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Effect of the Supplemental Use of Antioxidants Vitamin C, Vitamin E, and Coenzyme Q10 for the Prevention and Treatment of Cancer

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome written comments on this evidence report. They may be sent to: Director, Center for Practice and Technology Assessment, Agency for Healthcare Research and Quality, 540 Gaither Road, Suite 6000, Rockville, MD 20850.

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Structured Abstract

Objectives. The objective of this report was to conduct a comprehensive literature review and synthesis of evidence on the use of the supplements vitamin C, vitamin E, and coenzyme Q10 for the treatment and prevention of cancer.

Search Strategy. We performed a search of 13 databases through early 2001 using the terms coenzyme Q10, vitamin C, and vitamin E and their many pharmacological synonyms. The bibliographies of review articles were also searched, and experts were questioned to identify additional citations.

Selection Criteria. Reports were included in the synthesis of evidence if they focused on the use of supplements of coenzyme Q10, vitamin C, or vitamin E for the prevention and treatment of cancer and presented the results of clinical trials on human subjects. Language of publication was not a barrier to inclusion.

Data Collection and Analysis. All selected titles, abstracts, and articles, in all languages, were reviewed independently by two reviewers fluent in the appropriate language. Information was collected about patient demographics, disease state, intervention, study design, and outcomes. We focused on three primary outcomes: death, development of new tumors, and effect on colonic polyps. For deaths and new tumors, the trials were too heterogeneous to pool for meta-analyses. For colonic polyps, the trials were sufficiently homogeneous to support a meta-analysis.

We also identified a group of trials with intermediate outcomes, and these were reviewed in a qualitative analysis.

Main Results. We identified 432 articles for screening from which 35 articles met the criteria for inclusion in the analysis. These articles represented 37 unique studies and 22 unique trials, because many studies presented data on the same trial. The identified trials varied greatly in quality. For the doses and populations studied in the trials.

- There was no evidence found for assessing the efficacy of coenzyme Q10 for prevention or treatment of cancer.
- We identified three large trials assessing the effect of vitamin C and vitamin E in various combinations given to persons without cancer. No trial reported a statistically significant beneficial effect on death due to cancer. Subgroup analysis did identify a statistically significant 9% reduction in all cause mortality and a borderline significant 13% reduction in all-cancer mortality associated with supplemental vitamin E in combination with other micro-nutrients. All other trials showed no benefit for all other types of new tumor development except for one arm of the ATBC trial, which showed a decrease in the development of new prostate tumors.
- We identified seven trials that assessed the use of vitamin C in patients with advanced cancer. No trial reported a statistically significant mortality benefit.
- There was no decrease in risk of death for vitamin C as a treatment for advanced cancer.
We identified six trials assessing the effect of combinations of vitamin C and vitamin E with and without beta-carotene on the development of colonic polyps. No trial reported a statistically significant beneficial effect.

We identified six unique trials that reported on various intermediate outcomes.

The following beneficial results were reported from single trials:

a. Vitamin C was found to be beneficial in reducing the occurrence of new tumors in a single trial of patients with bladder cancer also treated with bacillus Calmette-Guerin (BCG).

Vitamin E in combination with omega-3 fatty acid increases survival in patients severely ill with a variety of malignancies.

A number of intermediate outcomes studies were positive.

Conclusions. For the interventions tested, in the populations described, there is scant evidence that vitamin C or vitamin E beneficially affects survival. Similarly, for the interventions tested, in the populations described, there are no results suggesting a benefit for the prevention of new tumors, which reach statistical significance with the exception of prostate cancer in subjects treated with alpha-tocopherol. One trial reported a benefit of a megadose vitamin therapy on the development of new tumors in patients with bladder cancer. However, the ability to infer from this finding is limited because the multi-component intervention limits our ability to attribute the reported efficacy to any particular component.

For the outcome for colonic polyps, four trials focusing on secondary polyp recurrence could be pooled for analysis and none used vitamins C or E as a single intervention. The combination of vitamins C and E was not clinically superior to placebo in secondary prevention. The combination of vitamins C and E with beta-carotene or vitamin A did show a trend favoring a reduction in polyp recurrence, but this finding was not statistically significant.

The systematic review of the literature does not support the hypothesis that the use of supplements of vitamin C or E or coenzyme Q10 generally help prevent and/or treat cancer. There were isolated findings of benefit, which require confirmation.

Future Research. Future research should be done to confirm the positive findings from the single trials identified here. Investigation should be undertaken to understand the discrepancy between the epidemiologic evidence and the clinical trial data. Additional research should include population (such as women) not well studied.

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Effect of the Supplemental Use of Antioxidants
Vitamin C, Vitamin E, and Coenzyme Q10 for the
Prevention and Treatment of Cancer

Summary

Overview

The objective of this report by the research team from the Southern California Evidence-based Practice Center (EPC) was to conduct a search of the published literature on the use of supplement forms of the antioxidants, vitamin C, vitamin E, and coenzyme Q10, for the treatment and prevention of cancer and, on the basis of that search, to evaluate the evidence for the efficacy of these antioxidants. A broad search revealed sufficient literature to support a detailed review of the use of two of these antioxidants for cancer.

Patients with cancer commonly try a variety of nontraditional treatments that fit the broad category known as Complementary and Alternative Medicine (CAM). However, evidence is lacking for the effectiveness of most CAM therapies for cancer. Among the CAM therapies publicized by the popular press for cancer treatment are several supplementary antioxidants: vitamin C, vitamin E, and coenzyme Q10.

It has long been argued that the adequacy of the vitamin supply to cells and tissues influences the development, progress, and outcome of cancers. A major challenge to the integrity and function of cells and tissues is thought to come from the uncontrolled formation of free radicals. Free radicals may, alone or in combination, attack cell membranes and DNA. The body has evolved antioxidant defenses to protect against free radical-induced damage. It is postulated that the antioxidant vitamins E and C and coenzyme Q10 are potentially involved in these antioxidant defenses and that some diseases might be prevented by increasing intake of antioxidants, either through increasing the dietary intake of antioxidant-rich foods or taking antioxidant supplements. However, it should be noted that while free radicals have been implicated in over 100 human diseases, this implication does not constitute proof of their role in disease formation or that preventing the formation or function of free radicals can prevent or cure disease.

Methodology

A panel of technical experts representing diverse disciplines was used by the Southern California Evidence-based Practice Center to advise on the search and inclusion criteria. The technical experts represented diverse disciplines including acupuncture, Ayurvedic medicine, chiropractic, dentistry, general internal medicine, gastroenterology, rheumatology, integrative medicine (the practice of combining alternative and conventional medicine), neurophysiology, pharmacology, psychiatry, psychoneuroimmunology, psychology, sociology, botanical medicine, and traditional Chinese medicine. The aim was to perform a meta-analysis whenever the literature was appropriate for such an analysis.

Search Strategy

1990-2002, and TGG Health & Wellness DB. Limiting the output to human studies, the team searched using the terms coenzyme Q10, vitamin E, and vitamin C, and their many pharmacological synonyms; the condition of interest (cancer); and study design or article type (randomized controlled trials, clinical controlled trials, meta-analyses, and systematic reviews).

Selection Criteria

Trials were included in the synthesis of evidence if they focused on vitamins C or E or coenzyme Q10 as supplements for the treatment or prevention of cancer and if they presented the results of clinical trials on human subjects or were a meta-analysis or systematic review or if they provided descriptive or background information about antioxidants. Language of publication was not a barrier to inclusion.

Reporting the Evidence

Searches of the literature yielded 1,337 articles, of which researchers were able to obtain 1,125. Based on a review by two physicians working independently, 432 articles were selected for screening, including clinical trials, meta-analyses, reviews, and reports that contained supplemental information. Twenty-two unique trials that met the inclusion criteria were included in the systematic review. Of these 22 trials, 19 included vitamin C, 14 included vitamin E, and none included coenzyme Q10 either for treatment or prevention of cancer. After reviewing the available evidence, the EPC research team focused on three primary outcomes: death from cancer, new tumors, and effect on colonic polyps, because these were the clinical outcomes that were most relevant and reported most frequently in the trials.

Data Collection and Analysis

All selected titles, abstracts, and articles, in all languages, were reviewed independently by two physician reviewers who were fluent in the appropriate language, and all disagreements were resolved by consensus. Information was collected about patient demographics, disease state, intervention, study design, and outcomes. Sufficient numbers of homogeneous trials did not exist to permit a meta-analysis of the efficacy of vitamins C or E or coenzyme Q10 for the outcomes of death or new tumor development. A meta-analysis was possible only for assessing the effect on colonic polyps. Additional qualitative reviews were done for trials that could not be pooled and for studies with intermediate outcomes.

Findings

Researchers identified 35 relevant articles corresponding to 37 studies. These 37 studies correspond to 22 unique trials, because many studies presented data on the same trial. The quality of the trials varied greatly as judged by the Jadad criteria. The distribution of trials across the three selected outcomes was as follows: 20 studies reported mortality outcomes; 15 studies reported the effect on new tumor development; and 8 studies reported the effect on colonic polyps. From these studies, the researchers were able to include data from six trials for the death analysis; four trials for the tumors analysis; and four trials for the pooled polyps analysis. Only the studies on colonic polyps were homogeneous enough to perform a meta-analysis. Seven studies also reported on a variety of intermediate outcomes.

Based on their analyses, the researchers made the following observations:

- No evidence was found for assessing the efficacy of coenzyme Q10 for prevention or treatment of cancer.
- Three large trials assessed the potential of vitamin C and vitamin E in various combinations to prevent cancer when given to persons without cancer. No trial reported a statistically significant beneficial effect on death due to cancer, nor did any trial show benefit for prevention of new tumor development, except for one arm of the ATBC trial, which showed a decrease in the development of new prostate tumors.
- Seven trials assessed the use of vitamin C in patients with advanced cancer. No trial reported a statistically significant mortality benefit: Vitamin C did not decrease the risk of death from advanced cancer.
- Six trials assessed the effect of combinations of vitamin C and vitamin E with and without beta-carotene on the development of colonic polyps. No trial reported a statistically significant beneficial effect.
- A number of intermediate outcomes studies reported positive results.
- A single trial of vitamin E in combination with omega-3 fatty acids showed increased survival of patients severely ill with a variety of malignancies.
- In a single trial of patients with bladder cancer who were also treated bacillus Calmette-Guerin (BCG) tuberculosis vaccine, Vitamin C was found to be beneficial in reducing the occurrence of new tumors.

This systematic review of the literature does not support the hypothesis that supplements of vitamins C or E or coenzyme Q10 generally help prevent or treat cancer. Isolated findings of benefit require confirmation.

Future Research

Results of the literature synthesis show generally disappointing results for the efficacy of antioxidant supplementation to prevent or treat cancer. Because this finding is in contrast to observational studies reporting benefits, additional research is needed to understand why these two
sources of evidence disagree. The positive findings from single clinical trials also need to be verified by further research.

Several factors should be considered when planning future research. Clinical trials should focus on populations not heretofore included—specifically, women with breast, cervical, and ovarian cancer—and study populations should be homogeneous with respect to condition and intervention. Additional research is needed to assess the benefit of antioxidant supplements for the secondary prevention of common cancers or for the modification of premalignant states. Based on the present analysis, the most promising antioxidants for future research are vitamins E and C. For coenzyme Q10, preliminary research is needed before a large clinical trial would be recommended. Finally, validated intermediate outcomes could be used as end points in future research, as they would provide a cost-effective method to gauge the efficacy of any planned clinical intervention.

Availability of the Full Report

The full evidence report from which this summary was taken was prepared for the Agency for Healthcare Research and Quality (AHRQ) by the Southern California Evidence-based Practice Center (EPC) under Contract No. 290-97-0001. Printed copies may be obtained free of charge from the AHRQ Clearinghouse by calling 800-358-9295. Requesters should ask for Evidence Report/Technology Assessment No. 75, Effect of the Supplemental Use of Antioxidants Vitamin C, Vitamin E, and the Coenzyme Q10 for the Prevention and Treatment of Cancer.
Chapter 1. Introduction

Purpose

Patients with cancer commonly try a variety of nontraditional treatments that fit the broad category known as Complementary and Alternative Medicine (CAM). However, evidence is lacking for the effectiveness of most CAM therapies for cancer. Among the CAM therapies publicized by the popular press for cancer treatment are several dietary antioxidants: vitamin C, vitamin E, and coenzyme Q10.

The purpose of our study was to conduct a systematic review of the scientific literature to identify and assess the evidence for the efficacy of these three antioxidants for the prevention and treatment of cancer.

Specific Aims

The National Center for Complementary and Alternative Medicine (NCCAM) and the Agency for Health Research Quality (AHRQ) established four specific aims for this study:

1. To identify all study reports on the efficacy of antioxidant supplements vitamin C, vitamin E, and coenzyme Q10 for preventing cancer;
2. To identify all study reports on the efficacy of antioxidant supplements vitamin C, vitamin E, and coenzyme Q10 for treating cancer;
3. To determine if sufficient evidence exists to recommend further study of these therapies;
4. To recommend the types of future research studies needed.

A Brief Review of the Use of CAM for Cancer Treatment

Antioxidants and Cancer

The April 2000 National Academy of Sciences/Institute of Medicine/Food and Nutrition Board report entitled Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids defined the term dietary antioxidant, provided Dietary Reference Intakes (DRIs) for the antioxidant vitamins and minerals, and reviewed the evidence supporting a role for these nutrients in preventing or treating a variety of chronic diseases. A dietary antioxidant is a substance in foods that significantly decreases the adverse effects of reactive species, such as reactive oxygen and nitrogen species, on normal physiological functions in humans.1 The DRIs provided by the report include four values: the Recommended Dietary Allowances (RDAs), the dietary intake level that is sufficient to meet the nutritional requirements of most healthy individuals in a particular age and gender group; Adequate Intakes (AIs), which are recommended intakes based on estimated or observed intake levels when data are inadequate to set an RDA; Tolerable Upper Limits (ULs), the highest level of nutrient intake that is likely to pose no adverse health risks for the majority of healthy individuals; and Estimated Average
Intakes (EARs), the intake that is estimated to meet the requirements of half the individuals in an age/gender group. The committee that authored the report found laboratory and epidemiological evidence that diets rich in fruits and vegetables (foods that are high in antioxidants) may be associated with the prevention of certain types of cancer, but found a lack of scientific basis for recommendations regarding any specific nutrient supplement. However, they were unable to establish a direct link between the intake of dietary antioxidants and the prevention of disease, recommending that further, large-scale studies were needed. It has been in the area of prevention of cancer rather than treatment of cancer that much of the discussion and work on antioxidants has focused.

The Origin of Ideas on Diet and Cancer Prevention

The discovery of the vitamins and their requirements in human nutrition was based on findings that the omission of these substances from the diet resulted in the acute appearance of constellations of symptoms. In preventing these symptoms, vitamins function as coenzymes and sometimes as hormones. However, in recent years, as some disease processes have been proposed to be the result of chemical oxidation, several of the vitamins have been found to have an additional set of functions, namely that of preventing such oxidation. The interest in a link between the intake of the antioxidant vitamins and chronic disease prevention is based on this proposed role for the antioxidant vitamins in human nutrition.

It has long been argued that the adequacy of the vitamin supply to cells and tissues influences the development, progress, and outcome of cancers. A major challenge to the integrity and function of cells and tissues is thought to come from chemical species called free radicals (defined as any atom or molecule whose nucleus has one or more unpaired electrons). The body produces these highly reactive species, such as the oxygen radical, as byproducts of some metabolic processes, the process of destroying foreign organisms, and in response to particular types of physical stress. The physiological processes that rid the body of toxins as well as those that metabolize drugs are also believed to lead to free-radical formation.

Free radicals may, in turn, join with other free radicals or react with non-radicals to cause chain reactions and form new radicals. These radicals can then attack cell membranes or their constituent lipoproteins, which is now believed to contribute to atherosclerosis. Free radicals can also attack the DNA, the chemical constituent of genes, causing mutations. The body has evolved antioxidant defenses to protect against free radical–induced damage; for example, cells manufacture repair enzymes that can “destroy free-radical-damaged proteins, remove oxidized fatty acids from membranes, and repair free-radical damage to DNA…” and additional, extracellular, antioxidant defenses also exist. Vitamins E and C, the carotenoids, and coenzyme Q10 are potentially involved in these antioxidant defenses. However, these defenses may not be totally effective. Thus, the concentration of free radicals in the body may continue to increase, more damage can occur, and, as a result, the body suffers oxidative stress. Severe oxidative stress may result in cell injury and destruction.
Given what we now know about the potential for free radicals to cause DNA damage and other types of destruction, a theory has developed that one possible cause of diseases such as cancer may be the uncontrolled effect of free radicals. For example, if the DNA damage were not repaired, mutations would result, which theoretically might lead to the development of cancers. If diseases could be caused by free-radical damage, it is also theoretically possible that these diseases could be prevented by increasing the dietary intake of antioxidant-rich foods, foods rich in vitamins E and C and other substances shown to reduce oxidative damage in the laboratory. Yet, as Halliwell notes, while free radicals have been implicated in over 100 human diseases, this implication does not constitute proof of their role in disease formation or proof that treatments aimed at preventing free radicals can prevent or cure disease.

Cancer Development

Research on the association between vitamins and cancer has focused largely on the potential for prevention (although some research focuses on the role of vitamins in cancer treatment). Based on animal studies, carcinogenesis (the development of cancer) has traditionally been viewed as a two-stage process. The first stage, initiation, involves irreversible mutation of genetic sequences, resulting in permanent changes to the genotype (the sequence of DNA carried by every cell). According to this model, this stage is necessary but not sufficient for cancer to develop. The second stage, promotion, involves a change in gene *expression* (the process by which genes are read and the proteins they encode are synthesized, resulting in a “visible” manifestation of the genotype), which requires a promoter substance and thus is believed to be reversible. Promoters enhance the expression of the mutated gene(s) and selectively stimulate the growth of cells that express these genes.

This two-stage model is now considered overly simplistic. Instead, carcinogenesis is now seen as a multistage process, however, the two-stage model conceptualizes the belief that cells must undergo a permanent genetic change followed by a stimulus that selectively allows these cells to divide and escape normal growth controls.

The genetic changes necessary for cancer initiation are thought to be caused by the actions of mutagenic chemicals or physical forces (such as high doses of radiation) acting on the DNA, processes that may require metabolic activation. As mentioned above, if the damaged DNA is not repaired quickly, it becomes a stable mutation during the next cycle of DNA replication. Alternatively, miscoding may occur during the repair process. Some mutations that may result in cancer include those that result in the activation of proto-oncogenes and those that inactivate tumor suppressor and other antimetastasis genes.

