Advanced Pharmaceutical Bulletin

Adv Pharm Bull, 2016, 6(4), 467-477
doi: 10.15171/apb.2016.061
http://apb.tbzmed.ac.ir

TUOMS Publishing Group

Review Article

Vitamins, Are They Safe?

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Article info

Article History:
Received: 2 June 2015
Revised: 9 October 2016
Accepted: 15 October 2016
ePublished: 22 December 2016

Keywords:
· Vitamins
· Dietary Supplements
· Drugs
· Complementary Therapies
· Safety
· Adverse effects

Abstract

The consumption of a daily multivitamin among people all over the world is dramatically increasing in recent years. Most of the people believe that if vitamins are not effective, at least they are safe. However, the long term health consequences of vitamins consumption are unknown. This study aimed to assess the side effects and possible harmful and detrimental properties of vitamins and to discuss whether vitamins can be used as safe health products or dietary supplements. We performed a MEDLINE/PubMed, EMBASE, Scopus and Google Scholar search and assessed reference lists of the included studies which were published from 1993 through 2015. The studies, with an emphasis on RCTs (randomized controlled clinical trials), were reviewed. As some vitamins such as fat-soluble vitamins (vitamin A, vitamin D, vitamin E), and also some of the water-soluble vitamins like folic acid may cause adverse events and some like vitamin C is widely taken assuming that it has so many benefits and no harm, we included relevant studies with negative or undesired results regarding the effect of these vitamins on health.

Our recommendation is that taking high-dose supplements of vitamins A, E, D, C, and folic acid is not always effective for prevention of disease, and it can even be harmful to the health.

Introduction

Most people all over the world use a daily multivitamin for treatment or prevention of chronic disease. Uncontrolled advertisements about the vitamins in addition to wide availability of these agents result in high prevalence of their consumption among people. Although the effectiveness of the multivitamins and minerals is unclear, the prevalence of the use of these supplements in many developed countries is widened.[1] The percentage of adults using any daily vitamin and mineral supplement has increased very rapidly in recent years. One third of adults and half of population aging more than 55 years report taking of at least one supplement per day.[2] An increase in supplement sales has been seen since 1997, reaching to $18.8 billion in the United States in 2003.[3]

Antioxidants such as α-tocopherol (vitamin E), ascorbic acid (vitamin C) and carotenoides attracted so many attentions over the past three decades. Free radicals can lead to the development of cancer and cardiovascular disease (CVD) by lipid peroxidation and DNA damage. Basic studies suggested that antioxidants deactivate excited oxygen molecules and organic free radicals, and consequently reduce cardiovascular disease. Antioxidants can prevent the formation of atherosclerotic plaque by inhibiting oxidation of low-density lipoprotein cholesterol (LDL-C), decreasing thrombotic potential, platelet activity modifying, and vascular reactivity modifying.[4,5] Most of the people believe that if vitamins are not effective, at least they are safe. In spite of various researches in cellular biologic function of vitamins and interesting massages about their roles on health, the long term health consequences of vitamins consumption are unknown.

This study aimed to assess the side effects and possible harmful and detrimental properties of vitamins and to discuss whether vitamins can be used as safe health products or dietary supplements. We performed a MEDLINE/PubMed, EMBASE, Scopus and Google Scholar search and assessed reference lists of the included studies which were published from 1993 through 2015. The studies, with an emphasis on RCTs (randomized controlled clinical trials), were reviewed. As some vitamins such as fat-soluble vitamins (vitamin A, vitamin D, vitamin E), and also some of the water-soluble vitamins like folic acid may cause adverse events and some like vitamin C is widely taken assuming that it has so many benefits and no harm, we included relevant studies with negative or undesired results regarding the effect of these vitamins on health. We have also shown recommended dietary allowance (RDA)/adequate intake (AI) and tolerable upper intake level (UL) of these vitamins in Table 1.

