CANADIAN TASK FORCE ON PREVENTIVE HEALTH CARE

GROUPE D'ÉTUDE CANADIEN SUR LES SOINS DE SANTÉ PRÉVENTIFS

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

Systematic Review and Recommendations

May 2003

TECHNICAL REPORT

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The Role of Vitamin E Supplements in the Prevention of Cardiovascular Disease and Cancer: Systematic Review and Recommendations

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Running Head: *Alkhenizan & Palda with CTF – Vitamin E Supplements*

ABSTRACT

Objectives: To establish evidence-based guidelines for the use of vitamin E in the prevention of cardiovascular disease (CVD) and cancer.

Options: Vitamin E supplementation in the primary and secondary prevention of CVD and primary prevention of cancer.

Outcomes: Total mortality, cardiac mortality, cancer mortality, incidence of non-fatal myocardial infarction, lung cancer and other cancers (prostate, urological, esophageal, stomach, colorectal).

Evidence: Ovid MEDLINE, PREMEDLINE, the Cochrane database, and EMBASE were searched for relevant English language randomized controlled trials (RCTs) to March 2003. Retrieved titles and abstracts were evaluated according to *a priori* inclusion criteria, and those included were critically appraised using established internal validity criteria.

Benefits, Harms, and Costs: No studies have shown a significantly reduced overall mortality associated with vitamin E use. No trials have found a benefit from vitamin E in reducing cardiovascular disease in either the primary or secondary prevention setting, but are limited by key internal study design flaws and generalizability. One of five trials found a reduction of CVD death and non-fatal myocardial infarction (RR= O.53, 95% CI 0.34-0.83) from vitamin E in the secondary prevention of coronary events in patients with established cardiovascular disease. The other cardiovascular endpoints were not reduced. Two good quality RCTs have not shown a reduction in lung cancer, and 2 studies of vitamin supplementation have not demonstrated benefit in cancer reduction for a number of cancer outcomes. In general, vitamin E was well tolerated with no significant adverse effects in the large RCTs reported in this review, with the exception of a trend toward increased risk of hemorrhagic stroke and increased risk of cardiovascular mortality seen in small trials.

Values: The strength of evidence was evaluated using the methods of the Canadian Task Force on Preventive Health Care.

Recommendations: There is insufficient evidence to recommend for or against the use of routine vitamin E supplementation for the primary prevention of CVD events in the general population and in male smokers (**I Recommendation**). The Task Force concludes that there is good evidence to recommend against the use of routine vitamin E supplementation for the

secondary prevention of CVD in patients with established CVD or risk factors for CVD (**D Recommendation**). There is good evidence to recommend against the use of routine vitamin E supplementation for the prevention of lung cancer (**D Recommendation**). The Task Force concludes that there is insufficient evidence to recommend for or against the use of routine vitamin E supplementation for the prevention of cancers other than lung cancer (esophageal, stomach, colorectal, urological, and prostate) in the general population (**I Recommendation**).

Validation: The members of the Canadian Task Force on Preventive Health Care reviewed these findings through an iterative process. The Task Force sent the final review and recommendations to selected external expert reviewers and their feedback was incorporated.

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BACKGROUND

Burden of Illness

Cardiovascular disease (CVD) and cancer are the leading causes of death in Canada, accounting for 37% and 27 % of all deaths respectively <StatsCan>. Premature death from cardiovascular disease is responsible for an estimated 294,000 years of life lost, and is third after that from injuries and cancer <Heart&Stroke>. Three types of cancer account for at least 50% of the new cases in each sex: prostate, lung, and colorectal cancers in males, and breast, lung, and colorectal cancers in females. 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 <Cdn cancer stats>. Simple, accessible and safe preventive therapies to decrease the incidence and mortality of CAD and cancer have the potential to exert a great effect on public health.

Epidemiologically, lower rates of heart disease and cancer have been noted among Vitamin E users <Rimm 1993; Stampfer 1993 ; Flagg 1995; Wald 1984; Menkes 1986>. It is hypothesized that Vitamin E's antioxidant properties are responsible for this association. Low Density Lipoproteins (LDL) cholesterol may be rendered atherogenic by oxidative modifications that allow it to accumulate in artery walls <Steinberg 1992>. Oxidative modification of LDL is an important step in the development and progression of atherosclerosis <Steinberg 1989>. Antioxidants such as vitamin E have been shown to slow atherosclerosis <Carew 1987>.

Several in vitro experiments with cells in culture exposed to pro-oxidant carcinogens showed antioxidant vitamins to have a significant protective role against cancer <Prasad 1990, Wattenberg 1992, Birt 1991>. In experimental animals deficiencies of certain nutrients such as vitamin E may enhance carcinogenesis, while supplementation of these nutrients may inhibit tumor formation <Prasad 1992, Shah 1994>. a-tocopherol is the most common naturally occurring compound of vitamin E <Dietary reference intakes 2000>.

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.

Rationale for this review

The purpose of the present review is to qualitatively review the randomized trial literature in this area in order to provide evidence-based guidance to practitioners on the use of vitamin E for prevention of cardiovascular events and cancer. The analytic framework and the key questions used to structure this review are illustrated in Appendix 1.

METHODS

A computerized search of Ovid MEDLINE, PREMEDLINE, the Cochrane database, and EMBASE for English language articles published between January 1966 and December 2000 was conducted using the MeSH terms "coronary disease", "vitamin E", "alpha-tocopherol", "vitamins", "myocardial ischemia", "neoplasms", "colonic polyps", "polyps", "prevention", "primary prevention", "side effects", "toxicities" and "secondary prevention". These terms were used in various combinations. Relevant articles were also retrieved through a manual review of references. The search was updated for key new evidence in March 2003. Trials were included if they were randomized controlled trial (RCT) design, looked at clinical (not surrogate) outcomes of CVD or cancer as a primary or a secondary end point, and included only adults (age > 18 years) Exclusion criteria were: studies with sample size <100, non-English language publications, and studies with more than 5 different supplements in the vitamin E arm.

The evidence was systematically reviewed using the methodology of the Canadian Task Force on Preventive Health Care (see Appendices 2 and 3).

RESULTS

Vitamin E Doses

The recommended dietary allowance of vitamin E is 15 mg daily for adult men and women. Each 1-mg of vitamin E equals to 1.5 IU of natural vitamin E and 2.2 IU of synthetic vitamin E <Dietary Reference Intakes 2000>. Vegetable oils, nuts, and green leafy vegetables are the main dietary sources of vitamin E. Fortified cereals are also an important source of vitamin E in the United States <Dietary Reference Intakes 2000>. Doses used in randomized trials vary from 50 mg/d to 600 mg/d <Virtamo 1998, Stephens 1996, ATBC 1994a, HPS 2002>. This is equivalent to a 5-40 fold increase over the recommended daily allowance. Serum a-tocopherol levels in these trials increase on average 1.5-2 fold. Vitamin E was well tolerated in the low and high doses used in the reviewed trials. The magnitude of vitamin E effects on cardiovascular outcomes, in which more trials available which used different doses of vitamin E, does not seem to correlate with the dose of vitamin E used. The optimal therapeutic/toxicity balance is therefore unknown.