The next phase, tumor promotion, enhances the probability of additional cumulative genetic damage, including endogenous mutations, by allowing expansion of the population of mutation-containing cells. The likelihood of cancer formation is further increased at this stage by exposure to other mutagenic agents.
The Antioxidant Supplements and Cancer Prevention

Oxidative processes have been implicated in both initiation and promotion of cancer. Likewise, animal studies have revealed effects of the antioxidant nutrients on both processes.

Vitamin E exhibits antioxidant properties by acting as a lipid-soluble free radical scavenger in cell membranes. Thus, vitamin E may be involved in both initiation and promotion stages. Among the other potentially anticarcinogenic effects of vitamin E are its ability to inhibit formation of the carcinogenic chemical nitrosamine from nitrites in some foods, and its ability to promote immune system function.⁶

Vitamin C (ascorbic acid) also acts as an antioxidant, and through its ability to scavenge free radicals, it may have protective effects on biopolymers such as DNA. Like vitamin E, vitamin C may be protective for both initiation and promotion of carcinogenesis. Also, like vitamin E, it is thought to prevent formation of nitrosamine (by converting nitrite to nitrous oxide)⁶ and to influence immune system function. Vitamin C has also been reported to affect liver enzymes responsible for detoxification and transformation of carcinogens.⁶

Coenzyme Q10 (also termed ubiquinone and ubidecarenone) is an endogenously synthesized chemical (called a quinone) that is also obtained through food intake. In addition to its role as an electron carrier in the mitochondrial electron transport chain, it can also function as a soluble antioxidant.⁸ No recommended daily intake has been established for Q10, no deficiency has ever been shown,⁵ and no side effects have been observed at any dose level.⁹ In addition to its role as an antioxidant (possibly in conjunction with vitamin E)¹⁰ and as a free radical scavenger, other roles have been proposed for Q10. These include acting as a nonspecific stimulant for the immune system,¹⁰ and playing a role in membrane stabilization, prostaglandin metabolism, inhibition of intracellular phospholipases, and stabilization of calcium-dependent slow channels.¹⁰ Decreased levels of Q10 have been noted with aging and in such disorders as congestive heart failure, cardiomyopathy, cancer, hypertension, Parkinson’s disease, spontaneous abortion, male infertility, chronic hemodialysis, and periodontal disease.¹⁰

As we have briefly reviewed, vitamins C and E and coenzyme Q10 have been implicated in a variety of potential anticarcinogenic processes. This report will review the evidence that supplements of these substances have the ability to prevent some types of cancer.
Chapter 2. Methodology

We synthesized evidence from the scientific literature on the effectiveness of vitamin C, vitamin E, and coenzyme Q10 for the prevention and treatment of cancer, using the evidence review and synthesis methods of the Southern California Evidence-based Practice Center (SCEPC). Established by the Agency for Healthcare Research and Quality (AHRQ), the center conducts systematic reviews and technology assessments of all aspects of health care; performs research on improving the methods of synthesizing the scientific evidence, developing evidence reports, and conducting technology assessments; and provides technical assistance to other organizations in their efforts to translate evidence reports and technology assessments into guidelines, performance measures, and other quality-improvement tools.

Project staff collaborated with the National Institutes of Health’s National Center for Complementary and Alternative Medicine (NCCAM), the Task Order Officer at AHRQ, and technical experts representing disciplines related to the intervention topic, conditions studied, and/or methods used.

Scope of Work

Our literature review process consisted of the following steps:

- Establish criteria for inclusion of articles in review.
- Identify sources of evidence in the scientific literature.
- Identify potential evidence with attention to controlled clinical trials using antioxidants.
- Evaluate potential evidence for methodological quality and relevance.
- Extract data from studies meeting methodological and clinical criteria.
- Synthesize the results.
- Perform further statistical analysis on selected studies.
- Perform pooled analysis where appropriate.
- Submit the results to technical experts for peer review.
- Incorporate reviewers’ comments into a final report for submission to AHRQ.

Objectives

Based on a discussion with the Task Order Officer for AHRQ, the Director of NCCAM, Co-Directors of SCEPC, and project staff, we selected, as the focus for this report, the use of vitamin C, vitamin E, and coenzyme Q10 to treat and prevent cancer.

The report was guided by the following research questions:

- What kinds and numbers of study reports were available that presented research on the use of antioxidants for treating and preventing cancer?
- Were interventions used for treatment, primary or secondary prevention, or in adjunct to conventional treatment?
• Were interventions used for treatment or modification of known risk factors for cancer or pre-malignant states?
• What types of outcomes were measured for the identified condition?
• What is the methodological quality of the studies identified?
• Can statistical results from the various studies be pooled?

Literature Search Design

Technical Expert Panel

The SCEPC is advised on CAM topics by a group of technical experts regarding the search and inclusion criteria and appropriate analyses. The technical experts represent diverse disciplines including acupuncture, Ayurvedic medicine, chiropractic, dentistry, general internal medicine, gastroenterology, rheumatology, integrative medicine (the practice of combining alternative and conventional medicine), neurophysiology, pharmacology, psychiatry, psychoneuroimmunology, psychology, sociology, botanical medicine, and traditional Chinese medicine. The technical experts assisted the project in several ways. They aided us in identifying potential topics for review, appropriate sources of relevant literature, and technical experts for peer review; assessing our search strategies; and addressing specific questions in their areas of expertise. Appendix A lists members of the expert panel along with their affiliations.

Identification of Literature Sources

Potential evidence for the report came from three areas: on-line library databases, the reference lists of all relevant articles, and other sources such as identified experts and the personal libraries of project staff and their associates. The reference librarian at RAND identified traditional biomedical databases as well as databases that focus on the condition of interest and alternative and complementary medicine (Table 1).

We conducted four searches specifically on the interventions of interest. The full search strategies are displayed in Appendix B. We utilized the National Library of Medicine’s controlled vocabulary thesaurus called Medical Subject Headings or “MeSH terms.” Limiting the output to human studies, we searched using the terms coenzyme Q10, vitamin E, vitamin C, and their many pharmacological synonyms (Table 2); the condition of interest (cancer); and study design or article type (randomized controlled trials, clinical controlled trials, meta-analyses, and systematic reviews). Because this report is focused on efficacy, clinical trials are preferred since they provide control groups which account for confounding factors. These searches yielded a total of 4595 titles, many of which were duplicates, because one article would appear repeatedly as each new search was added.
Two reviewers (a physician and a PhD) independently evaluated deduplicated lists of 1079 titles that the on-line database searches generated as well as 258 additional titles from other sources, such as professional libraries and reference mining. The reviewers read the lists of titles and accepted articles that:

- focused on vitamin C, vitamin E, or coenzyme Q10 for treatment or prevention of cancer, or the modification of a known risk factor for cancer or improvement in a pre-malignant state;
- focused on controlled trials on humans;
- presented a meta-analysis or systematic review of the interventions and condition;
- presented historical or descriptive background information about antioxidants and their use.

Articles that either reviewer classified as meeting these criteria were accepted. Articles were rejected that both reviewers considered:

- focused on a disease state that was not the topic of interest;
- contained animal or in vitro data unless human clinical trial information or significant background information was also included.

Language was not considered a barrier to inclusion.

From this stage of the screening process, the reviewers requested a total of 1337 articles, of which we were able to obtain 1125. Selected articles were further evaluated to see if they met the inclusion criteria. Based on this evaluation, we selected 432 that went on to further screening.

Using Microsoft Access database software, we tracked requests for articles. We used ProCite as a link to read the citations into the Access database as well as to manage our reference list. We also used the database to produce and store our data collection instruments. Table 3 summarizes the search strategy shown in Appendix B. The details of the screening process are discussed in the next section.

**Evaluation of Evidence**

Two physicians, each trained in the critical analysis of scientific literature, independently reviewed each article, abstracted data, and resolved disagreement by consensus. From the 432 articles accepted after the initial title screening, they accepted 36 articles for further study, based on the data collected using the screening form. These 36 articles were therefore included in the synthesis of evidence because they:

- focused on the antioxidants vitamin C, vitamin E or coenzyme Q10 and cancer;
- presented research on human subjects;
- reported the results of a clinical trial.
To be clear about our terminology: a “trial” refers to a controlled clinical trial; a “study” refers to a presentation of a specific portion of a trial’s results, e.g., focused on one outcome or at a particular follow-up time; and an “article” refers to a published document. Some articles may contain more than one study, particularly if they contain results from more than one trial. Some trials, especially large ones, have many associated studies and articles.

Two articles\textsuperscript{11, 12} described two different trials each, so a total of 38 unique studies were referred for detailed review. Many of these studies reported on three large trials—the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Trial, the Linxian General Population, and the Linxian Dysplasia Group Trials—which are discussed at length in the results section and displayed in the evidence table. We created a one-page data collection instrument that served as a screening form for this process. Appendix C contains a copy of this screening instrument.

**Extraction of Data**

Detailed information from each of the 38 studies was collected on a specialized data collection instrument (the Quality Review Form) designed for this purpose. This Quality Review Form (Appendix D) was developed in consultation with our technical experts. We included questions about the trial design; the quality of the trial; the number and characteristics of the patients; patient recruitment information; details on the intervention, such as the dose, route of administration, frequency, and duration; the types of outcome measures; and the time between intervention and outcome measurement. Two trained reviewers, working independently, extracted data in duplicate and resolved disagreements by consensus. A senior physician researcher on the project staff resolved any disagreements not resolved by consensus.

A note about equivalence of units for data extraction: dosages of vitamin E, often given as alpha-tocopherol, are reported in either milligrams or international units (IU). To interconvert these units, consider 1 milligram of alpha-tocopherol approximately equal to 1.5 IU of vitamin E.

To evaluate the quality of the trials, we collected information on the study design, appropriateness of randomization, blinding, description of withdrawals and dropouts and concealment of allocation.\textsuperscript{13} A score for quality was calculated for each trial using a system developed by Jadad.\textsuperscript{14} The Jadad score rates studies on a 0 to 5 scale.\textsuperscript{14} A score is based on the answer to three questions: Was the study described as randomized? Was the study described as double-blind? Was there a description of withdrawals and dropouts? One point is awarded for each “yes” answer, and no points are given for a “no” answer. An additional point is given if the randomization method described was appropriate. A point is deducted if the method is described but is not appropriate. A point is awarded if the method of blinding is appropriate and described, and one point is deducted if the blinding method is described, but inappropriate. Empirical evidence has shown that studies scoring 2 or less report exaggerated results compared with studies scoring 3 or more.\textsuperscript{15} Thus, studies with a Jadad score of 3 or more are referred to as “high” quality, and studies scoring 2 or less are referred to as “poor” quality.

The flow of articles from the point at which they entered our database, through the article ordering, screening, quality review, and statistical analysis stages is displayed in Figure 1. All articles that went on for abstraction were examined for inclusion in the data synthesis.
Selection of Studies for Meta-Analysis

Prior to the analysis, we entered all data on outcomes and treatments into the statistical program SAS. We analyzed this dataset to identify the clinically relevant outcomes that were reported most commonly and would therefore be appropriate for data synthesis. These outcomes were death, development of new tumors and progression of existing tumors, and development of adenomatous colonic polyps. The grouping of treatments and the appropriate comparison group, e.g., any combination of vitamins with vitamin E versus placebo, was based on clinical knowledge and was decided a priori. In addition to these three clinical outcomes, our review also examines intermediate outcomes. These are outcomes that are considered as precursors to such clinical outcomes as new tumor development and death, although they vary in the degree to which they are good predictors of those outcomes.

We defined the outcomes of interest as follows. “Death” from cancer was used as an outcome for any trial which gave survival results. “New tumors” includes the development of new tumors in a subject with no prior history of tumor as well as recurrence of tumor in a subject with a history of cancer or precancerous lesion. Adenomatous colonic polyps, or simply “colonic polyps” refers to new adenomatous polyps of the colon.

Several trials had multiple associated studies, so our first task was to discern what each study contained in terms of unique data for that trial. For example, two studies of the same trial might present data on deaths due to two different types of cancer, and therefore each contributed unique data to the analysis. Other studies contained duplicate data. Some studies did not contain sufficient data for a statistical analysis. The two primary causes of insufficient data were that only survival curves were presented graphically for death or new tumors rather than the number of outcomes at a specific follow-up time, or an outcome, e.g., number of deaths, was presented for all patients combined rather than separately by treatment group. After determining which studies could contribute to the analysis, we extracted data into the spreadsheet program Microsoft Excel and performed statistical and meta-analytic methods in the statistical package Stata.

All three outcomes were dichotomous and we used a risk ratio to summarize each individual study, so we discuss this statistical approach jointly for all outcomes. For death and new tumors, the studies were too heterogeneous to pool meta-analytically. We did pool the colonic polyp risk ratios, and we discuss this meta-analytic approach below.

Risk Ratio Analysis

For each of the three outcomes (death, tumors, and colonic polyps) that a trial reported, we estimated the log risk ratio comparing the relevant treatment group to either placebo or another comparison group as appropriate. We note that occasionally death or new tumor outcomes were further subdivided, e.g., death due to different types of cancers. We note further that some studies for the same trial would present comparisons in alternative ways. For example, one study might present death data for vitamin C and placebo groups separately, while another study presented death data for a different type of cancer for the vitamin E group versus all other study groups combined. The available data thus limited our ability to evaluate different comparisons.
for different outcomes. We also estimated the standard error of the log risk ratio for each trial and constructed a 95% confidence interval. We conducted the analysis on the log scale to stabilize the variance. We then back-transformed the log risk ratio and its confidence interval to the risk ratio scale for interpretability.

In summary, for each trial, comparison, and outcome for which data were available, we estimated the risk ratio (RR) and its 95% confidence interval. As an example of how to interpret a risk ratio, consider the outcome of all-cancer death when comparing the treatment of beta-carotene versus placebo. A risk ratio smaller than 1 indicates that a lower risk of death is associated with beta-carotene as compared to placebo.

For the death and new tumor outcomes, the trials were considered too heterogeneous to pool meta-analytically. For these outcomes, we present trial results individually with the separate outcomes defined as they appear in specific trial reports. In particular, three large trials (ATBC and the two Linxian Trials) were significantly different from each other and from the other small trials, so that meta-analytic pooling was not advisable. The main differences were study population (primary prevention versus treatment) and length of follow-up. For these large trials, we did consider whether we could combine related outcomes within trial. We note that we distinguish *pooling* results meta-analytically across trials from *combining* outcomes within a single trial. For example, a trial may report deaths due to different types of cancers separately. If clinically appropriate, we combined these deaths across all types of cancers reported, assuming that a patient’s death could not be attributed to more than one type of cancer, so that we were not double-counting deaths in the combined count. For this new combined cancer death outcome that we created, we estimated a risk ratio as described previously.

**Meta-Analysis for the Colonic Polyps Outcome**

The trials that examined colonic polyps as an outcome were considered clinically homogeneous enough to warrant meta-analysis. We performed meta-analysis for any subgroup of three or more trials that had similar designs and comparison groups, and that measured colonic polyps for a particular type of cancer over similar follow-up periods.

For each subgroup of trials that qualified for meta-analysis, we estimated the DerSimonian and Laird random effects\(^{19}\) pooled log risk ratio, and its confidence interval. We also present the chi-squared test for heterogeneity p-value.\(^{20}\) We back-transformed the pooled result to the risk ratio scale for interpretation, and present the pooled risk ratio, its 95% confidence interval, and associated forest plot. In this plot, each individual study risk ratio is shown with its confidence interval as a box whose area is inversely proportional to the estimated study variance. The pooled risk ratio and its confidence interval are shown as a diamond at the bottom of the plot with a dotted vertical line indicating the pooled estimate. A vertical solid line at a risk ratio of 1 indicates no treatment effect.
Publication Bias

For each subgroup of studies for which we conducted a meta-analysis, we assessed the possibility of publication bias by evaluating a funnel plot of the log risk ratios graphically for asymmetry resulting from the nonpublication of small, negative studies. Because graphical evaluation can be subjective, we also conducted an adjusted rank correlation test\textsuperscript{21} and a regression asymmetry test\textsuperscript{22} as formal statistical tests for publication bias.
Table 1. Biomedical and other databases searched.

<table>
<thead>
<tr>
<th>Database</th>
<th>Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allied &amp; Complementary Medicine</td>
<td>1984-2001 Feb</td>
</tr>
<tr>
<td>Biosis Previews</td>
<td>1969-2002 Jan</td>
</tr>
<tr>
<td>CAB Health</td>
<td>1983-2001 Dec</td>
</tr>
<tr>
<td>CancerLit</td>
<td>1975-2001 Oct</td>
</tr>
<tr>
<td>Cochrane Library</td>
<td>1922- 2001</td>
</tr>
<tr>
<td>Database of Systematic Reviews</td>
<td></td>
</tr>
<tr>
<td>Controlled Trials Register</td>
<td></td>
</tr>
<tr>
<td>Elsevier Biobase</td>
<td>1994-2002 Jan</td>
</tr>
<tr>
<td>Embase</td>
<td>1974-2002 Jan</td>
</tr>
<tr>
<td>MANTIS</td>
<td>1880-2001 Oct</td>
</tr>
<tr>
<td>Medline</td>
<td>1966-2002 Jan</td>
</tr>
<tr>
<td>Social SciSearch(R)</td>
<td>1972-2002 Jan</td>
</tr>
<tr>
<td>TGG Health&amp;Wellness DB</td>
<td>1976-2002 Dec</td>
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</table>

Table 2. Additional search items for antioxidants studied.