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Table 1. Dietary Reference Intake Values for vitamin E, C, A, D and folic acid

-	RDA/AI	UL
Vitamin E	15mg/d	1000mg/d
Vitamin C	Female: 75mg/d	2000mg/d
	Male: 90mg/d	-
Vitamin A	Female: 700µg/d	3000µg/d
	Male: 900µg/d	-
Folic acid	400µg/d	1000µg/d
Vitamin D	18-50 years: 5µg/d	-
	50-70 years: 10µg/d	50µg/d
	>70 years:15µg/d	-

RDA: Recommended Dietary Allowance; AI: Adequate Intake; UL: Tolerable Upper Intake Level; data based on the National Academy of Sciences

Vitamin E (α-tocopherol)

Vitamin E is a lipid-soluble vitamin and a major component in the cell antioxidant defense system. It is exclusively obtained from the diet.[6] As it has been shown that vitamin E can reduce oxidative stress, its supplementation have been assessed as a therapy to prevent many chronic diseases in many clinical trials. However, several studies could not find significant effectiveness of vitamin E on prevention of cancer,[4,7-25]reduction in cardiovascular diseases,[8,13,25-36] and overall mortality reduction.[5,15,19,25,27,37-39] In a randomized, double-blind, placebo-controlled trial (The Physicians' Health Study II), a total of 14641 male physicians aging more than 50 years were enrolled. They received supplements of vitamin E (400 IU) every other day and were followed for 8 years. Compared to placebo, vitamin E did not have any effect on prostate cancer incidence (HR=0.97; 95% CI=0.85-1.09; P=0.58) or total cancer incidence (HR=1.04; 95% CI=0.95-1.13; P=0.41). These data provided no support for vitamin E supplementation to prevent cancer in men aging more than 50 years.[10] This finding was confirmed in another study. In a multicenter randomized trial, around 35000 healthy men prescribed vitamin E (400 IU/d) or placebo were followed up for 7-12 years. Data analysis showed that prostate cancer prevalence was higher among men in vitamin E group (HR=1.17; 99% CI=1.004-1.36, P=0.008).[4,16] A prospective cohort study assessed daily use of supplemental vitamin E in 77721 women and men aging 50-76 years for 10 years. Use of vitamin E supplement lead to a small increase in lung cancer risk (HR was 1.05 for every 100 mg increase in dose per day; 95% CI=1.00-1.09; P=0.033). This risk of supplemental vitamin E was mostly shown in current smokers (for every 100-mg per day increase, the HR was 1.11; 95% CI=1.03-1.19; P<0.01) and was at the greatest level for non-small cell type of lung cancer (HR=1.07 for every 100-mg/d increase; 95% CI=1.02-1.12; P=0.004). This increased risk was equivalent to a 7% rise for every 100 mg/day. So, there will be a 28% increased risk of lung cancer with taking 400 mg/day of vitamin E for ten years.[40]

In 72829 nonsmoker Chinese female aging 40 to 70 years who were participating in Shanghai Women's Health Study (SWHS), the effect of tocopherol intake (from diet or supplements) and risk of lung cancer was assessed.

Total dietary tocopherol had an inverse association with risk of lung cancer in women receiving 14 mg/day (adequate intake of tocopherol) or more of tocopherol compared to those receiving less than this amount (HR=0.78; 95% CI=0.60–0.99). The protective effect of dietary tocopherol on risk of lung cancer was confined to women who were exposed to smoke (HR=0.53; CI=0.29–0.97; P=0.04). In contrast, use of vitamin E supplement was related with increased risk of lung cancer (HR=1.33; 95% CI=1.01–1.73), especially with risk of lung adenocarcinoma (HR=1.79; 95% CI=1.23–2.60). So, intake of dietary tocopherol may decrease lung cancer risk among non-smoker females; however, use of supplements may increase risk of lung adenocarcinoma.[41] Lonn et al in a randomized placebo-controlled trial showed that consumption of 400 IU/d vitamin E does not prevent cancer or cardiovascular disease and may even increase risk of heart failure in patients with diabetes mellitus or vascular disease.[8] Miller et al performed a meta-analysis on 19 clinical trials with 135967 participants and dosages of 16.5 to 2000 IU/d of vitamin E. They suggested that there is a dose-response relationship between vitamin E supplementation and all-cause mortality. The difference of all-cause mortality risk was 39 per 10,000 persons in high-dosage vitamin E trials (95% CI, 3 to 74 per 10,000 persons; P=0.035). The risk difference was -16 per 10,000 persons for low-dosage vitamin E trials (CI, -41 to 10 per 10,000 persons; P>0.2). A dose-response analysis revealed a statistically significant relationship between dosage of vitamin E and all-cause mortality, with increased risk of dosages >150 IU/d. A decreased risk of death was observed with lower doses of vitamin E (<400 IU) and an significant increased risk with high doses (≥400 IU).[38]