Primary and Secondary Prevention

Primary prevention aims to prevent disease before it occurs, while secondary prevention involves the early detection of disease in an asymptotic period and the treatment of that disease <Shah 1994>. Two RCTs addressed the role of vitamin E in primary prevention of cardiovascular disease in individuals at high risk, but who did not yet have cardiovascular disease <PPP 2001, Virtamo 1998>. Five RCTs addressed the role of vitamin E in the secondary prevention of coronary events in patients with established cardiovascular disease <Rapola 1997, Yusuf 2000, GISSI 1999, Stephens 1996, HPS 2002>. Three RCTs evaluated the role of vitamin E in the primary prevention of lung, stomach and esophageal cancer <ATBC 1994a, Albanes 1996, ATBC 1994b, Blot 1993, HPS 2002>.

The ATBC trial

The largest study addressing the effects of vitamin E and beta-carotene on both cardiovascular and cancer events, the ATBC trial, involved 29,133 participants, randomized to one of four treatment groups alpha-tocopherol (AT) alone, beta-carotene (BC) alone, AT and

BC, or placebo (2 x2 factorial design). The primary objective of the ATBC trial was to evaluate the effects of alpha-tocopherol and beta-carotene on lung cancer incidence. The secondary objectives were to evaluate the effects of alpha-tocopherol and beta-carotene on the incidence of other major cancers and the overall and cause-specific mortality. Cardiac outcomes were specifically mentioned in the ATBC major methodological publication as not featuring in the original study hypothesis <ATBC 1994b>. Participants were male, Finnish smokers, aged 50-69, recruited from the general population as these were deemed the highest risk population for lung cancer. Sample size was calculated to detect a 25% reduction in lung cancer incidence to obtain a study power of 85%, with 5% significance two-sided testing. All clinical events were identified from national hospital discharge and death registries in Finland. Validation was done in all cases of cancer and in a small sample for cardiovascular outcomes (found to carry a 94% PPV). Compliance was good, with approximately 90% of patients taking over 90% of their capsules. The dropout rate was high, at approximately 30%, but follow up was almost complete, and analysis was intention to treat for all outcomes. Different reports reported different disease outcomes, including: lung cancer <ATBC 1994a>, primary <Virtamo 1998> and secondary <Rapola 1997> prevention of cardiovascular disease, prostate cancer <Heinonen 1998>, colorectal cancer <Albanes 2000>, urothelial and renal cell cancer <Virtamo 2000>.

The study design and analysis met most of the standard quality review criteria (see Tables 2 and 5). The internal study quality for lung cancer outcomes, for which it was sufficiently powered, was ranked "good", but was ranked as "fair" for the outcomes of other cancer and cardiovascular disease. Although not an internal validity issue, the inclusion of only male smokers in a small age range and from a single country significantly limits the generalizability of this study.

The HPS study

The HPS trial was almost as large, enrolling over 20,000 participants, approximately 25% of whom were women. This study used a double blind 2x2 factorial design to allow the separate assessment of simvastatin 40 mg and of vitamin supplementation of 600 mg of vitamin E, 250 mg of vitamin C and 20 mg of beta-carotene. Although some patients with only "risk factors" for CAD were included, this trial can be considered mainly a secondary prevention trial as 65 % of participants had a pre-existing CAD, and 74% of participants had a pre-existing cardio vascular

disease (CAD or cerebrovascular disease). This trial was rated as a "Good" trial, as it met all quality criteria and cardiovascular and cancer outcomes were a priori primary or secondary outcomes (see Table 1).

Effect of Vitamin E on Total Mortality

Six large RCTs have evaluated the effect of vitamin E on total mortality. Three good quality trials demonstrated no effect of vitamin E on total mortality: the ATBC trial showed a relative risk of 1.02 (0.95-1.09) for vitamin E users, the HOPE trial revealed a RR of 1.0 (0.89-1.13), and the HPS trial revealed a RR of 1·04 (0·97–1·12) <ATBC 1994a, Yusuf 2000, HPS 2002>. Fair quality trials have produced more conflicting results: the CHAOS trial showed an elevated mortality risk, with an RR of 1.3 (0.78-2.17) <Stephens 1996>. There was a trend of reduction in total mortality in the GISSI trial (RR 0.86 (0.72-1.02) and a small marginally significant reduction in total mortality in Blot et al trial (RR 0.91 (0.84-0.99)) <GISSI 1999, Blot 1993>.

Association Between Vitamin E Supplements and CVD

Primary prevention

Two large RCTs addressed the effects of vitamin E on CVD mortality. Neither of the studies found a benefit from Vitamin E supplementation (see Table 2 for results). Both were rated as being of "fair" internal quality. In the Primary Prevention Project (PPP), a 2x2 factorial design examining the benefits of ASA, vitamin E, both or none, 300 mg of vitamin E over 6 years did not affect total CVD mortality (RR 0.86 (0.49-1.52)) nor the main outcome of combined CVD death, non-fatal MI, and non-fatal stroke (RR 1.07 (0.77-1.49)) <PPP 2001>. The secondary outcomes of total deaths, CVD deaths, all MI and non-fatal MI were likewise not different in the treatment groups. These results may represent a false negative as the study was insufficiently powered. Event rates were lower than expected and recruitment was terminated prematurely for safety and ethical considerations: a large benefit was demonstrated in the ASA group. Power and single blinding (open label design) resulted in a "fair", not a "good", internal quality rating. Generalizability is better in this study than the ATBC design, since half the study participants were female.

In the ATBC primary prevention subgroup trial, 50 mg of vitamin E alone or with beta-carotene did not affect major coronary events (RR 0.96(0.88-1.04)), CVD deaths (RR 0.92(0.81-1.05)) or non-fatal MI (RR 0.99(0.88-1.10)). As stated earlier, the study was designed to address lung cancer outcomes, but there was a high rate of cardiac outcomes and the power may be sufficient to rule out a 25% RRR. A low vitamin E dose was used in this trial and the length of follow up may be insufficient in the primary prevention setting.

These trials constitute fair evidence that vitamin E is not effective in the primary prevention of coronary events.

