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Vitamin and Mineral Supplements in the Primary Prevention of Cardiovascular Disease and Cancer: An Updated Systematic Evidence Review for the U.S. Preventive Services Task Force FREE

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See Also:

Oral High-Dose Multivitamins and Minerals After Myocardial Infarction: A Randomized Trial

Long-Term Multivitamin Supplementation and Cognitive Function in Men: A Randomized Trial

Enough Is Enough: Stop Wasting Money on Vitamin and Mineral Supplements

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Article | Figures | Tables | References | Supplements | Comments (3) | CME

Abstract

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Background: Vitamin and mineral supplements are commonly used to prevent chronic diseases.

Purpose: To systematically review evidence for the benefit and harms of vitamin and mineral supplements in community-dwelling, nutrient-sufficient adults for the primary prevention of cardiovascular disease (CVD) and cancer.

Data Sources: MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Database of Abstracts of Reviews of Effects were searched from January 2005 to 29 January 2013, with manual searches of reference lists and gray literature.

Study Selection: Two investigators independently selected and reviewed fair- and good-quality trials for benefit and fair- and good-quality trials and observational studies for harms.

Data Extraction: Dual quality assessments and data abstraction.

Data Synthesis: Two large trials (n = 27 658) reported lower cancer incidence in men taking a multivitamin for more than 10 years (pooled unadjusted relative risk, 0.93 [95% CI, 0.87 to 0.99]). The study that included women showed no effect in that group. High-quality studies (k = 24; n = 324 653) of single and paired nutrients (such as vitamins A, C, or D; folic acid; selenium; or calcium) were scant and heterogeneous and showed no clear evidence of benefit or harm. Neither vitamin E nor β-carotene

prevented CVD or cancer, and β-carotene increased lung cancer risk in smokers.

Limitations: The analysis included only primary prevention studies in adults without known nutritional deficiencies. Studies were conducted in older individuals and included various supplements and doses under the set upper tolerable limits. Duration of most studies was less than 10 years.

Conclusion: Limited evidence supports any benefit from vitamin and mineral supplementation for the prevention of cancer or CVD. Two trials found a small, borderline-significant benefit from multivitamin supplements on cancer in men only and no effect on CVD.

Primary Funding Source: Agency for Healthcare Research and Quality.

Vitamins and minerals are commonly used as dietary supplements to promote health and prevent chronic diseases (1). In the National Health and Nutrition Examination Survey III (1988–1994), nearly half of the U.S. population reported using a dietary supplement. A "multivitamin" was the most frequently used supplement (2). Americans spend an estimated $11.8 billion each year on vitamin and mineral supplements (3).

Cardiovascular disease (CVD) and cancer are the leading causes of illness and death in the United States (4). Cancer and CVD have several shared risk factors, including inflammation, oxidative stress, and methionine metabolism. The rationale for using these supplements is supported by many in vitro and animal studies showing that they protect against these damaging cellular mechanisms.

In 2003, the U.S. Preventive Services Task Force (USPSTF) concluded that there was insufficient evidence to recommend for or against the use of vitamins A, C, and E; multivitamins with folic acid; or antioxidant combinations for the prevention of CVD or cancer (5). The USPSTF recommended against the use of β-carotene supplements, either alone or in combination, because they found good-quality evidence that they not only carried no benefit but in fact caused harm among adults at an increased risk for lung cancer. To help the USPSTF update its recommendation, we identified and reviewed additional evidence on the benefits and harms of vitamin and mineral supplementation to prevent CVD and cancer in the general adult population.

Methods

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We developed an analytic framework (Appendix Figure 1 of the Supplement) with 4 key questions that we adapted from a 2006 review by Huang and colleagues (6). Our full report describes our methods in detail (7). We specifically sought studies of the following vitamins and minerals: vitamins A, B_1, B_2, B_6, B_{12}, C, D, and E; calcium; iron; zinc; magnesium; niacin; folic acid; β-carotene; and selenium. We included studies that evaluated single, paired, and combinations of 3 or more vitamins and minerals; we use the term "multivitamin" to refer to those combinations.