Of course, there is an inconsistency among different studies which can be due to the effect of the different isoforms of vitamin E. The most common isoform which is used in vitamin E supplements is α-Tocopherol whereas β-tocopherol and γ-tocopherol are the isoforms which are available in large quantities in the diet and are more efficient in trapping reactive oxygen species and reactive nitrogen species. Experimental studies shows that α-tocopherol can induce apoptosis in lesser amounts.[41] One possible mechanism for the harmful effects of vitamin E observed in the studies is that, although vitamin E is thought to be an antioxidant, it might have prooxidant effects in some conditions as well.[40]

In general, there is not any strong evidence in order to suggest vitamin E usage as a regular supplement for healthy people.

Vitamin C

Vitamin C or L-ascorbic acid is an indispensable nutrient for humans. It performs numerous physiological functions like antioxidant activity, modulation of the immune system, and synthesis of collagen, carnitine and neurotransmitters.[42-44] Patients and physicians have expected to overcome chronic disease such as cardiovascular disease or cancer by consumption of vitamin C, based on its antioxidant activities.[45] Previous studies were not able to show any benefit regarding the consumption of vitamin C and cancer prevention,[9-12,15,23-25] mortality reduction,[5,10,12,15,18,19,25,37,46] prevention of cardiovascular events,[25,28,29,32,33,36,46] urinary stone production[47] and reduction of common cold incidence.[48-50] Lee et al assessed the association between intake of vitamin C and mortality from cardiovascular disease in 1923 diabetic postmenopausal women. They concluded that intake of vitamin C from food had no association with mortality outcomes. In contrast, supplemental vitamin C intake of greater than 300 mg/d showed a positive relationship with cardiovascular disease.[46] Effect of vitamin C in treatment and prevention of common cold is a very challenging topic and there have been lots of controversies since 70 years ago.

Results of a recent meta-analysis on 29 clinical trial including 11306 subjects showed that regular supplementation with vitamin C in the ordinary population did not have any effect on the incidence of common cold. In another study comparing 31 clinical trials with 9745 common cold episodes, duration of common cold symptoms modestly decreased with regular intake of vitamin C. A systematic review was performed on 598 participants who were exposed to short durations of excessive physical stress (including marathon runners and skiers). It revealed that Vitamin C halved the risk of common cold. The intervention of these studies was at least 0.2g/d orally administered vitamin C for a single day or for a period.[50]

Although vitamin C is a vitamin with well-known and potent antioxidant capabilities, it has been shown that it can have prooxidant effects and can cause damage by stimulating lipid peroxidation.[46] In addition, short-term healthy effects of vitamin C may not be related to long-term beneficial effects and can even be harmful. One important point observed in some studies is that, vitamin C intake from food does not show the deleterious effects as seen with vitamin C intake from supplements. An explanation to this feature can be that the antioxidants which are naturally present in foods are biochemically balanced, which means that they are part of a combination of redox agents in oxidized and reduced forms, whereas this balance may be lacked in every supplement pill.