<table>
<thead>
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<th>Vitamin C</th>
<th>Vitamin E</th>
<th>Co-enzyme Q-10</th>
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</thead>
<tbody>
<tr>
<td>ascorbic acid</td>
<td>alpha tocopherol</td>
<td>ubiquinone</td>
</tr>
<tr>
<td>dehydroascorbic acid</td>
<td></td>
<td>ubiquedecarenon</td>
</tr>
<tr>
<td>ascorbate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>antiscorbutic vitamin</td>
<td></td>
<td>isoprostane</td>
</tr>
<tr>
<td>cevitamic acid</td>
<td></td>
<td></td>
</tr>
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</table>
**Table 3. Summary of search strategy.**

<table>
<thead>
<tr>
<th>Name</th>
<th>Description</th>
<th>Number of References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Search 1.1</td>
<td>Focused search on intervention (Co-enzyme Q-10), disease state, and human in on-line databases.</td>
<td>176</td>
</tr>
<tr>
<td>Search 1.2</td>
<td>Search on Cochrane databases for intervention (Co-enzyme Q-10).</td>
<td>111</td>
</tr>
<tr>
<td>Search 2.1</td>
<td>Focused search on intervention (Vitamin C), disease state, and human in on-line databases.</td>
<td>1987</td>
</tr>
<tr>
<td>Search 2.2</td>
<td>Search on Cochrane databases for intervention (Vitamin C) and disease state.</td>
<td>92</td>
</tr>
<tr>
<td>Search 3.1</td>
<td>Focused search on intervention (Vitamin E), disease state, type of therapy, and human in on-line databases.</td>
<td>1990</td>
</tr>
<tr>
<td>Search 3.2</td>
<td>Search on Cochrane databases for intervention (Vitamin E) and disease state.</td>
<td>112</td>
</tr>
<tr>
<td>Search 4.1</td>
<td>Search on synonyms for Co-enzyme Q-10 in on-line databases.</td>
<td>127</td>
</tr>
<tr>
<td>Total non-deduplicated references found:</td>
<td></td>
<td>4595</td>
</tr>
</tbody>
</table>
Figure 1. Literature Flow.

1337 Antioxidants articles requested

212 articles not found

432 Antioxidants for Cancer articles screened

Reasons for rejection:
Topic
Subject/Design
Population
Other reasons
Adverse events only

36 articles representing 38 studies on 23 unique trials

Death*  n = 21
Death rejected  n = 9
Polyps*  n = 8
Polyps rejected  n = 4
Tumors*  n = 16
Tumors rejected  n = 4

* Studies may be included in more than one analysis.
Chapter 3. Results

Description of the Evidence

We accepted from the screening process and submitted for further analysis 36 articles, which represented results from 38 studies on 23 unique trials. From the outcomes of the 38 studies, we found that 21 reported death as a primary outcome; 16 reported on new tumor development; eight focused on the development of colonic polyps; and seven reported on a variety of intermediate outcomes. An individual study may have contributed to more than one analysis, and seven studies reported only on intermediate, not primary, outcomes. Further, ten of these studies were from a large trial, Alpha-Tocopherol Beta Carotene Trial (ATBC), which evaluated the effects of antioxidant supplementation on Finnish, male, smokers. Seven were from 2 large multicenter intervention trials conducted in Linxian, China, focusing on the development of esophageal or gastric cancer in either a general population trial or a second trial in a high-risk population that already had dysplasia. All three large trials were primary prevention studies. All studies used interventions including vitamins C and E; no studies testing the use of coenzyme Q10 went on for further analysis based on study design (i.e. no controlled clinical trials).

The ATBC pilot trial scored five on the Jadad scale, but the intervention trial that followed scored three on the Jadad scale. (Please refer to the Methodology section for a description of the Jadad scale scoring system.) The Linxian Trials scored two for both the Dysplasia and for the General Population Trials. For the smaller trials reviewed, the frequency of Jadad scores was as follows: one trial scored zero; one trial scored one; five trials scored two; three trials scored three; seven trials scored four; and two had a score of five on the Jadad scale.14

Analysis of Studies Reporting on Death

Twenty-one studies corresponding to ten trials reported on the outcome of cancer-related death and were considered for a risk ratio analysis. These 21 studies were contained in 19 articles.11, 12, 23-38 Nine of these studies corresponding to seven articles were excluded for lack of sufficient information on outcome or insufficient statistics and thus were dropped from the analysis. For studies that only reported survival curves it was not possible to derive a risk ratio for death. From an article on a pilot study of the ATBC trial,23 we were unable to determine if the subjects of the pilot were included in the reports of the larger ATBC study. Thus, this study was not included in the analysis to avoid duplication of data and because, in addition, it had inadequate statistics for analysis. From the Linxian nutritional intervention trials, four studies reported in two articles11, 12 on either total death or total cancer death and did not separate the results by treatment arm. Three studies evaluated the effect of high-dose vitamin C on advanced cancer. Two of these27, 33 reported on survival times and did not provide sufficient detail on the number of deaths in each comparison group for our analysis; and the third study28 had insufficient statistics for analysis. The Moertel study33 also reported on death as well as survival time but reported on total death, not separated by treatment arm. A final study by Gogos et al,29 evaluating the effects of omega-3 fatty acids and vitamin E on survival of severely ill cancer patients, only reported on survival times. Therefore, due to inappropriate outcomes or
insufficient statistics, these studies were not included in this analysis. They will be discussed in more detail at the end of this section. In summary, six trials were included in the analysis.

**Studies Reporting on Death from the ATBC Trial**

The ATBC trial randomized 29,133 male smokers from Finland to receive one of four possible regimens: placebo, alpha-tocopherol alone (AT) (50 mg/day), beta-carotene (BC) alone (20 mg/day), or both vitamins. Patients were followed for a minimum of 5 years and a maximum of 8 years. Six studies from the ATBC trial reported on death due to a variety of different cancer types and reported sufficient data for analysis. Some, in addition, reported on all-cause mortality or all cancer mortality. Results from this analysis are included in Table 4. Please note that the results of the ATBC trial are reported in two different ways in Table 4.

Two studies looked at mortality from lung cancer but reported on this outcome in slightly different ways. Albanes et al\(^24\) reported on death from lung cancer in each of the four treatment arms. The risk ratio (RR) for AT only versus placebo was 0.93 (95% CI: 0.48, 2.47) and for AT combined with BC was 1.15 (95% CI: 0.91, 1.45). The second study\(^39\) combined arms so that results were reported as all arms using AT versus arms without AT. For all-cause mortality, the RR was 1.02 (95% CI: 0.96, 1.08) and for lung cancer death the RR was 1.02 (95% CI: 0.87, 1.2).

Three additional studies reported on death from a variety of other tumor types by individual treatment arms. Heinonen and colleagues\(^30\) reported on the mortality from prostate cancer. For AT versus placebo, the RR was 0.61 (95% CI: 0.29, 1.29), and for AT + BC versus placebo the RR was 0.67 (95% CI: 0.32, 1.38). In an article by Virtamo et al,\(^38\) deaths from urinary tract cancers were reported. For urothelial cell carcinoma, the RR of the AT versus placebo comparison was 1.20 (95% CI: 0.37, 3.93) and for AT + BC versus placebo comparison was 1.6 (95% CI: 0.52, 4.89). For renal cell carcinoma, the RR’s were 0.79 (95% CI: 0.36, 1.73) and 0.72 (95% CI: 0.32, 1.61), respectively. Albanes\(^25\) discussed deaths due to colorectal cancer. The RR for AT versus placebo was 1.09 (95% CI: 0.48, 2.47) and for AT + BC versus placebo was 1.18 (95% CI: 0.53, 2.64).

We calculated an RR for a combined death outcome, regardless of tumor type, for the four ATBC studies that reported their results for all four arms (this is not a meta-analysis because results are not pooled across trials).\(^24,25,30,38\) The RR for this combined outcome for AT versus placebo was 0.91 (95% CI: 0.74, 1.12) and for AT + BC versus placebo was 1.08 (95% CI: 0.89, 1.32).

Finally, a single additional study,\(^37\) which reported on mortality from pancreatic cancer, combined the treatment arms and reported all interventions with AT versus all interventions without AT. The RR for this comparison was 1.44 (95% CI: 0.93, 2.23).
Studies Reporting on Death from the Linxian Trials

The first Linxian Nutrition Intervention trial enrolled approximately 30,000 members of the general population of an area of central China that had a very high incidence of carcinoma of the esophagus and stomach. These patients (the General Population Group) were randomized to receive one of eight treatments. They were given either placebo, or formula A (retinol (5000 IU) and zinc oxide (22.5 mg)), or formula B (riboflavin (3.2 mg) and niacin (40 mg)), or formula C (ascorbic acid (120 mg) and molybdenum (30 µg)), or formula D (selenium (50 µg), and beta-carotene (15 mg), and alpha-tocopherol (30 mg)). These formulas were each given in combination with one of the other formulas and all four formulas were given together. No formula was given by itself alone. Interventions using formula C (containing vitamin C) in any combination and interventions using formula D (containing vitamin E) in any combination versus placebo are the comparisons of interest for this report. From the larger population, an additional population, already at higher risk of developing upper gastrointestinal tract cancers due to prior existence of dysplasia of the stomach and/or esophagus, was segregated for a separate trial. They were randomized to receive either a complex intervention—including beta-carotene (15 mg), vitamin A (10,000 IU), vitamin E (60 IU), vitamin C (180 mg), and multiple minerals daily—or placebo. This trial is referred to in the published literature as the Dysplasia Group. Patients were followed for 72 months in both the general study and the dysplasia study.

Two studies from the Linxian Trials had adequate statistics for further analysis. Blot et al report a RR for all-cause mortality in the general Linxian population for any group that took formula C (RR = 1.02 (95% CI: 0.93, 1.1)) and formula D (RR = 0.91 (95% CI: 0.84, 0.99)). Specifically for death due to cancer, the RR for formula C versus placebo was 1.06 (95% CI: 0.92, 1.21) and for formula D versus placebo was 0.87 (95% CI: 0.76, 1.00). This study also reported each of the combination arms individually. No comparison reported a statistically significant benefit. The lowest risk ratio reported for an individual arm was found in the Blot study in the A+D arm (cancer death RR = 0.75 (0.57, 1.00)).

Li and colleagues reported on the effect of the supplement intervention in the Dysplasia Group. The intervention was a combination of vitamins including both vitamins C and E. All-cause mortality had a RR of 0.94 (95% CI: 0.77, 1.16). All death due to all cancer had a RR of 0.98 (95% CI: 0.74, 1.31) and for death specifically due to esophageal cancer, the RR was 0.87 (95% CI: 0.56, 1.33).

Studies Reporting on Death from Trials Using Vitamin C as Treatment

Four studies, corresponding to four trials that tested the efficacy of vitamin C for treatment of patients with cancer, had sufficient statistics to proceed for further analysis. However, these trials were not pooled due to the heterogeneous nature of their populations and interventions.
Lamm et al\textsuperscript{21} evaluated the effect on patients with transitional cell carcinoma of the bladder of intravesicular and/or percutaneously administered bacillus Calmette-Guerin (BCG), a substance used to provoke an immune response, combined with either the recommended daily allowance (RDA) of a number of vitamins or a dose of the same supplements which exceeded the RDA (referred to by the authors as megadose). The daily RDA dosage included vitamin A (5,000 IU), vitamin C (60 mg), and vitamin E (30 IU), as well as other vitamins. The megadose intervention included an 800% increase in vitamin A (40,000 IU), and a 3,300% increase in vitamin C (2,000 mg), a 1,330% increase in vitamin E (400 IU) per day, as well as similar increases in other vitamins. The RR comparing the effect of RDA doses of vitamins to the megadoses of vitamins for all-cause death was 0.86 (95% CI: 0.37, 2.01). Two studies examined the effect of vitamin C alone on cancer. Investigators attempted to replicated results reported by Linus Pauling\textsuperscript{41} for the efficacy of high-dose vitamin C to prolong survival in cancer patients.\textsuperscript{35} They randomized patients with advanced carcinoma of the rectum and colon to receive either placebo or ten grams per day of vitamin C by mouth. The RR for all-cause mortality in this trial (vitamin C versus placebo) was 1.04 (95% CI: 0.69, 1.57). Another trial\textsuperscript{36} tested the effects of three grams per day of vitamin C or placebo in a group of 27 breast cancer patients who had already received conventional therapy. The risk ratio for all-cause mortality comparing vitamin C versus placebo is 1.52 (95% CI: 0.72, 3.23). A final trial, the Heart Protection Study Collaboration Group,\textsuperscript{34} randomly assigned 20, 536 adults (ages 40-80) to receive either antioxidant vitamin supplements (600 mg synthetic vitamin E, 250 mg vitamin C, and 20 mg beta-carotene daily) or a placebo. The study was primarily designed to assess cardiovascular endpoints in a high-risk population, however, all cause mortality was reported as well. The RR reported for this study was 1.04 (95% CI: 0.97, 1.11).

**Summary of Results from the Analysis of Death**

The results of all of the studies included in this analysis are summarized in Table 5. For the interventions tested, in the populations described, there is no evidence for a benefit for survival.

**Trials Not Included in the Death Analysis**

Nine studies were considered for the preceding analysis because they appeared to report on death, but they then were excluded due to insufficient statistics or other reasons. These studies will be briefly discussed here.

Albanes et al\textsuperscript{23} reported on a pilot of the ATBC trial. Although the main focus of the pilot study was to assess enrollment and compliance issues, dropouts due to death or cancer were mentioned. These results were not separated either by outcome or intervention and thus were not amenable to analysis. In addition, it is not clear if these subjects were then included in the main study and had results reported again. This pilot study had a Jadad score of 5.

Two articles, corresponding to four studies from the Linxian General Population and Dysplasia Trials, were excluded. The first\textsuperscript{11} represented two studies because it presented the methodology for the General Population Trial as well as the Dysplasia Trial that is described earlier in this section. The results of these pilot studies demonstrated that it was feasible to conduct these trials.
The third and fourth studies reported in the article from the Linxian Trial\textsuperscript{2} reported that the total number of deaths for the general and intervention trials combined was 2,100; of those, 37\% of the total deaths were due to cancer. In addition, the authors reported that none of the four combination supplements in the General Population Trial produced a significant reduction in the prevalence of death from esophageal, gastric, or other cancer.

Three studies corresponding to three unique trials involving the use of vitamin C from the same research group\textsuperscript{27, 28, 33} and one additional study of the efficacy of vitamin E to treat advanced stage cancer\textsuperscript{29} were not included in the analysis. These results are described briefly here.

Creagan, Moertel, O’Fallon, and colleagues\textsuperscript{27} reported on a randomized, double-blinded trial of 150 patients with proven terminal cancer of a variety of types, all of whom had previously received conventional care, including cytotoxic drugs. The intervention group received high-dose vitamin C (10 g daily), whereas the control group received a placebo. The two groups did not differ significantly in survival (mean survival for both groups was approximately 7 weeks). Because only survival-curve data were provided, it was not possible to include these results in the death risk ratio analysis.

This same research team published an abstract of what appears to be a subset of the previous trial.\textsuperscript{42} They had enrolled the first 128 of the expected 160 patients.

Finally, Moertel, Fleming, Creagan, and colleagues\textsuperscript{33} conducted a second prospective, randomized, double-blind, controlled trial on the effect of high-dose vitamin C (2500 mg daily) in 100 patients with advanced colorectal cancer. In contrast to the previous study by this group, none of the patients in this trial had received prior treatment with cytotoxic drugs. The patients were followed as long as they could take the oral medications or until there was evidence of marked progression of the malignant disease. They were assessed at 4 weeks and every 8 weeks thereafter. Because only total deaths were reported, the results of the study could not be included in the pooled analysis. The vitamin C therapy showed no advantage over the placebo for either tumor progression or survival, and no patient with measurable disease had objective improvement.

The final treatment trial not included in the analysis was by Gogos et al\textsuperscript{29} and focused on the effect of supplementation with omega-3 polyunsaturated fatty acids plus vitamin E on immune parameters in severely ill cancer patients. In a prospective, randomized, controlled study, 60 patients with generalized solid tumors were given either 200 mg of vitamin E daily plus 18 grams of fish oil daily or placebo until their deaths. None of the patients had received chemotherapeutic or immunomodulating agents during the 4 months prior to the study, and none were being treated for their tumors at the time of the study. Because only the survival curve was reported and showed the results could not be pooled in the death analysis.
Analysis of Studies Reporting on New Tumor Development

Sixteen studies, corresponding to 14 articles and four unique trials, were considered for further analysis of the development of new tumors or recurrence of tumors. Four studies from the Linxian Trials were excluded for inadequate statistics. The RRs were reported as adjusted risk ratios and insufficient data were given to be able to convert them to unadjusted risk ratios and make the results comparable to those reported for other trials. This study will be discussed briefly at the end of this section.

Studies Reporting on New Tumor Development from the ATBC Trial

Seven studies of the ATBC trial reported on the development of a variety of new tumors. Results of this analysis are summarized in Table 6. Details of the design of the ATBC trial are discussed earlier in the section entitled Studies Reporting on Death from the ATBC trial.

An article by Varis et al reported on the risk of developing carcinoma (all cell types). They analyzed their data separately for each of the four interventions. For developing a new carcinoma, they reported a RR of 1.04 (95% CI: 0.15, 7.32) for the AT versus placebo comparison and 1.84 (95% CI: 0.34, 10.01) for the AT + BC comparison.

Two studies reported on development of new lung carcinomas in the ATBC trial but in slightly different ways. The ATBC study analyzed the results of the ATBC trial by combining all arms that had a particular intervention. Thus, their analysis reported on the relative risk of developing a new lung cancer in groups that did or did not take alpha-tocopherol without separating the AT-only group from the AT + BC group. Additionally, in the BC versus no BC comparison, the BC + AT group and the BC groups are combined. The RR for this study was 0.98 (95% CI: 0.86, 1.11). The second study to look at the development of new lung tumors, reported on in Albanes et al., analyzed each of the four arms separately. They reported a RR for the development of new lung cancers for the AT versus placebo comparison of 0.98 (95% CI: 0.81, 1.19) and for AT + BC of 1.16 (95% CI: 0.96, 1.39).

All of the remainder of the ATBC studies analyzed each of the four intervention arms separately and focused on the development of a variety of different tumor types. Heinonen and colleagues reported on the development of new prostate cancers. For the AT versus placebo comparison, the RR was 0.64 (95% CI: 0.44, 0.94), and for the AT + BC versus placebo comparison, the RR was 0.84 (95% CI: 0.59, 1.19). Virtamo et al assessed the effects of AT and BC on development of urinary tract cancers. For development of urothelial cancers, the AT versus placebo comparison had a RR of 1.27 (95% CI: 0.83, 1.95), and for AT + BC the RR was 1.14 (95% CI: 0.73, 1.77). For development of renal cell cancer, the AT versus placebo comparison had a RR of 1.00 (95% CI: 0.59, 1.70), and for AT + BC, the RR was also 1.00 (95% CI: 0.59, 1.71).
For development of new pancreatic carcinomas, Rautalahti and colleagues\textsuperscript{37} analyzed data from each of four arms separately as well as by combining all AT arms together. The RR for the AT versus placebo comparison was 0.96 (95% CI: 0.56, 1.66); for AT + BC versus placebo was 1.00 (95% CI: 0.58,1.72); and for AT versus no AT was 1.34 (95% CI: 0.88, 2.04). Albanes et al\textsuperscript{25} reported on the development of new colorectal cancers. The RR for AT versus placebo was 0.78 (95% CI: 0.48, 1.27) and for AT + BC versus placebo was 0.81 (95% CI: 0.50, 1.31).