Data Sources and Searches

We reviewed all included studies from 3 USPSTF reviews published in 2003 (8–10) and the review conducted by Huang and colleagues (6). We searched MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Database of Abstracts of Reviews of Effects from January 2005 through 29 January 2013, to identify articles published since the review conducted by Huang and colleagues (6). We also searched the bibliographies of relevant reviews and meta-analyses, as well as the Web sites of government agencies and professional organizations, for any relevant research published outside of peer-reviewed journals. We obtained additional references from outside experts.

Study Selection

Two investigators independently reviewed each study's abstract against prespecified inclusion criteria. We included fair- and good-quality randomized, controlled trials that assessed the effectiveness or safety of supplements in the primary prevention of CVD, cancer, or all-cause mortality in the general adult population without a history of CVD or cancer. We included fair- and good-quality secondary prevention trials if they hypothesized effects on outcomes included in this review and not present at baseline in the study (for example, a trial of secondary skin cancer prevention that also reported on other cancers). We included only studies that were conducted among community-dwelling, nutrient-sufficient adults who had no chronic disease and were performed in countries with a Human Development Index of "very high" (11). We also required supplement doses to be lower than the upper tolerable limit set by the U.S. Food and Nutrition Board (12). We included both fair- and good-quality trials and observational studies, without limitations on study sample size or duration, to assess potential harms in order to increase our likelihood of detecting serious harms that are rare or that develop only after long periods (13). Serious harms included paradoxical increases in CVD, cancer, or mortality and events defined as "serious" by study investigators. We also considered adverse events in trials that reported less serious harms if they were common (that is, occurred in >5% of persons and were statistically significantly higher among those

receiving supplements).

Data Extraction and Quality Assessment

One investigator abstracted study design information, baseline population characteristics, intervention details, disease incidence, mortality, and harms data from all included studies into a standardized evidence table. A second investigator checked these data for accuracy. Two investigators independently assessed each study's quality as “good,” “fair,” or “poor” by using predefined quality criteria based on USPSTF methods (14). We excluded all poor-quality randomized, controlled trials and observational studies. In general, a good-quality study met all prespecified criteria. A fair-quality study did not meet at least 1 criterion but also did not have a known limitation that could invalidate its results. A poor-quality study had a fatal flaw or multiple important limitations. We supplemented the USPSTF criteria with criteria from the National Institute for Health and Clinical Excellence for the quality assessment of observational studies (15). We resolved any disagreements through discussion.

Data Synthesis and Analysis

We qualitatively described and summarized the evidence. We stratified results by supplement and synthesized the results of included studies by examining estimates of effects. We conducted meta-analyses to estimate the effect size of supplementation on CVD incidence, cancer incidence, and all-cause mortality at the longest follow-up time point by using the metan procedure of Stata software, version 11.2 (Stata Corp., College Station, Texas) (16). For all cases, we analyzed unadjusted relative risks based on the number of events and nonevents. We used the fixed-effects Mantel–Haenszel method because few trials could be combined and to help avoid bias associated with rare events (1% to 10% of participants in most trials) (17–18).

Role of Funding Source

The Agency for Healthcare Research and Quality funded this review under a contract to support the work of the USPSTF. Members of the USPSTF and an AHRQ medical officer assisted in defining this review's scope. Although approval from AHRQ was required before the manuscript could be submitted for publication, the authors are solely responsible for its content and the decision to submit it for publication.