Secondary prevention

All major coronary events

Five RCTs evaluated the effects of vitamin E on all major coronary events <Rapola 1997, Yusuf 2000, GISSI 1999, Stephens 1996, HPS 2002>. Non-fatal MI and fatal coronary events were not reduced by vitamin E supplements in three RCTs. In the ATBC subset trial 50 mg of vitamin E over 5.3 years did not affect all major coronary events in male smokers who had a previous MI (RR 1.16 (0.89-1.52)) <Rapola 1997>. This trial was rated as a "fair" trial, because cardiac outcomes were a secondary endpoint of this study. In the Heart Outcomes Prevention Evaluation (HOPE) trial 400 IU of vitamin E over 4.5 years had no effect on MI, stroke or death from CVD causes in high-risk patients with established CAD (RR 0.94 (0.7-1.25)) <Yusuf 2000>. In the GISSI trial 300 mg of vitamin E over 3.5 years showed a trend of a non-significant reduction of CVD death, non-fatal MI, non-fatal stroke (RR 0.88 (0.72-1.02)) in patients surviving recent (< 3 months) MI <GISSI 1999>. The GISSI trial received a "fair" quality rating, because it was an open label trial, in which a blinded committee assessed outcomes.

In the CHAOS trial 400-800 IU of vitamin E over 1.4 years showed a statistically significant reduction of CVD death and non-fatal MI (RR= O.53, 95% CI 0.34-0.83, P= 0.005) in patients with angiographically proven atherosclerosis <Stephens 1996>. This benefit was due to a reduction in the risk of non-fatal MI, but not in cardiovascular deaths, indeed there was a non-significant increase in cardiovascular deaths among vitamin E recipients (RR 1.18 (0.62-2.27)) <Stephens 1996>. In this trial there were small differences between active treatment and placebo

groups in sex ratio, serum total cholesterol, systolic blood pressure, presence of diabetes, and the proportion of patients taking B-blockers, all these differences weighted risk in favor of the placebo group. Additionally, this trial included patients who, although potentially asymptomatic, all were at high risk of coronary events, given angiographically proven disease. Because of these differences, this trial only received a "fair" quality rating.

The results of these large trials were combined in the analysis of the HOPE trial, which showed that vitamin E did not reduce MI, stroke, or death from CVD causes (RR 0.97 (0.92-1.02)) <Yusuf 2000>. The HOPE trial received a "good" quality rating.

In the HPS trial, vitamin supplementation of 600 mg of vitamin E over 5 years did not affect all major coronary events among all patients (RR 1·00 (0·94–1·06)). In a sub-group analysis of patients with pre-existing CAD (65% of the participants) vitamin E did not affect all major coronary events (RR 1·0 (0·95–1·06)).

CVD mortality

Five RCTs addressed the effects of vitamin E on CVD mortality <Rapola 1997, ATBC 1994a, Yusuf 2000, GISSI 1999, Stephens 1996, HPS 2002 >. In the ATBC subset trial, there was a statistically significant increase in CAD mortality among patients receiving vitamin E 50 mg (and ß-carotene 20 mg) (RR 1.51 95% CI (1.02-2.24)) <Rapola 1997>. This finding remained but lost its statistical significance when direct comparison between the vitamin E (alone) and placebo groups were made (RR 1.33 (0.86-2.05)) <Rapola 1997>. In the larger parent ATBC trial, which received a "good" quality rating, 50 mg of vitamin E did not affect CVD mortality either (RR 1.02 (0.95-1.09)) <ATBC 1994a>. Vitamin E showed no beneficial effects on CVD mortality in the HOPE and CHAOS trials, with RRs of 1.05 (0.9-1.22) and 1.18 (0.62-2.27) respectively <Yusuf 2000, Stephens 1996>. In the GISSI trial, the group that took 300 mg of vitamin E plus 1 g of n-3 PUFA did not have a lower rate of CVD deaths, RR 0.94 (0.81-1.1), but a marginally significant reduction of CVD deaths was found in the vitamin E only group, when compared to placebo (RR 0.8 (0.65- 0.99)) <GISSI 1999>. Table 5 shows the results for the 2-way analysis comparing all patients taking vitamin E (2 groups) to all patients not taking vitamin E (2 groups). In the HPS trial 600 mg of vitamin E showed no beneficial effects on CVD mortality among all participants (RR 1·05 (0·95–1·15)).

Myocardial Infarction

Five trials evaluated the effects of vitamin E on MI, or non-fatal CVD events <Rapola 1997, Yusuf 2000, GISSI 1999, Stephens 1996, HPS 2002>. Only the CHAOS trial showed significant changes in the rate of non-fatal myocardial infarction (RR 0.23 (0.11-0.47)) <Stephens 1996>. In the HOPE and ATBC subset trials, vitamin E did not reduce MI rates (RR1.02 (0.9-1.15)) <Yusuf 2000>, and the HPS trial showed no beneficial effects on non-fatal MI (RR 1.0 (0.87-1.12) among all participants. In the GISSI trial, non-fatal CVD events were not reduced by vitamin E (RR 1.02 (0.81-1.28)) <GISSI 1999>.

Summary for Cardiac Outcomes

The numerical results for secondary prevention trials for the three major outcomes of total mortality, cardiac mortality and non-fatal MIs are shown in Table 3. Results of trends are illustrated in Table 4 for all groups and subgroups of these trials. One fair quality RCT does show a reduction in non-fatal MI rate <Stephens 1996>. This significant large reduction in non-fatal MI in the CHOAS trial within a relatively short time (1.4 years) was not found in other large fair and good quality trials. Many authors have attributed this finding to chance or co-intervention in this group of patients at high risk of subsequent cardiac events. The vast majority of outcomes studied has failed to reveal a significant effect, either positive or negative, from vitamin E. Power in the studies was mostly adequate to detect large treatment effects. If vitamin E offered, for example, a 10% relative risk reduction of outcomes, the available studies would not be able to detect this. A meta-analysis could potentially address this issue. Insufficient length of therapy has also been cited as another reason why vitamin E trials have produced inconclusive results. Ongoing trials of vitamin E therapy may also provide further clarification of outcome results.

Cancer Prevention

Cancer incidence and mortality

Three RCTs trial have evaluated the role of vitamin E on all-cancer mortality. In Blot et al trial, a there was a marginally significant reduction of total cancer mortality (RR 0.87 (0.75-1.00)) in the vitamin E group, without a statistically significant reduction in total cancer

incidence (RR 0.93 (0.83-1.03) <Blot 1993> (Table 6). In the ATBC trial there was no effect of vitamin E on total cancer incidence or mortality (RR1.03 (0.81-1.11), and RR 1.08(0.96-1.21) respectively) <ATBC 1994a>. The HPS study, likewise, detected no change in either total cancer incidence (RR 0·98 (0·89–1·08)), or mortality (RR1.03 (0.81-1.11)).