We combined the tumor outcomes of the five studies that reported on results by separate arms\textsuperscript{24, 25, 30, 37, 38} regardless of tumor type (this is not a meta-analysis because results are not pooled across trials). The resulting RR for the AT versus placebo comparison was 0.93 (95% CI: 0.81, 1.07); and for the AT + BC versus placebo, the RR was 1.05 (95% CI: 0.92, 1.20).

**Studies Reporting on New Tumor Development from the Linxian Trials**

Four studies from the Linxian Trials reported on the outcome of new tumor development. One study\textsuperscript{12} reported on the development of new gastric and esophageal cancers in the General Population Trial. Three of these studies\textsuperscript{12, 32, 43} reported on similar outcomes from the Dysplasia portion of the Linxian Trial. One of these studies\textsuperscript{12} could not be included in the analysis due to insufficient statistics. The details of this analysis are summarized in Table 7. Details of the designs of the Linxian General Population and Dysplasia Group Trials are included in the earlier section entitled Studies Reporting on Death from the Linxian Trials.

Taylor and colleagues\textsuperscript{12} did not report directly on new tumors in the entire General Population Trial sample, although they noted that a total of 1,298 incident cancers were identified in this group. Instead, they reported on new tumor development in a subset of the entire General Population Trial sample who received an endoscopy with gastric and esophageal biopsies at the completion of the 5.25-year trial. This intervention was designed to find cancers that had not been identified by usual means during the course of the trial. The RR for presence of an additional new carcinoma on esophageal biopsy for the C versus no C comparison was 1.18 (95% CI: 0.27, 5.20) and for the D versus no D comparison was 0.71 (95% CI: 0.17, 2.95). The RR for the presence of a new tumor on gastric biopsy was 2.71 (95% CI: 0.55, 13.25) for the C versus no C comparison and was 1.22 (95% CI: 0.31, 4.79) for the D versus no D comparison.

Three studies also reported data on new tumor development in the Dysplasia Trial. Taylor and colleagues\textsuperscript{12} noted that a total of 448 incident cancers were found in the Dysplasia Trial but did not separate the results by intervention. No additional analysis was performed on this group and the results were not reported in sufficient detail to permit further analysis. Li and colleagues\textsuperscript{32} reported risk ratios for the development of either esophageal or gastric cancer after 72 months of treatment. For esophageal cancer the RR was 0.96 (95% CI: 0.76, 1.22); for gastric cancer the RR was 1.19 (95% CI: 0.89, 1.58); and for all cancers combined the RR was 1.03 (95% CI: 0.87, 1.22).

Dawsey and colleagues\textsuperscript{43} reported on the results of biopsies done of the gastric and esophageal areas during the Linxian Dysplasia Trial (30 months) and at the end of the trial (6 years). The number of cancers reported is smaller than in the Li\textsuperscript{32} study, because this study does not report on all incident cancers identified during the trial, just the cases identified by biopsy.
The RR for the presence of new esophageal tumors during the midpoint of the trial was overall 0.99 (95% CI: 0.60, 1.64); for the esophagus only it was 0.78 (95% CI: 0.41, 1.49); and for the stomach only it was 1.63 (95% CI: 0.75, 3.52). At the completion of the trial, the RR for the overall rate of the presence of a new tumor was 0.92 (95% CI: 0.54, 1.57); for the esophagus alone it was 1.53 (95% CI: 0.51, 4.58); and for the stomach only it was 0.91 (95% CI: 0.49, 1.68).

Studies Reporting on New Tumor Development from Other Trials

Two trials besides the ATBC and Linxian Trials reported on the outcome of new tumor development. Lamm et al\textsuperscript{31} was a treatment secondary prevention trial as opposed to a primary prevention trial. It tested the effect of vitamin supplementation on the development of new bladder tumors in patients previously treated for transitional cell carcinoma of the bladder. (The details of this study design are discussed earlier in the section entitled Studies Reporting on Death from Trials Using Vitamin C as Treatment.) Compared to RDA doses of vitamins, megadoses of vitamins were associated with a reduced RR of 0.50 for new bladder tumors (95% CI: 0.32, 0.78). The Heart Protection Study Collaboration Group,\textsuperscript{34} randomly assigned 20,536 adults (ages 40-80) to receive either antioxidant vitamin supplements (600 mg synthetic vitamin E, 250 mg vitamin C, and 20 mg beta-carotene daily) or a placebo. The study was primarily designed to assess cardiovascular endpoints in a high-risk population, however, new tumor development was reported as well. The RR reported for this study was 0.98 (95% CI: 0.89, 1.08).

Summary of Results from the Analysis of New Tumor Development Outcome

The results of all of the studies included in this analysis are summarized in Table 7. For the interventions tested, in the populations described, there is no evidence for a benefit for primary prevention of new tumors except for a single arm of the ATBC trial, AT versus placebo for the development of new prostate cancers. The single treatment/secondary prevention trial discussed did report that the addition of megadose vitamins conferred a benefit. However, the ability to generalize from this finding is limited because the intervention was multicomponent, preventing attribution of efficacy to any particular component. Additionally, all groups also received BCG, a major confounder.

Studies Not Included in the New Tumor Development Analysis

Four studies from the Linxian Trial were not included in the new tumor analysis.\textsuperscript{11} (Studies A&B), \textsuperscript{12} (Study A), \textsuperscript{40, 46} Blot’s study reported adjusted risk ratios for the development of gastric or esophageal cancer. Insufficient information was given to calculate unadjusted risk ratios; therefore, these data were not included in the previous analysis. However, the adjusted risk ratios for this trial (adjusted for age and sex), reported by individual arm, were for all cancer (C versus no C) 1.06 (95% CI: 0.95, 1.18), and for D versus no D 0.93 (95% CI: 0.83, 1.03). For esophageal cancer (C versus no C), the adjusted RR was 1.06 (95% CI: 0.91, 1.24) and for D versus no D was 1.02 (95% CI: 0.87, 1.19). For gastric cancer, (C versus no C) the adjusted RR was 1.10 (95% CI: 0.92, 1.30) and for D versus no D was 0.84 (95% CI: 0.71, 1.00).
Li and colleagues’ article\textsuperscript{11} presents the methodology for the Linxian General Population and Dysplasia Trials. These studies and their new tumor results are described in the death analysis. As noted earlier, the study by Taylor\textsuperscript{12} on the Linxian Dysplasia Trial could also not be included due to insufficient statistics.

**Analysis of Trials Reporting on Development of Colonic Polyps**

The presence of adenomatous polyps of the colon is considered a significant risk factor for the development of colon cancer. Thus, interventions that would decrease the rate of polyp formation would be of interest in decreasing the risk of colon cancer. Eight studies corresponding to 8 articles and 7 unique trials reported on the development of adenomatous polyps of the colon and were considered for pooled analysis.\textsuperscript{47-54} Two studies by Roncucci\textsuperscript{50, 51} corresponded to the same trials and presented duplicate data; therefore, only the first study was included in the analysis. The remaining six studies corresponded to six unique trials.

One trial focused on the primary prevention of new colonic polyps in a general population\textsuperscript{52} while two trials\textsuperscript{53, 54} considered the effects of an antioxidant intervention on polyp recurrence in patients with familial polyposis, a condition characterized by extensive polyps in the colon and a greatly increased risk of developing colon cancer. Finally, four trials\textsuperscript{47-50} evaluated the ability of antioxidants to decrease the recurrence of colonic polyps in nonfamilial polyposis patients with preexisting adenomatous colonic polyps. The four trials that focused on the secondary prevention of recurrent colonic polyps in patients with previous colonic polyps were judged sufficiently homogeneous to attempt a pooled analysis. The results of trials not included in this analysis will be discussed following the next section.

**Meta-Analysis for Secondary Prevention of Polyp Formation**

Interventions in these four trials varied. There were no trials that used either vitamins C or E as single interventions. All treatment arms were not pooled because it was felt that vitamins C and E, with and without beta-carotene or vitamin A, were not equivalent interventions. Within the groupings of vitamins C and E with and without beta-carotene or vitamin A, there were insufficient studies to perform an analysis stratified based on dosage.

Specifically, the interventions and doses for these trials are herein discussed. Greenberg and his colleagues\textsuperscript{67} gave 864 patients either placebo or beta-carotene (25 mg daily) or vitamin C (1 gm daily) and vitamin E (400 mg daily) or all three vitamins in a two-by-two factorial design for 4 years. McKeown-Eyssen et al\textsuperscript{49} randomly assigned 200 patients to receive either placebo or vitamin C (400 mg daily) and alpha-tocopherol (400 mg daily) for 2 years. Hofstad and colleagues\textsuperscript{48} gave 116 patients either placebo or a mixture of beta-carotene (15 mg), vitamin C (150 mg), vitamin E (75 mg), selenium 101 µg, and calcium (1.6 gm) daily for 3 years. For the trial performed by Roncucci and his colleagues,\textsuperscript{50} 225 individuals were given either no treatment or lactulose (20 gm/day) or a combination of vitamin A (30,000 IU), vitamin C (1 gm), and vitamin E (70 mg) per day for an average of 18 months.
Trials Featuring Combinations of Vitamins C and E Only for Secondary Prevention of Polyp Formation

Two trials\(^47\) of the four considered for pooled analysis had treatment arms that involved the combination of vitamins C and E without beta-carotene or vitamin A. Details of these trials are summarized in the Evidence Table. Because there were only two trials, a pooled analysis was not performed. The estimated risk ratios for these two trials, along with their 95% confidence intervals, are summarized in Table 8. A lower RR in this analysis favors treatment because it represents a lower likelihood of forming new colonic polyps as compared to placebo.

The RRs for the Greenberg and the McKeown-Eyssen trials are not significantly different from 1; therefore there is no evidence that the combinations of vitamins C and E tested are more effective than placebo in the secondary prevention of recurrent adenomatous polyps of the colon.

Trials Featuring Combinations of Vitamins C and E with Beta-Carotene or Vitamin A for Secondary Prevention of Polyp Formation

Three trials of the four considered for pooled analysis used combinations of vitamins C and E with carotenoids compared with a placebo. Two trials were placebo-controlled. Details of these trials are summarized in the Evidence Table. The three interventions were considered sufficiently equivalent to allow pooling—even though calcium, which was included in the intervention used in the Hofstad trial,\(^48\) has activity of its own in prevention of polyp formation, and vitamin A (not beta-carotene) was used in the Roncucci trial. The estimated RRs for these three studies, along with their 95% confidence intervals and the pooled estimate, are summarized in Table 9 and in Figure 2.

The pooled estimate yields a RR of 0.6, which is clinically important but not statistically significant (p = 0.13). In addition, the chi-squared test of heterogeneity is significant (p = 0.001), indicating a high degree of heterogeneity among these trials. Sensitivity analyses to account for heterogeneity could not be performed due to the small number of trials, but a visual inspection of Figure 2 suggests that heterogeneity may be due to the differences in population size and numbers of outcomes observed between Roncucci\(^50\) versus Greenberg\(^47\) and Hofstad.\(^48\) For example, Hofstad has the smallest total sample size (n = 93) but has a number of outcomes that are proportionally greater than either of the other two trials. Conversely, for a relatively large total number of patients (n = 209), Roncucci develops many fewer new colonic polyps. It is likely, therefore, that a significant amount of this heterogeneity is due to patient population selection.

Assessing publication bias with so few trials is difficult at best. The funnel plot represented in Figure 3, although limited, shows no obvious bias. In addition, formal statistical tests revealed no statistically significant bias.
Trials Reporting on Polyp Formation Not Included in the Above Analysis

Three trials were not included in the prior analysis.\textsuperscript{52-54} The details of these trials are included in the Evidence Table, and their salient features will be briefly discussed here.

The primary prevention trial reported by Malila and colleagues,\textsuperscript{52} as part of the ATBC Trial, was not appropriate for pooling with other secondary prevention trials on the grounds of clinical issues and study design. The other 2 trials\textsuperscript{53-54} study populations at extraordinarily high risk of developing polyps. They were felt to be clinically dissimilar enough to preclude pooling of their data with populations with average risk. Malila and colleagues evaluated a subgroup (15,538) of the 29,133 male Finnish smokers enrolled in the trial. Subjects who were not known to have colonic polyps at the start of the trial were randomly assigned to one of four groups: vitamin E (50 mg/day, n = 3,890); beta-carotene (20 mg/day, n = 3,883); both supplements (n = 3,878); placebo (n = 3,887). Patients were followed for an average of 6.2 years. Whereas vitamin E supplementation resulted in a statistically significant increase in the risk for development of new adenomas (RR 1.66; 95% CI: 1.19, -2.32), it did not increase the risk for developing colorectal cancer. Beta-carotene had no effect on the risk of developing adenomas (RR 0.97; 95% CI: 0.69, -1.38) or cancer.

Bussey, DeCosse, Deschner, and colleagues\textsuperscript{54} reported on a randomized, double-blind trial of 47 patients with polyposis coli, a familial condition that causes extensive polyp formation in the colon and leads to a high risk of cancer formation, who received either vitamin C (3 gm daily) or a placebo. At 21 months, rectal mucosal biopsies were taken from 31 subjects. The results showed a reduction in the polyp area for the vitamin C arm at the 9-month follow-up (p < 0.03) and trends toward a reduction in both the number and area of rectal polyps during the middle of the trial.

DeCosse, Miller, and Lesser\textsuperscript{53} reported on a randomized, double-blind trial in 58 patients with familial adenomatous polyposis (polyposis coli) who had undergone a total colectomy with ileorectal anastomosis at least 1 year prior to the commencement of the trial and had a residual section of rectum and sigmoid colon (of on average 15 cm) that would be susceptible to new tumor formation. Patients were given either vitamin C (4 gm/day) and vitamin E (400 IU/day) or high-dose fiber (22.5 gm/day), or assigned to a control group that had only low-dose fiber (2.2g/day) plus placebo. The trial lasted 4 years, during which patients received serial proctosigmoidoscopies (total of 18). All new colonic polyps (recurrence) and growth in preexisting colonic polyps (progression) were recorded. The results suggested a limited effect of the supplements on rectal polyp recurrence and progression.

Trials Reporting on Intermediate Outcomes

Seven studies corresponding to seven trials (one of these studies reports on the ATBC trial) reported on a variety of intermediate outcomes relevant to the development of cancer or improvements in the risk factors for development of a particular type of cancer.\textsuperscript{55-61}
Two trials evaluated the effects of antioxidants on the development or progression of risk factors for gastric cancer.\textsuperscript{56, 62} One of the widely recognized precursors to intestinal gastric carcinoma is chronic atrophic gastritis with intestinal metaplasia. Zullo, Rinaldi, Hassan, and colleagues\textsuperscript{56} conducted a randomized, controlled trial using vitamin C in patients with chronic atrophic gastritis. Following eradication of \textit{Helicobacter pylori}, 66 patients with documented metaplasia received either vitamin C (500 mg/day) or no treatment (the method of randomization was not described) for 6 months. At the end of the trial, endoscopic examination demonstrated a significant decrease in the appearance of intestinal metaplasia in the vitamin C group compared with the control group. In addition, among those who presented with chronic inactive pangastritis with widespread metaplasia at entry, less extensive antritis with intestinal metaplasia was seen in the intervention group. The researchers concluded that vitamin C helps resolve intestinal metaplasia and may, by implication, be effective for primary prevention of gastric carcinoma in this high-risk group.

In a trial of patients with two precancerous, multifocal atrophic gastritis and dysplasia,\textsuperscript{62} subjects (n = 631 who completed at 72 months) were randomly assigned to one of 8 arms of the study: placebo; anti-\textit{Helicobacter pylori} triple therapy; beta-carotene; vitamin C; anti-\textit{Helicobacter pylori} plus beta-carotene; anti-\textit{Helicobacter pylori} plus vitamin C; beta-carotene plus vitamin C; anti-\textit{Helicobacter pylori}, plus beta-carotene plus vitamin C. The dosage was 30 mg per day for beta-carotene and 1 g twice a day for vitamin C. The anti-\textit{Helicobacter pylori} therapy consisted of amoxicillin (500 mg 3 times daily), metronidazole (375 mg 3 times daily), and bismuth subsalicylate (262 mg 3 times per day). Patients were evaluated at 36 and 72 months. All three basic interventions (\textit{H. pylori} treatment, beta-carotene, and vitamin C) in this high-risk population resulted in significant increases in the rates of regression. (RRs were 4.8; 5.1, and 5.0, respectively). The authors concluded that all three treatments might interfere with a precancerous process and provide benefit in a high-risk population.

Two trials evaluated the effects of an antioxidant intervention on the development of oral leukoplakia, which is considered to be a risk factor for the development of oral cancer.\textsuperscript{55, 63} Smoking increases the occurrence of oral leukoplakia and increases the number of keratinized cells in the epithelium of the tongue and palate, even when the mucosa in these areas is clinically normal. However, the link between these intermediate outcomes and cancer is not as clearly established as the link with other intermediate outcomes such as the presence of adenomatous polyps with adenocarcinoma of the colon. Nevertheless, the ATBC trial by Liede, Hietanen, Saxen, and colleagues\textsuperscript{63} studied the impact of vitamin E and beta-carotene on the prevalence of oral mucosal lesions in smokers in a randomized, double-blind study. A random sample of 409 participants in a cancer prevention study (the ATBC study) was chosen to receive supplementation with either vitamin E (50 mg/day), beta-carotene (20 mg/day), or a placebo for 6 years. An oral examination was performed at the end of the trial. No statistically significant differences were found among any of the groups in the prevalence of oral mucosal lesions. In fact, only 24 patients in total had leukoplakia (5.9% of the total population) and only 7 of those 24 lesions were dysplastic.
In a randomized, controlled, double-blind fashion, 532 men between 50 to 69 years of age with oral leukoplakia and/or chronic esophagitis were given either riboflavin, or retinol with beta-carotene and vitamin E, both, or a placebo. A significant reduction in oral leukoplakia was noted after 6 months for those receiving retinol, beta-carotene and vitamin E. After 20 months, no effect was seen in chronic esophagitis—although the risk for progression was lower in the retinol, beta-carotene and vitamin E group. Doses of 100,000 IU of retinol, 80 mg vitamin E, and 80 mg of riboflavin were administered weekly. The complexity of the intervention and difference in response between groups make interpretation of the efficacy of any single item difficult.