Vitamin A (Retinol) and beta-carotene

Vitamin A is one of the lipid-soluble vitamins that have antioxidant functions. It is provided by the diet in two forms: preformed vitamin A (which is naturally found just in animal products) and carotenoid vitamin A precursors (found primarily in foods of plant origin). Beta-carotene is the main precursor of vitamin A which also has anti-oxidant properties. Vitamin A is an essential agent for vision, embryogenesis, reproduction, the integrity of membrane structures, epithelial differentiation, growth, and development.[51,52] Epidemiologic studies have shown a reduced risk of various chronic diseases, particularly cancers of lung, gastrointestinal tract, bladder, breast and pancreas and cardiovascular disease with dietary consumption of various carotenoids.[53-61] However, randomized clinical trials have not shown any consistent reduction in the incidence of cancers or cancer deaths, or of cardiovascular disease.[7,62-66] Worse still, an elevated risk of lung cancer in high-risk individuals (asbestos workers and smokers) who were given high doses of beta-carotene alone or in combination with other antioxidants has been reported.[7,64] The Alpha-Tocopherol Beta-Carotene Cancer Prevention (ATBC) Trial and the Beta-Carotene and Retinol Efficacy Trial (CARET) were planned to assess beta-carotene effect on incidence of lung cancer. ATBC tested the combination of alpha-tocopherol (50 mg) and beta-carotene(20 mg) in 29133 male current cigarette smokers.[7]CARET compared the combination of retinyl palmitate (25000 IU) and beta-carotene (30 mg) with placebo in more than 18000 current and recent ex-smokers (male and female) and asbestos workers (male).[63] After 6.1 years of follow-up, ATBC showed a 16% increase in incidence of lung cancer and 8% increase in deaths from all causes in individuals receiving beta-carotene compared to placebo-receiving subjects.[7,66] After 4 years of follow-up, CARET showed a 28% increased incidence of lung cancer and 17% increase in all-cause mortality and greater mortality from cardiovascular disease in vitamin-receiving group than placebo group.[64] It is obvious from these two studies that beta-carotene containing supplements can have adverse effects such as increased incidence of lung cancer and greater mortality in cigarette smokers. Another concern about Vitamin A is its teratogenic effect. A study performed by Rothman et al on 22748 pregnant women showed that the prevalence of cranial-neural-crest tissue defects was 3.5 times in babies whose mothers consumed >15000 IU/d vitamin A from food and supplements compared to the babies whose mothers consumed ≤5000 IU/d (95% CI, 1.7 to 7.3). They concluded that high doses of vitamin A can be teratogenic and almost 1 in 57 infants whose mothers took >10000 IU/d of vitamin A supplements had a malformation.[52]

Vitamin A intake in abundant amounts can have deleterious effects on bone via induction of osteoporosis. This can cause an increased fracture risk,

especially in those with previous osteoporosis risk. Some studies have shown that intake of high amounts of vitamin A can lead to an elevated risk of fracture in hip.[67,68] A study showed that there is a 68%-increased risk of hip fracture for each 1-mg increase in daily intake of retinol (95% CI, 18% to 140%; P for trend, 0.006). For intake >1.5 mg/d compared with intake < 0.5 mg/d, bone mineral density was reduced by 10% at the femoral neck (P = 0.05), 14% at the lumbar spine (P = 0.001), and 6% for the total body (P = 0.009) and risk for hip fracture was doubled (odds ratio, 2.1 [CI, 1.1 to 4.0]).[67] In a prospective study involving 72337 postmenopausal women, women in the highest quintile of total vitamin A intake (>/=3000 µg/d of retinol equivalents [RE]) had a significantly elevated relative risk (RR) of hip fracture (RR, 1.48; 95% CI, 1.05-2.07; P for trend =.003) compared with women in the lowest quintile of intake (<1250 µg /d of RE).[68] In a prospective study of more than 2000 men, a 1.64-fold greater risk of any fracture (95% CI, 1.12 to 2.41) and 2.47-fold greater risk of hip fracture (95% CI, 1.15 to 5.28) was seen with serum retinol level in the highest quantile.[69]

In the Iowa Women's Health Study, there was a greater risk of hip fracture in vitamin A users, but no apparent dose-response. They prospectively followed 34703 postmenopausal women for a duration of almost 9.5 years. It was shown that risk of hip fracture was 1.18 fold in vitamin A supplement users compared to nonusers (95% CI, 0.99 to 1.41), but there was not a greater risk of all fractures among the users of vitamin A supplement.[70]

The importance of vitamin A in the bone remodeling process has been shown in various studies. Vitamin A deficiency results in retarded bone growth, but in the other hand hypervitaminosis A leads to accelerated bone resorption, bone fragility, and spontaneous fracture. Both osteoblasts and osteoclasts express the nuclear receptors for retinoic acid (retinoic acid receptors and retinoid X receptors). Retinoic acid inhibits osteoblast activity, stimulates osteoclast formation, and induces bone resorption.[51, 67]

Folic acid

Folate is a member of vitamin B family and a water-soluble vitamin. It is used for nucleotide biosynthesis, DNA replication, and methylation reactions in body. Folic acid is synthetic folate which is the form used in fortified foods and supplements. It is used alone or combined with other B vitamins in treatment or prevention of cardiovascular disease, macrocytic anemia and neural tube deficiency.[71] Experimental studies have shown that folate deficiency may initiate early stages of carcinogenesis, whilst high doses can enhance the growth of cancer cells.[72,73]

