

Canadian Task Force on Preventive Health Care

RECOMMENDATION STATEMENT: The Role of Vitamin E Supplements in the Prevention of Cardiovascular Disease and Cancer

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RECOMMENDATIONS

The CTFPHC concludes that there is insufficient evidence to recommend for or against the use of routine vitamin E supplementation for the primary prevention of CVD events (**I Recommendation**). There is good evidence to recommend against the use of vitamin E for the secondary prevention of CVD in patients with established CVD or risk factors for CVD (**D Recommendation**). The CTFPHC concludes that there is good evidence to recommend against the use of routine vitamin E supplementation for the prevention of lung cancer (**D Recommendation**). There is insufficient evidence to recommend for or against the use of routine vitamin E supplementation for the prevention of cancers in the general population (**I Recommendation**).

BACKGROUND

Cardiovascular disease (CVD) and cancer are the leading causes of death in Canada, accounting for 37% and 27% of all deaths respectively.¹ Premature death from cardiovascular disease is responsible for an estimated 294,000 years of life lost.² Almost one-third of the cancer deaths in men and almost one-quarter in women are due to lung cancer alone. Cancer was the leading cause of potential years of life lost (PYLL) for men and women: 894,000 potential years were lost due to cancer, representing 29% of the PYLL resulting from all causes of death.³ Simple, accessible and safe preventive therapies that will decrease the incidence and mortality of CAD and cancer are expected to have a great effect on public health.

Epidemiologically, lower rates of heart disease and cancer have been noted among Vitamin E users.⁴⁻⁸ Vitamin E's antioxidant properties are felt to be responsible for this association. Oxidative modification of Low Density Lipoproteins (LDL) is an important step in the development and progression of atherosclerosis.^{9,10} Antioxidants such as vitamin E have been shown to slow atherosclerosis.¹¹

Several in vitro experiments with cells in culture exposed to pro-oxidant carcinogens showed antioxidant vitamins to have a significant protective role against cancer.¹²⁻¹⁴ In experimental animals deficiencies of certain nutrients such as vitamin E may enhance carcinogenesis, while supplementation of these nutrients may inhibit tumor formation.^{15,16} α -tocopherol is the most common naturally occurring compound of vitamin E.¹⁷

Given the high prevalence of both cardiovascular disease and cancer, the potential population at risk is broad. In the last 5 years, multiple randomized trials have been published examining the effect of vitamin E in the primary prevention of cancer and cardiovascular disease as well as the secondary prevention of cardiac events.

MANEUVERS

- Use of vitamin E for the prevention of cardiovascular events and cancer.

POTENTIAL BENEFITS & HARMS

Benefits

- Reduction of total mortality
- Primary prevention of cardiovascular disease
- Secondary prevention of coronary events in patients with established cardiovascular disease
- Primary prevention of lung, stomach, esophageal, colorectal, genitourinary and prostate cancer

Harms

- Increase in mortality from hemorrhagic stroke
- Increase in CVD mortality
- A small but statistically significant increase of total cholesterol levels

EVIDENCE & CLINICAL SUMMARY

- Vitamin E did not have beneficial effects on the primary prevention of CVD events.
- The evidence regarding the effects of vitamin E on the secondary prevention of CVD is conflicting, but mostly does not show benefit.
- In the ATBC trial there was a significant increase in mortality from hemorrhagic stroke in patients taking vitamin E (RR 1.49 (1.03-3.17)).^{18,19} This finding was based on a small number of events and it was not reported in other large vitamin E trials.
- There was a significant increase in CVD mortality (age adjusted) in the ATBC subset trial (RR 1.51 (1.02-2.24)) in the vitamin E group (with B-carotene), which remained but lost its statistical significance in the vitamin E group (alone) (RR 1.33 (0.86-2.05)).²⁰ Additionally, this association was not noted in the original cohort: CVD mortality in the ATBC trial was not affected in the vitamin E (with B-carotene) group (RR 0.98 (0.89-1.08)).¹⁸ This finding was not replicated in other large trials, which evaluated the role of vitamin E in the primary or secondary prevention of CVD.
- In the HPS trial, participants allocated to the vitamin group had a small but statistically significant increase of total cholesterol levels (mean difference 0.15 mmol/L, p=0.024).²¹
- Vitamin E did not affect the incidence or mortality of lung cancer. Half of the participants in the vitamin E group of the ATBC trial received B-carotene which might mask any protective effect of vitamin E against lung cancer. B-carotene was shown to increase the risk of lung cancer in two large RCTs, the ATBC trial and in the CARET trial (RR 1.16 (1.02-1.33) and RR 1.28 P <0.05, respectively).^{18,22}
- There is one fair quality RCT, which showed a marginal benefit of vitamin E (with B-carotene), in the reduction of prostate cancer incidence, but the discernment of this secondary endpoint is not well defined.²³ This finding was not replicated in the large HPS trial (RR 0.9 (0.74 - 1.1)).²¹
- There is conflicting evidence to recommend for or against the use of vitamin E for the prevention of stomach cancer. In one large good quality trial there was a marginal significant reduction of stomach cancer mortality and morbidity in patients taking vitamin E (with B-carotene and