Results

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We screened 12 766 abstracts, reviewed 277 full-text articles, and included 103 articles (26 studies) (Appendix Figure 2 of the Supplement). Four trials (19–22) and 1 cohort study (23) examined the benefits and harms of multivitamin supplementation (Supplement). Twenty-two trials and 2 cohort studies examined the benefits and harms of individual or paired supplements (Supplement): 6 studies of β-carotene (24–29), 6 studies of vitamin E (22, 24, 30–33), 3 studies of selenium (33–35), 5 studies of vitamin A (23, 29, 36–38), 2 studies of vitamin C (30–31), 1 study of folic acid (39), 3 studies of vitamin D (40–42), 2 studies of vitamin D in combination with calcium (43–44), and 4 studies of calcium (40, 43, 45–46). The study sizes ranged from 128 to 72 337 individuals with average ages ranging from 22 to 77 years, although in most studies the mean age was older than 50 years (Supplement). Six studies were conducted among women only, 5 were conducted among men only, and the remaining studies were in mixed populations (24.2% to 84.7% women). The effects of the supplements were examined between 6 months and 16 years; most studies provided less than a decade of follow-up.

Multivitamin Studies

We identified 4 good-quality trials (n = 28 607) (19–22) and 1 good-quality cohort study (n = 72 337) (23) that evaluated a multivitamin's effect on cardiovascular, cancer, and mortality outcomes or harms (Table and Supplement) (47–55). Two of the 4 multivitamin trials were large (n = 27 658): SUpplementation in VItamins and Mineral AntioXidants Study (SU.VI.MAX) and the Physicians' Health Study II (PHS-II). SU.VI.MAX was conducted among 13 017 men and women living in France and examined a 5-ingredient multivitamin (19). PHS-II tested the efficacy of a 30-ingredient commercial multivitamin among 14 641 U.S. male physicians (21). Neither SU.VI.MAX nor PHS-II reported that supplements affected all-cause mortality after 7.5 and 11.2 years of follow-up, respectively (Figure 1). A third trial, the Roche European American Cataract Trial (REACT), reported more deaths in the intervention group (n = 9) than in the control group (n = 3) after 3 years, but this difference was not statistically significant (P = 0.07) (20). We found no effect on all-cause mortality when we pooled the results of these trials (Figure 1).

Figure 1.

Unadjusted RR for all-cause mortality at longest follow-up only, by supplement.

RR = relative risk.

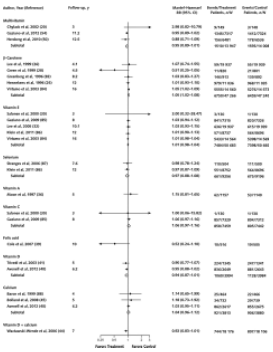

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Table. Multivitamin Evidence Summary

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Multivitamins had no effect on fatal and nonfatal CVD events overall (Figure 2 and Appendix Table 1). PHS-II found a borderline statistically significant benefit for fatal myocardial infarction (adjusted hazard ratio, 0.61 [95% CI, 0.38 to 0.995]; *P* = 0.048) (which could be a type I error due to multiple testing) and no effect for combined fatal and nonfatal myocardial infarction (adjusted hazard ratio, 0.93 [CI, 0.80 to 1.09]; *P* = 0.39]).

Appendix Table 1. CVD and Cancer Incidence and Mortality Among Multivitamin Studies

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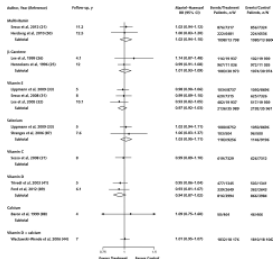
Figure 2.

Unadjusted RR for cardiovascular disease at longest follow-up only, by supplement.

RR = relative risk.



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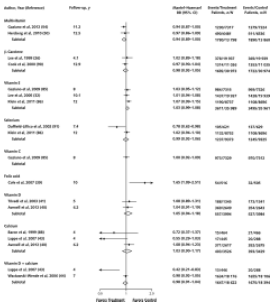
PHS-II found that multivitamins reduced overall cancer incidence after 11.2 years of follow-up (Appendix Table 1) (54). SU.VI.MAX did not find that multivitamins affected total cancer incidence after an initial follow-up of 7.5 years or during posttreatment follow-up for an additional 5 years (51) (Figure 3). This study stratified randomization by sex and tested for a sex–by–treatment group interaction, which was statistically significant (*P* = 0.02). The sex-specific subgroup analysis showed a protective effect among men (adjusted relative risk, 0.69 [CI, 0.53 to 0.91]) but not women. When SU.VI.MAX's findings in men were pooled with the PHS-II results, the unadjusted relative risk for all cancer incidence was reduced over 10 years of follow-up (unadjusted pooled relative risk, 0.93 [CI, 0.87 to 0.99]).