In a study performed on 6837 patients suffering from ischemic heart disease, increased incidence of lung cancer (HR, 1.21; 95% CI, 1.03-1.41; P=0.02), cancer-related mortality (HR, 1.38; 95% CI, 1.07-1.79; P=0.01) and all-cause mortality (HR, 1.18; 95% CI, 1.04-1.33; P=0.01) was seen in subjects treated with 0.8 mg/d folic acid plus 0.4 mg/d vitamin B_{12}.[74]

Figueiredo et al showed increased risk of prostate cancer in men supplemented with 1 mg/d folic acid for 10 years (HR=2.63, 95% CI=1.23 to 5.65, P=0.01).[75]

Zhang et al randomized 5442 women with cardiovascular disease and supplemented them with a mixture of folic acid, vitamin B_6, and vitamin B_{12} (2.5 mg, 50 mg and 1 mg, respectively) or placebo. They observed no effect of these agents on risk of total invasive cancer (HR=0.97; 95% CI=0.79-1.18; P=0.75) or breast cancer (HR=0.83; 95% CI=0.60-1.14; P=0.24).[76] Cole et al performed a clinical trial on almost 1000 men and women with a history of colorectal adenomas. They indicated that 1 mg/d folic acid for 6 years, does not decrease the colorectal adenoma formation risk (RR, 1.13; 95% CI, 0.93-1.37; P =0.23). In addition, a significant excess of prostate cancers was observed in the folate group (7.3% in the folic acid group versus 2.8% in the placebo group [P=0.01]).[77] Bazzanoet al performed a meta-analysis on 12 randomized controlled trials evaluating the effect of folic acid supplementation on risk of cardiovascular diseases. They found that supplementation with folic acid does not decrease the risk of cardiovascular events in patients with previous history of vascular disease. The overall relative risks (95% CI) of outcomes for patients treated with folic acid supplementation compared with controls were 0.95 (0.88-1.03) for cardiovascular diseases, 1.04 (0.92-1.17) for coronary heart disease, 0.86 (0.71-1.04) for stroke, and 0.96 (0.88-1.04) for all-cause mortality.[78] Albert et al in a randomized trial on 5442 women with CVD history showed that supplementation with folic acid and B vitamins for 7.3 years did not reduce cardiovascular events (P=0.65).[79] Graat et al performed a randomized control trial on 652 men taking physiological doses of multivitamins including 200µg/d of folic acid. They found that these agents had no effect on incidence of acute respiratory tract infections and their severity (P=0.58).[80]

These findings highlight the potentially complex role of folate in carcinogenesis. Folate plays a dual role in carcinogenesis. When folate is administered to individuals with suboptimal folate status or in the early stages of carcinogenesis, it prevents tumor initiation; but when it is administered to individuals with high folate intake or in later stages of carcinogenesis (ie, once premalignant lesions are established), it promotes tumor development.[72]

Vitamin D

In most trials, the effects of calcium and vitamin D could not be separated because of their high correlation. Observational epidemiologic studies suggest that higher intake of calcium and vitamin D is associated with a decreased risk of colorectal cancer and polyp recurrence.[81-86] However, in a randomized controlled

trial, daily supplementation of 36282 postmenopausal women with 1000 mg of elemental calcium and 400 IU of vitamin D3 for seven years did not have any effect on the incidence of colorectal cancer (HR, 1.08; 95% CI, 0.86 to 1.34; P=0.51).[87] Although the association between high calcium and vitamin D intake and high levels of 25-hydroxyvitamin D (25-OH D) with lower breast cancer risk has been reported in some observational studies,[88-90] findings of clinical trials do not support this relationship. In a study performed by Chlebowski et al on 36282 postmenopausal women receiving calcium and vitamin D3 (1000 mg/d and 400 IU/d, respectively) for almost 7.0 years, incidence of invasive breast cancer did not reduce with supplementation. Moreover, 25-OH D levels were not associated with further risk of breast cancer (HR, 0.96; 95% CI, 0.85 to 1.09).[91] The effect of vitamin D and calcium intake on bone density and risk of fracture remains equivocal and studies have shown mixed results. Michaëlsson et al assessed the relationship between dietary vitamin D and calcium intake with osteoporotic fracture risk. They used data from a population-based cohort study in 60689 Swedish women, aged 40-74 years and showed that intake of vitamin D was not related to risk of fracture. In addition, age-adjusted RR of all fractures was 1.02 for women in the highest quintiles compared to the women in the lowest quintiles of calcium and vitamin D intake (95% CI 0.88-1.17). They concluded that intake of calcium or vitamin D from diet did not seem to be important for osteoporotic fractures prevention in these women.[92] Nieves et al assessed the effect of vitamin D and calcium intake on bone density and risk of fracture in 76507 postmenopausal Caucasian women. They showed that higher intake of vitamin D and calcium could reduce the odds of osteoporosis (OR = 0.75; 95% CI, 0.68, 0.82 and OR = 0.73; 95% CI, 0.0.66, 0.81; respectively) but did not reduce the 3-year fracture risk in these women.[93]