selenium).²⁴ This study was done in Linxian, a rural area in china with a population that has a high rate of gastric cancer and subclinical deficiencies of several micronutrients including vitamin E.^{25,26} In addition, it is not clear if the beneficial effect comes from vitamin E alone or with selenium and B-carotene or with these supplements combined. The findings of this trial were not replicated in the large ATBC and HPS trials.^{18,21}

- There is an insufficient evidence to make a recommendation about the role of vitamin E in the prevention of esophageal, colorectal, urothelial (bladder, renal pelvis, ureter) and renal cell cancer.

RECOMMENDATIONS OF OTHERS

In 2003, the US Preventive Services Task Force concluded that the evidence is insufficient to recommend for or against the use of supplements of vitamins A, C, or E; multivitamins with folic acid; or antioxidant combinations for the prevention of cancer or cardiovascular disease.²⁷

Authorship Contributions:

Abdullah Alkhenizan and Valerie A. Palda co-authored the original systematic evidence review and the current article.

The Canadian Task Force on Preventive Health Care critically reviewed the evidence and developed the recommendations according to its methodology and consensus development process.

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References:

1. Selected leading causes of death by sex. Ottawa: Statistics Canada; 1997. Available from: URL: <http://www.statcan.ca/english/Pgdb/health36.htm>
2. Heart disease and stroke in Canada. Ottawa (ON): Heart and Stroke Foundation of Canada; 1997. Available from URL: http://www.hc-sc.gc.ca/hpb/lcdc/bcrdd/hdsc97/s02_e.html.
3. Canadian cancer statistics 2000. Toronto (ON): National Cancer Institute of Canada; 2000. Available from URL: http://www.cancer.ca/ccs/internet/standard/0,3182,3172_12851_langId-en,00.html.
4. Rimm EB, Stampfer MJ, Ascherio A, Giovannucci E, Colditz GA, Willett WC. Vitamin E consumption and the risk of coronary heart disease in men. *N Engl J Med* 1993;328(20):1450-6.
5. Stampfer MJ, Hennekens CH, Manson JE, Colditz GA, Rosner B, Willett WC. Vitamin E consumption and the risk of coronary disease in women. *N Engl J Med* 1993;328(20):1444-9.
6. Flagg EW, Coates RJ, Greenberg RS. Epidemiologic studies of antioxidants and cancer in humans. *J Am Coll Nutr* 1995;14(5):419-27.
7. Wald NJ, Boreham J, Hayward JL, Bulbrook RD. Plasma retinal, beta-carotene and vitamin E levels in relation to the future risk of breast cancer. *Br J Cancer* 1984;49(3): 321-4.
8. Menkes MS, Comstock GW, Vuilleumier JP, Helsing KJ, Rider AA, Brookmeyer R. Serum beta-carotene, vitamins A and E, selenium, and the risk of lung cancer. *N Engl J Med*. 1986;315(20):1250-4.
9. Steinberg D, and Workshop Participants. Antioxidants in the prevention of human atherosclerosis. Summary of the proceedings of a National Heart, Lung & Blood Institute workshop: September 5-6, 1991, Bethesda, Maryland. *Circulation* 1992;85(6):2337-44.
10. Stampfer MJ, Hennekens CH, Manson JE, Colditz GA, Rosner B, Willett WC. Vitamin E consumption and the risk of coronary disease in women. *N Engl J Med* 1993;328(20):1444-9.
11. Carew TE, Schwenke DC, Steinberg D. Antiatherogenic effect of probucol unrelated to its hypercholesteremic effect: evidence that antioxidants in vivo can selectively inhibit low density lipoprotein degradation in macrophage rich fatty streaks and slow the progression of atherosclerosis in the watanabe heritable hyperlipidemic rabbit. *Proc Natl Acad Sci USA* 1987;84(21):7725-9.
12. Prasad KN, Edwards-Prasad J. Expressions of some molecular cancer risk factors and their modification by vitamins. *J Am Coll Nutr* 1990;9(1):28-34.
13. Wattenberg LW. Inhibition of carcinogenesis by minor dietary constituents. *Cancer Res* 1992;52(7 Suppl):2085s-91s.
14. Birt DF, Bresnick E. Chemoprevention by non-nutrient components of vegetables and fruits. In: Alfin-Slater RB, Kritchevsky D, editors. *Cancer and nutrition*. New York (NY): Plenum Press; 1991. p. 221-61.
15. Prasad KN, Edwards-Prasad J. Vitamin E and cancer prevention: recent advances and future potentials. *J Am Coll Nutr*. 1992;11(5):487-500.
16. Shah CP, with Shah SS and Shah RR. *Public Health and Preventive Medicine in Canada*. 3rd ed. Toronto (ON): C.P. Shah; 1994.
17. Dietary reference intakes for vitamin C, vitamin E, selenium and carotenoids: a report of the Panel on Dietary Antioxidants and Related Compounds, Subcommittees on Upper Reference Levels of

