Evidence Report/Technology Assessment

Number 75

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

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
http://www.ahrq.gov

Contract No. 290-97-0001

Prepared by:
Southern California Evidence-based Practice Center
Paul Shekelle, MD, PhD
EPC Director

Ian Coulter, PhD
Mary Hardy
Principal Investigators

Sally C. Morton, PhD
EPC Co-Director/Senior Statistician

Jay Udani, MD
Myles Spar, MPH, MD
Karen Oda, MD
Lara K. Jungvig, BA
Wenli Tu, MS
Roberta Shanman, MLS
Sydne Newberry, PhD
Louis R. Ramirez, BA
Di Valentine, JD
Investigators

AHRQ Publication No. 04-E003
August 2003

This report may be used, in whole or in part, as the basis for development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies. Endorsement by the Agency for Healthcare Research and Quality (AHRQ) or the U.S. Department of Health and Human Services (DHHS) of such derivative products may not be stated or implied.

AHRQ is the lead Federal agency charged with supporting research designed to improve the quality of health care, reduce its cost, address patient safety and medical errors, and broaden access to essential services. AHRQ sponsors and conducts research that provides evidence-based information on health care outcomes; quality; and cost, use, and access. The information helps heath care decisionmakers—patients and clinicians, health system leaders, and policymakers—make more informed decisions and improve the quality of health care services.

ISBN: 1-58736-091-5

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.

Carolyn Clancy, M.D.
Director
Agency for Healthcare Research and Quality

Jean R. Slutsky, P.A., M.S.P.H.
Acting Director
Center for Practice and Technology Assessment
Agency for Healthcare Research and Quality

The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services of a particular drug, device, test, treatment, or other clinical service.

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 Calmetee-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.

Suggested Citation:
Coulter I, Hardy M, Shekelle P, et al. Effect of the Supplemental Use of Antioxidants Vitamin C, Vitamin E, and Coenzyme Q10 for the Prevention and Treatment of Cancer. Evidence Report/Technology Assessment Number 75. (Prepared by Southern California Evidence-based Practice Center under Contract No. 290-97-0001.) AHRQ Publication No. 04-E003. Rockville, MD: Agency for Healthcare Research and Quality. August 2003.

Contents

Agency for Healthcare Research and Quality

Evidence Report/Technology Assessment

Number 75

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

Thirteen biomedical databases were searched through early 2002: Allied and Complementary Medicine, BIOSIS Previews®, CAB HEALTH®, CANCER LIT®, Cochrane Library, Elsevier Biobase, EMBASE, MANTIS™, MEDLINE®, SciSearch® Cited Ref Sci 1974-1989, Social SciSearch® 1972-2002, SciSearch® Cited Ref Sci

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES • Public Health Service

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*.

www.ahrq.gov
AHRQ Pub. No. 04-E002
October 2003

ISSN 1530-440X

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.[1] 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.[2] 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.[3] 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.[4] 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…"[4] 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.[5] 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[4] 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.[6] 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[7] 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.[5] 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.[6]

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,[9] 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 Pro-Cite 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[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.[13] A score for quality was calculated for each trial using a system developed by Jadad.[14] The Jadad score rates studies on a 0 to 5 scale.[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.[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.[16] 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[17] and performed statistical and meta-analytic methods in the statistical package Stata.[18]

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 that 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[21] and a regression asymmetry test[22] as formal statistical tests for publication bias.

Table 1. Biomedical and other databases searched.

Database	Years
Allied & Complementary Medicine	1984-2001 Feb
Biosis Previews	1969-2002 Jan
CAB Health	1983-2001 Dec
CancerLit	1975-2001 Oct
Cochrane Library Database of Systematic Reviews Controlled Trials Register	1922- 2001
Elsevier Biobase	1994-2002 Jan
Embase	1974-2002 Jan
MANTIS	1880-2001 Oct
Medline	1966-2002 Jan
SciSearch Cited Ref Sci	1974-1989 Dec
Social SciSearch(R)	1972-2002 Jan
SciSearch Cited Ref Sci	1990-2002 Jan
TGG Health&Wellness DB	1976-2002 Dec

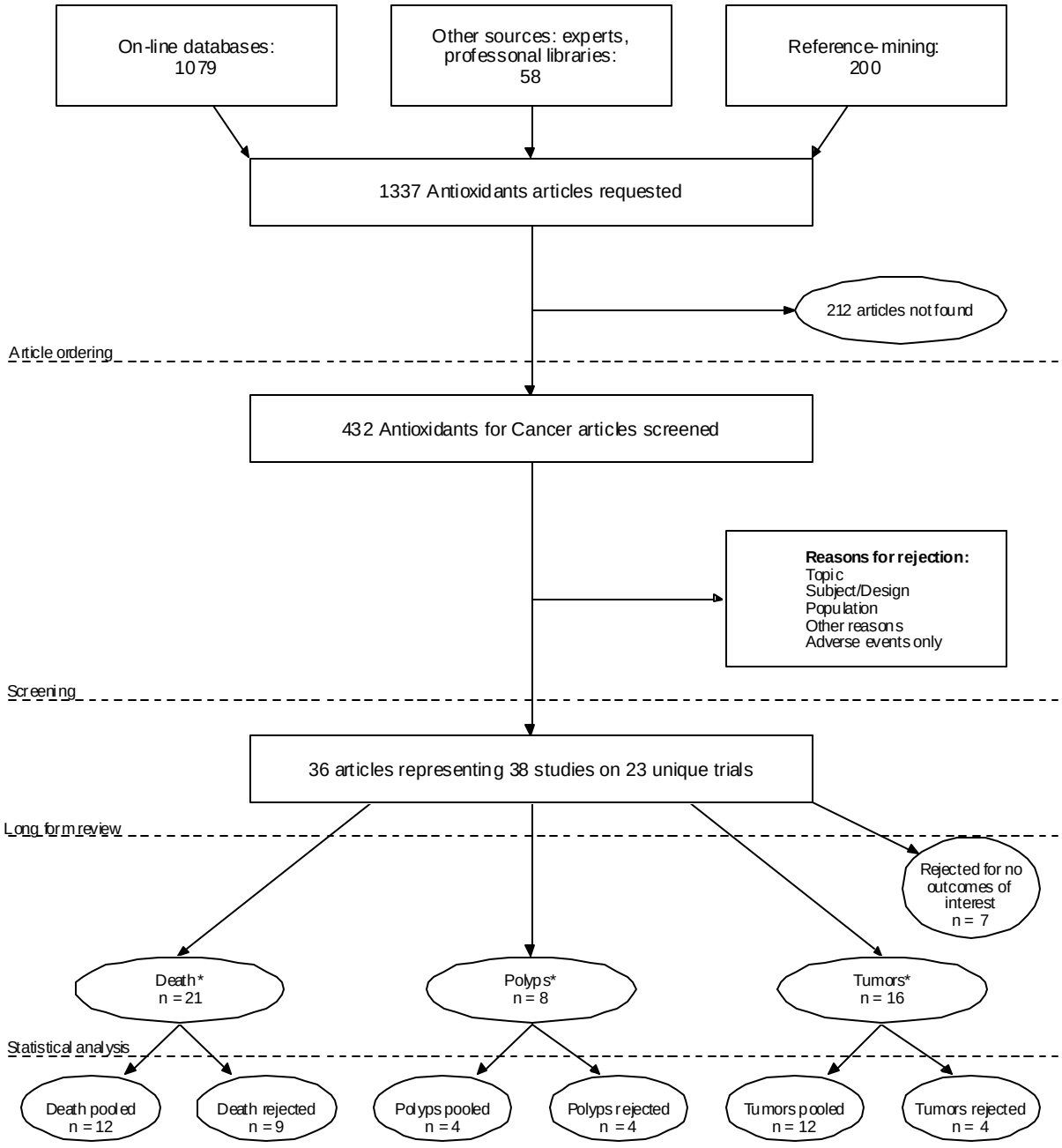
Table 2. Additional search items for antioxidants studied.

Vitamin C	Vitamin E	Co-enzyme Q-10
ascorbic acid	alpha tocopherol	ubiquinone
dehydroascorbic acid		ubidecarenone
ascorbate		ubidecarenon
antiscorbutic vitamin		isoprostane
cevitamic acid		

Table 3. Summary of search strategy.

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

Figure 1. Literature Flow.



***** *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 articles[11, 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 these[27, 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 study[28] had insufficient statistics for analysis. The Moertel study[33] 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.[32] 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[40] 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[40] study in the A+D arm (cancer death RR = 0.75 (0.57, 1.00)).

Li and colleagues32 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[31] evaluated the effect on patients with transitional cell carcinoma of the bladder of intravesicular and/or percutaneously administered bacillus Calmetee-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[41] for the efficacy of high-dose vitamin C to prolong survival in cancer patients.[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[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,[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[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[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[12] 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[27, 28, 33] and one additional study of the efficacy of vitamin E to treat advanced stage cancer[29] were not included in the analysis. These results are described briefly here.

Creagan, Moertel, O'Fallon, and colleagues[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.[42] They had enrolled the first 128 of the expected 160 patients.

Finally, Moertel, Fleming, Creagan, and colleagues[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[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.[11 (Studies A&B), 12 (Study A), 24, 31, 33, 34, 37-40, 43-45] Four studies from the Linxian Trials were excluded for inadequate statistics.[11, 12, 40] 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[45] 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[39] 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,[24] 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[30] 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[38] 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[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[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[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[12] reported on the development of new gastric and esophageal cancers in the General Population Trial. Three of these studies[12, 32, 43] reported on similar outcomes from the Dysplasia portion of the Linxian Trial. One of these studies[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[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[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[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[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[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[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,[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.[11 (Studies A&B), 12 (Study A), 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[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[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.[47-54] Two studies by Roncucci[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[52] while two trials[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[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[47] 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[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[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,[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, 49] 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 McKeowen-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.[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,[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[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[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[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.[55-61]

Two trials evaluated the effects of antioxidants on the development or progression of risk factors for gastric cancer.[56, 62] One of the widely recognized precursors to intestinal gastric carcinoma is chronic atrophic gastritis with intestinal metaplasia. Zullo, Rinaldi, Hassan, and colleagues[56] conducted a randomized, controlled trial using vitamin C in patients with chronic atrophic gastritis. Following eradication of *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,[62] subjects (n = 631 who completed at 72 months) were randomly assigned to one of 8 arms of the study: placebo; anti-*Helicobacter pylori* triple therapy; beta-carotene; vitamin C; anti-*Helicobacter pylori* plus beta-carotene; anti-*Helicobacter pylori* plus vitamin C; beta-carotene plus vitamin C; anti-*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-*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 (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.[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[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[55] 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.[57] Mackerras et al[57] 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 l. 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.[58] 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[64] 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.