Figure 3.

Unadjusted RR for cancer at longest follow-up only, by supplement.

RR = relative risk.



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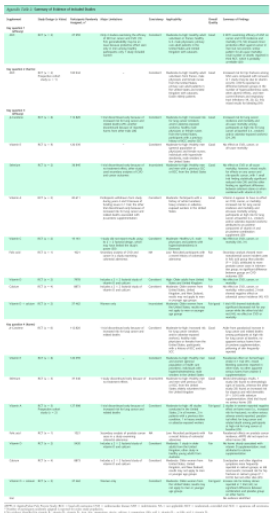
Our 5 included studies showed no consistent pattern of harms from nutritional dosages of multivitamins (19–20, 22–23, 54). Some individual studies or subgroup analyses, however, did find possible harms. For example, there was an increase in melanomas among women enrolled in SU.VI.MAX, and the Nurse's Health Study found higher hip fracture rates (23). The fifth study, by Graat and colleagues, examined only effects on respiratory illness in the elderly and reported no harms (22).

Single and Paired Vitamins and Minerals

We identified 24 studies (*n* = 324 653) of single and paired nutrients. Overall, we found little consistent evidence to support or refute a health effect on all-cause mortality or the incidence of CVD or cancer for supplementation with vitamins A, C, or D; folic acid; selenium; or calcium (Appendix Table 2; Figures 1, 2, and 3; and Supplement). For most nutrients, however, we found 3 or fewer studies. Trials often varied considerably in principal aims, study design, and recruitment criteria. Such a small body of evidence makes a type II error more likely. In addition, for some supplements the evidence of no benefit was inconsistent. In 1 of 2 studies of selenium, for example, cancer risk decreased (33–34). Likewise, 1 of 2 studies of calcium plus vitamin D supplementation in women found a decreased cancer risk (43–44).

Appendix Table 2. Summary of Evidence of Included Studies



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We found consistent null results for CVD incidence and cancer incidence across 6 trials of β-carotene (Figures 1 and 3) (24–29). We found a probable increase in lung cancer incidence in high-risk subgroups (smokers and asbestos workers). We found 5 trials for vitamin E supplementation that showed no effect on the 3 outcomes (Figures 1, 2, and 3) (24, 30–33).

Six trials evaluated the effects of vitamin D and calcium supplementation on CVD and cancer incidence when used alone or in combination. Four of these trials provided data on calcium supplementation without vitamin D (40, 43, 45–46) and reported no statistically significant effect on CVD or cancer incidence or on all-cause mortality (Figures 1, 2, and 3). Although the overall cancer rate reported for calcium supplementation was lower than the rate in the placebo group in 2 trials (43, 46), the opposite was observed in another trial (40); neither difference was statistically significant (Figure 3). Vitamin D plus calcium supplementation was specifically studied in 2 trials (43–44), 1 of which examined CVD incidence and found no effect (44). Both of these trials reported cancer outcomes, and while the smaller trial found a

statistically significant decrease in overall cancer incidence over 4 years (43), the larger trial did not (44). The pooled unadjusted relative risk was 0.98 (CI, 0.91 to 1.04). Another trial examined vitamin D and calcium supplementation under a 2 × 2 factorial design and also found no main effect for either supplement (40).

We found little consistent evidence of harm across studies. Although vitamin A use in 1 trial was associated with increased risk for lung cancer, it was combined with β-carotene (29). Two cohort studies also implicated vitamin A use for increased risk for hip fracture (23, 38), although the total fracture rate was not higher in the study that reported this outcome (38). One study assessed folic acid supplementation in patients with prior colorectal adenomas and found that folic acid supplementation was associated with an increase in prostate cancer incidence (39). Incidence of colorectal cancer in the calcium group was increased in a pooled analysis of 2 trials of calcium supplementation, but this was a post hoc subgroup analysis (40, 43). The large trial of vitamin D and calcium supplementation found a small increase in kidney stones in the supplement group (44).