In the studies mentioned above, a significant relationship between vitamin D intake and risk of cancer or fracture is not observed. The most attractive explanation for these results might be that higher intakes of vitamin D are required for fracture or cancer prevention.[91-93]

Discussion

In recent decade, use of nutritional supplements has rapidly increased. One third of adults and half of population aging more than 55 years report taking of at least one supplement per day. In the present review, we evaluated the long term effects of some vitamins consumption on prevention or treatment of some chronic disease and the adverse effects of these supplements.

As vitamin A, E, D, C and folic acid are shown to have some deleterious effects in various studies, we focused on them in this narrative review. Results from related literature, summarized in Table 2, showed that daily consumption of these vitamins in some cases not only had no benefit but also increased the risk of disease. With concern to results of these studies, there is a main question; should we quit taking these vitamins or should we use them wisely and just with physician order or pharmacists consults?

It was implied that adverse effects of some vitamins such as vitamin E may be dose related. Due to the unlimited access of people to vitamins and also lack of patient's attention into multivitamins ingredients and their doses, it may be high probable that a patient use vitamins in higher doses. It can be suggested that vitamin administration should be under the control of health provider professionals like pharmacists and only be marketed by pharmacies in order to provide critical information for patients about appropriate vitamins use. In addition, labeling of vitamins should include information on recommended upper intake, safe dosing and possible toxicities.

Table 2. List of the mentioned studies with no or negative effects of multi-vitamins on prevention or treatment of disease

Name of Study (reference number)	Populations (N/Properties)	Vitamins/minerals (Dose)	Duration of supplement treatment/follow up period(years)	Results
Klein EA et al (4)	35533 men	Selenium (200 µg/day)Vitamin E (400 IU/day)	7-12	Increased risk of prostate cancer
Heinonen OP et al (7)	29,133 male smokers	Alpha-tocopherol (50 mg /day), beta carotene (20 mg/day)	5-8	No reduction in the incidence of lung cancer
Lonn E et al (8)	9541patients with vascular disease or diabetes mellitus	Daily dose of natural source vitamin E (400 IU)	7	Increase the risk of heart failure
Coulter ID et al (9)	357 articles	Vitamin C(120-180mg/day) and E(400 -600 IU/day)	-	No prevention and/or treatment of cancer
Gaziano J et al(10)	14641 male with a history of prior cancer	Vitamin E(400 IU/day) and vitamin C (500 mg /day)	8	No reduction in risk of prostate and total cancer
Hunter DJ et al (11)	89494 women	Vitamins C, E (≥ 23,000 IU per day), and A(10,000 IU/day)	8	No influence on incidence of breast cancer
Kirsh VA et al (12)	29361 men	Vitamin E(>400 IU/day), beta-carotene(2000 microg/day), and vitamin C	8	No prevention on incidence of prostate cancer
the Women's Health Study ,Lee IM et al(13)	39876 healthy women	Vitamin E (600 IU)	10.1	No effect on cardiovascular events, cancer and total mortality
Liede K et al(14)	409 white male cigarette smokers,	Alpha-tocopherol (50 mg/day), beta-carotene (20 mg/ day)	5-7	No effect on preventing oral mucosal changes in smokers