Study	Author, Year	Type of death	Intervention	Sample Size	FU Time	# of deaths	RR (95% CI)
ATBC	Albanes, 1996[24]	Lung cancer	AT	7286	6.1 yrs	125	0.93 (0.73, 1.19)
			AT+BC	7278		154	1.15 (0.91, 1.45)
			Placebo	7287		134	
	Heinonen, 1998[30]	Prostate cancer	AT	7286	6.1 yrs	11	0.61 (0.29, 1.29)
			AT+BC	7278		12	0.67 (0.32, 1.38)
			Placebo	7287		18	
	Albanes, 2000[25]	Colorectal cancer	AT	7286	6.1 yrs	12	1.09 (0.48, 2.47)
			AT+BC	7278		13	1.18 (0.53, 2.64)
			Placebo	7287		11	
	Virtamo, 2000[38]	Urothelial cancer	AT	7286	6.1 yrs	6	1.20 (0.37, 3.93)
			AT+BC	7278		8	1.60 (0.52, 4.89)
			Placebo	7287		5	
	Virtamo, 2000[38]	Renal cell cancer	AT	7286	6.1 yrs	11	0.79 (0.36, 1.73)
			AT+BC	7278		10	0.72 (0.32, 1.61)
			Placebo	7287		14	
	Albanes, 1996,[24] 2000[25]; Virtamo, 2000[38]	Combined cancer (lung, colorectal, urothelial, and renal cell)	AT	7286	6.1 yrs	165	0.91 (0.74, 1.12)
			AT+BC	7278		197	1.08 (0.89, 1.32)
			Placebo	7287		182	
	Alpha-Tocopherol, 1994[39]	All cause	AT	14564	6.1 yrs	1798	1.02 (0.96, 1.08)
			no AT	14569		1768	
		Lung cancer	AT	14564	6.1 yrs	285	1.02 (0.87, 1.20)
			no AT	14569		279	
	Rautalahti, 1999[37]	Pancreas cancer	AT	14564	6.1 yrs	49	1.44 (0.93, 2.23)
			no AT	14569		34	

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.

Study	Author, Year	Type of death	Intervention	Sample Size	FU Time	# of deaths	RR (95% CI)
Linxian Dysplasia	Li, 1993[32]	All cause	Supplement	1657	6 yrs	157	0.94 (0.77, 1.16)
			Placebo	1661		167	
	Li, 1993[32]	Cancer	Supplement	1657		87	0.98 (0.74, 1.31)
			Placebo	1661		89	
	Li, 1993[32]	Esophageal Cancer	Supplement	1657		38	0.87 (0.56, 1.33)
			Placebo	1661		44	
Linxian General Population	Blot, 1993[40]	All cause	*A+B*	3701	5.25 yrs	265	0.94 (0.80, 1.11)
			A+C	3694		296	1.05 (0.90, 1.23)
			A+D	3703		250	0.89 (0.75, 1.05)
			B+C	3691		268	0.95 (0.81, 1.12)
			B+D	3699		263	0.93 (0.79, 1.10)
			C+D	3705		249	0.88 (0.75, 1.04)
			A+B+C+D	3712		256	0.91 (0.77, 1.07)
			Placebo	3679		280	
			C	14802		1069	1.01 (0.93, 1.10)
			No *C*	14782		1058	
			D	14819		1018	0.91 (0.84, 0.99)
			No *D*	14765		1109	
	Blot, 1993[40]	Cancer death	*A+B*	3701	5.25 yrs	94	0.87 (0.66, 1.15)
			A+C	3694		121	1.13 (0.87, 1.45)
			A+D	3703		81	0.75 (0.57, 1.00)
			B+C	3691		101	0.94 (0.72, 1.23)
			B+D	3699		103	0.96 (0.73, 1.25)
			C+D	3705		90	0.84 (0.63, 1.10)
			A+B+C+D	3712		95	0.88 (0.67, 1.16)
			Placebo	3679		107	
			C	14802		407	1.06 (0.92, 1.21)
			No *C*	14782		385	
			D	14819		369	0.87 (0.76, 1.00)
			No *D*	14765		423	
Other trials	Lamm, 1994[31]	All cause	Megadose vitamins	35	45 mos	8	0.86 (0.37, 2.01)
			RDA	30		8	
	MRC/BHF, 2002[34]		Vitamins	10269	5 yrs	1446	1.04 (0.97, 1.11)
	Nutr Rev, 1985[35]	All cause	*C*	25	1 yr	51	1.04 (0.69, 1.57)
			Placebo	23		49	
	Poulter, 1984[36]	All cause	*C*	27	5 yrs	12	1.52 (0.72, 3.23)
			Control	24		7	

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.

Study	Lead Author, Yr	Type of Tumor	Intervention	Sample size	FU time	# of patients with new tumor	RR (95% CI)
ATBC	Albanes, 1996[24]	Lung cancer	AT	7286	6.1 yrs	204	0.98 (0.81, 1.19)
			AT+BC	7278		240	1.16 (0.96, 1.39)
			Placebo	7287		208	
	Albanes, 2000[25]	Colorectal cancer	AT	7286	6.1 yrs	29	0.78 (0.48, 1.27)
			AT+BC	7278		30	0.81 (0.50, 1.31)
			Placebo	7287		37	
	Heinonen, 1998[30]	Prostate cancer	AT	7286	6.1 yrs	43	0.64 (0.44, 0.94)
			AT+BC	7278		56	0.84 (0.59, 1.19)
			Placebo	7287		67	
	Rautalahti, 1999[37]	Pancreas cancer	AT	7286	6.1 yrs	25	0.96 (0.56, 1.66)
			AT+BC	7278		26	1.00 (0.58, 1.72)
			Placebo	7287		26	
			AT	14564		51	1.34 (0.88, 2.04)
			no AT	14569		38	
	Virtamo, 2000[38]	Urothelial cancer	AT	7286	6.1 yrs	47	1.27 (0.83, 1.95)
			AT+BC	7278		42	1.14 (0.73, 1.77)
			Placebo	7287		37	
	Virtamo, 2000[38]	Renal cell cancer	AT	7286	6.1 yrs	27	1.00 (0.59, 1.70)
			AT+BC	7278		27	1.00 (0.59, 1.71)
			Placebo	7287		27	
	Albanes 1996[24] and 2000,[25] Heinonen, 1998,[30] Rautalahti, 1999,[37] Virtamo, 2000[38]	Combined types of tumor: (lung, colorectal, prostate, pancreas, urothelial and renal cell)	AT	7286	6.1 yrs	375	0.93 (0.81, 0.81)
			AT+BC	7278		421	1.05 (0.92, 1.20)
			Placebo	7287		402	
	Alpha-Tocopherol, 1994[39]	Lung cancer	AT	14564	6.1 yrs	433	0.98 (0.86, 1.11)
			no AT	14569		443	
	Varis, 1998[45]	Carcinoma	AT	321	6.1 yrs	2	1.04 (0.15, 7.32)
			BC	329		3	1.52 (0.26, 9.03)
			AT+BC	361		4	1.84 (0.34, 10.01)
			Placebo	333		2	

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

Study	Lead Author, Year	Type of Tumor	Intervention	Sample size	*FU time*	# of patients with new tumor	RR (95% CI)
Linxian Dysplasia	Dawsey, 1994[43]	Esophageal cancer	Supplement	392	30 mos	16	0.78 (0.41, 1.49)
			Placebo	362		19	
			Supplement	195	6 yrs	8	1.53 (0.51, 4.58)
			Placebo	186		5	
	Dawsey, 1994[43]	Gastric cancer	Supplement	43	30 mos	13	1.63 (0.75, 3.52)
			Placebo	43		8	
			Supplement	202	6 yrs	18	0.91 (0.49, 1.68)
			Placebo	194		19	
	Dawsey, 1994[43]	Overall biopsy	Supplement	400	30 mos	29	0.99 (0.60, 1.64)
			Placebo	368		27	
			Supplement	202	6 yrs	23	0.92 (0.54, 1.57)
			Placebo	194		24	
	Li, 1993[32]	All cancer	Supplement	1657	6 yrs	227	1.03 (0.87, 1.22)
			Placebo	1661		221	
	Li, 1993[32]	Esophageal cancer	Supplement	1657	6 yrs	123	0.96 (0.76, 1.22)
			Placebo	1661		128	
	Li, 1993[32]	Stomach cancer	Supplement	1657	6 yrs	96	1.19 (0.89, 1.58)
			Placebo	1661		81	
Linxian General Population	Taylor, 1994[12]	Esophageal cancer	*C*	201	6 yrs	4	1.18 (0.27, 5.20)
			No *C*	178		3	
			D	173		3	0.71 (0.17, 2.95)
			No *D*	206		5	
	Taylor, 1994[12]	Gastric cancer	*C*	205	6 yrs	6	2.71 (0.55, 13.25)
			No *C*	185		2	
			D	176		4	1.22 (0.31, 4.79)
			No *D*	214		4	
Other Trials	Lamm, 1994[31]		Megadose vitamins	35	6 yrs	14	0.50 (0.32, 0.78)
			RDA	30		24	
	MRC/BHF, 2002[34]		Vitamins	10269	5 yrs	800	0.98 (0.89, 1.08)
			Placebo	10267		817	

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

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

Article	Intervention	Total n	Risk Ratio	95% CI	
Greenberg, 1994[47]	C+E only	751	1.06	(0.82,	1.37)
McKeown-Eyssen, 1988[49]	C+E only	137	0.82	(0.57,	1.18)

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

Article	Intervention	Total n	Risk Ratio	95% CI	
Greenberg, 1994[47]	C+AT+BC	751	1.04	(0.79,	1.36)
Hofstad, 1998[48]	C+AT+BC+Ca	93	0.71	(0.50,	1.01)
Roncucci, 1993[50]	C+AT+A	209	0.16	(0.06,	0.43)
Pooled Random Effects Estimate			0.60[(1)]	(0.31,	1.16)

[(1)] 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.