A single trial evaluated the effect of an intervention vitamin C with and without beta-carotene, and all groups were compared to placebo in women with cervical abnormalities that, if untreated, may progress to cervical carcinoma. Mackerras et al conducted a randomized double-blind study with a placebo in 141 women with confirmed minor squamous atypia or cervical epithelial neoplasia (CIN) stage I. The subjects were assigned randomly to an oral daily dose of 30 mg beta-carotene or 500 mg vitamin C, both, or neither. Over 2 years of follow-up, there was no statistically significant difference in the regression of the lesions. Therefore, the researchers concluded that high doses of either compound increases the rate of regression or decreases the progression of minor atypia or CIN I. Again, because the outcome measured is not fully developed cancer per se, it was not included in the pooled analysis.

A different intermediate end point was used in the trial by Cahill, O’Sullivan, Mathias, and colleagues. Colonic crypt cell proliferation and a shift in the proliferative zone in the crypt are precursors to colon carcinoma. Following colonoscopy and colon biopsy, ten patients were randomly assigned to each of four intervention arms: arm 1 of the trial received no supplementation, arm 2 received vitamin E (160 mg/day), arm 3 received vitamin C (750 mg/day), and arm 4 received beta-carotene (9 mg/day). Twenty subjects with a normal colonoscopy and normal colonic mucosa were included as a control group. After 1 month, colonic biopsies were repeated. Both vitamin C and beta-carotene significantly reduced the total proliferation, but vitamin E had no effect. Beta-carotene reduced the colonic cell proliferation only at the base of the crypts, whereas vitamin C reduced proliferation in all crypt compartments from the apex to the base, when compared to age- and gender-matched controls.

A rising prostate specific antigen (PSA) level is a widely used diagnostic method for identifying possible presence of early prostate cancer. This is not an intermediate outcome or a risk factor for a particular cancer per se, but it does have interest as a possible way to detect early tumors. The reliability and utility of PSA to screen for prostate cancer is controversial however it is used as a tumor marker in patients who have undergone prostatectomy. In a randomized, double-blinded, crossover, prevention trial, Schroder, Kranse, Dijik, and colleagues examined the impact of a dietary intervention on prostate cancer in a sample of 37 men with rising PSA levels after undergoing radical prostatectomy, radiotherapy, and pelvic node dissection, but no endocrine treatment. The dietary intervention included soy extract, tea extract, carotenoids, phytosterols, selenium, and vitamin E (doses not given) in addition to a regular diet. The effect of the diet on PSA levels was assessed relative to that of a placebo during a two-week run-in period followed by two 6-week crossover periods that alternated with two washout periods. The results showed that during the supplement treatment periods, the slope of the normal rise in PSA
was decreased, which translated into an 8-week delay in the rise of the PSA with a 6-week course of supplements. The effect of such a delay on prostate cancer mortality on other clinical outcomes is not known.
Table 4. Risk Ratios for Death Outcome for ATBC Trial.

<table>
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<tr>
<th>Study Author, Year</th>
<th>Type of death</th>
<th>Intervention</th>
<th>Sample Size</th>
<th>FU Time</th>
<th># of deaths</th>
<th>RR (95% CI)</th>
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<tr>
<td>ATBC Albanes, 1996\textsuperscript{24}</td>
<td>Lung cancer</td>
<td>AT</td>
<td>7286</td>
<td>6.1 yrs</td>
<td>125</td>
<td>0.93 (0.73, 1.19)</td>
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<td>154</td>
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<td>Prostate cancer</td>
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<td>Albanes, 2000\textsuperscript{25}</td>
<td>Colorectal cancer</td>
<td>AT</td>
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<td>6.1 yrs</td>
<td>12</td>
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<td>Virtamo, 2000\textsuperscript{38}</td>
<td>Urothelial cancer</td>
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<td>Combined cancer (lung, colorectal, urothelial, and renal cell)</td>
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<td>0.91 (0.74, 1.12)</td>
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<td>All cause</td>
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<td>1798</td>
<td>1.02 (0.96, 1.08)</td>
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<td>6.1 yrs</td>
<td>285</td>
<td>1.02 (0.87, 1.20)</td>
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<td>Pancreas cancer</td>
<td>AT</td>
<td>14564</td>
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<td>49</td>
<td>1.44 (0.93, 2.23)</td>
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<td>14569</td>
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</table>

Additional studies for which risk ratios could not be calculated are discussed in the text and displayed in the Evidence Table.

*AT: alpha-tocopherol; BC: beta-carotene; CI: confidence interval; RR: risk ratio*
Table 5. Risk Ratios for Death Outcome for Linxian and Other Trials.

<table>
<thead>
<tr>
<th>Study</th>
<th>Author, Year</th>
<th>Type of death</th>
<th>Intervention</th>
<th>Sample Size</th>
<th>FU Time</th>
<th># of deaths</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linxian</td>
<td>Li, 199332</td>
<td>All cause</td>
<td>Supplement</td>
<td>1657</td>
<td>6 yrs</td>
<td>157</td>
<td>0.94 (0.77, 1.16)</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>Placebo</td>
<td>1661</td>
<td></td>
<td>167</td>
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</tr>
<tr>
<td>Dysplasia</td>
<td>Li, 199332</td>
<td>Cancer</td>
<td>Supplement</td>
<td>1657</td>
<td>8 yrs</td>
<td>87</td>
<td>0.98 (0.74, 1.31)</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>Placebo</td>
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<td>Li, 199332</td>
<td>Esophageal</td>
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<td>38</td>
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<td></td>
<td>Placebo</td>
<td>1661</td>
<td></td>
<td>44</td>
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</tr>
<tr>
<td>Linxian</td>
<td>Blot, 199340</td>
<td>All cause</td>
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<td>3701</td>
<td>5.25 yrs</td>
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<td>B+D</td>
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<td>C+D</td>
<td>3705</td>
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<td>249</td>
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<td>A+B+C+D</td>
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<td></td>
<td></td>
<td></td>
<td>C</td>
<td>14802</td>
<td></td>
<td>1069</td>
<td>1.01 (0.93, 1.10)</td>
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<td>D</td>
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<td>103</td>
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<td>Megadose</td>
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<td>0.86 (0.37, 2.01)</td>
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<td>Vitamins</td>
<td>10269</td>
<td>5 yrs</td>
<td>1446</td>
<td>1.04 (0.97, 1.11)</td>
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<tr>
<td>Nutr Rev, 19853</td>
<td>All cause</td>
<td>C</td>
<td>25</td>
<td>1 yr</td>
<td>51</td>
<td>1.04 (0.69, 1.57)</td>
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<td>Poultier, 19846</td>
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<td>5 yrs</td>
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<td>Control</td>
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</table>

Additional studies for which risk ratios could not be calculated are discussed in the text and displayed in the Evidence Table.

A: retinol plus zinc; B: riboflavin plus niacin; C: vitamin C (ascorbic acid) plus molybdenum; CI: confidence interval; D: beta-carotene plus vitamin E and selenium; RR: risk ratio
Table 6. Risk Ratios for New Tumors for ATBC Trial.

<table>
<thead>
<tr>
<th>Study</th>
<th>Lead Author, Yr</th>
<th>Type of Tumor</th>
<th>Intervention</th>
<th>Sample size</th>
<th>FU time</th>
<th># of patients with new tumor</th>
<th>RR (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>ATBC</td>
<td>Albanes, 1996²⁴</td>
<td>Lung cancer</td>
<td>AT</td>
<td>7286</td>
<td>6.1 yrs</td>
<td>204</td>
<td>0.98 (0.81, 1.19)</td>
</tr>
<tr>
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<td></td>
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<td>AT+BC</td>
<td>7278</td>
<td></td>
<td>240</td>
<td>1.16 (0.96, 1.39)</td>
</tr>
<tr>
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<td>Placebo</td>
<td>7287</td>
<td></td>
<td>208</td>
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</tr>
<tr>
<td></td>
<td>Albanes, 2000²⁵</td>
<td>Colorectal cancer</td>
<td>AT</td>
<td>7286</td>
<td>6.1 yrs</td>
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<td>0.78 (0.48, 1.27)</td>
</tr>
<tr>
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<td></td>
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<td>AT+BC</td>
<td>7278</td>
<td></td>
<td>30</td>
<td>0.81 (0.50, 1.31)</td>
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<td></td>
<td>Placebo</td>
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<td></td>
<td>37</td>
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<td></td>
<td>Heinonen, 1998³⁰</td>
<td>Prostate cancer</td>
<td>AT</td>
<td>7286</td>
<td>6.1 yrs</td>
<td>43</td>
<td>0.64 (0.44, 0.94)</td>
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<td>56</td>
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</tr>
<tr>
<td></td>
<td>Rautalahti, 1999³⁷</td>
<td>Pancreas cancer</td>
<td>AT</td>
<td>7286</td>
<td>6.1 yrs</td>
<td>25</td>
<td>0.96 (0.56, 1.66)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AT+BC</td>
<td>7278</td>
<td></td>
<td>26</td>
<td>1.00 (0.58, 1.72)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>7287</td>
<td></td>
<td>26</td>
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</tr>
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<td></td>
<td></td>
<td>AT</td>
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<td></td>
<td>51</td>
<td>1.34 (0.88, 2.04)</td>
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<td>14569</td>
<td></td>
<td>38</td>
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<tr>
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<td>Virtamo, 2000³⁸</td>
<td>Urothelial cancer</td>
<td>AT</td>
<td>7286</td>
<td>6.1 yrs</td>
<td>47</td>
<td>1.27 (0.83, 1.95)</td>
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<td>7278</td>
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<td>42</td>
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<td>Placebo</td>
<td>7287</td>
<td></td>
<td>37</td>
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</tr>
<tr>
<td></td>
<td>Virtamo, 2000³⁸</td>
<td>Renal cell cancer</td>
<td>AT</td>
<td>7286</td>
<td>6.1 yrs</td>
<td>27</td>
<td>1.00 (0.59, 1.70)</td>
</tr>
<tr>
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<td>AT+BC</td>
<td>7278</td>
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<td></td>
<td>Placebo</td>
<td>7287</td>
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<td>Albanes 1996²⁴ and 2000²⁵, Heinonen, 1998³⁰, Rautalahti, 1999³⁷, Virtamo, 2000³⁸</td>
<td>Combined types of tumor: (lung, colorectal, prostate, pancreas, urothelial and renal cell)</td>
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<td>433</td>
<td>0.98 (0.86, 1.11)</td>
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</table>

Additional studies for which risk ratios could not be calculated are discussed in the text and displayed in the evidence table.

AT: alpha-tocopherol; BC: beta-carotene; CI: confidence interval; FU: follow-up; RR: risk ratio
Table 7. Risk Ratios for New Tumor Outcome for Linxian and Other Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Lead Author, Year</th>
<th>Type of Tumor</th>
<th>Intervention</th>
<th>Sample size</th>
<th>FU time</th>
<th># of patients with new tumor</th>
<th>RR (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Linxian</td>
<td>Dawsey, Esophageal cancer</td>
<td>Supplement</td>
<td>392</td>
<td>30 mos</td>
<td>16</td>
<td>0.78 (0.41, 1.49)</td>
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<td>19</td>
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<tr>
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<td>Supplement</td>
<td>195</td>
<td>6 yrs</td>
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<td>1.53 (0.51, 4.58)</td>
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<td>Supplement</td>
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<td>6 yrs</td>
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<td>Li, All cancer</td>
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<td>Li, Esophageal cancer</td>
<td>Supplement</td>
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<td>6 yrs</td>
<td>123</td>
<td>0.96 (0.76, 1.22)</td>
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</tr>
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<td>6 yrs</td>
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<td>1.19 (0.89, 1.58)</td>
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<tr>
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<td>81</td>
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<td>Taylor, Esophageal cancer</td>
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<td>201</td>
<td>6 yrs</td>
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<td>Population</td>
<td>D</td>
<td>173</td>
<td>3</td>
<td></td>
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<td></td>
<td>No D</td>
<td>206</td>
<td>5</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Taylor, Gastric cancer</td>
<td>C</td>
<td>205</td>
<td>6 yrs</td>
<td>6</td>
<td>2.71 (0.55, 13.25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No C</td>
<td>185</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>176</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No D</td>
<td>214</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Other</td>
<td>Lamm, Megadose vitamins</td>
<td>35</td>
<td>6 yrs</td>
<td>14</td>
<td>0.50 (0.32, 0.78)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trials</td>
<td>RDA</td>
<td>30</td>
<td>24</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>MRC/BHF, Vitamins</td>
<td>10269</td>
<td>5 yrs</td>
<td>800</td>
<td>0.98 (0.89, 1.08)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>10267</td>
<td>817</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Additional studies for which risk ratios could not be calculated are discussed in the text and displayed in the Evidence Table.

C: vitamin C (ascorbic acid) plus additional vitamins; CI: confidence interval; D: vitamin D; FU: follow-up; RR: risk ratio

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### Table 8. Risk Ratios for Polyps Outcome for Vitamins C + E versus Placebo

<table>
<thead>
<tr>
<th>Article</th>
<th>Intervention</th>
<th>Total n</th>
<th>Risk Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greenberg, 1994&lt;sup&gt;47&lt;/sup&gt;</td>
<td>C+E only</td>
<td>751</td>
<td>1.06</td>
<td>(0.82, 1.37)</td>
</tr>
<tr>
<td>McKeown-Eyssen, 1988&lt;sup&gt;49&lt;/sup&gt;</td>
<td>C+E only</td>
<td>137</td>
<td>0.82</td>
<td>(0.57, 1.18)</td>
</tr>
</tbody>
</table>

C: vitamin C (ascorbic acid); CI: confidence interval; E: vitamin E (alpha-tocopherol)

### Table 9. Risk Ratios for Polyps Outcome for the use of vitamins C + E with carotenoids versus placebo: Pooled Results

<table>
<thead>
<tr>
<th>Article</th>
<th>Intervention</th>
<th>Total n</th>
<th>Risk Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greenberg, 1994&lt;sup&gt;47&lt;/sup&gt;</td>
<td>C+AT+BC</td>
<td>751</td>
<td>1.04</td>
<td>(0.79, 1.36)</td>
</tr>
<tr>
<td>Hofstad, 1998&lt;sup&gt;48&lt;/sup&gt;</td>
<td>C+AT+BC+Ca</td>
<td>93</td>
<td>0.71</td>
<td>(0.50, 1.01)</td>
</tr>
<tr>
<td>Roncucci, 1993&lt;sup&gt;50&lt;/sup&gt;</td>
<td>C+AT+A</td>
<td>209</td>
<td>0.16</td>
<td>(0.06, 0.43)</td>
</tr>
</tbody>
</table>

Pooled Random Effects Estimate: 0.60<sup>(1)</sup> (0.31, 1.16)

<sup>(1)</sup> Chi-squared test of heterogeneity p-value = 0.001

A: vitamin A; AT: alpha-tocopherol; BC: beta-carotene; C: vitamin C (ascorbic acid); Ca: calcium; CI: confidence interval
Figure 2. Meta-Analysis for Polyps Outcome.

Figure 3. Publication Bias for Polyps Outcome.
Chapter 4. Conclusions

This evidence report assessed the evidence for the efficacy of coenzyme Q10, vitamin C, and vitamin E for the prevention and/or treatment of cancer.

We identified a body of literature and were able to make the following observations from the literature’s trials:

- There were no controlled trials found in the literature that presented data on the efficacy of coenzyme Q10 for prevention or treatment of cancer and therefore no conclusions, either positive or negative, can be drawn.
- There were the following results found for the use of vitamin C and vitamin E in these doses, various combinations, and populations:
  - no decrease risk of death due to cancer;
  - no decrease of new tumor formation for populations studied, except for one arm of the ATBC study and one tumor type (AT for prevention of prostate cancer).
  - There was no decrease in risk of death for vitamin C in the doses as treatment for advanced cancer.
  - There was no benefit for the development of new colonic polyps in the doses, populations tested; the combination of vitamins C and E was not clinically superior to placebo in secondary prevention and the combination of vitamins C and E with betacarotene or vitamin A did show a trend favoring a reduction in polyp recurrence, but this finding was not statistically significant.
  - There were several single trials which separately showed:
    - Vitamin C was found to be beneficial in single trial bladder cancer used in conjunction with BCG for new tumors.
    - Vitamin E in combination with omega-3 fatty acid increases survival.
    - A number of intermediate outcomes studies were positive.
    - The systematic review of the literature does not support the hypothesis that the use of supplements of vitamins C or E or coenzyme Q10 in the doses tested generally help prevent and/or treat cancer in the populations studied. There were isolated findings of benefit, which require confirmation.

Limitations of the Review

Heterogeneity

A number of issues potentially limit the effectiveness of this review. Methodologically, there was marked heterogeneity in the size of the population, the intent of the trial, the types of outcomes, and follow-up times. We identified three large primary prevention trials (ATBC, Linxian General Population and Linxian Dysplasia Group) that each reported on a number of separate outcomes. The majority of remaining trials were studies of much smaller numbers of people. They included not only secondary prevention trials but also treatment trials such as vitamin C for treatment of cancer. In addition, the populations varied from representatives of the healthy population to subjects identified at high risk for the development of cancer or who in fact
already had cancer. The observed heterogeneity in study populations and designs deterred us from conducting a meta-analysis in two of our three outcome domains—death and new tumors—and also excluded some studies from our colonic polyps analysis. In the face of this heterogeneity, we provide individual study risk ratios and discuss the studies descriptively. We cannot assess the relationship between the possible heterogeneity in treatment effects and study or population characteristics, due to the small numbers of studies available.

**Quality of the Trials**

Given the consistent positive effects from the observational literature, the number of clinical trials as well as their depth and quality was disappointing. The quality of these studies varied as well. More than half of the trials had a Jadad score of less than three. The presence of Jadad scores of less than three has been associated in the literature with bias. In addition, we excluded from consideration case series, cohort studies and epidemiologic assessments. While these would have expanded the data base, they do not provide the most direct evidence of efficacy.

**Publication Bias**

We conducted a comprehensive literature search, including hand-searching reference lists of identified articles, and contacting experts. We also searched databases that include unpublished studies, such as the Cochrane registry of trials and the so-called “grey literature” (unpublished data, conference proceedings, and abstracts). Although we were unable to find any unpublished literature, we were able to include a number of conference proceedings in our analysis. Research by McAuley and colleagues has demonstrated that the exclusion of the “grey literature” exaggerates the estimates of the effects of interventions that are being tested. Therefore, to the degree that there is significant unpublished or non-indexed literature pertinent to this topic that we did not find, this review is limited. Language was not an exclusion criterion for our search.