Cancer incidence

Lung cancer

The ATBC trial evaluated as its main outcome the incidence of lung cancer. Vitamin E did not demonstrate an effect on the incidence or mortality of lung cancer in this patient group (RR 0.99 (0.87- 1.13) and RR 1.02 (0.86-1.2), respectively) <ATBC 1994a, Albanes 1996, ATBC 1994b> (see Table 6). Women were not included in this study, limiting its generalizability to half the population. A low vitamin E dose was used in this trial and the length of treatment may be insufficient in primary prevention setting for lung cancer, which is considered to have a latency of about 20 years. The lung cancer incidence rate was also lower than expected, perhaps limiting the power of this study. Interestingly, the Beta-carotene group was found to have a higher mortality when compared to placebo.

In the HPS trial there was no effect of vitamin E on the incidence of lung cancer (RR 1.03 (0.81-1.11) <HPS 2002>.

Prostate cancer

Prostate cancer is the only cancer that has been noted to be reduced by vitamin E supplementation in Western populations. Fifty mg of vitamin E showed a marginal statistically significant reduction in the incidence of and mortality from prostate cancer (RR 0.68 (0.53-0.88) and RR 0.59 (0.35-99), respectively), a secondary outcome in the study <Heinonen 1998> (see Tables 5 and 6). This difference was not significant for latent, non-clinical (stage 0) cancers, or advanced cancer, but was noted for early clinical cancers (RR 0.60 (95% CI 0.45-0.80)), suggesting a preventive effect on clinically meaningful cancers versus a stage shift. The reduction in mortality also supports this effect.

In the HPS trial there was no effect of vitamin E on the incidence of prostate cancer (RR 0.9 (0.74 - 1.1) <HPS 2002>.

Urinary tract cancer

Another secondary outcome of the ATBC trial was to evaluate the effects of vitamin E supplementation on urothelial cancer (bladder, renal pelvis, ureter) and renal cell cancer. In this trial, 50 mg of vitamin E (with B-carotene) did not affect the incidence of urothelial cancer or renal cell cancer (RR 1.1 (0.8-1.5) and RR 1.1 (0.7-1.6), respectively) <Virtamo 2000> (see Table 7). In the HPS trial the trend toward reduction of the incidence of genitourinary cancer in the vitamin E group did not reach significance (RR 0.86 (0.72 - 1.01). <HPS 2002>

Esophageal and stomach cancers

The nutrition intervention trials in Linxian, China studied the effects of various vitamin supplementation regimens on the populations of 4 communes in this region, in an area with an epidemic rate of esophageal and stomach cancer. In this area, 32% of deaths were due to esophageal or stomach cancer, which is approximately 100 times the rates seen in North America. The authors also noted that although this population was not overtly nutritionally deficient, dietary intake of fruit and meat was much lower than the national Chinese average. These two factors limit the generalizability of this otherwise well-conceived study. This study received a "fair" internal validity rating (see Table 5), because diagnostic confirmatory data for the review committee was missing in 15% of the patients (diagnosis made by family doctors clinically), and the inability of the analysis to account for supplement interaction. The study consisted of 4 possible vitamin combinations, one of which was vitamin E plus beta-carotene plus selenium (their notation for this combination was "D"). Patients were then randomized to a 2x8 factorial design, in which they might receive, among other combinations, D plus one other nutritional supplement combination (retinol plus zinc, or riboflavin plus niacin, or ascorbic acid plus molybdenum), all nutritional supplement combinations, or none. No effect was noted for 30 mg of vitamin E (with B-carotene and selenium) on esophageal cancer incidence (RR 1.02 (0.87-1.19)) and no effect on esophageal cancer mortality (RR 0.96 (0.78-1.18)) <Blot 1993> (see Table 6). There was a marginal significant reduction of stomach cancer incidence (RR 0.84

(0.71-1.00)) and a marginal significant reduction of stomach cancer mortality (RR 0.79 (0.64-0.99)).

The ATBC trial also reported on the incidence of stomach cancer, but found no reduction (RR 1.26, P>0.05) <ATBC 1994a>. In the HPS trial there was no effect of vitamin E on the incidence of stomach cancer (RR 1.2 (0.83 - 1.74), or total gastrointestinal cancer (RR 1 (0.8 – 1.2) <HPS 2002>.

Colorectal cancer

The ATBC trial has been the only RCT to examine vitamin E's effects on the incidence and mortality of colorectal cancer. No effects of 50 mg of vitamin E were found on colorectal cancer incidence or mortality (RR 0.78(0.55-1.09) and RR 0.92 (0.51-1.64), respectively) <Albanes 2000> (see Table 6).

Potential Harms

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)) <ATBC 1994a, Jha 1995>. This finding was based on a small number of events and it was not reported in other large vitamin E trials. In ATBC report on cardiac outcomes, among a subgroup of patients who had a history of a previous MI, there was a significant increase in CVD mortality (age adjusted) (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)) <Rapola 1997>. 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)) <ATBC 1994a>. This finding was not replicated in other large trials, which evaluated the role of vitamin E in the primary or secondary prevention of CVD. A small significant reduction of CVD deaths was found in the GISSI trial (RR 0.8 (0.65- 0.99)) <GISSI 1999>. Treatment with vitamin E alone or with other antioxidant vitamins in these large trials was well tolerated with no difference between the treatment groups in other side effects. Side effect rates were reported in 0.9-2.9% of patients <Yusuf 2000>. 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), with a small, but

statistically significant increase of LDL levels (mean difference 0.08, p=0.019), and a small but statistically significant increase in triglyceride levels (mean difference 0.21mmol/L, p=0.027). in addition there was a small but statistically significant decrease in HDL levels (mean difference -0.03 mmol/L, p=0.007) among patients allocated to the vitamin group.

INTERPRETATION

Summary of Key Evidence

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 some of the best quality literature available, 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 masked 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) <ATBC 1994a, Omenn 1996>.

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 <Heinonen 1998>.

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). 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 <Yang 1982; Zheng 1989>. In addition, it is not clear if the beneficial effect comes from vitamin E alone or with selenium and B-carotene or with theses supplements combined. The findings of this trial were not replicated in the large ATBC and HPS trials, which involved a population of white male smokers. There is an insufficient evidence to make a recommendation about the role of vitamin E in the prevention of esophageal, urothelial (bladder, renal pelvis, ureter) and renal cell cancer.

Alkhenizan & Palda with CTF – Vitamin E Supplements

The one trial looking at colorectal cancer incidence and mortality is insufficiently powered to make recommendations.

Canadian Task Force Recommendations (Table 7)

CVD events

Primary prevention: The Canadian Task Force 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 in the general population and male smokers (**I Recommendation**).

Secondary prevention: The CTF concludes that 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**).

Cancer

Lung cancer: The Task Force concludes that there is good evidence to recommend against the use of routine vitamin E supplementation for the prevention of lung cancer (**D Recommendation**).

Other cancers: The Task Force concludes that there is insufficient evidence to recommend for or against the use of routine vitamin E supplementation for the prevention of cancers other than lung cancer (esophageal, stomach, colorectal, urological, and prostate) in the general population (**I Recommendation**).