Nutrients and Interpretation and Uses of Dietary Reference Intakes, and the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. Washington, DC: National Academy Press; 2000.

18. The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancer in male smokers. *N Engl J Med* 1994;330(15):1029-35.
19. Jha P, Flather M, Lonn E, Farkouh M, Yusuf S. The antioxidant vitamins and cardiovascular disease. A critical review of epidemiologic and clinical trial data. *Ann Intern Med* 1995;123(11):860-72.
20. Rapola JM, Virtamo J, Ripatti S, Huttunen JK, Albanes D, Taylor PR, et al. Randomised trial of alpha-tocopherol and beta-carotene supplements on incidence of major coronary events in men with previous myocardial infarction. *Lancet* 1997;349(9067):1715-20.
21. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of antioxidant supplementation in 20,536 high risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;360(9326):23-33.
22. Omenn GS, Goodman GE, Thornquist MD, Balmes J, Cullen MR, Glass A, et al. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. *N Engl J Med* 1996;334(18):1150-5.
23. Heinonen OP, Albanes D, Virtamo J, Taylor PR, Huttunen JK, Hartman AM, et al. Prostate cancer and supplementation with alpha-tocopherol and beta-carotene: incidence and mortality in a controlled trial. *J Natl Cancer Inst* 1998;90(6):440-6.
24. Blot WJ, Li JY, Taylor PR, Guo W, Dawsey S, Wang GQ, et al. Nutrition intervention trials in Linxian, China: supplementation with specific vitamin/mineral combinations, cancer incidence, and disease-specific mortality in the general population. *J Natl Cancer Inst* 1993;85(18):1483-92.
25. Yang CS, Miao J, Yang W, Huang M, Wang T, Xue H, et al. Diet and vitamin nutrition of the high esophageal cancer risk population in Linxian, China. *Nutr Cancer* 1982;4(2):154-64.
26. Zheng SF, Ershow AG, Yang CS, Li GY, Li RS, Li H, et al. Nutritional status in Linxian, China: effects of season and supplementation. *Int J Vitam Nutr Res* 1989;59(2):190-9.
27. US Preventive Services Task Force. Routine vitamin supplementation to prevent cancer and cardiovascular disease: recommendations and rationale. *Ann Intern Med* 2003;139(1):51-5.