We could only test formally for publication bias in the single setting for which we did a meta-analysis, and based on only three studies. In this setting, we found no evidence of publication bias but have little statistical power given the small number of studies. We acknowledge that publication bias may still exist despite our best efforts to conduct a comprehensive search, and the lack of statistical evidence of existence.

**Diverse Interventions**

Clinically, a number of potential limitations could be identified as well. Few studies evaluated single agents for efficacy. There was no standard amount of either vitamins C or E given, nor were the multi-vitamin formulas consistent from study to study. Some of this variation may be due to differences in the populations assessed; however, it also reflects lack of consensus on recommended doses of these vitamins to be used therapeutically. Given the small number of studies and the differences in doses and formulas, no assessment could be made regarding effectiveness of varying dosage levels or combinations of individual supplements.
However, the ability to infer from this finding is limited because the multicomponent intervention limits our ability to attribute the reported efficacy to any particular component. However, there will always be problems of confounding variables when studies are not designed to isolate effects of single nutrients. However, take single nutrients for treating cancer, making it a challenge to test the efficacy of almost any of the treatments being used in practice.

The role of these clinical trials in understanding anti-oxidants in cancer can be expressed in a series of logical steps:

- Cellular/molecular evidence has shown that oxidation is associated with DNA and other molecular damage.
- Cellular/molecular evidence relates DNA damage to the development of cancer.
- Epidemiologic data supports a relationship between consumption of diets rich in anti-oxidants and decreased rates of cancer.
- However, the randomized controlled trials (RCTs) reviewed here failed to support the hypothesis that anti-oxidant supplements help prevent cancer.

In trying to resolve the RCT results with the cellular/molecular and the epidemiologic data there are several possible explanations:

1. The type of antioxidants used in the trials was different (synthetic vs. natural).
2. The dose used was wrong.
3. The results were due to something other than the single anti-oxidants or combinations that were tested in the trials.
4. The duration of treatment was too short.
5. The observed epidemiologic association is not causal in the same way in which the recent demonstration that epidemiologic studies relating the use of hormonal replacement therapy to potential cardiac effects in post-menopausal women was not confirmed by a definitive RCT.

The conclusion of the review is that the negative results only apply to the anti-oxidants tested, in the doses tested, and for the populations tested and do not constitute “proof” that anti-oxidants do not influence cancer. However, the generally negative results from the RCTs do place the burden of proof on the proponents of anti-oxidant supplements to identify the specific supplement, the dosage and the population combination that is efficacious.

Other Limitations

In addition, it will be difficult to generalize from this body of work, because insufficient numbers of female patients were included for study. Also, few trials were conducted on cancers specific to women, such as breast or cervical cancer. Finally, the lack of any published studies on coenzyme Q10 appropriate for inclusion in this analysis limit the ability to assess this popular therapy. Unfortunately, the only literature identified involved uncontrolled clinical trials, case series and case reports.
Chapter 5. Future Research

The results of our literature synthesis show generally disappointing results for the efficacy of these antioxidant supplements in these doses to prevent, modify risks or treat cancer in these populations. This result is in contrast to the numerous observational studies reporting benefits in persons consuming diets that are high in these same antioxidants. Therefore, additional research is needed to understand why these two sources of evidence disagree.

Future research should include populations that were not included in the previous studies. Specifically, future research should include female subjects and should also focus on cancers particular to women such as breast, cervix, and ovarian cancer. Additionally, populations enrolled in future clinical trials should be homogeneous with respect to condition and intervention. The majority of the large trials studied here focused on primary prevention in high-risk populations. Additional research would be needed to ascertain the benefit for the secondary prevention of common cancers or for the modification of premalignant states. Research into other popular antioxidants such as selenium might also yield deterrent results.

We did find evidence of certain associations of vitamin C and E and certain cancers or intermediate outcomes that require replication before definitive conclusions of efficacy can be reached. These results need to be confirmed in larger studies.

For coenzyme Q10, preliminary research needs to be done before clinical trials would be recommended. Molecular and animal model studies need to establish a plausible reason in terms of mechanisms, dose and duration of treatment before proceeding to clinical trials.

The utilization of antioxidants to mitigate the negative effects of standard cancer therapy would also be useful to study. We would recommend, initially, that a review of antioxidants as adjunctive cancer therapy be considered.

Finally, a number of intermediate outcomes are becoming established for development of cancer. If these outcomes become validated for common cancers, it would be much more cost-effective to use these end points to gauge efficacy of any planned clinical intervention prior to undertaking large clinical trials. We would also recommend the continuing development of more appropriate and sensitive biomarkers of nutritional status.
References


## Antioxidants For Cancer Prevention/Treatment

<table>
<thead>
<tr>
<th>First Author Year</th>
<th>Trial name Study Design Quality Population Comorbidities</th>
<th>Interventions Dosage Data</th>
<th>Sample Size</th>
<th>Summary of Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Albanes 1986</strong></td>
<td>Named trial: ATBC pilot RCT</td>
<td>1 Placebo Placebo for 8 Months</td>
<td>n Entered: N/D</td>
<td>Excluded from statistical analysis because of insufficient statistics. This pilot study for the ATBC lung cancer prevention trial showed the feasibility of conducting the larger trial. Death and development of cancers were reported as explanations for dropouts, but these data were not broken down by type of intervention.</td>
</tr>
<tr>
<td></td>
<td>Jadad Score: 5 Population: smokers Comorbidities: N/D</td>
<td>2 Beta-carotene 20 mg orally for 8 Months</td>
<td>n Entered: N/D</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 Vitamin E 50 mg orally for 8 Months</td>
<td>n Entered: N/D</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 Beta-carotene 20 mg orally for 8 Months</td>
<td>n Entered: N/D</td>
<td></td>
</tr>
<tr>
<td><strong>Albanes 1996</strong></td>
<td>Named trial: ATBC RCT</td>
<td>1 Placebo Placebo for 6.1 Years</td>
<td>n Entered: 7287</td>
<td>Statistical pooling performed: Death: relative risk at 6.1 years (average follow-up) New tumor: relative risk at 6.1 years (average follow-up)</td>
</tr>
<tr>
<td></td>
<td>Jadad Score: 3 Population: smokers Comorbidities: N/D</td>
<td>2 Beta-carotene 20 mg orally for 6.1 Years</td>
<td>n Entered: 7282</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>3 Vitamin E 50 mg orally for 6.1 Years</td>
<td>n Entered: 7286</td>
<td></td>
</tr>
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<td></td>
<td></td>
<td>4 Beta-carotene 20 mg orally for 6.1 Years</td>
<td>n Entered: 7278</td>
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<td>Statistical pooling performed: Death: relative risk at 6.1 years (average follow-up) New tumor: relative risk at 6.1 years (average follow-up)</td>
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<td>n Entered: 7286</td>
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</tr>
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<td></td>
<td>4 Vitamin E 50 mg orally for 6.1 Years</td>
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N/D = not described
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<th>Trial name Study Design Quality Population Comorbidities</th>
<th>Arm</th>
<th>Interventions Dosage Data</th>
<th>Sample Size</th>
<th>Summary of Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATBC Prevention Study Group 1994</td>
<td>Named trial: ATBC RCT</td>
<td>1</td>
<td>Placebo Placebo for 6.1 Years</td>
<td>n Entered: 7287, n Analyzed: 7287</td>
<td>Statistical pooling performed: Death: relative risk at 6.1 years (average follow-up) New tumor: relative risk at 6.1 years (average follow-up)</td>
</tr>
<tr>
<td></td>
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<td>2</td>
<td>Vitamin E 50 mg orally for 6.1 Years</td>
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<td>Beta-carotene 20 mg orally for 6.1 Years</td>
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<tr>
<td></td>
<td></td>
<td>4</td>
<td>Vitamin E 50 mg orally for 6.1 Years Beta-carotene 20 mg orally for 6.1 Years</td>
<td>n Entered: 7278, n Analyzed: 7278</td>
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<table>
<thead>
<tr>
<th>First Author Year</th>
<th>Trial name Study Design Quality Population Comorbidities</th>
<th>Arm</th>
<th>Interventions Dosage Data</th>
<th>Sample Size</th>
<th>Summary of Results</th>
</tr>
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<tbody>
<tr>
<td>Blot 1993</td>
<td>Named trial: Linxian (General Population Trial) RCT</td>
<td>1</td>
<td>Placebo Placebo for 5.25 Years</td>
<td>n Entered: N/D n Analyzed: 3679</td>
<td>Statistical pooling performed: Death: relative risk at 5.25 years follow-up</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>Niacin 40 mg orally for 5.25 Years Multi-vitamin Multi-vitamin orally for 5.25 Years</td>
<td>n Entered: N/D n Analyzed: 3701</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>Vitamin C 120 mg orally for 5.25 Years Multi-vitamin Multi-vitamin orally for 5.25 Years</td>
<td>n Entered: N/D n Analyzed: 3694</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4</td>
<td>Vitamin C 120 mg orally for 5.25 Years Multi-vitamin Multi-vitamin orally for 5.25 Years</td>
<td>n Entered: N/D n Analyzed: 3703</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5</td>
<td>Vitamin E 30 mg orally for 5.25 Years Multi-vitamin Multi-vitamin orally for 5.25 Years</td>
<td>n Entered: N/D n Analyzed: 3691</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>6</td>
<td>Vitamin C 120 mg orally for 5.25 Years Vitamin E 30 mg orally for 5.25 Years Multi-vitamin Multi-vitamin orally for 5.25 Years</td>
<td>n Entered: N/D n Analyzed: 3699</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>7</td>
<td>Vitamin C 120 mg orally for 5.25 Years Vitamin E 30 mg orally for 5.25 Years Multi-vitamin Multi-vitamin orally for 5.25 Years</td>
<td>n Entered: N/D n Analyzed: 3705</td>
<td></td>
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N/D = not described
## Antioxidants For Cancer Prevention/Treatment

<table>
<thead>
<tr>
<th>First Author Year</th>
<th>Trial name Study Design Quality Population Comorbidities</th>
<th>Interventions Dosage Data</th>
<th>Sample Size</th>
<th>Summary of Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bussey 1982</strong></td>
<td>Named trial: No RCT Jadad Score: 4 Population: N/D Comorbidities: N/D</td>
<td>8 Vitamin E 30 mg orally for 5.25 Years Multi-vitamin Multi-vitamin orally for 5.25 Years</td>
<td>n Entered: N/D n Analyzed: 3712</td>
<td>Excluded from polyps meta-analysis because of insufficient statistics. Individuals all had polyposis coli. Those in Arm 2 exhibited reduction of colonic polyp area (p &lt; 0.03) at 9 months and had a nonsignificant trend towards reduction in number and area of rectal polyps.</td>
</tr>
<tr>
<td><strong>Cahill 1993</strong></td>
<td>Named trial: No RCT Jadad Score: 2 Population: N/D Comorbidities: N/D</td>
<td>1 Control or Usual care No dosage data reported</td>
<td>n Entered: 10 n Analyzed: 10</td>
<td>Excluded from statistical analysis because there were no outcomes of interest. Reduction in cell proliferation in colonic crypts in patients with adenomatous polyps was found with vitamin C in all crypt components and with beta-carotene at the base only. There was no significant effect on cell proliferation from vitamin E supplementation.</td>
</tr>
<tr>
<td><strong>Correa 2000</strong></td>
<td>Named trial: No RCT Jadad Score: 5 Population: N/D Comorbidities: N/D</td>
<td>1 Placebo Placebo for 6 Years</td>
<td>n Entered: 117 n Analyzed: 76</td>
<td>Excluded from statistical analysis because there were no outcomes of interest. Within this study of metaplasia, there was no statistically significant difference among treatment groups in progression or regression of dysplasia.</td>
</tr>
</tbody>
</table>

N/D = not described
## Antioxidants For Cancer Prevention/Treatment

<table>
<thead>
<tr>
<th>First Author Year</th>
<th>Study Design</th>
<th>Quality</th>
<th>Population</th>
<th>Comorbidities</th>
<th>Interventions</th>
<th>Dosage Data</th>
<th>Sample Size</th>
<th>Summary of Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>30 mg orally for 6 Years</td>
<td>Beta-carotene</td>
<td>n Entered: 126</td>
<td>n Analyzed: 88</td>
<td>H. pylori treatment</td>
<td>N/D dose orally for 6 Years</td>
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<tr>
<td>6</td>
<td>N/D dose orally for 6 Years</td>
<td>H. pylori treatment</td>
<td>n Entered: 111</td>
<td>n Analyzed: 72</td>
<td>Vitamin C</td>
<td>2 gm orally for 6 Years</td>
<td></td>
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<tr>
<td>7</td>
<td>30 mg orally for 6 Years</td>
<td>Beta-carotene</td>
<td>n Entered: 121</td>
<td>n Analyzed: 79</td>
<td>Vitamin C</td>
<td>2 gm orally for 6 Years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>N/D dose orally for 6 Years</td>
<td>H. pylori treatment</td>
<td>n Entered: 134</td>
<td>n Analyzed: 81</td>
<td>Beta-carotene</td>
<td>30 mg orally for 6 Years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Placebo</td>
<td>Placebo taken until death</td>
<td>Placebo</td>
<td>n Entered: N/D</td>
<td>n Analyzed: N/D</td>
<td></td>
<td></td>
<td></td>
<td>Excluded from statistical analysis because of insufficient statistics. No difference was found between the treatment groups in terms of symptoms, functional status, appetite, weight, or survival among subjects with advanced cancer.</td>
</tr>
<tr>
<td>2 Vitamin C</td>
<td>10 gm orally until death</td>
<td>n Entered: N/D</td>
<td>n Analyzed: N/D</td>
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**Evidence Table**

**57**
<table>
<thead>
<tr>
<th>First Author Year</th>
<th>Trial name</th>
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<th>Population</th>
<th>Comorbidities</th>
<th>Interventions</th>
<th>Dosage Data</th>
<th>Sample Size</th>
<th>Summary of Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creagan 1979(Sep)</td>
<td>Named trial: No</td>
<td>RCT</td>
<td>Jadad Score: 4</td>
<td>N/D</td>
<td>N/D</td>
<td>1 Placebo</td>
<td>No dosage data reported</td>
<td>n Entered: 75 n Analyzed: 63</td>
<td>Excluded from death analysis because of insufficient statistics: Study only reported survival curve. All subjects had various forms of advanced cancer. No significant difference was shown between the two groups in terms of changes in symptoms, performance status, appetite, weight or survival.</td>
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<tr>
<td>Dawsey 1994</td>
<td>Named trial: Linxian (Dysplasia trial)</td>
<td>RCT</td>
<td>Jadad Score: 2</td>
<td>N/D</td>
<td>N/D</td>
<td>1 Placebo</td>
<td>Placebo for 6 Years</td>
<td>n Entered: N/D n Analyzed: 368</td>
<td>Statistical pooling performed: New tumor: relative risk at 30 months and 6 years follow-up</td>
</tr>
<tr>
<td>DeCosse 1989</td>
<td>Named trial: No</td>
<td>RCT</td>
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<td>N/D</td>
<td>N/D</td>
<td>1 Fiber</td>
<td>2.2 gm orally for 4 years</td>
<td>n Entered: 22 n Analyzed: 21</td>
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N/D = not described
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<th>Sample Size</th>
<th>Summary of Results</th>
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<tr>
<td>Gogos 1998</td>
<td>Vitamin C</td>
<td>RCT</td>
<td>1</td>
<td>N/D</td>
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<td>2</td>
<td>4030 mg orally for 4 Years</td>
<td>n Entered: 16</td>
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<td></td>
<td>Vitamin E</td>
<td></td>
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<td>2</td>
<td>400 mg orally for 4 Years</td>
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<td></td>
<td>Fiber</td>
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<td>2</td>
<td>2.2 gm orally for 4 Years</td>
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<td>Vitamin A</td>
<td></td>
<td></td>
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<td>2000 IU orally for 4 Years</td>
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<td>Placebo</td>
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<td>No dosage data reported</td>
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<td>Vitamin C</td>
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<td>4030 mg orally for 4 Years</td>
<td>n Entered: 20</td>
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<td>Vitamin E</td>
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<td>400 mg orally for 4 Years</td>
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<td></td>
<td>Fiber</td>
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<td>2</td>
<td>22.5 gm orally for 4 Years</td>
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<td></td>
<td>Vitamin A</td>
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<td>2</td>
<td>2000 IU orally for 4 Years</td>
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<tr>
<td></td>
<td>Fish oil</td>
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<td>2</td>
<td>18 gm orally, duration N/D</td>
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<td>2</td>
<td>200 mg orally, duration N/D</td>
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Excluded from death analysis because of insufficient statistics: Study only reported survival curve. All subjects had various types of solid tumors. Those receiving the active intervention had prolonged survival (p < 0.025) compared with placebo. This group also exhibited higher TNF production (p < 0.05) in malnourished subjects.
## Antioxidants For Cancer Prevention/Treatment

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<thead>
<tr>
<th>First Author Year</th>
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<tr>
<td></td>
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<td>Beta-carotene 25 mg orally for 4 Years</td>
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<td>Vitamin C 1 gm orally for 4 Years Vitamin E 400 mg orally for 4 Years</td>
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<td>Vitamin C 1 gm orally for 4 Years Vitamin E 400 mg orally for 4 Years Beta-carotene 25 mg orally for 4 Years</td>
<td>n Entered: N/D n Analyzed: 175</td>
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<td>Beta-carotene 20 mg orally for 6.1 Years</td>
<td>n Entered: 7282 n Analyzed: 7282</td>
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<td></td>
<td>Vitamin E 50 mg orally for 6.1 Years</td>
<td>n Entered: 7286 n Analyzed: 7286</td>
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<td></td>
<td>Vitamin E 50 mg orally for 6.1 Years Beta-carotene 20 mg orally for 6.1 Years</td>
<td>n Entered: 7278 n Analyzed: 7278</td>
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## Antioxidants For Cancer Prevention/Treatment