Recommendation of Others

The Canadian Task Force on Preventive Health Care did not previously have recommendations regarding vitamin E supplementation. 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 <USPSTF 2003>.

Research Agenda

Large-scale randomized trials designed to assess the effects of vitamin E therapy on cardiovascular disease are underway (see Table 8)<Buring 1992, Manson 42, Hercberg 1999>. These large RCTs may provide the additional length of study required in a wider range of participants to clarify the role of vitamin E, especially in the prevention of cancers.

Members of the Canadian Task Force on Preventive Health Care

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Table 1: Summary of Quality Criteria for RCTs that Evaluate the Role of Vitamin E in the Prevention of CVD

Study	Quality	Comparative Group	Reliable Outcomes/ Measurement/ Instrumentation	Blinded/ Outcome/ Assessment	Addresses Confounding Factors and Contamination	Adequate Power	Analysis/ Intention To Treat	Adequate Follow-up
Heart Protection Study, 2002	GOOD	Baseline characteristics were similar among treatment groups **YES**	Central ascertainment of death and coronary events were done by The Oxford coordinating centre. Log-rank analysis was used in the statistical analysis. **YES**	**YES**	No confounding factors noted, Contamination rate was not provided, but the average plasma concentration of ∝-tocopherol was doubled in the vitamins allocated group compared to the placebo group. **YES**	**YES** 90%	**YES**	F/U 99%, 5 years (mean) **YES**
PPP, 2001	FAIR	Baseline characteristics were well balanced across the groups **YES**	Yes, copies of physicians' and hospital records and death certificates were reviewed by the committee for event validation according to WHO standard definition criteria. **YES**	Open label trial, Single blinding – clinicians not blinded to Rx, records reviewed by outcome assessors masked Rx **NO**	ASA interaction-addressed in 2x2 design -0.2% of no vitamin E group were taking vitamin E **YES**	Not adequate-45% RRR detected for ASA. Designed to pick-up 25% RRR CVD events BUT event rate lower than expected and recruitment stopped early due to ASA finding **NO**	**YES**	Follow-up 92%, 6 yrs (mean), 4 yrs (median) **uncertain**

Study	Quality	Comparative Group	Reliable Outcomes/ Measurement/ Instrumentation	Blinded/ Outcome/ Assessment	Addresses Confounding Factors and Contamination	Adequate Power	Analysis/ Intention To Treat	Adequate Follow-up
ATBC Virtamo et al., 1998	FAIR	Baseline characteristics similar among groups **YES**	Death and coronary events identified from national hospital discharge and death registries in Finland. Validation done in small sample 94% PPV. BUT, cardiac outcomes were originally recorded as SIDE EFFECTS, not even as an outcome, as was designed as a cancer trial **NO**	Double blinding **YES**	Duration of supplementation/serum concentration/ Dietary intake of vit E and beta-carotene interaction all analysed for - no effect **YES**	Sufficient events, so power probably OK **uncertain**	**YES**	Follow-up >80% 5-8 years, median 6.1 **uncertain**
HOPE Yosuf et al., 2000	GOOD	Baseline characteristics were similar among treatment groups. **YES**	Clinical outcomes assessed by standard criteria. Regular F/U with study investigators (every 6 months) **YES**	Double- blind **YES**	Other vitamin use recorded. No mention of serum levels. No interaction with ramipril. 3.4% of patients in placebo group Were taking vit E **YES**	>90% power to detect 13% RRR in 1° outcome **YES**	ITT **YES**	89.2%(mean 4.5 yrs) **YES**
GISSI, 1999	FAIR	Patient's characteristics were well balanced across the groups **YES**	Diagnosis on health records or death certificate was used. Clinical outcomes were validated by a committee of experts blinded to patient's treatment assignment. 15% women in all groups **YES**	Single-blind – open label Clinical outcomes validated by a committee of experts blinded to patient's treatment assignment **NO**	PUFA interaction tested for. 2 patients not assigned to Vitamin E taking supplements. **YES**	80% power to detect a 20% RRR Drop-out rates 7.3% and 26.2% in both vitamin E groups **uncertain**	ITT **YES**	Follow-up 99.9%(3.5yrs) **YES**

Study	Quality	Comparative Group	Reliable Outcomes/ Measurement/ Instrumentation	Blinded/ Outcome/ Assessment	Addresses Confounding Factors and Contamination	Adequate Power	Analysis/ Intention To Treat	Adequate Follow-up
CHAOS Stephens et al., 1996	FAIR	Small difference between active treatment and placebo groups. Differences weighted risk in favor of the placebo group. **uncertain**	Yes, outcomes were assessed by examination of ECG, cardiac enzymes, and case notes over the hospital admission. MI was defined according to the MONICA criteria, the cause of death was classified according to ICD, 9th revision. Endpoints were collected by tracking admissions of study patients, and sending questionnaires to patients and their family physicians **YES**	Double-blind **YES**	49% compliance in both groups. No asssociatino between serum levels and event rate **YES**	80% power to detect RRR 25% at 1.5 years **YES**	ITT **YES**	Median 510 days 98% follow-up (1.4 yrs median follow-up.) **YES**
ATBC Rapola et al., 1997	FAIR	Median age ranged from 59-60.2 yrs between the four groups (p=0.005), else OK **YES**	Death and coronary events identified from national hospital discharge and death registries in Finland. Validation done in small sample 94% PPV. But cardiac outcomes were originally recorded as SIDE EFFECTS, not even as an outcome, as was designed as a cancer trial **NO**	Double blinding **YES**	serum concentration and beta-carotene interaction analysed for: interaction found between Beta-carotene and vit E for non-fatal MI Multivariate risk adjustment also done. **YES**	Study designed to address lung cancer outcomes, but high rate of cardiac outcomes: power may be sufficient to r/o 25% RRR **uncertain**	ITT **YES**	Follow-up 100% (median follow-up 5.3 yrs) 24% drop-out rate **YES**

Table 2: The Effect of Vitamin E Supplementation on Prevention of Cardiac Events – Summary of Published RCTs

Study	N	Intervention	Outcome	1°or 2°	Number of events		RR (95% CI)	Median follow-up (yrs)	Serum concentration (µmol/L)	Quality rating	Comments
					vit E	no vit E					
Primary prevention											
PPP, 2001	4495	AT 300 mg, ECASA 100 mg, both or none. 2x2 factorial placebo controlled	CVD deaths + non-fatal MI + non-fatal stroke.	1°	56	53	1.07 (0.74-1.56)	4		FAIR	About half male, all with one or more of the followingsignificant CAD risk factors No interaction between Vit E and beta-carotene for combined outcome of all major CV events Loses GOOD rating because insufficiently powered-stopped early due to effect of ASA, and smaller than expected event rates; single blinding
			Total deaths	2°			1.07 (0.77-1.49)				
			CVD deaths				0.86 (0.49-1.52)				
			Total CVD events*				0.94 (0.77-1.16)				
			All MI				0.86 (0.52-1.58)				
			Non-fatal MI				1.01 (0.56-2.03)				
ATBC Virtamo et al., 1998	27271 Finnish, all male, white, smokers 50-69 yrs old.	Vitamin E 50mg ß-carotene, both or none 2x2 factorial placebo controlled	"Major coronary events"	2°	1030	1081	0.96(0.88-1.04)	6.1	26.7 initial 40.2 final	FAIR	Length of f/u may be insufficient in primary prevention setting. Loses GOOD because cardiac outcomes post hoc analysis/ secondary
			CVD deaths		434	473	0.92(0.81-1.05)				
			Non-fatal MI		596	608	0.99(0.88-1.10)				
Secondary prevention											