Discussion

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This review included 26 studies (24 randomized, controlled trials and 2 cohort studies) that examined the benefits and harms of using vitamin and mineral supplements for primary prevention of CVD, cancer, or all-cause mortality in healthy individuals without known nutritional deficiencies. We found no consistent evidence that the included supplements affected CVD, cancer, or all-cause mortality in healthy individuals without known nutritional deficiencies. Other systematic reviews have arrived at this same conclusion (56–66). The certainty of this result is tempered, however, because few fair- or good-quality studies are available for all supplements except vitamin E and β-carotene. For vitamin E, we identified 6 fair- to good-quality trials that produced clearly null effects on these end points. This result is consistent with the conclusions of other systematic reviews and meta-analyses of vitamin E (67–71). Our review also confirmed the established harm of β-carotene supplementation on lung cancer incidence and death for individuals at high risk for lung cancer (24, 29, 72). Further, we identified 6 trials that failed to detect any benefit from β-carotene supplementation for any individuals.

The results of vitamin supplementation trials have been disappointing at best, despite having a solid mechanistic basis (73). One explanation for this result could be that the physiologic systems affected by vitamins and other antioxidant supplements are so complex that the effects of supplementing with only 1 or 2 components is generally ineffective or actually does harm (74). This hypothesis is compatible with our finding that the best support for benefit of supplementation came from 2 multivitamin trials that used physiologic doses of a wider variety of agents.

Two good-quality trials of multivitamin supplementation found lower cancer incidence in men (19, 54). The SU.VI.MAX trial included women and did not find an effect in this subgroup (19). We found a statistically significant protective effect from multivitamin supplementation when we pooled data for men in these 2 trials. The borderline significance level in both studies and the lack of an effect in women in SU.VI.MAX suggest we should not try to overgeneralize these results. The SU.VI.MAX investigators speculate that the observed sex difference in multivitamin effects on cancer incidence in their trial may have been due to lower baseline antioxidant status in men than women (19). A baseline difference in blood levels, however, was found only for β-carotene and not for vitamins E and C, selenium, or zinc (19), although blood levels may not fully reflect nutritional status. Other behavioral or biological factors might modify the effects of antioxidant supplements on men and women; however with only 1 study available it would be better to reconfirm the sex difference before speculating on its cause.

The simplest way to interpret the vitamin D and calcium results is that these vitamins have no effect on CVD or cancer. A systematic review by Wang and colleagues came to a similar conclusion (59). Our data do suggest, however, that the effects of calcium on these end points may differ from the effects of vitamin D. When we pooled the 2 vitamin D trials (40–41), for example, we found lower mortality in the supplement groups (unadjusted relative risk, 0.94 [CI, 0.87 to 1.01]). In contrast, the point estimates for calcium were all greater than 1, although CIs for all estimates were wide. These findings support the idea that future research should include separate studies of calcium and vitamin D.

Recently, several investigators have posited that calcium intake or supplementation has harmful effects on CVD outcomes (75–80). Much of this speculation, however, derives from 2 meta-analyses that used different sets of trials (75–76) and were heavily influenced by data from a reanalysis of the Women's Health Initiative (WHI) trial (77). The WHI reanalysis identified harms only in the subgroup of women *not* taking calcium or vitamin D at baseline. Such post hoc subgroup analyses, however, can be misleading (81). Indeed, the WHI investigators found no evidence of harm for CVD or cancer in their own reanalysis of their trial results, even when results were stratified by baseline supplement use and the results of their large observational study were added (78). Two other recent studies included only observational data. These studies did not show consistent findings across studies, between sexes, or between dietary and supplemental calcium use (79–80). Although available studies are insufficiently consistent to permit the

conclusion that calcium supplementation is harmful, future controlled trials should address this question.