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<td>Holstad 1998</td>
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<td>RCT</td>
<td>Jadad Score: 3</td>
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<td>Comorbidities: N/D</td>
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<td>Placebo</td>
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<td>2</td>
<td>Vitamin E</td>
<td>75 mg orally for 3 Years</td>
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<td></td>
<td>Vitamin C</td>
<td>150 mg orally for 3 Years</td>
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<td></td>
<td>Beta-carotene</td>
<td>15 mg orally for 3 Years</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ca</td>
<td>1.6 gm orally for 3 Years</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Selenium</td>
<td>101 µg orally for 3 Years</td>
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<tr>
<td>Lamm 1994</td>
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<td>RCT</td>
<td>Jadad Score: 4</td>
<td>Population: N/D</td>
<td>Comorbidities: N/D</td>
<td>1</td>
<td>Multi-vitamin</td>
<td>Multi-vitamin orally for 40 Months</td>
<td>n Entered: 30</td>
<td>n Analyzed: 30</td>
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<td>2</td>
<td>Vitamin E</td>
<td>430 IU orally for 49 Months</td>
<td>n Entered: 35</td>
<td>n Analyzed: 35</td>
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<td>Vitamin C</td>
<td>2060 mg orally for 49 Months</td>
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<td></td>
<td>Vitamin A</td>
<td>45000 IU orally for 49 Months</td>
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<td></td>
<td>Multi-vitamin</td>
<td>Multi-vitamin orally for 49 Months</td>
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<tr>
<td>First Author Year</td>
<td>Trial name Study Design Quality Population Comorbidities</td>
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<tr>
<td><strong>Study A</strong></td>
<td>Named trial: Linxian (Dysplasia Trial) RCT</td>
<td>1 Placebo Placebo for 6 Years</td>
<td>n Entered: 1661 n Analyzed: N/D</td>
<td>Excluded from statistical analysis because of duplicate data, same data as another report. This paper describes the design and methods of the Linxian trials. Deaths and development of cancers were reported for the total population, but these data were not broken down by type of intervention.</td>
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<tr>
<td>Li, Bing 1993</td>
<td>Jadad Score: 2</td>
<td>2 Vitamin C 180 mg orally for 6 Years Vitamin E 60 IU orally for 6 Years Multi-vitamin Multi-vitamin orally for 6 Years Beta-carotene 15 mg orally for 6 Years Vitamin A 10000 IU orally for 6 Years Selenium 50 µg orally for 6 Years</td>
<td>n Entered: 1657 n Analyzed: N/D</td>
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<tr>
<td><strong>Study B</strong></td>
<td>Named trial: Linxian (General Population Trial) RCT</td>
<td>1 Placebo Placebo for 6 Years</td>
<td>n Entered: 1661 n Analyzed: N/D</td>
<td>Excluded from statistical analysis because of insufficient statistics. This is a pilot study for the Linxian General Population trial.</td>
<td></td>
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</tr>
<tr>
<td>Li, Bing 1993</td>
<td>Jadad Score: 2</td>
<td>2 Vitamin C 180 mg orally for 6 Years Vitamin E 60 IU orally for 6 Years Multi-vitamin Multi-vitamin orally for 6 Years Beta-carotene 15 mg orally for 6 Years Vitamin A 10000 IU orally for 6 Years Selenium 50 µg orally for 6 Years</td>
<td>n Entered: 1657 n Analyzed: N/D</td>
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<th>Interventions Dosage Data</th>
<th>Sample Size</th>
<th>Summary of Results</th>
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</thead>
<tbody>
<tr>
<td>Li, Jun-Yao 1993</td>
<td>Named trial: Linxian (Dysplasia Trial) RCT Jadad Score: 2 Population: N/D Comorbidities: N/D</td>
<td>1 Placebo Placebo for 6 Years</td>
<td>n Entered: 1661 n Analyzed: 1661</td>
<td>Statistical pooling performed: Death: relative risk at 6 years follow-up New tumor: relative risk at 6 years follow-up</td>
</tr>
<tr>
<td></td>
<td>2 Vitamin C 180 mg orally for 6 Years Vitamin E 60 IU orally, duration N/D Multi-vitamin Multi-vitamin orally, duration N/D Beta-carotene 15 mg orally, duration N/D Vitamin A 10000 IU orally, duration N/D Selenium 50 µg orally, duration N/D</td>
<td>n Entered: 1657 n Analyzed: 1657</td>
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<tr>
<td>Liede 1998</td>
<td>Named trial: ATBC RCT Jadad Score: 3 Population: Smokers Comorbidities: N/D</td>
<td>1 Placebo Placebo for 6 Years</td>
<td>n Entered: 119 n Analyzed: N/D</td>
<td>Excluded from statistical analysis because there were no outcomes of interest. No significant difference was found among any of the four groups in the incidence of any oral mucosal lesions evaluated including leukoplakia, keratoses, hyperplasia and mucosal dysplasia.</td>
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<tr>
<td></td>
<td>2 Vitamin E 50 mg orally for 6 Years</td>
<td>n Entered: 95 n Analyzed: N/D</td>
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<tr>
<td></td>
<td>3 Vitamin E 50 mg orally for 6 Years Beta-carotene 20 mg orally for 6 Years</td>
<td>n Entered: 96 n Analyzed: N/D</td>
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<tr>
<td></td>
<td>4 Beta-carotene 20 mg orally for 6 Years</td>
<td>n Entered: 99 n Analyzed: N/D</td>
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### Antioxidants For Cancer Prevention/Treatment

#### Evidence Table

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<tr>
<td>Mackerras 1999</td>
<td>Placebo</td>
<td>RCT</td>
<td>Female</td>
<td>N/D</td>
<td>Placebo</td>
<td>Placebo for 2 Years</td>
<td>n Entered: N/D, n Analyzed: 35</td>
<td>Excluded from statistical analysis because there were no outcomes of interest. There was no significant difference found among the groups in terms of regression or progression of cervical intraepithelial neoplasia (CIN) I.</td>
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<tr>
<td></td>
<td>Beta-carotene</td>
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<td>30 mg orally for 2 Years</td>
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<tr>
<td></td>
<td>Vitamin C</td>
<td></td>
<td></td>
<td></td>
<td>518 mg orally for 2 Years</td>
<td>n Entered: N/D, n Analyzed: 35</td>
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<tr>
<td></td>
<td>Vitamin C</td>
<td></td>
<td></td>
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<td>518 mg orally for 2 Years</td>
<td>n Entered: N/D, n Analyzed: 35</td>
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<tr>
<td>Malila 1999</td>
<td>Placebo</td>
<td>RCT</td>
<td>Smokers</td>
<td>N/D</td>
<td>Beta-carotene</td>
<td>20 mg orally for 6.3 Years</td>
<td>n Entered: 3887, n Analyzed: N/D</td>
<td>Excluded from polyps analysis because of insufficient statistics: Statistics too heterogeneous to pool. Vitamin E increased the risk for colorectal adenoma (RR 95% CI 1.19-2.32) among participants. There was no interaction between vitamin E and beta-carotene on risk for adenoma.</td>
</tr>
<tr>
<td></td>
<td>Beta-carotene</td>
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<td></td>
<td></td>
<td>20 mg orally for 6.3 Years</td>
<td>n Entered: 3883, n Analyzed: N/D</td>
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<td>Vitamin E</td>
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<td>50 mg orally for 6.3 Years</td>
<td>n Entered: 3878, n Analyzed: N/D</td>
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<tr>
<td>McKeown-Eyssen 1988</td>
<td>Placebo</td>
<td>RCT</td>
<td>N/D</td>
<td>N/D</td>
<td>Vitamin E</td>
<td>50 mg orally for 6.3 Years</td>
<td>n Entered: 89, n Analyzed: 67</td>
<td>Statistical pooling performed: Polyps: meta-analysis at 2 years follow-up</td>
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<tr>
<td></td>
<td>Vitamin C</td>
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<td>400 mg orally for 2 Years</td>
<td>n Entered: 96, n Analyzed: 70</td>
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### Evidence Table

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<tr>
<td>Moertel 1985</td>
<td>Named trial: No RCT Jadad Score: 3</td>
<td>Population: N/D Comorbidities: N/D</td>
<td>1 Placebo Placebo for 3.6 Months</td>
<td>n Entered: 49 n Analyzed: 49</td>
<td>Excluded from death analysis because of insufficient statistics: study only reported total death. All subjects had advanced colorectal cancer. No significant difference was shown between the groups in terms of disease progression or survival.</td>
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N/D = not described
### Antioxidants For Cancer Prevention/Treatment

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<tr>
<td>Poulter 1984</td>
<td>Control or Usual care</td>
<td>n Entered: 25 n Analyzed: 24</td>
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<td>Statistical pooling performed: Death: relative risk at 5 years follow-up</td>
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<td>Control or Usual care for 5 Years</td>
<td>n Analyzed: 24</td>
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<td>Vitamin C 3 gm orally for 5 Years</td>
<td>n Analyzed: 27</td>
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<td></td>
<td>Placebo for 6.1 Years</td>
<td>n Analyzed: 7287</td>
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<td>Vitamin E 50 mg orally for 6.1 Years</td>
<td>n Analyzed: 7286</td>
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<td>Beta-carotene 20 mg orally for 6.1 Years</td>
<td>n Analyzed: 7282</td>
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<tr>
<td></td>
<td>Vitamin E 50 mg orally for 6.1 Years</td>
<td>n Analyzed: 7278</td>
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<tr>
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<td>Beta-carotene 20 mg orally for 6.1 Years</td>
<td>n Analyzed: 7278</td>
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<td>Rautalahti 1999</td>
<td>Placebo</td>
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<td>Placebo for 6.1 Years</td>
<td>n Analyzed: 7286</td>
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<td>50 mg orally for 6.1 Years</td>
<td>n Analyzed: 7282</td>
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<td>50 mg orally for 6.1 Years</td>
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<td>Beta-carotene 20 mg orally for 6.1 Years</td>
<td>n Analyzed: 7278</td>
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<tr>
<td>Roncucci, Di Donato 1993</td>
<td>Placebo</td>
<td>n Entered: N/D n Analyzed: 78</td>
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<td>Statistical pooling performed: Polyps: meta-analysis at 12 months follow-up</td>
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<td>Placebo for 18 Months</td>
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<td>Lactulose 20 gm orally for 18 Months</td>
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<td>1 gm orally for 18 Months</td>
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<th>Dosage Data</th>
<th>Sample Size</th>
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<tbody>
<tr>
<td>Roncucci 1993</td>
<td>Named trial: No</td>
<td>RCT</td>
<td>Jadad Score: 2</td>
<td>Population: N/D</td>
<td>Comorbidities: N/D</td>
<td>1 Control or Usual care</td>
<td>n Entered: 78</td>
<td>n Analyzed: 78</td>
<td>Excluded from polyps meta-analysis because study reported data duplicated in another included study (Roncucci, Di Donato 1993)</td>
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<tr>
<td>Schroder 2000</td>
<td>Named trial: No</td>
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<td>Comorbidities: N/D</td>
<td>1 Placebo</td>
<td>n Entered: 37</td>
<td>n Analyzed: N/D</td>
<td>Excluded from statistical analysis because there were no outcomes of interest. The slope of the rise of PSA and PSA doubling times decreased among those receiving antioxidant supplementation (29.5 vs. 60 weeks doubling time, p&lt;0.05) in prostate cancer patients with rising PSA values post prostatectomy or radiotherapy.</td>
</tr>
<tr>
<td>Taylor 1994 Study A</td>
<td>Named trial: Linxian (Dysplasia Trial)</td>
<td>RCT</td>
<td>Jadad Score: 2</td>
<td>Population: N/D</td>
<td>Comorbidities: N/D</td>
<td>1 Placebo</td>
<td>n Entered: 1661</td>
<td>n Analyzed: 1661</td>
<td>Excluded from new tumor analysis because of insufficient statistics. Subjects in the dysplasia trial all had esophageal dysplasia without malignancy. This report describes the methods of the dysplasia trial but reports no results from it.</td>
</tr>
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## Evidence Table

<table>
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<tr>
<th>First Author Year</th>
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<th>Population Comorbidities</th>
<th>Arm</th>
<th>Interventions Dosage Data</th>
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<th>Summary of Results</th>
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<td>2 Niacin 40 mg orally for 5.25 Years Multi-vitamin Multi-vitamin orally for 5.25 Years</td>
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<td></td>
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<td>n Entered: N/D n Analyzed: 3694</td>
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<td>4 Vitamin C 120 mg orally for 5.25 Years Multi-vitamin Multi-vitamin orally for 5.25 Years</td>
<td>n Entered: N/D n Analyzed: 3703</td>
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<td>7 Vitamin C 120 mg orally for 5.25 Years Vitamin E 30 mg orally for 5.25 Years Multi-vitamin Multi-vitamin orally for 5.25 Years</td>
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N/D = not described
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<th>Summary of Results</th>
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<td>3 Vitamin E 50 mg orally for 5.1 Years</td>
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<td></td>
<td>4 Beta-carotene 20 mg orally for 5.1 Years</td>
<td>n Entered: 361 n Analyzed: 361</td>
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<td></td>
<td>2 Vitamin E 50 mg orally for 6.1 Years</td>
<td>n Entered: 7286 n Analyzed: 7286</td>
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<td>3 Beta-carotene 20 mg orally for 6.1 Years</td>
<td>n Entered: 7282 n Analyzed: 7282</td>
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<td>4 Vitamin E 50 mg orally for 6.1 Years</td>
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N/D = not described
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<th>Interventions Dosage Data</th>
<th>Sample Size</th>
<th>Summary of Results</th>
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<tbody>
<tr>
<td>Zaridze 1993</td>
<td>Named trial: No RCT Jadad Score: 4 Population: N/D Comorbidities: N/D</td>
<td>1</td>
<td>Placebo Placebo for 20 Months</td>
<td>n Entered: N/D, n Analyzed: N/D</td>
<td>Excluded from statistical analysis because there were no outcomes of interest. Among men with oral leukoplakia and/or chronic esophagitis, those in arm 3 exhibited a decreased OR for oral leukoplakia after 6 months ((5% CI 0.39-0.98) as compared with placebo. There was no significant difference in risk of progression of chronic esophagitis after 20 months.</td>
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<td>Riboflavin 11.4 mg orally for 20 Months</td>
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<tr>
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<td></td>
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<td>n Entered: N/D, n Analyzed: N/D</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4</td>
<td>Riboflavin 11.4 mg orally for 20 Months Vitamin E 11.4 mg orally for 20 Months Vitamin A 14285 IU orally for 20 Months Beta-carotene 40 mg orally for 20 Months</td>
<td>n Entered: N/D, n Analyzed: N/D</td>
<td></td>
</tr>
<tr>
<td>Zullo 2000</td>
<td>Named trial: No RCT Jadad Score: 2 Population: N/D Comorbidities: N/D</td>
<td>1</td>
<td>Control or Usual care Control or Usual care for 6 Months</td>
<td>n Entered: 33, n Analyzed: 29</td>
<td>Statistical pooling performed: Excluded from statistical analysis because there were no outcomes of interest.</td>
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<tr>
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<td>Vitamin C 500 mg orally for 6 Months</td>
<td>n Entered: 32, n Analyzed: 29</td>
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</table>


Anderson D. Factors that contribute to biomarker responses in humans including a study in individuals taking Vitamin C supplementation. *Mutat Res.* 2001;480-481:337-47.


Collins R. Randomized trial of cholesterol-lowering therapy and antioxidant vitamin supplementation in over 20,000 higher-risk patients. J Am Coll Cardiol. 1999;33(2 suppl A):263A.


Herman ZS. The application of the Hardin Jones-Pauling biostatistical theory of survival analysis for cancer patients to a clinical trial purporting to test the efficacy of vitamin C in lengthening the survival times of patients with advanced colorectal cancer. J Orthomol Med. 1998;13(4):225-32.


Appendix A. Acknowledgments

Reviewers

We gratefully acknowledge the following individuals who reviewed the initial draft of this report and provided us with constructive feedback. Acknowledgments are made with the explicit statement that this does not constitute endorsement of the report.

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Los Angeles CA
Appendix B. Search Methodologies

Coenzyme Q10 And Cancer Prevention/Treatment
Search Methodology

SEARCH #1 (PERFORMED 11/16/01)

DATABASES SEARCHED/TIME PERIOD COVERED:

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<td>CAB HEALTH</td>
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<td>Biosis Previews</td>
<td>1969-2001/Nov W2</td>
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<tr>
<td>EMBASE</td>
<td>1974-2001/Nov W2</td>
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<tr>
<td>Social SciSearch</td>
<td>1972-2001/Nov W3</td>
</tr>
<tr>
<td>ELSEVIER BIOBASE</td>
<td>1994-2001/Nov W2</td>
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SEARCH STRATEGY:
ubiquinone OR ubidecarenone OR coenzyme q10 OR co-enzyme q10 OR coenzyme q 10 OR co-enzyme q 10 OR coenzyme q-10 OR co-enzyme q-10

AND

neoplasms(exploded) from Medline OR malignant neoplastic disease(exploded) from Embase OR cancer* in title or subject heading field from all other databases (exception – In CancerLit the terms for cancer were omitted and just the total of “coenzyme q-10” terms were used”)

AND

Human

TOTAL NUMBER OF ITEMS RETRIEVED: 176
Vitamin C And Cancer Prevention/Treatment
Search Methodology

SEARCH #2a (PERFORMED 11/27/01)

DATABASES SEARCHED/TIME PERIOD COVERED:
- MEDLINE       1966-2001/Dec W4
- MANTIS       1880-2001/Aug
- Allied & Complementary Medicine 1984-2001/Dec
- CancerLit       1975-2001/Oct
- CAB HEALTH       1983-2001/Oct
- TGG Health&Wellness DB 1976-2001/Nov W2
- Biosis Previews 1969-2001/Nov W3
- EMBASE       1974-2001/Nov W3
- Social SciSearch 1972-2001/Nov W4
- ELSEVIER BIOBASE 1994-2001/Nov W4

SEARCH STRATEGY:
- ascorbic acid (exploded) from Medline, Embase OR ascorbic acid from all other databases OR dehydroascorbic acid* OR ascorbate OR vitamin c OR antiscorbutic vitamin* OR cevitamic acid*

AND

- neoplasms (exploded) from Medline OR malignant neoplastic disease (exploded) from Embase OR (cancer OR neoplasm*) in subject heading field from BIOSIS OR cancer* in title or subject heading field from all other databases OR neoplasm* from all other databases (exception – in CancerLit the terms for cancer were omitted and just the total of the “vitamin c” terms were used)

AND

- (prevention OR preventive OR therapy OR therapeutic OR treatment) in title, subject heading fields

AND

- human

TOTAL NUMBER OF ITEMS RETRIEVED: 1987
SEARCH #2b (PERFORMED 11/7/01)

DATABASES SEARCHED:
Cochrane Library

SEARCH STRATEGY:
vitamin c OR ascorbic acid OR ascorbate OR antiscorbutic vitamin OR cevitamic acid OR dehydroascorbic acid

AND

neoplasms(exploded)

TOTAL NUMBER OF ITEMS RETRIEVED:

The Cochrane Controlled Trials Register (CENTRAL/CCTR)
References - 92
Vitamin E And Cancer Prevention/Treatment
Search Methodology

SEARCH #3a (PERFORMED 12/13/01)

DATABASES SEARCHED/TIME PERIOD COVERED:
MEDLINE 1966-2001/Jan W1
MANTIS 1880-2001/Oct
Allied & Complementary Medicine 1984-2001/Jan
CancerLit 1975-2001/Oct
CAB HEALTH 1983-2001/Oct
TGG Health&Wellness DB 1976-2001/Nov W4
Biosis Previews 1969-2001/Dec W2
EMBASE 1974-2001/Dec W2
ELSEVIER BIOBASE 1994-2001/Dec W2

SEARCH STRATEGY:
Vitamin e (exploded) from Medline OR vitamin e OR alpha tocopherol* OR D1 alpha tocopherol* OR d alpha tocopherol OR rrr alpha tocopherol* OR all rac alpha tocopherol*

AND

neoplasms(exploded) from Medline OR malignant neoplastic disease(exploded) from Embase OR (cancer OR neoplasm*) in subject heading field from BIOSIS OR cancer* in title or subject heading field from all other databases OR neoplasm* from all other databases (exception – in CancerLit the terms for cancer were omitted and just the total of the “vitamin e” terms were used)

AND

(prevention OR preventive OR therapy OR therapeutic OR treatment) in title,subject heading fields

AND

human

TOTAL NUMBER OF ITEMS RETRIEVED: 1990
SEARCH #3b (PERFORMED 12/19/01)

DATABASES SEARCHED/TIME PERIOD COVERED:
Cochrane Library 1922-2001

SEARCH STRATEGY:
vitamin-e
AND
neoplasms (exploded) OR cancer*

TOTAL NUMBER OF ITEMS RETRIEVED:
Database of Abstracts of Reviews of Effectiveness
Abstracts of quality assessed systematic reviews: 1
The Cochrane Controlled Trials Register (CENTRAL/CCTR)References: 112
Co Q10 Synonyms + Cancer
Search Methodology

SEARCH #4 (PERFORMED 1/18/02)

DATABASES SEARCHED/TIME PERIOD COVERED:

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<td>1972-2002/Jan W3</td>
</tr>
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<td>ELSEVIER BIOBASE</td>
<td>1994-2002/Jan W2</td>
</tr>
</tbody>
</table>

SEARCH STRATEGY:
ubidecarenon? OR isoprostane? OR f2(2w)isoprostane?