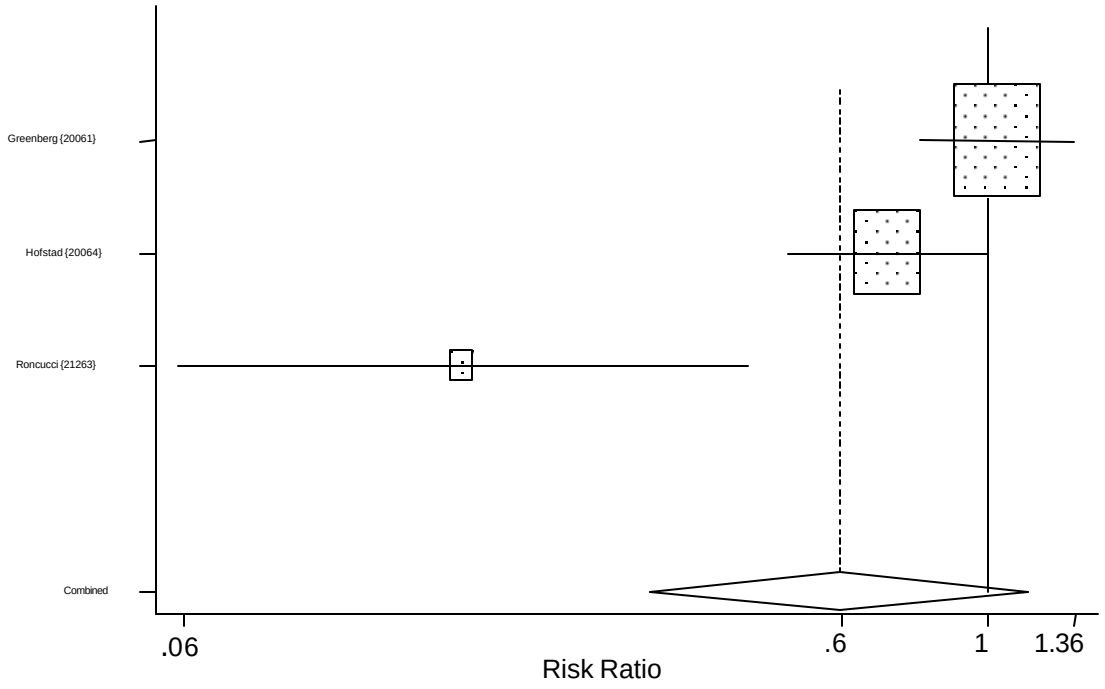
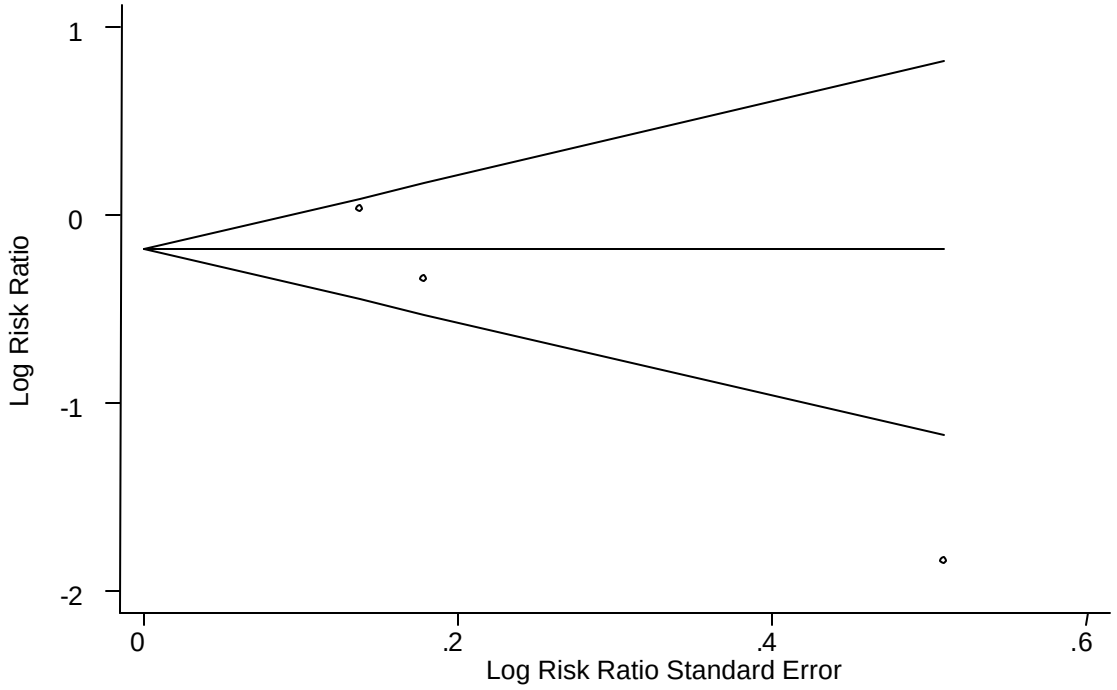


Figure 3. Publication Bias for Polyps Outcome.



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 beta-carotene 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.[14] 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[65] 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

1. IOM (Institute of Medicine); Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids. Washington, DC: National Academy Press; 2000.

2. Block G, Levine M. Vitamin C: a new look. Ann Intern Med. 1991;114:909-10.

3. Young VR, Newberne PM. Vitamins and cancer prevention: issues and dilemmas. Cancer. 1981;47(suppl 5):1226-40.

4. Halliwell B. Free radicals, antioxidants, and human disease: curiosity, cause or consequence? Lancet. 1994;344:721-24.

5. Uddin S, Ahmad S. Antioxidants protection against cancer and other human diseases. Compr Ther. 1995;21(1):41-5.

6. van Poppel G, van den Berg H. Vitamins and cancer. Cancer Lett. 1997;114(1-2):195-202.

7. van Zandwijk N, Pastorino U, de Vries N. Chemoprevention of cancer. Eur Respir J. 1993;6(3):322-4.

8. Overvad K, Diamant B, Holm L, Holmer G, Mortensen SA, Stender S. Coenzyme Q10 in health and disease. Eur J Clin Nutr. 1999;53(10):764-70.

9. Hattersley JG. Coenzyme Q10 and cancer. J Orthomol Med. 1996;11. 2:111-2.

10. Pepping J. Coenzyme Q10. Am J Health Syst Pharm. 1999;56(6):519-21.

11. Li B, Taylor PR, Li JY, et al. Linxian nutrition intervention trials: design, methods, participant characteristics, and compliance. Ann Epidemiol. 1993;3:577-85.

12. Taylor PR, Li B, Dawsey SM, et al. Prevention of esophageal cancer: the nutrition intervention trials in Linxian, China. Linxian Nutrition Intervention Trials Study Group Cancer Res. 1994;54(suppl 7):2029s-2031s.

13. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA. 1995;273(5):408-12.

14. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17(1):1-12.

15. Moher D, Pham B, Jones A, et al. Does the poor quality of reports of randomized trials exaggerate estimates of intervention effectiveness reported in meta-analyses. Lancet. 1998;352(9128):609-613.

16. SAS Institute. SAS/STAT [computer program]. Version 8. Cary, NC: SAS Institute Inc.; 1999.

17. Microsoft Excel for Windows 2000 [computer program]. Redmond, WA: Microsoft Corporation; 2000.

18. Stata Statistical Software: Release 6.0 [computer program]. Version 6.0. College Station, TX: Stata Corporation; 1999.

19. DerSimonian R, Laird N. Meta-analysis in clinical trials Controlled Clinical Trials. 1986;7(3):177-188.

20. Hedges LV, Olkin I; Statistical Methods for Meta-Analysis. San Diego, CA: Academic Press, Inc.; 1985.

21. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994;50 (4):1088-1101.

22. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629-634.

23. Albanes D, Virtamo J, Rautalahti M, et al. Pilot study: The US-Finland lung cancer prevention trial. J Nutr Growth Cancer. 1986;3:207-14.

24. Albanes D, Heinonen OP, Taylor PR, et al. Alpha-Tocopherol and beta-carotene supplements and lung cancer incidence in the alpha-tocopherol, beta-carotene cancer prevention study: effects of base-line characteristics and study compliance. J Natl Cancer Inst. 1996;88(21):1560-70.

25. Albanes D, Malila N, Taylor PR, et al. Effects of supplemental alpha-tocopherol and beta-carotene on colorectal cancer: results from a controlled trial (Finland). Cancer. Causes Control. 2000;11(3):197-205.

26. Blot W. Preventing cancer by disrupting progression of precancerous lesions. J Natl Cancer. Inst. 2000;92(23):1868-9.

27. Creagan ET, Moertel CG, O'Fallon JR, et al. Failure of high-dose vitamin C (ascorbic acid) therapy to benefit patients with advanced cancer: a controlled trial. N Engl J Med. 1979;301(13):687-90.

28. Creagan, E T , Moertel, C G, Schutt A J, and O'Connell M J. Vitamin-c (ascorbic-acid) therapy of pre-terminal cancer-patients. [abstract]. *Proc Am Assoc Cancer Res.* 79;20:355.

29. Gogos CA, Ginopoulos P, Salsa B, Apostolidou E, Zoumbos NC, Kalfarentzos F. Dietary omega-3 polyunsaturated fatty acids plus vitamin E restore immunodeficiency and prolong survival for severely ill patients with generalized malignancy: a randomized control trial. Cancer. 1998;82(2):395-402.

30. Heinonen OP, Albanes D, Virtamo J, et al. Prostate cancer and supplementation with alpha-tocopherol and beta-carotene: incidence and mortality in a controlled trial. J Natl Cancer Inst. 1998;90 :414-15.

31. Lamm D, Riggs DR, Shriver JS, vanGilder PF, Rach JF, DeHaven JI. Megadose vitamins in bladder cancer: a double-blind clinical trial. J Urol. 1994;151(1):21-6.

32. Li J, Taylor P, Li B, et al. Nutrition intervention trials in Linxian, China: multiple vitamin/mineral supplementation, cancer incidence, and disease-specific mortality among adults with esophageal dysplasia. J Natl Cancer Inst. 1993;85(18):1492-8.

33. Moertel CG, Fleming TR, Creagan ET, Rubin J, O'Connell MJ, Ames MM. High-dose vitamin C versus placebo in the treatment of patients with advanced cancer who have had no prior chemotherapy: a randomized double-blind comparison. N Engl J Med. 1985;312(3):137-41.

34. MRC/BHF Heart Protection Study Collaborative group. MRC/BHF Heart Protection Study of antioxidant vitamin supplementation in 20536 high-risk individuals: a randomised placebo-controlled trial. Lancet. 2002;360:23-33.

35. Ascorbic acid does not cure cancer. Nutr Rev. 1985;43(5):146-7.

36. Poulter JM, White WF, Dickerson JW. Ascorbic acid supplementation and five year survival rates in women with early breast cancer. Acta Vitaminol Enzymol. 1984;6(3):175-82.

37. Rautalahti MT, Virtamo JR, Taylor PR, et al. The effects of supplementation with alpha-tocopherol and beta-carotene on the incidence and mortality of carcinoma of the pancreas in a randomized, controlled trial. Cancer. 1999;86(1):37-42.