Study	N	Intervention	Outcome	1°or 2°	Number of events		RR (95% CI)	Median follow-up (yrs)	Serum concentration (µmol/L)	Quality rating	Comments
					vit E	no vit E					
Heart Protection Study, 2002	20536 (15,454 men and 5, 082 women)	2x2 factorial design of simvastatin 40 mg/ cocktail of 600 mg of vitamin E, 250 mg of vitamin C and 20 mg of beta-carotene.	Total Mortality	1°	1446	1389	1·04 (0·97–1·12)	5 (mean)	the average plasma concentration of ∝-tocopherol was doubled in the vitamins allocated group compared to the placebo group.	Good	52% of participants were ≥ 65 years old. 74% of participants had pre-existing cardiovascular disease.
			Major vascular event	1°	2306	2312	1·00 (0·94–1·06)				
			Total stroke	2°	511	518	99 (0·87–1·12)				
			Major coronary events	2°	1063	1047	1·02 (0·94–1·11)				
			CVS Mortality	2°	878	840	1·05 (0·95–1·15)				
			Non-fatal MI	2°	464	467	1 (0.87 – 1.12)				
HOPE Yosuf et al., 2000	9541	Vitamin E 400 IU (268mg), ramipril , both or none, 2x2factorial design	MI + stroke + CVD deaths	1°	772	739	1.05 (0.95-1.16)	4.5	Not reported	GOOD	Participants were high-risk patients with CVD or DM, and one other risk factors, ≥ 55 years old. 27% women
			Total deaths	2°	535	537	1.00(0.89-1.13)				
			CVD deaths		342	328	1.05 (0.90-1.22)				
			Total MIs		532	524	1.02 (0.90-1.15),				
			Stroke		209	218	1.17 (0.95-1.42),				

Study	N	Intervention	Outcome	1°or 2°	Number of events		RR (95% CI)	Median follow-up (yrs)	Serum concentration (µmol/L)	Quality rating	Comments
					vit E	no vit E					
GISSI, 1999	11324	Vitamin E 300 mg, n-3 PUFA 1 g, both or none. 2x2 factorial placebo controlled	Deaths + non-fatal MI + stroke	1°	730	770	0.95 (0.86-1.05)	3.5	Not reported	FAIR	Patients with recent ≤3 months MI. The study population had Mediterranean dietary habits.15% women
			CVD deaths + non-fatal MI + non-fatal stroke		571	584	0.98 (0.87-1.1)				
			Total deaths	2°	488	529	0.92 (0.82-1.04)				
			CVD deaths		247	243	0.94 (0.81-1.1),				
			Non-fatal CVD events		294	284	1.04(0.88.-1.22)				
CHAOS Stephens et al., 1996	2002	Vitamin E 800 IU(537mg) (546 patients) 400 IU(268 mg) (489 patients), vs, placebo	CVD deaths + non-fatal MI	1°	41	64	0.53 (0.34-0.83) P = 0.005	1.4	34.2 initial 51.1 final	FAIR	Patients included were with angiographically proven coronary atherosclerosis. 15% women
			non-fatal MI		14	41	0.23 (0.11-0.47), P=0.001				
			Total mortality	2°	36	26	1.3 (0.78-2.17)				
			CVD deaths		27	23	1.18 (0.62-2.27)				

Study	N	Intervention	Outcome	1°or 2°	Number of events		RR (95% CI)	Median follow-up (yrs)	Serum concentration (µmol/L)	Quality rating	Comments
					vit E	no vit E					
ATBC Rapola et al., 1997	1862	Vitamin E 50mg ß-carotene, both or none 2x2 factorial placebo controlled	The first major coronary event after randomization	2°	94	94	0.90 (0.67-1.22)	5.3	28.5 initial 42.5 final	FAIR	Finnish, all male, white, smokers 50-69 yrs old. Loses GOOD because cardiac outcomes post hoc analysis/secondary, and power likely insufficient (few outcomes, multiple analyses) Multivariate risk adjustment did not change outcomes Interaction between Beta-carotene and Vit E found in non-fatal MI group
			CVD deaths		54	39	1.33 (0.86-2.05)				
			Non-fatal MI		40	55	0.68 (0.45-1.02)				

*(CVD deaths, non-fatal MI, non-fatal stroke, angina pectoris, TIA, PAD, revascularization procedure); PUFA= polyunsaturated fatty acids

Table 3. Summary by Outcome of RCTs Addressing Effects of Vitamin E on Cardiac Events

Study	N	Outcome								
		Total mortality			CVD deaths			Non-fatal MI		
		Rx	Ctrl	RR	Rx	Ctrl	RR	Rx	Ctrl	RR
HOPE	9,541	535	537	1.00(0.89-1.13)	342	328	1.05 (0.90 - 1.22)	532	524	1.02 (0.90 - 1.15)*
GISSI	11,324	488	529	0.92 (0.82-1.04)	247	243	0.94 (0.81 - 1.10)	294	284	1.04(0.88. - 1.22)**
CHAOS	2002	36	26	1.3 (0.78-2.17)	27	23	1.18 (0.62 - 2.27)	14	41	0.23 (0.11 - 0.47), P=0.001
ATBC Subset	1862				121	113	1.05(0.80 - 1.37)	96	94	0.89(0.67-1.20)
HPS	20,536	1446	1389	1·04 (0·97–1·12)	878	840	1·05 (0·95– 1·15)	464	467	1 (0.87 – 1.12)

*all MIs, **not specified, CVD events presumed to be equivalent to MIs as no other CVD outcomes measured

Table 4: Summary of the Effects of Vitamin E on CVD Outcomes

Study	Quality	N	Intervention	All major coronary events	CVD mortality	Fatal and/or non-fatal MI	Total mortality
ATBC Heinonen et al., 1994	GOOD	29,133			?		?
ATBC Virtamo et al., 1998	FAIR	27,271	Vitamin E 50 mg and 20 mg B-carotene	?	?	?	
			Vitamin E 50 mg	?	?	?	
ATBC subset trial Rapola et al., 1997	FAIR	1862	Vitamin E 50 mg and 20 mg B-carotene	?	? NNH=22	?	
			Vitamin E 50 mg	?	?	?	
HOPE Yosuf et al., 2000	GOOD	9541	Vitamin E 400 IU	?	?	?	?
CHAOS Stephens et al., 1996	FAIR	2002	Vitamin E 400-800 mg	? NNT=38	?	? NNT=35	?
GISSI, 1999	FAIR	11324	Vitamin E 300 mg and n-3 PUFA 1 g vs. placebo	?	?	?	?
			Vitamin E 300 mg	?	? NNT=77	?	
PPP, 2001	FAIR	4495	Vitamin E 300 mg	?	?	?	?
HPS, 2002	GOOD	20536	600 mg of vitamin E, 250 mg of vitamin C and 20 mg of beta-carotene	?	?	?	?