Name of Study (reference number)	Populations (N/Properties)	Vitamins/minerals (Dose)	Duration of supplement treatment/follow up period(years)	Results
Lin J et al (15)	8171 women at high risk for CVD	Vitamins C (500 mg/day) and E (600 IU/day) and beta carotene (50 /day)	4-8	No benefits in prevention of cancer
Lippman SM et al (16)	35533 men	Selenium (200 microg/day) and vitamin E(400 IU/day)	5.46	No prevention of prostate cancer
Wright MEet al(17)	29133 male smokers, free of cancer	Alpha-tocopherol (50 mg /day), beta carotene (20 mg/day)	-	No protective effect on upper aerodigestive tract cancers
Huang HY et al (18)	3710 potentially eligible articles	Multivitamin and mineral supplement(daily)	-	No benefits in preventing cancer and chronic disease
Hercberg S et al (19)	13017 adults	combination of 120 mg of ascorbic acid, 30 mg of vitamin E, 6 mg of beta carotene, 100 mug of selenium, and 20 mg of zinc	7.5	low total cancer incidence and all-cause mortality in men but not in women
Cook NR et al (20)	22071 male physicians	Beta-carotene (50 mg)	13	No overall effect on total cancer
Wright ME et al (21)	295344 cancer-free men	Vitamin E	5	No protection against prostate cancer
Greenberg ER et al (22)	864 colorectal adenoma patients	Beta carton(25 mg daily) , vitamin C (1 g daily) and vitamin E (400 mg daily)	4	No prevention of colorectal cancer
Larsson SCet al(23)	35329 cancer-free women	Multivitamins	9.5	Increased risk of breast cancer
Lawson KA et al (24)	295344 cancer-free men	Multivitamins	5	Increased risk of advanced and fatal prostate cancers
Neuhouser ML et al (25)	182099 participants	Multivitamin (daily)	8	No influence on cancer and CVD
Yusuf Set al(26)	2545 women and 6996 men	400 IU of vitamin E daily	4.5	No effect on cardiovascular outcomes
Vivekananthan DP et al(27)	81788 patients in vitamin E trials and 138113 in beta carotene trials	Vitamin E 50-800 IU, and beta carotene 15-50 mg	1.4 to 12.0	No benefit of vitamin E in mortality/ increase in mortality with beta carotene
Sesso HD et al (28)	14641 male physicians	Vitamin E (400 IU /day and vitamin C (500 mg/day)	8	No reduction in risk of major cardiovascular events
Salonen RM et al(29)	520 smoking and nonsmoking men and postmenopausal women	136 IU of vitaminE plus 250 mg of slow-release vitaminC twice daily	6	slowing down atherosclerotic progression
Rapola JM et al (30)	1795 male smokers who had angina pectoris	Alpha tocopherol (50 mg/day) and beta carotene (20 mg/day)	4	No beneficial effect on angina pectoris
Rapola JM et al (31)	29133 male smokers	50 mg/d of alpha tocopherol, 20 mg/d of betacarotene	4.7	No beneficial effect on angina pectoris
Kushi LH et al(32)	34486 postmenopausal women	Vitamins A, E, and C	7	No effect on mortality from coronary disease
Cook NR et al (33)	8171 female health professionals	Ascorbic acid (500 mg/d), vitamin E (600 IU every other day), and beta carotene (50 mg every other day)	2-3	No effect on cardiovascular events
Ascherio A et al(34)	43738 men	Vitamin E (411 IU/d), C (1167 mg/d)	8	No reduction in risk of stroke
Waters DD et al (35)	423 postmenopausal women	400 IU of vitamin E plus 500 mg of vitamin C twice daily	-	No cardiovascular benefit
Bleys J et al(36)	2311 articles	Antioxidants (vitamins E and C, beta-carotene, or selenium) and trials using B vitamins (folate, vitamin B-6, or vitamin B-12)	0.3 and 7.2	No evidence of a protective effect on the progression of atherosclerosis
Pocobelli G et al (37)	77673persons	Multivitamins, vitamin C, and vitamin E(dose depend on BMI	10	Not associated with cancer mortality
Miller ER 3rd et al (38)	135967 participants in 19 clinical trials	Vitamin E (150-400 IU/d)	-	High doses increase death risk
Hayden KM et al (39)	A defined population aged 65 years or older	VitaminE	-	unrelated to mortality, even increased mortality in severe CVD
Slatore CG et al (40)	77721 men and women	Multivitamins, vitaminC, vitaminE, and folate	10	Not associated with decreased risk of lung cancer
Wu QJ et al (41)	72,829 nonsmoker female	Vitamin E	12.02	increased risk of lung adenocarcinom
Lee DH et al (46)	1923 postmenopausal women with diabetes	Vitamin C	-	Increased risk of CVD mortality
Traxer O et al (47)	12 normal subjects and 12 CaOxstone formers	2 g ascorbic acid daily	2, 6-day phases	No change in urinary pH but an increase in urinary oxalate
Douglas RM et al (48)	29 trial comparisons involving 11077 study participants	Vitamin C (0.2 g per day or more)	-	Failure n reduction of common colds
Douglas RM et al (49)	30 trial comparisons involving 11350 study participants	Vitamin C (0.2 g per day or more)	-	Failure in reduction of common colds
Hemilä Het al(50)	29 trial comparisons involving 11306 participant	Vitamin C (0.2 g per day or more)	-	Failure in reduction of common colds
HennekensCH et al(62)	22071 male	Supplementation with beta carotene (50 mg on alternate days)	-	Neither benefit nor harm in malignant neoplasms
Omenn GS et al (64)	18314 smokers, and workers exposed to asbestos	Beta carotene (30 mg) and vitamin A(25,000 IU)	2	No benefit on lung cancer