38. Virtamo J, Edwards BK, Virtanen M, et al. Effects of supplemental alpha-tocopherol and beta-carotene on urinary tract cancer: incidence and mortality in a controlled trial (Finland). Cancer Causes Control. 2000;11(10):933-9.

39. Alpha-Tocopherol B-CCPSG. The effects of vitamin E and beta-carotene on the incidence of lung cancer and other cancers in male smokers. N Engl J Med. 1994;330:1029-35.

40. Blot W, Li JY, Taylor PR, et al. Nutrition intervention trials in Linxian, China: supplementation with specific vitamin/mineral combinations, cancer incidence, and disease-specific mortality in the general population. J Natl Cancer Inst. 1993;85(18):1483-92.

41. Pauling L, Moertel C. A proposition: megadoses of vitamin C are valuable in the treatment of cancer. Nutr Rev. 1986;44(1):28-32.

42. Creagan ET, Moertel CG. Vitamin C therapy of advanced cancer. N Engl J Med. 1979;301(25):1399.

43. Dawsey SM, Wang GQ, Taylor PR, et al. Effects of vitamin/mineral supplementation on the prevalence of histological dysplasia and early cancer of the esophagus and stomach: results from the Dysplasia Trial in Linxian, China. Cancer Epidemiol Biomarkers Prev. 1994;3(2):167-72.

44. Heinonen OP, Albanes D, Virtamo J, et al. Prostate cancer and supplementation with alpha-tocopherol and beta-carotene: incidence and mortality in a controlled trial. J Natl Cancer Inst. 1998;90 :414-15.

45. Varis K, Taylor PR, Sipponen P, et al. Gastric cancer and premalignant lesions in atrophic gastritis: a controlled trial on the effect of supplementation with alpha-tocopherol and beta-carotene. The Helsinki Gastritis Study Group. Scand J Gastroenterol. 1998;33(3):294-300.

46. Li B, Taylor PR, Li JY, et al. Linxian nutrition intervention trials: design, methods, participant characteristics, and compliance. Ann Epidemiol. 1993;3:577-85.

47. Greenberg ER, Baron JA, Tosteson TD, et al. A clinical trial of antioxidant vitamins to prevent colorectal adenoma. N Engl J Med. 1994; 331:141-47.

48. Hofstad B, Almendingen K, Vatn M, et al. Growth and recurrence of colorectal polyps: a double-blind, three-year intervention with calcium and antioxidants. Digestion. 1998;59:148-56.

49. McKeown-Eyssen G, Holloway C, Jazmaji V, Bright-See E, Dion P, Bruce WR. A randomized trial of vitamins C and E in the prevention of recurrence of colorectal polyps. Cancer Res. 1988;48(16):4701-5.

50. Roncucci L, Di Donato P, Carati L, et al. Antioxidant vitamins or lactulose for the prevention of the recurrence of colorectal adenomas. Colorectal Cancer Study Group of the University of Modena and the Health Care District 16. Dis Colon Rectum. 1993;36(3):227-34.

51. Roncucci L, Ponz de Leon M. Antioxidant vitamins or lactulose as chemopreventive agents for colorectal cancer. In: Waldron K, Johnson I, Fenwick G, eds. *Food and Cancer Prevention: Chemical and Biological Aspects*. Cambridge, UK: Royal Society of Cambridge; 1993:p.147-150.

52. Malila N, Virtamo J, Virtanen M, Albanes D, Tangrea JA, Huttunen JK. The effect of alpha-tocopherol and beta-carotene supplementation on colorectal adenomas in middle-aged male smokers. Cancer Epidemiol Biomarkers Prev. 1999;8(6):489-93.

53. DeCosse JJ, Miller HH, Lesser ML. Effect of wheat fiber and vitamins C and E on rectal polyps in patients with familial adenomatous polyposis. J Natl Cancer Inst. 1989;81(17):1290-7.

54. Bussey HJ, DeCosse JJ, Deschner EE, et al. A randomized trial of ascorbic acid in polyposis coli. Cancer. 1982;50(7):1434-9.

55. Zaridze D, Evstifeeva T, Boyle P. Chemoprevention of oral leukoplakia and chronic esophagitis in an area of high incidence of oral and esophageal cancer. Ann Epidemiol. 1993;3(3):225-34.

56. Zullo A, Rinaldi V, Hassan C, et al. Ascorbic acid and intestinal metaplasia in the stomach: a prospective, randomized study. Aliment Pharmacol Ther. 2000;14(10):1303-9.

57. Mackerras D, Irwig L, Simpson JM, et al. Randomized double-blind trial of beta-carotene and vitamin C in women with minor cervical abnormalities. Br J Cancer. 1999;79(9-10):1448-53.

58. Cahill RJ, O'Sullivan KR, Mathias PM, Beattie S, Hamilton H, O'Morain C. Effects of vitamin antioxidant supplementation on cell kinetics of patients with adenomatous polyps. Gut. 1993;34(7):963-7.

59. Zullo A, Rinaldi V, Hassan C, et al. Ascorbic acid and intestinal metaplasia in the stomach: a prospective, randomized study. Aliment Pharmacol Ther. 2000;14(10):1303-9.

60. Liede K, Hietanen J, Saxen L, et al. Long-term supplementation with alpha-tocopherol and beta-carotene and prevalence of oral mucosal lesions in smokers. Oral Dis. 1998;4(2):78-83.

61. Schroder FH, Kranse R., Dijk M.A., et al. Tertiary prevention of prostate cancer by dietary intervention: results of a randomised, double blind, placebo controlled, cross-over study. European Urology. 2000;37(2 suppl):24.

62. Correa P, Fontham ET, Bravo JC, et al. Chemoprevention of gastric dysplasia: randomized trial of antioxidant supplements and anti-helicobacter pylori therapy. J Natl Cancer Inst. 2000;92(23):1881-8.

63. Liede K, Hietanen J, Saxen L, et al. Long-term supplementation with alpha-tocopherol and beta-carotene and prevalence of oral mucosal lesions in smokers. Oral Dis. 1998;4(2):78-83.

64. Schroder FH, Kranse R., Dijk M.A., et al. Tertiary prevention of prostate cancer by dietary intervention: results of a randomised, double blind, placebo controlled, cross-over study. European Urology. 2000;37(2 suppl):24.

65. McAuley L, Pham B, Tugwell P, Moher D. Does the inclusion of the grey literature influence estimates of intervention effectiveness reported in meta-analyses? Lancet. 2000;356:1228-1231.

First Author Year	Trial name Study Design Quality Population Comorbidities	Arm	Interventions Dosage Data	Sample Size		Summary of Results
Albanes 1986	Named trial: ATBC pilot RCT Jadad Score: 5 Population: Smokers Comorbidities: N/D	1	Placebo Placebo for 8 Months	n Entered: n Analyzed:	N/D N/D	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.
		2	Beta-carotene 20 mg orally for 8 Months	n Entered: n Analyzed:	N/D N/D	
		3	Vitamin E 50 mg orally for 8 Months	n Entered: n Analyzed:	N/D N/D	
		4	Beta-carotene 20 mg orally for 8 Months Vitamin E 50 mg orally for 8 Months	n Entered: n Analyzed:	N/D N/D	
Albanes 1996	Named trial: ATBC RCT Jadad Score: 3 Population: Smokers Comorbidities: N/D	1	Placebo Placebo for 6.1 Years	n Entered: n Analyzed:	7287 7287	Statistical pooling performed: Death: relative risk at 6.1 years (average follow-up) New tumor: relative risk at 6.1 years (average follow-up)
		2	Beta-carotene 20 mg orally for 6.1 Years	n Entered: n Analyzed:	7282 7282	
		3	Vitamin E 50 mg orally for 6.1 Years	n Entered: n Analyzed:	7286 7286	
		4	Beta-carotene 20 mg orally for 6.1 Years Vitamin E 50 mg orally for 6.1 Years	n Entered: n Analyzed:	7278 7278	
Albanes 2000	Named trial: ATBC RCT Jadad Score: 3 Population: Smokers Comorbidities: N/D	1	Placebo Placebo for 6.1 Years	n Entered: n Analyzed:	7287 7287	Statistical pooling performed: Death: relative risk at 6.1 years (average follow-up) New tumor: relative risk at 6.1 years (average follow-up)
		2	Beta-carotene 20 mg orally for 6.1 Years	n Entered: n Analyzed:	7282 7282	
		3	Vitamin E 50 mg orally for 6.1 Years	n Entered: n Analyzed:	7286 7286	
		4	Vitamin E 50 mg orally for 6.1 Years Beta-carotene 20 mg orally for 6.1 Years	n Entered: n Analyzed:	7278 7278	

N/D = not described

Antioxidants For Cancer Prevention/Treatment

First Author Year	Trial name Study Design Quality Population Comorbidities	Arm	Interventions Dosage Data	Sample Size	Summary of Results
ATBC Prevention Study Group 1994	Named trial: ATBC RCT Jadad Score: 3 Population: Smokers Comorbidities: N/D	1	Placebo Placebo for 6.1 Years	n Entered: 7287 n Analyzed: 7287	Statistical pooling performed: Death: relative risk at 6.1 years (average follow-up) New tumor: relative risk at 6.1 years (average follow-up)
		2	Vitamin E 50 mg orally for 6.1 Years	n Entered: 7286 n Analyzed: 7286	
		3	Beta-carotene 20 mg orally for 6.1 Years	n Entered: 7282 n Analyzed: 7282	
		4	Vitamin E 50 mg orally for 6.1 Years Beta-carotene 20 mg orally for 6.1 Years	n Entered: 7278 n Analyzed: 7278	

N/D = not described

First Author Year	Trial name Study Design Quality Population Comorbidities	Arm	Interventions Dosage Data	Sample Size	Summary of Results
Blot 1993	Named trial: Linxian (General Population Trial) RCT Jadad Score: 2 Population: N/D Comorbidities: N/D	1	Placebo Placebo for 5.25 Years	n Entered: N/D n Analyzed: 3679	Statistical pooling performed: Death: relative risk at 5.25 years follow-up
		2	Niacin 40 mg orally for 5.25 Years Multi-vitamin Multi-vitamin orally for 5.25 Years	n Entered: N/D n Analyzed: 3701	
		3	Vitamin C 120 mg orally for 5.25 Years Multi-vitamin Multi-vitamin orally for 5.25 Years	n Entered: N/D n Analyzed: 3694	
		4	Vitamin C 120 mg orally for 5.25 Years Multi-vitamin Multi-vitamin orally for 5.25 Years	n Entered: N/D n Analyzed: 3703	
		5	Vitamin E 30 mg orally for 5.25 Years Multi-vitamin Multi-vitamin orally for 5.25 Years	n Entered: N/D n Analyzed: 3691	
		6	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	n Entered: N/D n Analyzed: 3699	
		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	n Entered: N/D n Analyzed: 3705	

