Carotene Supplementation vs No Beta-Carotene Supplementation for outcome Occurrence of Prostate

Study or Subgroup	Beta-carotene supplements Events	Total	No Beta-Carotene Suppleme Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Heinonen 1998	80	7282	67	7287	32.9%	1.20 [0.86, 1.66]
Kirsh 2006	537	12203	801	12813	35.3%	0.69 [0.62, 0.77]
Zhang 2009	63	108	1338	3367	31.8%	2.12 [1.44, 3.13]
Total (95% CI)		**19593**		**23467**	**100.0%**	**1.18 [0.61, 2.30]**
Total events	680		2206			

Heterogeneity: Tau² = 0.32; Chi² = 36.62, df = 2 (P < 0.00001); I² = 95%
Test for overall effect: Z = 0.49 (P = 0.62)

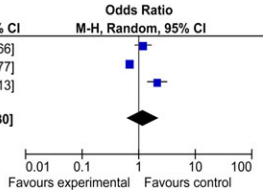


FIGURE 2 *Continued*

Discussion

Individually, some of the studies we included in this review did show an association between the consumption of supplemental vitamins and minerals and the occurrence of prostate cancer. However, these associations were often weak and some studies showed a positive influence while others showed a negative influence on prostate cancer. As well, two studies showed a relationship only in smokers.

Overall, when all the identified eligible studies were combined in meta-analyses, there was no effect of any of the vitamins or multivitamins on the occurrence or severity of prostate cancer.

Clinical implications

While some studies suggest benefit with some vitamins, other studies show potential harm. There is no convincing evidence from this review that clinicians should recommend multivitamins, vitamin E, vitamin C, zinc, selenium or beta-carotene to their male patients in an attempt to prevent prostate cancer nor any evidence that these vitamins and minerals will help in secondary prevention in men who have a diagnosis of prostate cancer.

Limitations

The major limitation is the conduct of a meta-analysis in the presence of high heterogeneity among the studies. While we used a random effects model to try to mitigate the heterogeneity as an issue, and while our sensitivity analyses did not change the results, it is possible that an unidentified subgroup may benefit from, or be harmed by, vitamin supplementation.

Declarations

Ethical approval: Not required at our institution for systematic reviews.
Funding: Non-funded research.
Conflict of interest: No conflicts of interest.

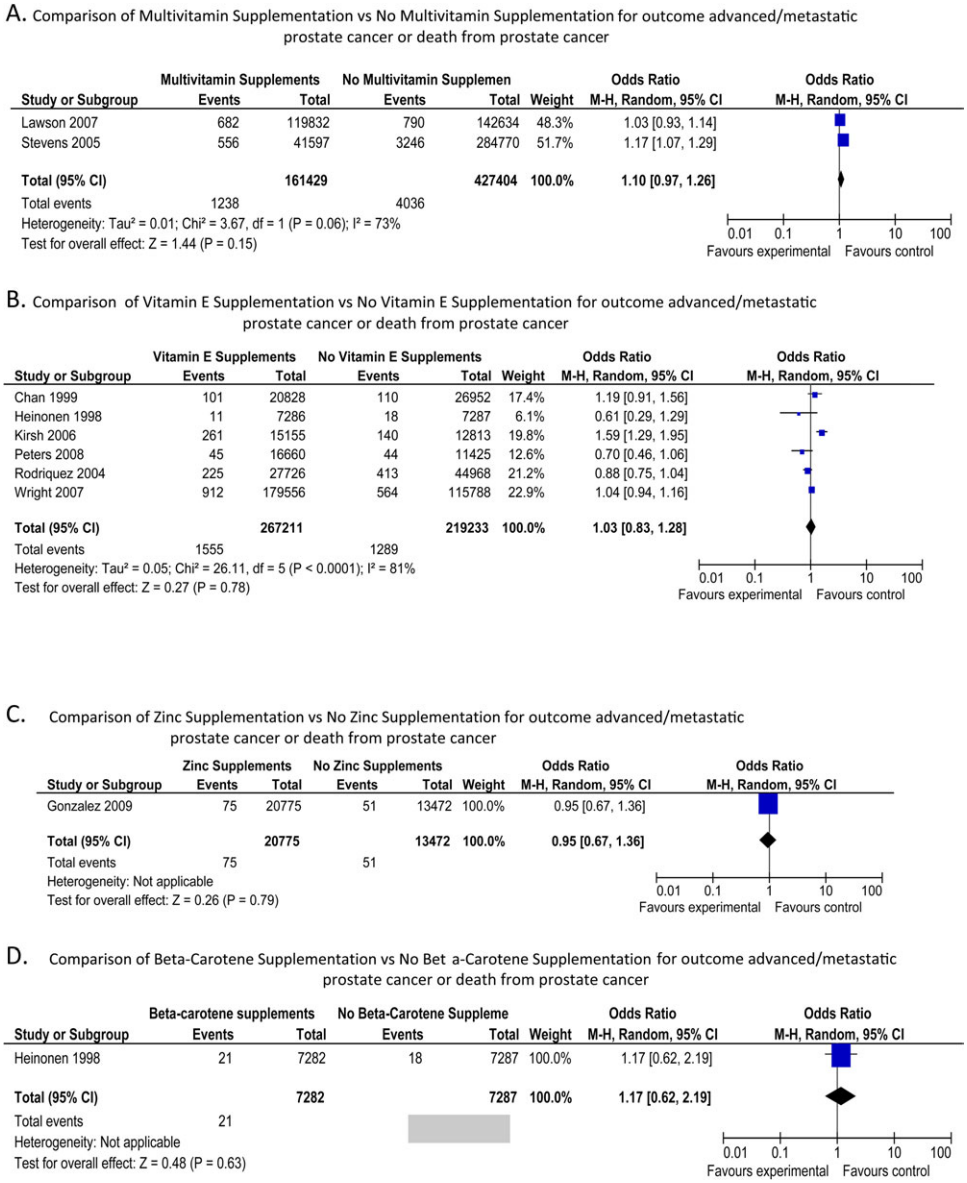


FIGURE 3 *Forest plots for outcome: advanced/metastatic prostate cancer or death from prostate cancer. (A) Comparison of multivitamin supplementation versus no multivitamin supplementation for outcome advanced/metastatic prostate cancer or death from prostate cancer. (B) Comparison of vitamin E supplementation versus no vitamin E supplementation for outcome advanced/metastatic prostate cancer or death from prostate cancer. (C) Comparison of zinc supplementation versus no zinc supplementation for outcome advanced/metastatic prostate cancer or death from prostate cancer. (D) Comparison of beta-carotene supplementation versus no beta-carotene supplementation for outcome advanced/metastatic prostate cancer or death from prostate cancer.*

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