Our analysis has some limitations. We considered only primary prevention interventions in generally healthy people and excluded secondary and tertiary prevention trials and treatment studies. Thus, our results do not apply to the targeted use of nutrients in deficient or higher-risk individuals. Only 2 trials of multivitamin supplements were included for efficacy, even though we broadly defined a multivitamin as 3 or more ingredients. Those 2 trials studied very different supplements (19, 21). Because the only multivitamin trial to include women used a supplement with 5 ingredients (19), it could be argued that there are no data on a "true" multivitamin in women. Most of the included vitamin trials provided less than a decade of follow-up, and vitamin effects on CVD and cancer may take longer to manifest. The small number of studies in each pooled analysis made it difficult to evaluate between-study heterogeneity. We limited our examination of harms to fair- and good-quality trials and observational studies and thus may have underestimated harms. In addition, we did not assess harms from higher doses of vitamins and minerals than the upper tolerable limit set by the U.S. Food and Nutrition Board.

This is a review of trials, a study design used primarily to evaluate drug therapy. The design might not be ideally suited to evaluating nutrients (82). The control group in a placebo-controlled trial of medications is not exposed to the medication. In a nutrient supplementation study, however, the control group is exposed to some level of the nutrient because it is designed to answer a different question: Does exposure to an optimal level of the nutrient produce better health outcomes than exposure to the usual level? To conduct this type of study, one must know both the usual and optimal level of exposure. In practice, however, exposure to the nutrient in the control group may change during the course of a trial as societal norms change, complicating interpretation of the trial results. Women in the WHI control group, for example, had twice the average calcium intake of that anticipated when the trial was designed, and the vitamin D dose was lower than many now think is necessary to achieve optimal blood levels.

Few studies have evaluated the effectiveness of vitamin and mineral supplements in the primary prevention of CVD and cancer in nutrient-sufficient adults. Published studies have used a wide variety of supplements, in different doses, with different study objectives and populations, and usually for short duration. Although 2 relatively large trials examined the efficacy of a multivitamin in the primary prevention of CVD and cancer in a general population, population selection and potential sex-specific findings limit the applicability of their results. Future studies of multivitamin supplements should recruit from a general population with representation of multiple minority groups and both sexes, use a multivitamin that is reasonably similar to the popular brands in the current market, continue for at least a decade, and include enough participants to provide adequate power to detect benefits and harms within important subgroups, including men and women. This is a tall order, and any such study would also face other difficulties, including agreement on the content of the multivitamin, so the results of the trial might be dismissed by observers who felt that an important ingredient was omitted. The wide availability of multivitamins could result in substantial crossover, and the large number of participants and long follow-up needed would result in an expensive trial. Still, the U.S. public is devoting major financial resources to multivitamins, so such a trial could have a large public health impact, whatever the outcome.

Despite its limitations, the current literature on single or paired vitamins and minerals is sufficient to discourage additional studies of β-carotene or vitamins A, C, and E in general populations not deficient in the nutrients. Future studies of selenium should clearly separate individuals with adequate and low baseline selenium levels. Future studies of vitamin D should be done separately from studies of calcium. Vitamin D and calcium studies should include the full range of hypothesized benefits, including fracture prevention, to allow a comprehensive comparison of overall benefits and harms.

In conclusion, we found no evidence of an effect of nutritional doses of vitamins or minerals on CVD, cancer, or mortality in healthy individuals without known nutritional deficiencies for most supplements we examined. In most cases data are insufficient to draw any conclusion, although for vitamin E and β-carotene a lack of benefit is consistent across several trials. We identified 2 multivitamin trials that both found lower overall cancer incidence in men (19, 21). Both trials were methodologically sound, but the lack of an effect for women (albeit in 1 trial), the borderline significance in men in both trials, and the lack of any effect on CVD in either study makes it difficult to conclude that multivitamin supplementation is beneficial.

References

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