N/D = not described

First Author Year	Trial name Study Design Quality Population Comorbidities	Arm	Interventions Dosage Data	Sample Size	Summary of Results
		8	Vitamin E 30 mg orally for 5.25 Years Multi-vitamin Multi-vitamin orally for 5.25 Years	n Entered: N/D n Analyzed: 3712	
Bussey 1982	Named trial: No RCT Jadad Score: 4 Population: N/D Comorbidities: N/D	1	Placebo Placebo for 2 Years	n Entered: 22 n Analyzed: 17	Excluded from polyps meta-analysis because of insufficient statistics. Individuals all had polyposis coli. Those in Arm 2 exhibited reduction of colonic polyp area ($p < 0.03$) at 9 months and had a nonsignificant trend towards reduction in number and area of rectal polyps.
		2	Vitamin C 3 gm orally for 2 Years	n Entered: 25 n Analyzed: 19	
Cahill 1993	Named trial: No RCT Jadad Score: 2 Population: N/D Comorbidities: N/D	1	Control or Usual care No dosage data reported	n Entered: 10 n Analyzed: 10	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.
		2	Beta-carotene 9 mg orally for 1 Month	n Entered: 10 n Analyzed: 10	
		3	Vitamin E 160 mg orally for 1 Month	n Entered: 10 n Analyzed: 10	
		4	Vitamin C 750 mg orally for 1 Month	n Entered: 10 n Analyzed: 10	
Correa 2000	Named trial: No RCT Jadad Score: 5 Population: N/D Comorbidities: N/D	1	Placebo Placebo for 6 Years	n Entered: 117 n Analyzed: 76	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.
		2	H. pylori treatment N/D dose orally for 6 Years	n Entered: 120 n Analyzed: 79	
		3	Beta-carotene 30 mg orally for 6 Years	n Entered: 117 n Analyzed: 65	
		4	Vitamin C 2 gm orally for 6 Years	n Entered: 130 n Analyzed: 91	

N/D = not described

First Author Year	Trial name Study Design Quality Population Comorbidities	Arm	Interventions Dosage Data	Sample Size	Summary of Results
		5	Beta-carotene 30 mg orally for 6 Years H. pylori treatment N/D dose orally for 6 Years	n Entered: 126 n Analyzed: 88	
		6	H. pylori treatment N/D dose orally for 6 Years Vitamin C 2 gm orally for 6 Years	n Entered: 111 n Analyzed: 72	
		7	Beta-carotene 30 mg orally for 6 Years Vitamin C 2 gm orally for 6 Years	n Entered: 121 n Analyzed: 79	
		8	H. pylori treatment N/D dose orally for 6 Years Beta-carotene 30 mg orally for 6 Years Vitamin C 2 gm orally for 6 Years	n Entered: 134 n Analyzed: 81	
Creagan 1979(Mar)	Named trial: No RCT Jadad Score: 4 Population: N/D Comorbidities: Cancer	1	Placebo Placebo taken until death	n Entered: N/D n Analyzed: N/D	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.
		2	Vitamin C 10 gm orally until death	n Entered: N/D n Analyzed: N/D	

N/D = not described

First Author Year	Trial name Study Design Quality Population Comorbidities	Arm	Interventions Dosage Data	Sample Size	Summary of Results
Creagan 1979(Sep)	Named trial: No RCT Jadad Score: 4 Population: N/D Comorbidities: N/D	1	Placebo No dosage data reported	n Entered: 75 n Analyzed: 63	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.
		2	Vitamin C 10 gm orally, duration N/D	n Entered: 75 n Analyzed: 60	
Dawsey 1994	Named trial: Linxian (Dysplasia trial) RCT Jadad Score: 2 Population: N/D Comorbidities: N/D	1	Placebo Placebo for 6 Years	n Entered: N/D n Analyzed: 368	Statistical pooling performed: New tumor: relative risk at 30 months and 6 years follow-up
		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	n Entered: N/D n Analyzed: 400	
DeCosse 1989	Named trial: No RCT Jadad Score: 5 Population: N/D Comorbidities: N/D	1	Fiber 2.2 gm orally for 4 years Vitamin C 4030 mg orally for 4 Years Vitamin A 2000 IU orally for 4 Years Placebo Placebo for 4 years	n Entered: 22 n Analyzed: 21	

N/D = not described

First Author Year	Trial name Study Design Quality Population Comorbidities	Arm	Interventions Dosage Data	Sample Size	Summary of Results
		2	Vitamin C 4030 mg orally for 4 Years Vitamin E 400 mg orally for 4 Years Fiber 2.2 gm orally for 4 Years Vitamin A 2000 IU orally for 4 Years	n Entered: 16 n Analyzed: 14	
		3	Vitamin C 4030 mg orally for 4 Years Vitamin E 400 mg orally for 4 Years Fiber 22.5 gm orally for 4 Years Vitamin A 2000 IU orally for 4 Years	n Entered: 20 n Analyzed: 19	
Gogos 1998	Named trial: No RCT Jadad Score: 1 Population: N/D Comorbidities: N/D	1	Placebo No dosage data reported Vitamin C 4030 mg orally for 4 Years	n Entered: 30 n Analyzed: 30 n Entered: 16 n Analyzed: 14	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.
		2	Vitamin E 200 mg orally, duration N/D Fish oil 18 gm orally, duration N/D	n Entered: 30 n Analyzed: 30	

N/D = not described

First Author Year	Trial name Study Design Quality Population Comorbidities	Arm	Interventions Dosage Data	Sample Size		Summary of Results
Greenberg 1994	Named trial: No RCT Jadad Score: 4 Population: N/D Comorbidities: N/D	1	Placebo Placebo for 4 Years	n Entered: n Analyzed:	N/D 187	Statistical pooling performed: Polyps: meta-analysis at 1 year follow-up
		2	Beta-carotene 25 mg orally for 4 Years	n Entered: n Analyzed:	N/D 184	
		3	Vitamin C 1 gm orally for 4 Years Vitamin E 400 mg orally for 4 Years	n Entered: n Analyzed:	N/D 205	
		4	Vitamin C 1 gm orally for 4 Years Vitamin E 400 mg orally for 4 Years Beta-carotene 25 mg orally for 4 Years	n Entered: n Analyzed:	N/D 175	
Heinonen 1998	Named trial: ATBC RCT Jadad Score: 3 Population: Smokers Comorbidities: N/D	1	Placebo Placebo for 6.1 Years-+	n Entered: n Analyzed:	7287 7287	Statistical pooling performed: Death: relative risk at 6.1 years (average follow-up) New tumor: relative risk at 6.1 years (average follow-up)
		2	Beta-carotene 20 mg orally for 6.1 Years	n Entered: n Analyzed:	7282 7282	
		3	Vitamin E 50 mg orally for 6.1 Years	n Entered: n Analyzed:	7286 7286	
		4	Vitamin E 50 mg orally for 6.1 Years Beta-carotene 20 mg orally for 6.1 Years	n Entered: n Analyzed:	7278 7278	

N/D = not described

First Author Year	Trial name Study Design Quality Population Comorbidities	Arm	Interventions Dosage Data	Sample Size	Summary of Results
Hofstad 1998	Named trial: No RCT Jadad Score: 3 Population: N/D Comorbidities: N/D	1	Placebo Placebo for 3 Years	n Entered: 51 n Analyzed: 51	Statistical pooling performed: Polyps: meta-analysis at 3 years follow-up
		2	Vitamin E 75 mg orally for 3 Years Vitamin C 150 mg orally for 3 Years Beta-carotene 15 mg orally for 3 Years Ca 1.6 gm orally for 3 Years Selenium 101 µg orally for 3 Years	n Entered: 42 n Analyzed: 42	
Lamm 1994	Named trial: No RCT Jadad Score: 4 Population: N/D Comorbidities: N/D	1	Multi-vitamin Multi-vitamin orally for 40 Months Vitamin E 30 IU orally for 40 Months Vitamin C 60 mg orally for 40 Months Vitamin A 5000 IU orally for 40 Months	n Entered: 30 n Analyzed: 30	Statistical pooling performed: Death: relative risk at 45 months follow-up
		2	Vitamin E 430 IU orally for 49 Months Vitamin C 2060 mg orally for 49 Months Vitamin A 45000 IU orally for 49 Months Multi-vitamin Multi-vitamin orally for 49 Months	n Entered: 35 n Analyzed: 35	

N/D = not described

First Author Year	Trial name Study Design Quality Population Comorbidities	Arm	Interventions Dosage Data	Sample Size	Summary of Results
Li, Bing 1993 Study A	Named trial: Linxian (Dysplasia Trial) RCT Jadad Score: 2 Population: N/D Comorbidities: N/D	1	Placebo Placebo for 6 Years	n Entered: 1661 n Analyzed: N/D	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.
		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	n Entered: 1657 n Analyzed: N/D	
Li, Bing 1993 Study B	Named trial: Linxian (General Population Trial) RCT Jadad Score: 2 Population: N/D Comorbidities: N/D	1	Placebo Placebo for 6 Years	n Entered: 1661 n Analyzed: N/D	Excluded from statistical analysis because of insufficient statistics. This is a pilot study for the Linxian General Population trial.
		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	n Entered: 1657 n Analyzed: N/D	

N/D = not described

First Author Year	Trial name Study Design Quality Population Comorbidities	Arm	Interventions Dosage Data	Sample Size	Summary of Results
Li, Jun-Yao 1993	Named trial: Linxian (Dysplasia Trial) RCT Jadad Score: 2 Population: N/D Comorbidities: N/D	1	Placebo Placebo for 6 Years	n Entered: 1661 n Analyzed: 1661	Statistical pooling performed: Death: relative risk at 6 years follow-up New tumor: relative risk at 6 years follow-up
		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	n Entered: 1657 n Analyzed: 1657	
Liede 1998	Named trial: ATBC RCT Jadad Score: 3 Population: Smokers Comorbidities: N/D	1	Placebo Placebo for 6 Years	n Entered: 119 n Analyzed: N/D	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 mocosal lesions evaluated including leukoplakia, keratoses, hyperplasia and mucosal dysplasia.
		2	Vitamin E 50 mg orally for 6 Years	n Entered: 95 n Analyzed: N/D	
		3	Vitamin E 50 mg orally for 6 Years Beta-carotene 20 mg orally for 6 Years	n Entered: 96 n Analyzed: N/D	
		4	Beta-carotene 20 mg orally for 6 Years	n Entered: 99 n Analyzed: N/D	