? = no change

Table 5: Summary of Quality Criteria for RCTs of Vitamin E Role in the Prevention of Cancer

Study	Quality	Comp. Group	Reliable Outcomes measurement Instrument.	Blinded. Outcome Assessment.	Confounding Factors Contamination	Power	Analysis. ITT	Follow-up
ATBC (ATBC 1994a, Albanes 2000, Virtamo 2000, Heinonen 1998)	GOOD for lung cancer FAIR for other outcomes	Baseline characteristics were similar among treatment groups **YES**	Cases of cancer were identified through the Finnish Cancer Registry. To enhance the ascertainment of cases a chest film was obtained at a study visit every 28 months and at each participants exit from the study. All diagnostic information for each case of lung cancer was reviewed by the Clinical Review Committee for confirmation and staging. Other types of cancer were identified through the Finnish Cancer Registry, with medical records reviewed at the central study office. **YES**	Double blind trial **YES**	Interaction with beta-carotene analyzed and found non-signifcant. Also looked ateffect of serum concentration/smoking cessatino/alcohol intake. Contamination unlikely a major facotr since serume levels unchanged in placebo group. **YES**	lung cancer **YES,** other outcomes **NO**	ITT **YES**	86% (5-8 yrs, median 6.1) **YES**
Chinese Blot et al., 1993	FAIR	Baseline characteristics were similar among treatment groups **YES**	Yes, mortality among trial participants was ascertained via follow up with village doctors. Diagnosis of cancer were ascertained through local commune and county hospitals and supplemented by a study medical team that provided clinical and diagnostic services including endoscopy. 85% of cancer cases had diagnostic data. **uncertain**	Double-blind trial, but whether outcome assessors blinded to treatment is not specified **uncertain**	Vitamin E given in same pill with beta-carotene and selenium. Also, multiple combinations of vitamins given –2x8 design – interactions not tested for. Smoking/fam Hx of cancer addressed. Contamination unlikely – nutrient levels higher in treated groups **NO**	0.90? **YES**	ITT **YES**	5.25 Yrs, follow-up >90% **YES**

Heart Protection Study, 2002	Good	**Yes,** baseline characteristics were similar among treatment groups	**Yes**, central ascertainment of death and any registered non-fatal cancers was done by The Oxford coordinating centre from the Office of Population Censuses and Surveys (OPCS) Central Registry. Cancer-related outcomes were among the secondary outcomes.	Double blinding **YES**	Contamination rate was not provided, but the average plasma concentration of ∝-tocopherol was doubled in the vitamins allocated group compared to the placebo group.	Sufficient events, so power **probably OK**	ITT **YES**	F/U 99%, The mean follow up was 5 years. **YES**

Table 6: The Effect of Vitamin E Supplementation on Prevention of Cancer Events – Summary of Published RCTs

Study	N	Intervention	Outcome	1°or 2°	Incidence RR (95% CI)	Mortality RR (95% CI)	Median Follow-up (yrs)	Quality rating
ATBC (ATBC 1994a, Albanes 2000, Virtamo 2000, Heinonen 1998)	29,133	Vitamin E 50mg ß-carotene, both or none 2x2 factorial placebo controlled	Lung cancer	1°	0.99(0.87-1.13)	1.02 (0.86-1.2)	6.1	GOOD
			Total cancers			1.08 (0.96-1.21)		
			Total mortality		N/A*	1.02 (0.95-1.09).		
			Prostate cancer	2°	0.68 (0.53-0.88)	0.59 (0.35-0.99)		
			Urothelial cancer (bladder, pelvis, ureter)		1.1 (0.8- 1.5),	0.99(0.88-1.10)		
			Renal cell cancer		1.1 (0.7-1.6)			
			Colorectal cancer		0.78(0.55-1.09)	0.92 (0.51-1.64)		
Chinese Blot et al., 1993	29,584	Vitamin E 30mg, ß-carotene 15mg, selenium 50ug +/- other supplements, in a 2x8 factorial design	Total mortality	1°	N/A	0.91 (0.84-0.99), P=0.03 [not in text]	5.25	FAIR
			Total cancers		0.93 (0.83-1.03)	0.87 (0.75-1.00)		
			Esophageal cancer	2°	1.02(0.87- 1.19)	0.96 (0.78-1.18)		
			Stomach cancer		0.84 (0.71-1.00)	0.79(0.64-0.99)		
			CVAs			0.90(0.76-1.07)		
Heart Protection Study, 2002	20,536	600 mg of vitamin E, 250 mg of vitamin C and 20 mg of beta-carotene	Total Mortality	1°	N/A	1·04 (0·97–1·12)	5 (mean)	GOOD
			Total cancers	2°	0·98 (0·89–1·08)	1.03 (0.81-1.11)		
			Stomach cancer	2°	1.2 (0.83 - 0.74).			
			Genitourinary cancer	2°	0.86 (0.72 - 1.01).			
			Prostate cancer	2°	0.9 (0.74 - 1.1).			
			Lung cancer	2°	1.03 (0.81-1.11).			
			Total Gastrointestinal cancer	2°	1.0 (0.8 – 1.2)			

*N/A = not applicable

Table 7: Recommendation Table: Vitamin E Supplementation for the Prevention of CVD & Cancer