AND

neoplasms(exploded) from Medline, Embase OR cancer* in title or subject heading field OR neoplasm* from all other databases (exception – in CancerLit the terms for cancer were omitted)

AND

human

TOTAL NUMBER OF ITEMS RETRIEVED: 127
### Appendix C. Antioxidant Screener

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<th>RAND EPC Alternative Medicine</th>
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</tr>
<tr>
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<td>Assigned on: mm/dd/yy</td>
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{article author, title, journal, date, vol, pages}

1. **Data Source:**
   - Article ............................................................ 1
   - Abstract of article .......................................... 2
   - Conference proceeding.................................. 3
   - Other (Specify_____________________) .... 4

2. **What topic does the article study:**
   - Vitamin C....................................................... π
   - Vitamin E....................................................... π
   - Co-Enzyme Q10 .............................................. π
   - Other (Specify______________________) .. π (STOP)
   - Unclear........................................................... π

3. **Condition(s) and/or disease(s) studied in article:**
   - Cancer ............................................................. π
   - Cardiovascular Disease.................................... π
   - No condition/disease...................................... π (STOP)
   - Other (Specify______________________) ... π (STOP)
   - Unclear.................................................................. π

4. **Subject Population:**
   - Human............................................................ π
   - In vitro / In vivo .............................................. π (STOP)
   - Animal ..................................................................... π (STOP)
   - Other (Specify______________________) .... π (STOP)
   - Unclear .................................................................. π

5. **Article Type:**
   - Historical/Descriptive/System/Bkgrd ............ π
   - Review/Meta-analysis...................................... π
   - Pharmacological .............................................. π
   - Clinical Study
     - Trial........................................................ π
     - Cohort.................................................. π
     - Other clinical study................................ π
     - Other (Specify______________________) .... π
     - Unclear........................................................... π

6. **How is the intervention being used in the study?**
   - Treatment....................................................... 1
   - Primary prevention........................................ 2
   - Secondary prevention..................................... 3
   - Adjunct to conventional treatment.............. 4
   - Other (Specify______________________) .... 5
   - Unclear........................................................... 6

7. **Language of Article:**
   - English........................................................... 1
   - Foreign........................................................... 2

**NOTES:**

---

**Abstract:**

---
 RAND EPC, CAM Project  
Quality Review Form, Topic = ANTIOXIDANT

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<th>Reviewer: ______________</th>
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<td>(Last Name Only)</td>
</tr>
<tr>
<td>Study Number: __ of ____</td>
<td>Description: ___________</td>
</tr>
<tr>
<td>(Enter ‘1 of 1’ if only one)</td>
<td>(if more than one study)</td>
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</table>

1. Design:  
   (circle one)  
   RCT .............................................................. 1  
   CCT .............................................................. 2  
   Other ........................................................... 3 (STOP)  
   *(If not RCT or CCT, change study design on cover sheet and STOP)*

2. What topic(s) does the study report on? ..............(check all that apply)  
   Vitamin C .......................................................... □  
   Vitamin E .......................................................... □  
   Co-Q10 ............................................................. □  
   None of the above ............................................. □ (STOP)

3. What condition(s) does the study report on?  
   (circle one)  
   Cardiovascular ................................................. 1  
   Cancer ............................................................ 2  
   Both .................................................................... 3  
   None .................................................................... 4 (STOP)

4. Is the study described as randomized?  
   (circle one)  
   Yes ....................................................................... 1  
   No ......................................................................... 2  

5. If the study was randomized, was the method of randomization 
   appropriate?  
   (circle one)  
   Yes ....................................................................... 1  
   No ......................................................................... 2  
   Method not described ........................................ 8  
   Not applicable ................................................. 9

6. If reported, was the method of double blinding appropriate?  
   (circle one)  
   Yes ....................................................................... 1  
   No ......................................................................... 2  
   Double blinding method not described ..................... 8  
   Not applicable ................................................. 9

7. If study was randomized, did the method of randomization 
   provide for concealment of allocation?  
   (circle one)  
   Yes ....................................................................... 1  
   No ......................................................................... 2  
   Concealment not described .................................... 8  
   Not applicable ................................................. 9

8. Are withdrawals (W) and dropouts (D) described?  
   (circle one)  
   Yes, reason described for all W and D .................... 1  
   Yes, reason described for some W and D ............... 2  
   Not described ...................................................... 8  
   Not applicable ................................................. 9

9. Is this a cross-over study design?  
   (circle one)  
   Yes ....................................................................... 1  
   No ......................................................................... 2  
   Not described ...................................................... 8
10. Does the study population include a purposefully selected group of individuals chosen because they have any of the following characteristics? (check all that apply)
   Race:
   - African-American ........................................... (01)
   - Asian ............................................................. (02)
   - Hispanic ........................................................... (03)
   Gender:
   - Male ....................................................................... (04)
   - Female ....................................................................... (05)
   Age:
   - Children (under 18) ............................................ (06)
   - Elderly (over 65) ................................................... (07)
   Miscellaneous:
   - Smokers ............................................................... (08)
   Other:
   - (Enter code: __ __, __ __, __ __, __ __, __ __, __ __, __ __, __ __, __ __)
   - None of the above ................................................. (97)

11. Does the study population include a purposefully selected group of individuals chosen because they have any of the following comorbidities? 
   (enter code or circle)
   Code: __ __, __ __, __ __, __ __, __ __, __ __
   Not applicable ......................................................... 99

12. Does the study population include a purposefully selected group of individuals chosen because they have any of the following predisposing factors? 
   (enter code or circle)
   Code: __ __, __ __, __ __, __ __, __ __, __ __
   Not applicable ......................................................... 99

13. If this study is from a larger trial, please note the name of original trial. 
   (circle one or enter code)
   ADMT ................................................................. (01)
   ATBC ................................................................. (02)
   CGPPP ................................................................. (03)
   CHAOS ............................................................... (04)
   GISSI/GIZZI ......................................................... (05)
   HOPE ................................................................. (06)
   MRC/BHF ............................................................. (07)
   PHS II ................................................................. (08)
   SPACE ............................................................... (09)
   SU.VI.MAX ........................................................... (10)
   WHI ................................................................. (11)
   WHS ................................................................. (12)
   Code: __ __
   Not from a larger trial ............................................. (99)
### Patient Characteristics – CARDIOVASCULAR

14. What type of cardiovascular disease did the study report on? (check all that apply and/or add code)

- CAD ........................................... (01)
- CVA/TIA ..................................... (02)
- PVD .......................................... (03)
- CHF .......................................... (04)
- Angina ...................................... (05)

   Code: _____ _____
   _____ _____
   _____ _____
   _____ _____

- Not Applicable ................................ (99)

15. What was the severity of the disease?

Enter code: _____ _____
(enter 99 if not applicable)

### Patient Characteristics – CANCER

16. What type of cancer did the study report on? (check all that apply and/or add code)

- Breast ........................................... (01)
- Lung ........................................... (02)
- Prostate ....................................... (03)
- Oral ............................................ (04)
- Cervix ......................................... (05)
- Gastric ........................................ (06)
- Colon .......................................... (07)

   Code: _____ _____
   _____ _____
   _____ _____
   _____ _____

- Not Applicable ................................ (99)

17. What was the severity of the disease? (check all that apply and/or add code)

- Pre-cancerous ................................ (01)
- Localized ..................................... (02)
- Metastatic .................................... (03)

   Other code: _____ _____

- Not Applicable ................................ (99)
If the study has a control/usual care arm, enter that data in arm 1. Otherwise, enter data for the groups in order of first mention.

18. What type of arm is this? (circle one)
   - Placebo ................................................................. 1
   - Usual care .............................................................. 2
   - Primary Antioxidant ............................................... 3
   - Other active treatment ......................................... 4

19. What was the sample size in this arm?  
   ___ ___ ___  ___ ___ ___  ___ ___ ___  ___ ___ ___  
   (Enter 999,999 if not reported.)

20. Intervention:

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Daily Dose</th>
<th>Units</th>
<th>Route of administration</th>
<th>Duration</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>___</td>
<td>___</td>
<td>taken</td>
<td>___</td>
<td>___</td>
</tr>
<tr>
<td>2</td>
<td>___</td>
<td>___</td>
<td>taken</td>
<td>___</td>
<td>___</td>
</tr>
<tr>
<td>3</td>
<td>___</td>
<td>___</td>
<td>taken</td>
<td>___</td>
<td>___</td>
</tr>
<tr>
<td>4</td>
<td>___</td>
<td>___</td>
<td>taken</td>
<td>___</td>
<td>___</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Enter code</th>
<th>Enter a number</th>
<th>1. µg</th>
<th>1. PO</th>
<th>Enter a number</th>
<th>1. Hour</th>
<th>8. Mean Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>998. ND</td>
<td>3. gm</td>
<td>8. ND</td>
<td>998. ND</td>
<td>3. Week</td>
<td>10. Maximum Month</td>
<td></td>
</tr>
<tr>
<td>8. ND</td>
<td>9. NA</td>
<td></td>
<td></td>
<td>5. Year</td>
<td>12. Maximum Year</td>
<td></td>
</tr>
<tr>
<td>9. NA</td>
<td></td>
<td></td>
<td></td>
<td>6. Mean Month</td>
<td>13. Minimum Year</td>
<td></td>
</tr>
</tbody>
</table>

Arm 1 of ___  Description: ___________________________
If the study has a control/usual care arm, enter that data in arm 1. Otherwise, enter data for the groups in order of first mention.

| Arm 2 of ___ | Description:______________________________ |

18. What type of arm is this? (circle one)
- Placebo .......................................................... 1
- Usual care .......................................................... 2
- Primary Antioxidant ........................................... 3
- Other active treatment ....................................... 4

19. What was the sample size in this arm?

___ ___ ___ , ___ ___ ___ , ___ ___ ___
Entering Completing

(Enter 999,999 if not reported.)

20. Intervention:

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Daily Dose</th>
<th>Units</th>
<th>Route of administration</th>
<th>Duration</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>_______</td>
<td>_______</td>
<td>taken</td>
<td>_______</td>
<td>_______</td>
</tr>
<tr>
<td>2</td>
<td>_______</td>
<td>_______</td>
<td>taken</td>
<td>_______</td>
<td>_______</td>
</tr>
<tr>
<td>3</td>
<td>_______</td>
<td>_______</td>
<td>taken</td>
<td>_______</td>
<td>_______</td>
</tr>
<tr>
<td>4</td>
<td>_______</td>
<td>_______</td>
<td>taken</td>
<td>_______</td>
<td>_______</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Enter code</th>
<th>Enter a number</th>
<th>1. µg</th>
<th>1. PO</th>
<th>Enter a number</th>
<th>1. Hour</th>
<th>8. Mean Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>998. ND</td>
<td>2. mg</td>
<td>2. IV</td>
<td></td>
<td></td>
<td>2. Day</td>
<td>9. Median Year</td>
</tr>
<tr>
<td>999. NA</td>
<td>3. gm</td>
<td>8. ND</td>
<td>998. ND</td>
<td></td>
<td>3. Week</td>
<td>10. Maximum Month</td>
</tr>
<tr>
<td>9. NA</td>
<td>8. ND</td>
<td></td>
<td></td>
<td></td>
<td>5. Year</td>
<td>12. Maximum Year</td>
</tr>
<tr>
<td></td>
<td>9. NA</td>
<td></td>
<td></td>
<td></td>
<td>6. Mean Month</td>
<td>13. Minimum Year</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7. Median Month</td>
<td>98. ND</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>99. NA</td>
</tr>
</tbody>
</table>

109
If the study has a control/usual care arm, enter that data in arm 1. Otherwise, enter data for the groups in order of first mention.

| Arm 3 of ___ | Description: ________________________________ |

18. What type of arm is this? (circle one)
- Placebo ................................................. 1
- Usual care .............................................. 2
- Primary Antioxidant ............................... 3
- Other active treatment ......................... 4

19. What was the sample size in this arm?

   ___ ___ ___ Enter a number
   ___ ___ ___  ___ ___ ___ Completing
(Enter 999,999 if not reported.)

20. Intervention:

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Daily Dose</th>
<th>Units</th>
<th>Route of administration</th>
<th>Duration</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 _______</td>
<td>_______</td>
<td>______</td>
<td>taken</td>
<td>_______</td>
<td>______</td>
</tr>
<tr>
<td>2 _______</td>
<td>_______</td>
<td>______</td>
<td>taken</td>
<td>_______</td>
<td>______</td>
</tr>
<tr>
<td>3 _______</td>
<td>_______</td>
<td>______</td>
<td>taken</td>
<td>_______</td>
<td>______</td>
</tr>
<tr>
<td>4 _______</td>
<td>_______</td>
<td>______</td>
<td>taken</td>
<td>_______</td>
<td>______</td>
</tr>
</tbody>
</table>

Enter code  

Enter a number  

1. µg  1. PO  1. Hour  8. Mean Year
2. mg  2. IV  2. Day  9. Median Year
3. gm  8. ND  998. ND  3. Week 10. Maximum Month
998. ND  3. gm  8. ND  998. ND  3. Week 10. Maximum Month
If the study has a control/usual care arm, enter that data in arm 1. Otherwise, enter data for the groups in order of first mention.

<table>
<thead>
<tr>
<th>Arm 4 of ___</th>
<th>Description: ________________________________</th>
</tr>
</thead>
</table>

18. What type of arm is this? (circle one)
- Placebo .......................................................... 1
- Usual care ......................................................... 2
- Primary Antioxidant .......................................... 3
- Other active treatment ....................................... 4

19. What was the sample size in this arm?

(Enter 999,999 if not reported.)

---

20. Intervention:

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Daily Dose</th>
<th>Units</th>
<th>Route of administration</th>
<th>Duration</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>___</td>
<td>_____</td>
<td>taken</td>
<td>_____</td>
<td>_____</td>
</tr>
<tr>
<td>2</td>
<td>___</td>
<td>_____</td>
<td>taken</td>
<td>_____</td>
<td>_____</td>
</tr>
<tr>
<td>3</td>
<td>___</td>
<td>_____</td>
<td>taken</td>
<td>_____</td>
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<tr>
<td>4</td>
<td>___</td>
<td>_____</td>
<td>taken</td>
<td>_____</td>
<td>_____</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Enter code</th>
<th>Enter a number</th>
<th>1. µg</th>
<th>1. PO</th>
<th>Enter a number</th>
<th>1. Hour</th>
<th>8. Mean Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>998. ND</td>
<td>3. gm</td>
<td>8. ND</td>
<td>998. ND</td>
<td>3. Week</td>
<td>10. Maximum Month</td>
<td></td>
</tr>
<tr>
<td>8. ND</td>
<td>9. NA</td>
<td>999. NA</td>
<td>5. Year</td>
<td>12. Maximum Year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>99. NA</td>
<td></td>
<td></td>
<td>6. Mean Month</td>
<td>13. Minimum Year</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>7. Median Month</td>
<td>98. ND</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>99. NA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---
### Outcomes

21. Type of outcomes measured:

<table>
<thead>
<tr>
<th>Enter the code for each outcome measured.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

### Evaluation

22. When, relative to the start of the intervention, were outcomes reported?

Enter the number and letters in the appropriate box

<table>
<thead>
<tr>
<th>Number</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>follow-up</td>
</tr>
<tr>
<td>2nd</td>
<td>follow-up</td>
</tr>
<tr>
<td>3rd</td>
<td>follow-up</td>
</tr>
<tr>
<td>4th</td>
<td>follow-up</td>
</tr>
<tr>
<td>5th</td>
<td>follow-up</td>
</tr>
<tr>
<td>6th</td>
<td>follow-up</td>
</tr>
<tr>
<td>Additional follow-ups:</td>
<td></td>
</tr>
</tbody>
</table>

Use the following abbreviations for units:

- MI minute
- HR hour
- DY day
- WK week
- MO month
- YR year
- YRMN mean for year
- YRME median for year
- YRMI minimum for year
- MOMN mean for month
- MOME median for month
- MOMX maximum for month
- MOMI minimum for month
- ND not described
- NA not applicable

23. Is there a sub-group analysis? **(circle one)**

- Yes ................................................................. 1
- No ............................................................... 2

If yes, code

| _____ _____ |
| _____ _____ |
| _____ _____ |
| _____ _____ |