N/D = not described

First Author Year	Trial name Study Design Quality Population Comorbidities	Arm	Interventions Dosage Data	Sample Size		Summary of Results
Mackerras 1999	Named trial: No RCT Jadad Score: 4 Population: Female Comorbidities: N/D	1	Placebo Placebo for 2 Years	n Entered: n Analyzed:	N/D 35	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.
		2	Beta-carotene 30 mg orally for 2 Years	n Entered: n Analyzed:	N/D 36	
		3	Vitamin C 518 mg orally for 2 Years	n Entered: n Analyzed:	N/D 35	
		4	Vitamin C 518 mg orally for 2 Years Beta-carotene 30 mg orally for 2 Years	n Entered: n Analyzed:	N/D 35	
Malila 1999	Named trial: ATBC RCT Jadad Score: 3 Population: Smokers Comorbidities: N/D	1	Placebo Placebo for 6.3 Years	n Entered: n Analyzed:	3887 N/D	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.
		2	Beta-carotene 20 mg orally for 6.3 Years	n Entered: n Analyzed:	3883 N/D	
		3	Beta-carotene 20 mg orally for 6.3 Years Vitamin E 50 mg orally for 6.3 Years	n Entered: n Analyzed:	3878 N/D	
		4	Vitamin E 50 mg orally for 6.3 Years	n Entered: n Analyzed:	3890 N/D	
McKeown-Eyssen 1988	Named trial: No RCT Jadad Score: 3 Population: N/D Comorbidities: N/D	1	Placebo Placebo for 2 Years	n Entered: n Analyzed:	89 67	Statistical pooling performed: Polyps: meta-analysis at 2 years follow-up
		2	Vitamin C 400 mg orally for 2 Years Vitamin E 400 mg orally for 2 Years	n Entered: n Analyzed:	96 70	

N/D = not described

Antioxidants For Cancer Prevention/Treatment

First Author Year	Trial name Study Design Quality Population Comorbidities	Arm	Interventions Dosage Data	Sample Size	Summary of Results
Moertel 1985	Named trial: No RCT Jadad Score: 3 Population: N/D Comorbidities: N/D	1	Placebo Placebo for 3.6 Months	n Entered: 49 n Analyzed: 49	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.
		2	Vitamin C 10 gm orally for 2.5 Months	n Entered: 51 n Analyzed: 51	
MRC/BHF 2002	Named trial: Other RCT Jadad Score: 5 Population: Unspecified Comorbidities: DM	1	Placebo Placebo for 5 Years	n Entered: 10267 n Analyzed: 10228	Statistical pooling performed
		2	Vitamin E 600 mg orally for 5 Years Vitamin C 250 mg orally for 5 Years Beta-carotene 20 mg orally for 5 Years	n Entered: 10269 n Analyzed: 10241	
Nutrition Review 1985	Named trial: No RCT Jadad Score: 2 Population: N/D Comorbidities: Cancer	1	Placebo No dosage data reported	n Entered: 49 n Analyzed: 49	Statistical pooling performed: Death: relative risk at 1 year follow-up
		2	Vitamin C 10 gm orally, duration N/D	n Entered: 51 n Analyzed: 51	

N/D = not described

First Author Year	Trial name Study Design Quality Population Comorbidities	Arm	Interventions Dosage Data	Sample Size	Summary of Results
Poulter 1984	Named trial: No CCT Jadad Score: 0 Population: Female Comorbidities: N/D	1	Control or Usual care Control or Usual care for 5 Years	n Entered: 25 n Analyzed: 24	Statistical pooling performed: Death: relative risk at 5 years follow-up
		2	Vitamin C 3 gm orally for 5 Years	n Entered: 27 n Analyzed: 27	
Rautalahti 1999	Named trial: ATBC RCT Jadad Score: 3 Population: Smokers Comorbidities: N/D	1	Placebo Placebo for 6.1 Years	n Entered: 7287 n Analyzed: 7287	Statistical pooling performed: Death: relative risk at 6.1 years (average follow-up) New tumor: relative risk at 6.1 years (average follow-up)
		2	Vitamin E 50 mg orally for 6.1 Years	n Entered: 7286 n Analyzed: 7286	
		3	Beta-carotene 20 mg orally for 6.1 Years	n Entered: 7282 n Analyzed: 7282	
		4	Vitamin E 50 mg orally for 6.1 Years Beta-carotene 20 mg orally for 6.1 Years	n Entered: 7278 n Analyzed: 7278	
Roncucci, Di Donato 1993	Named trial: No RCT Jadad Score: 2 Population: N/D Comorbidities: N/D	1	Control or Usual care No dosage data reported	n Entered: N/D n Analyzed: 78	Statistical pooling performed: Polyps: meta-analysis at 12 months follow-up
		2	Lactulose 20 gm orally for 18 Months	n Entered: N/D n Analyzed: 61	
		3	Vitamin C 1 gm orally for 18 Months Vitamin E 70 mg orally for 18 Months Vitamin A 30000 IU orally for 18 Months	n Entered: N/D n Analyzed: 70	

N/D = not described

First Author Year	Trial name Study Design Quality Population Comorbidities	Arm	Interventions Dosage Data	Sample Size	Summary of Results
Roncucci 1993	Named trial: No RCT Jadad Score: 2 Population: N/D Comorbidities: N/D	1	Control or Usual care Control/Usual care for 18 Months	n Entered: 78 n Analyzed: 78	Excluded from polyps meta-analysis because study reported data duplicated in another included study (Roncucci, Di Donato 1993)
		2	Lactulose 20 gm orally for 18 Months	n Entered: 61 n Analyzed: 61	
		3	Vitamin E 70 mg orally for 18 Months Vitamin C 1 gm orally for 18 Months Vitamin A 30000 IU orally for 18 Months	n Entered: 70 n Analyzed: 70	
Schroder 2000	Named trial: No RCT Jadad Score: 2 Population: N/D Comorbidities: N/D	1	Placebo Placebo for 6 Weeks	n Entered: 37 n Analyzed: N/D	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<0.05) in prostate cancer patients with rising PSA values post prostatectomy or radiotherapy.
		2	Vitamin E N/D dose orally for 6 Weeks Selenium N/D dose orally for 6 Weeks Multi-vitamin Multi-vitamin orally for 6 Weeks	n Entered: 37 n Analyzed: N/D	
Taylor 1994 Study A	Named trial: Linxian (Dysplasia Trial) RCT Jadad Score: 2 Population: N/D Comorbidities: N/D	1	Placebo Placebo for 6 Years	n Entered: 1661 n Analyzed: 1661	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.
		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	n Entered: 1657 n Analyzed: 1657	

N/D = not described

First Author Year	Trial name Study Design Quality Population Comorbidities	Arm	Interventions Dosage Data	Sample Size		Summary of Results
Taylor 1994 Study B	Named trial: Linxian (General Population Trial) RCT Jadad Score: 2 Population: N/D Comorbidities: N/D	1	Placebo Placebo for 5.25 Years	n Entered: n Analyzed:	N/D 3679	Statistical pooling performed: New tumor: relative risk at 5.25 years follow-up.
		2	Niacin 40 mg orally for 5.25 Years Multi-vitamin Multi-vitamin orally for 5.25 Years	n Entered: n Analyzed:	N/D 3701	
		3	Vitamin C 120 mg orally for 5.25 Years Multi-vitamin Multi-vitamin orally for 5.25 Years	n Entered: n Analyzed:	N/D 3694	
		4	Vitamin C 120 mg orally for 5.25 Years Multi-vitamin Multi-vitamin orally for 5.25 Years	n Entered: n Analyzed:	N/D 3703	
		5	Vitamin E 30 mg orally for 5.25 Years Multi-vitamin Multi-vitamin orally for 5.25 Years	n Entered: n Analyzed:	N/D 3691	
		6	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	n Entered: n Analyzed:	N/D 3699	
		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	n Entered: n Analyzed:	N/D 3705	

N/D = not described

First Author Year	Trial name Study Design Quality Population Comorbidities	Arm	Interventions Dosage Data	Sample Size	Summary of Results
		8	Vitamin E 30 mg orally for 5.25 Years Multi-vitamin Multi-vitamin orally for 5.25 Years	n Entered: N/D n Analyzed: 3712	
Varis 1998	Named trial: ATBC RCT Jadad Score: 3 Population: Smokers Comorbidities: N/D	1	Placebo Placebo for 5.1 Years	n Entered: 333 n Analyzed: 333	Statistical pooling performed: New tumor: relative risk at 6.1 years (average follow-up)
		2	Beta-carotene 20 mg orally for 5.1 Years	n Entered: 329 n Analyzed: 329	
		3	Vitamin E 50 mg orally for 5.1 Years	n Entered: 321 n Analyzed: 321	
		4	Beta-carotene 20 mg orally for 5.1 Years Vitamin E 50 mg orally for 5.1 Years	n Entered: 361 n Analyzed: 361	
Virtamo 2000	Named trial: ATBC RCT Jadad Score: 3 Population: Smokers Comorbidities: N/D	1	Placebo Placebo for 6.1 Years	n Entered: 7287 n Analyzed: 7287	Statistical pooling performed: Death: relative risk at 6.1 years (average follow-up) New tumor: relative risk at 6.1 years (average follow-up)
		2	Vitamin E 50 mg orally for 6.1 Years	n Entered: 7286 n Analyzed: 7286	
		3	Beta-carotene 20 mg orally for 6.1 Years	n Entered: 7282 n Analyzed: 7282	
		4	Vitamin E 50 mg orally for 6.1 Years Beta-carotene 20 mg orally for 6.1 Years	n Entered: 7278 n Analyzed: 7278	

N/D = not described

First Author Year	Trial name Study Design Quality Population Comorbidities	Arm	Interventions Dosage Data	Sample Size	Summary of Results
Zaridze 1993	Named trial: No RCT Jadad Score: 4 Population: N/D Comorbidities: N/D	1	Placebo Placebo for 20 Months	n Entered: N/D n Analyzed: N/D	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.
		2	Riboflavin 11.4 mg orally for 20 Months	n Entered: N/D n Analyzed: N/D	
		3	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	n Entered: N/D n Analyzed: N/D	
		4	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	n Entered: N/D n Analyzed: N/D	
Zullo 2000	Named trial: No RCT Jadad Score: 2 Population: N/D Comorbidities: N/D	1	Control or Usual care Control or Usual care for 6 Months	n Entered: 33 n Analyzed: 29	Statistical pooling performed: Excluded from statistical analysis because there were no outcomes of interest.
		2	Vitamin C 500 mg orally for 6 Months	n Entered: 32 n Analyzed: 29	

N/D = not described

Bibliography

Ascorbic acid does not cure cancer. *Nutr Rev.* 1985;43(5):146-7.