Name of Study (reference number)	Populations (N/Properties)	Vitamins/minerals (Dose)	Duration of supplement treatment/follow up period(years)	Results
van Zandwijk Net al(65)	2592 patients	Vitamin A (300000 IU daily for 1 year followed by 150000 IU for a 2nd year), N-acetylcysteine (600 mg daily)	2	No benefit for patients with head and neck cancer or with lung cancer
Albanes D et al (66)	29133 smoker men	Alpha-tocopherol (50 mg), beta-carotene (20 mg)	5-8	increased lung cancer incidence in cigarette smokers
Melhus H et al(67)	175 women for the cross-sectional study, 247 women for the nested case-control study	Retinol	-	Increased osteoporosis
Feskanich D et al(68)	72 337 postmenopausal women	Vitamin A	18	development of osteoporotic hip fractures
Michaëlsson K et al (69)	2322 men	Retinol	30	1.6-fold increased risk of any fracture and 2.5-fold increased risk of hip fracture
Lim LSet al(70)	34703 postmenopausal women	Vitamin A	9.5	1.18-fold increased risk of hip fracture
Ebbing M et al (74)	6837 patients with ischemic heart disease	Folic acid (0.8 mg/d) and vitamin B_{12} (0.4 mg/d), vitamin B_6 (40 mg/d)	9	Increased cancer risk
Figueiredo JC et al (75)	643 men	1 mg of folic acid	10.8	Increased risk of prostate cancer
Zhang SM et al (76)	5442 female health professionals	Combination of folicacid, vitamin B6, and vitamin B12	7.3	No effect on overall risk of total invasive cancer or breast cancer
Cole BF et al(77)	1021 men and women with a recent history of colorectal adenomas	1 mg/d of folic acid	3	No reduction in colorectal adenoma risk
Bazzano LAet al(78)	16958 participants with preexisting vascular disease	Folic acid(0.5-15mg/day)	-	No reduction in cardiovascular diseases or all-cause mortality
Albert CM et al (79)	5442 women	Combination of folicacid, vitamin B6, and vitamin B12	7.3	No reduction in cardiovascular events
Graat JM et al (80)	652 non-institutionalized individuals	Physiological doses of multivitamin-minerals, 200 mg of vitaminE	1.3	No effect on incidence and severity of respiratory tract infections
Wactawski-Wende Jet al(87)	36282 postmenopausal women	1000 mg of elemental calcium and 400 IU of vitamin D3	7	No effect on the incidence of colorectal cancer
Chlebowski RTet al(91)	36282 postmenopausal women	1000 mg of elemental calcium with 400 IU of vitamin D(3)	7	No reduction in invasive breast cancer incidence
Michaëlsson K et al (92)	60689 women	Calcium and vitamin D	-	No prevention of osteoporotic fractures
Nieves JW et al (93)	76507 postmenopausal women	calcium and vitamin D	-	Reduction in the odds of osteoporosis but not the 3-year risk of fracture

Conclusion

In conclusion, taking supplements of vitamin E, A, C, D, and folic acid for prevention of disease or cancer is not always effective, and can even be harmful to the health. So, it would be rational to limit these supplements consumption to those having deficiencies of the mentioned vitamins.

Ethical Issues

Not applicable.

Conflict of Interest

The Authors report no declaration of interest.

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