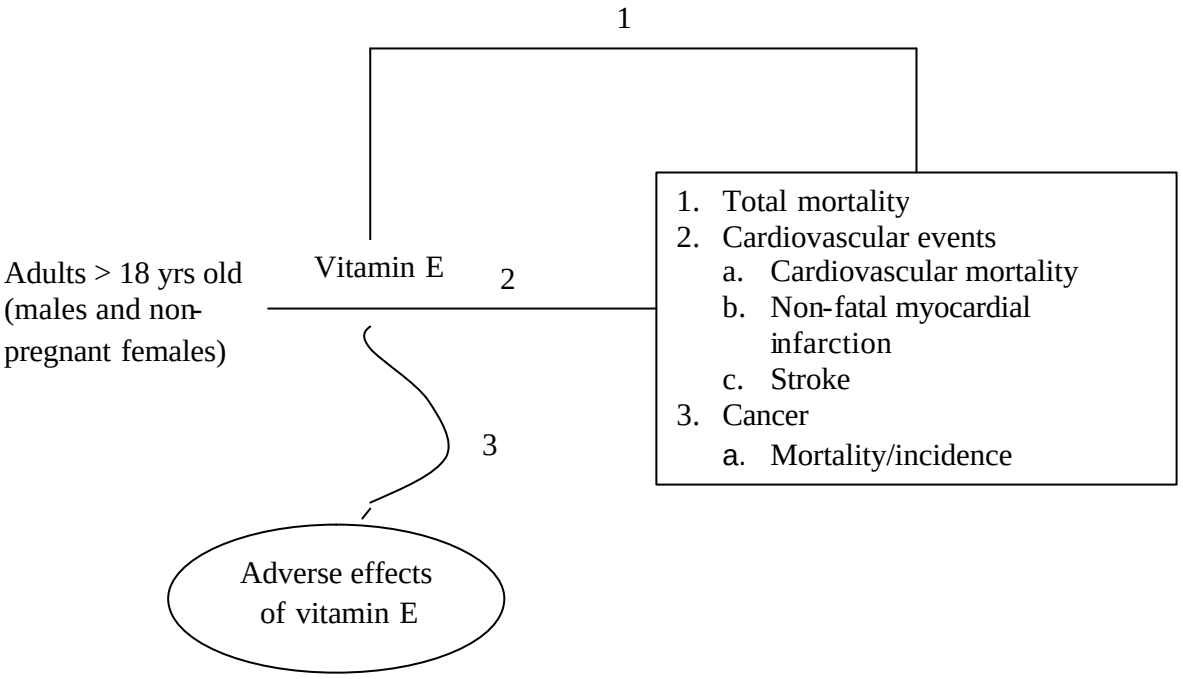
Maneuver	Effectiveness	Level of Evidence* <refs>	Recommendation*
Vitamin E for the primary prevention of CVD	No studies showed significant results for the primary prevention of CVD	I-Good <HPS 2002> I-Fair <PPP 2001, Virtamo 1998>	The CTF concludes that there is insufficient evidence to recommend for or against the use of routine vitamin E supplementation for the primary prevention of CVD events in the general population and in male smokers (**I Recommendation**).
Vitamin E for the secondary prevention of CVD in patients with established CVD or risk factors for CVD	The majority of trials showed no benefit. Only 1 trial showed a positive result for non-fatal MI (RR=0.23)	I-Good <HPS 2002, Yusuf 2000> I-Fair <Virtamo 1998, Rapola 1997, GISSI 1999, Stephens 1996>	The CTF concludes that 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**).
Vitamin E for the prevention of lung cancer	No studies showed significant results for the prevention of lung cancer	I-Good <ATBC 1994a, HPS 2002>	The CTF concludes that there is good evidence to recommend against the use of routine vitamin E supplementation for the prevention of lung cancer (**D Recommendation**).
Vitamin E for the prevention of other cancers (esophageal, stomach, colorectal, urological, and prostate)	No studies showed significant results for the prevention of other cancers	I-Good <HPS 2002> I-Fair <ATBC 1994a, Blot 1993, Roncucci 1993, Albanes 2000, Virtamo 2000, Heinonen 1998>	The CTF concludes that 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**).

*See Appendix 2 for definitions of the levels of evidence, quality ratings and grades of recommendation.

Table 8: Ongoing RCTs

Trial	Participants	Intervention	Outcomes
Women's Health Study (Buring 1992)	40000 postmenopausal US nurses	Vitamin E 600 mg/d, B-carotene 50 mg every other day	MI, stroke, CVD mortality
Women's Atherosclerosis Cardiovascular Study (Manson 1995)	800 female nurses with previous cardiovascular disease	Vitamin E 400 mg or vitamin C 1 g, or B-carotene 20 mg /d	MI, stroke, death from CVD
The Supplementation en Vitamins et Mineraux Antioxydants SU VI MAX (Hercberg 1999)	12,735 French adult men and women 35-60 years old	Daily multivitamin and mineral supplements containing: Vitamin E 30mg, B-carotene 6000ug; vitamin C 120mg;selenium 100ug; and zinc 20mg.	Incidence of cancer (all sites) and ischemic heart disease incidence, overall and cause specific mortality.

Appendix 1: Analytic Framework and Key Questions



Key Questions:

1. What is the direct evidence that vitamin E reduces adverse clinical outcomes in the general population?
    a. What is the direct evidence that vitamin E reduces total mortality?
    b. What is the direct evidence that vitamin E reduces cardiovascular outcomes?
    c. What is the direct evidence that vitamin E reduces cancer outcomes?
2. What is the optimal dose of vitamin E in the prevention of CVD and cancer?
3. What are the short-term and long-term side effects and toxicity of vitamin E?

Appendix 2: Criteria for Rating Individual Studies

Good: Comparable groups were assembled initially and maintained throughout the study. Follow up at least 80 %. Reliable and valid measurements are used and applied equally to the groups, interventions are spelled out clearly. All-important outcomes were considered. Appropriate attention to confounders in analysis and intention to treat analysis.

Fair: If any or all of the following problems occur, without the fatal flaws noted in the poor category. Generally comparable groups were assembled initially but some (although not major) differences occurred; measurement instruments were accepted (but not the best); some but not all important outcomes considered; intention to treat was don; and some but not all potential confounders were accounted for.

Poor: If any of the following fatal flaws exists: groups assembled were not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments were used or not applied at all equally among groups (including not masking outcomes assessment); and key confounders were given a little or no attention; and if intention to treat is lacking.

Appendix 3: Canadian Task Force on Preventive Health Care Levels of Evidence and Quality Ratings of Individual Studies*

Levels of Evidence

A. Research design rating

I: Evidence from at least one randomized controlled trial.

II-1: Evidence from controlled trial(s) without randomization.

II-2: Evidence from cohort or case–control analytic studies, preferably from more than one centre or research group.

II-3: Evidence from comparisons between times or places with or without the intervention; dramatic results from uncontrolled studies could be included here.

III: Opinions of respected authorities, based on clinical experience; descriptive studies or reports of expert committees.

B. Quality (internal validity) rating†

Good: A study that meets all design- specific criteria well.

Fair: A study that does not meet (or it is not clear that it meets) at least one design-specific criterion* but has no known "fatal flaw".

Poor: A study that has at least one design-specific "fatal flaw", or an accumulation of lesser flaws to the extent that the results of the study are not deemed able to inform recommendations.

*The Canadian Task Force methodology is described in Woolf et al. or available from the Canadian Task Force website: http://www.ctfphc.org, under History and Methods.

†General design specific criteria by study type, are outlined in Harris et al.