NIA study: Vitamin E may have protective effects in older adults. *Geriatr.* 1995;50(1):20-21.

Use of vitamin C for bone metastasis. *Postgrad Med.* 1972;52(2):24.

Abdel-Galil AM. Preventive effect in vitamin C (L-ascorbic acid) on methylcholanthrene-induced soft tissue sarcomas in mice. *Oncol.* 1986;43(5): 335-7.

Adler SR, Foskett JR. Disclosing complementary and alternative medicine use in the medical encounter: a qualitative study in women with breast cancer. *J Fam Pract.* 1999;48:453-8.

Akar H, Sarac A, Konuralp C, Yildiz L, Kolbakir F. 2001.

Alberts DS, Meyskens Jr F.L, Garewal H, et al. Fourth International Conference on Prevention of Human Cancer: Nutrition and chemoprevention controversies Tucson, Arizona, June 3-6, 1992. *Prev Med.* 1993;22(5):629-641.

Ambrosone CB, Marshall JR, Vena JE, et al. Interaction of family history of breast cancer and dietary antioxidants with breast cancer risk (New York, United States). *Cancer Causes Control.* 1995;6(5):407-15.

Ames BN. Micronutrient deficiencies. A major cause of DNA damage. *Ann N Y Acad Sci.* 1999;889:87-106.

Ames BN. The prevention of dna damage: the role of nutrition. *Mutat Res.* 1997;379(suppl 1):S172.

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.

Anderson JW, Gowri MS, Turner J, et al. Antioxidant supplementation effects on low-density lipoprotein oxidation for individuals with type 2 diabetes mellitus. *J Am Coll Nutr.* 1999;18 (5):451-61.

Anderson R. Assessment of the roles of vitamin C, vitamin E and beta-carotene in the modulation of oxidant stress mediated by cigarette smoke-activated phagocytes. *Am J Clin Nutr.* 1991;53 :S358-61.

Angell M, Kassirer JP. Alternative medicine--the risks of untested and unregulated remedies. *N Engl J Med.* 1998;339(12):839-41.

Arad Y, Newstein D, Roth M, Guerci A.D. Rationale and design of the St. Francis Heart Study: A randomized clinical trial of atorvastatin plus antioxidants in asymptomatic persons with elevated coronary calcification. *Control Clin Trials.* 2001;22(5):553-572.

Astin JA. Why patients use alternative medicine: results of a national study. *JAMA.* 1998;279(19):1548-53.

Aubertin A. Vitamin C: how it may protect against cancer is unclear. *J Natl Cancer Inst.* 1991;83(6):396-7.

Azen SP, Qian D, Mack WJ, et al. Effect of supplementary antioxidant vitamin intake on carotid arterial wall intima-media thickness in a controlled clinical trial of cholesterol lowering. *Circulation.* 1996;94(10):2369-72.

Bakemeier AH. The potential role of vitamins A, C, and E and selenium in cancer prevention. *Oncol Nurs Forum.* 1988;15(6):785-91.

Ballmer PE, Reinhart WH, Jordan P, Buhler E, Moser UK, Gey KF. Depletion of plasma vitamin C but not of vitamin E in response to cardiac operations. *J Thorac Cardiovasc Surg.* 1994;108(2):311-20.

Barber DA, Harris S.R. Oxygen free radicals and antioxidants: A review. *Am Pharm.* 1994;34(9):26-35.

Barone J, Taioli E, Hebert J, Wynder EL. Vitamin supplement use and risk for oral and esophageal cancer. *Nutr Cancer.* 1992;18(1):31-41.

Bartsch H, Ohshima H, Pignatelli B. Inhibitors of endogenous nitrosation. Mechanisms and implications in human cancer prevention. *Mutat Res.* 1988;202(2):307-24.

Batist G. Clinical evaluation of vitamin C and other micronutrients in the treatment of cancer. *J Orthomol Med*. 2000;15(4):189-92.

Beer D, Stoner G. Clinical models of chemoprevention for the esophagus. *Hematol Oncol Clin North Am.* 1998;12(5):1055-77.

Begbie J, Wood J, Anderson P, Latchman D. Specific up-regulation of the POU domain transcription factor Oct-2 following axotomy. *Neurosci Lett.* 1996;207(3):183-6.

Begbie S, Kerestes Z, Bell D. Patterns of alternative medicine use by cancer patients. *Med J Aust.* 1996;165(10):545-8.

Beltramino R, Penenory A, Buceta AM. An open-label, randomized multicenter study comparing the efficacy and safety of Cyclo 3 fort(R) versus hydroxyethyl rutoside in chronic venous lymphatic insufficiency. *Angiol*. 2000;51(7):535-544.

Bendich A, Langseth L. The health effects of vitamin C supplementation: a review. *J Am Coll Nutr.* 1995;14 (2):124-36.

Benner SE, Pastorino U, Lippman S.M, Waun Ki Hong. Second International Cancer Chemoprevention Conference. *Cancer Res.* 1994;54(3):854-856.

Berenson M, Groshen S, Miller H, DeCosse J. Subject-reported compliance in a chemoprevention trial for familial adenomatous polyposis. *J Behav Med*. 1989;12(3):233-47.

Bertram JS, Kolonel LN, Meyskens FLJ. Rationale and strategies for chemoprevention of cancer in humans. *Cancer Res.* 1987;47(11):3012-31.

Birt DF. Update on the effects of vitamins A, C and E and selenium on carcinogenesis. *Proc Soc Exp Biol Med*. 1986;183:311-20.

Block G. The data support a role for antioxidants in reducing cancer risk. *Nutr Rev.* 1992;50:207-13.

Block G. Epidemiologic evidence regarding vitamin C and cancer. *Am J Clin Nutr*. 1991;54(suppl 6):1310S-1314S.

Block G. Vitamin C and cancer prevention: the epidemiologic evidence. *Am J Clin Nutr*. 1991;53(suppl 1):270S-282S.

Block G. Vitamin C and reduced mortality. *Epidemiol*. 1992;3(3):189-91.

Block G. Vitamin C status and cancer. Epidemiologic evidence of reduced risk. *Ann N Y Acad Sci*. 1992;669:280-90.

Block G, Levine M. Vitamin C: a new look. *Ann Intern Med.* 1991;114:909-10.

Blot W. Preventing cancer by disrupting progression of precancerous lesions. *J Natl Cancer Inst.* 2000;92(23):1868-9.

Blot W, Li JY, Taylor PR, et al. Nutrition intervention trials in Linxian, China: supplementation with specific vitamin/mineral combinations, cancer incidence, and disease-specific mortality in the general population. *J Natl Cancer Inst.* 1993;85(18):1483-92.

Boon H, Stewart M, Kennard M, et al. Use of complementary/alternative medicine by breast cancer survivors in Ontario: prevalence and perceptions. *J Clin Oncol*. 2000;18(13):2515-21.

Boone CW. Current strategies of cancer chemoprevention: 13th Sapporo Cancer Seminar. *Cancer Res.* 1994;54(12):3315-3318.

Bostick RM, Potter JD, McKenzie DR, et al. Reduced risk of colon cancer with high intake of vitamin E: the Iowa Women's Health Study. *Cancer Res.* 1993;53(18):4230-7.

Botterweck AA, van den Brandt PA, Goldbohm RA. Vitamins, carotenoids, dietary fiber, and the risk of gastric carcinoma: results from a prospective study after 6.3 years of follow-up. *Cancer.* 2000;88(4):737-48.

Bourgeault I. Physicians' attitudes toward patients' use of alternative cancer therapies. *CMAJ.* 1996;155(12):1679-85.

Breaux T, Jamison James M, Summers Jack L, et al. Vitamin c: k3 combinations induce a novel form of non-apoptotic cell death in bladder cancer. *J Urol.* 2001;165(suppl 5):116.

Bright-See E. Vitamin C and cancer prevention. *Semin Oncol.* 1983;10(3):294-8.

Brock KE, Berry G, Mock PA, MacLennan R, Truswell AS, Brinton LA. Nutrients in diet and plasma and risk of in situ cervical cancer. *J Natl Cancer Inst.* 1988;80(8):580-5.

Brown BG, Xue-Qiao Z, Chait A, et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *New Engl J Med.* 2001;345(22):1583-92.

Bruckdorfer KR. Antioxidants, lipoprotein oxidation, and arterial function. *Lipids.* 1996;31(suppl 3):S83-S85.

Buiatti E. *Intervention Trials of Cancer Prevention: Results and New Research Programming*. Lyon, France: IARC Press; 1994.

Burstein H, Gelber S, Guadagnoli E, Weeks J. Use of alternative medicine by women with early-stage breast cancer. *N Engl J Med.* 1999;340(22):1733-9.

Bussey HJ, DeCosse JJ, Deschner EE, et al. A randomized trial of ascorbic acid in polyposis coli. *Cancer.* 1982;50(7):1434-9.

Butterworth CEJ, Norris D. Folic acid and vitamin C in cervical dysplasia. *Am J Clin Nutr.* 1983;37(2):332-3.

Byers T, Perry G. Dietary carotenes, vitamin C, and vitamin E as protective antioxidants in human cancers. *Annu Rev Nutr.* 1992;12:139-59.

Cahill RJ, O'Sullivan KR, Mathias PM, Beattie S, Hamilton H, O'Morain C. Effects of vitamin antioxidant supplementation on cell kinetics of patients with adenomatous polyps. *Gut.* 1993;34(7):963-7.

Cai L, Koropatnick J, Cherian MG. Roles of vitamin C in radiation-induced DNA damage in presence and absence of copper. *Chem Biol Interact.* 2001;137(1):75-88.

Calabrese EJ. Conjoint use of laetrile and megadoses of ascorbic acid in cancer treatment: possible side effects. *Med Hypotheses.* 1979;5(9):995-7.

Calzada C, Bruckdorfer KR, Rice-Evans CA. The influence of antioxidant nutrients on platelet function in healthy volunteers. *Atheroscler.* 1997;128(1):97-105.

Cameron E. Protocol for the use of vitamin C in the treatment of cancer. *Med Hypotheses.* 1991;36(3):190-4.

Cameron E, Campbell A. Innovation vs. quality control: an 'unpublishable' clinical trial of supplemental ascorbate in incurable cancer. *Med Hypotheses.* 1991;36(3):185-9.

Cameron E, Campbell A. The orthomolecular treatment of cancer. II. Clinical trial of high-dose ascorbic acid supplements in advanced human cancer. *Chem Biol Interact.* 1974;9(4):285-315.

Cameron E, Campbell A, Jack T. The orthomolecular treatment of cancer. III. Reticulum cell sarcoma: double complete regression induced by high-dose ascorbic acid therapy. *Chem Biol Interact.* 1975;11(5):387-93.

Cameron E, Pauling L. The orthomolecular treatment of cancer. I. The role of ascorbic acid in host resistance. *Chem Biol Interact.* 1974;9(4):273-83.

Cameron E, Pauling L. Supplemental ascorbate in the supportive treatment of cancer: reevaluation of prolongation of survival times in terminal human cancer. *Proc Natl Acad Sci USA.* 1978;75:4538-42.

Campbell A, Jack T, Cameron E. Reticulum cell sarcoma: two complete 'spontaneous' regressions, in response to high-dose ascorbic acid therapy. A report on subsequent progress. *Oncol.* 1991;48(6):495-7.

Campion EW. Why unconventional medicine? *N Engl J Med.* 1993;328(4):282-3.

Carr AC, Frei B. Toward a new recommended dietary allowance for vitamin C based on antioxidant and health effects in humans. *Am J Clin Nutr.* 1999;69(6):1086-107.

Cascinu S, Ligi M, Del Ferro E, et al. Effects of calcium and vitamin supplementation on colon cell proliferation in colorectal cancer. *Cancer Invest.* 2000;18(5):411-6.

Cassileth BR. Unorthodox cancer medicine. *Cancer Invest.* 1986;4(6):591-8.

Cassileth BR, Lusk EJ, Guerry D, et al. Survival and quality of life among patients receiving unproven as compared with conventional cancer therapy. *N Engl J Med.* 1991;324(17):1180-5.

Cassileth BR, Lusk EJ, Strouse TB, Bodenheimer BJ. Contemporary unorthodox treatments in cancer medicine. A study of patients, treatments, and practitioners. *Ann Intern Med*. 1984;101(1):105-12.

Chamiec T, Herbaczynska-Cedro K, Ceremuzynski L. Effects of antioxidant vitamins C and E on signal-averaged electrocardiogram in acute myocardial infarction. *Am J Cardiol*. 1996;77(4):237-41.

Chappell LC, Seed PT, Briley AL, et al. Effect of antioxidants on the occurrence of pre-eclampsia in women at increased risk: a randomised trial. *Lancet*. 1999;354:810-6.

Charleux JL. Beta-carotene, vitamin C, and vitamin E: the protective micronutrients. *Nutr Rev*. 1996;54(11 Pt 2):S109-14.

Chen LH, Boissonneault GA, Glauert HP. Vitamin C, vitamin E and cancer (review). *Anticancer Res*. 1988;8(4):739-48.

Cherubini A, Polidori MC, Bregnocchi M, et al. Antioxidant profile and early outcome in stroke patients. *Stroke*. 2000;31(10):2295-300.

Chevion S, Or R, Berry EM. The antioxidant status of patients subjected to total body irradiation. *Biochem Mol Biol Int*. 1999;47(6):1019-27.

Chisolm IGM. Antioxidants and atherosclerosis: A current assessment. *Clin Cardiol*. 1991;14(2 suppl 1):I-25-I-30.

Christen WG, Gaziano JM, Hennekens CH. Design of Physicians' Health Study II--a randomized trial of beta-carotene, vitamins E and C, and multivitamins, in prevention of cancer, cardiovascular disease, and eye disease, and review of results of completed trials. *Ann Epidemiol*. 2000;10(2):125-34.

Clifton PM. Antioxidant vitamins and coronary heart disease risk. *Curr Opin Lipidology*. 1995;6(1):20-24.

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.

Conklin KA. Dietary antioxidants during cancer chemotherapy: impact on chemotherapeutic effectiveness and development of side effects. *Nutr Cancer*. 2000;37(1):1-18.

Cooke JP. Nutriceuticals for cardiovascular health. *Am J Cardiol*. 1998;82(10A):43S-46S.

Coppes MJ, Anderson RA, Egeler RM, Wolff JE. Alternative therapies for the treatment of childhood cancer. *N Engl J Med*. 1998;339(12):846-7.

Correa P, Fontham ET, Bravo JC, et al. Chemoprevention of gastric dysplasia: randomized trial of antioxidant supplements and anti-helicobacter pylori therapy. *J Natl Cancer Inst*. 2000;92(23):1881-8.

Coss RA, McGrath P, Caggiano V. Alternative care. Patient choices for adjunct therapies within a cancer center. *Cancer Pract*. 1998;6(3):176-81.

Costa A, Santoro G, Assimakopoulos G. Cancer chemoprevention. A review of ongoing clinical studies. *Acta Oncol*. 1990;29(5):657-63.

Creagan ET, Moertel C. Vitamin C therapy of advanced cancer. *N Engl J Med*. 1979;301(25):1399.

Creagan ET, Moertel CG, O'Fallon JR, et al. Failure of high-dose vitamin C (ascorbic acid) therapy to benefit patients with advanced cancer. A controlled trial. *N Engl J Med*. 1979;301(13):687-90.

Creagan, E. T., Moertel C.G., Schutt A.J., and Oconnell M.J. Vitamin-c (ascorbic-acid) therapy of pre-terminal cancer-patients. [abstract]. Proc Am Assoc Cancer Res. 79;20:355.

D'Avanzo B, Ron E, La Vecchia C, Francaschi S, Negri E, Zleglar R. Selected micronutrient intake and thyroid carcinoma risk. *Cancer*. 1997;79(11):2186-92.

Daniel TA, Nawarskas J.J. Vitamin C in the prevention of nitrate tolerance. *Annals of Pharmacotherapy*. 2000;34(10):1193-1197.

Daugherty A, Roselaar S.E. Lipoprotein oxidation as a mediator of atherogenesis: Insights from pharmacological studies. *Cardiovasc Res*. 1995;29(3):297-311.

Daughters K, Waxman K, Gassel A, Zommer S. Anti-oxidant treatment for shock: Vitamin E but not vitamin C improves survival. *Am Surg*. 1996;62(10):789-792.

Dawsey SM, Wang GQ, Taylor PR, et al. Effects of vitamin/mineral supplementation on the prevalence of histological dysplasia and early cancer of the esophagus and stomach: results from the Dysplasia Trial in Linxian, China. *Cancer Epidemiol Biomarkers Prev.* 1994;3 (2):167-72.

de Stefani E, Boffetta P, Deneo-Pellegrini H, et al. Dietary antioxidants and lung cancer risk: a case-control study in Uruguay. *Nutr Cancer.* 199;34(1):100-10.

DeCosse JJ, Adams MB, Kuzma JF, Lo Gerfo P, Condon RE. Effect of ascorbic acid on rectal polyps of patients with familial polyposis. *Wis Med J.* 1976;75(1):S8.

DeCosse JJ, Miller HH, Lesser ML. Effect of wheat fiber and vitamins C and E on rectal polyps in patients with familial adenomatous polyposis. *J Natl Cancer Inst.* 1989;81(17):1290-7.

Diaz MN, Frei B, Vita JA, Keaney JF. Antioxidants and atherosclerotic heart disease. *N Engl J Med.* 1997;337:408-16.

DiPaola R, Zhang H, Lambert G, et al. Clinical and biologic activity of an estrogenic herbal combination (PC- SPES) in prostate cancer. *N Engl J Med.* 1998;339(12):785-91.

Diplock AT. Antioxidant nutrients and disease prevention. *Am J Clin Nutr.* 1991;53:S189-93.

Diplock AT. Dietary supplementation with antioxidants. Is there a case for exceeding the recommended dietary allowance? *Free Radic Biol Med.* 1987;3:199-201.

Drake IM, Davies MJ, Mapstone NP, et al. Ascorbic acid may protect against human gastric cancer by scavenging mucosal oxygen radicals. *Carcinog.* 1996;17(3):559-62.

Draper HH, Bird RP. Micronutrients and cancer prevention: are the RDAs adequate? *Free Radic Biol Med.* 1987;3(3):203-7.

Driarsh P. Ascorbic acid protects lipids in human plasma and low-density lipoprotein against oxidative damage. *Am J Clin Nutr.* 1991;54:S1113-18.

Duchesne J. Cancer prevention and therapy. *Med Hypotheses.* 1981;7(4):429-32.

Duffy SJ, Gokce N, Holbrook M, et al. Effect of ascorbic acid treatment on conduit vessel endothelial dysfunction in patients with hypertension. *Am J Physiol Heart Circ Physiol.* 2001;280(2 49-2):H528-H534.

Duffy SJ, Gokce N, Holbrook M, et al. Treatment of hypertension with ascorbic acid. *Lancet.* 1999;354:2048-9.

Duthie G, Bellizzi MC. Effects of antioxidants on vascular health. *Br Med Bull.* 1999;55(3):568-577.

Dwyer J. Dietary fiber and colorectal cancer risk. *Nutr Rev.* 1993;51(5):147-8.

Dyke GW, Craven JL, Hall R, Garner RC. Effect of vitamin C supplementation on gastric mucosal DNA damage. *Carcinog.* 1994;15(2):291-5.

Egan DA, Garg R, Wilt TJ, et al. Rationale and design of the Arterial Disease Multiple Intervention Trial (ADMIT) Pilot Study. *Am J Cardiol.* 1999;83(4):569-75.

Eichholzer M, Stahelin HB, Ludin E, Bernasconi F. Smoking, plasma vitamins C, E, retinol, and carotene, and fatal prostate cancer: seventeen-year follow-up of the prospective basal study. *Prostate.* 1999;38(3):189-98.

Eisenberg DM, Davis R, Ettner SL, et al. Trends in alternative medicine use in the United States, 1990-1997: results of a follow-up national survey. *JAMA.* 1998;280(18):1569-75.

el-Bayoumy K. Evaluation of chemopreventive agents against breast cancer and proposed strategies for future clinical intervention trials. *Carcinog.* 1994;15(11):2395-420.

Elsendoorn TJ, Weijl NI, Mithoe S, et al. Chemotherapy-induced chromosomal damage in peripheral blood lymphocytes of cancer patients supplemented with antioxidants or placebo. *Mutat Res.* 2001;498(1-2): 145-58.

Enstrom JE, Kanim LE, Klein MA. Vitamin C intake and mortality among a sample of the United States population. *Epidemiol.* 1992;3:194-202.

Erhola M, Kellokumpu-Lehtinen P, Metsa-Ketela T, Alanko K, Nieminen MM. Effects of anthracyclin-based chemotherapy on total plasma antioxidant capacity in small cell lung cancer patients. *Free Radic Biol Med.* 1996;21(3):383-90.

Ernst E, Cassileth BR. The prevalence of complementary/alternative medicine in cancer: a systematic review. *Cancer*. 1998;83(4):777-82.

Fahey PJ, Boltri JM, Monk JS. Key issues in nutrition. Disease prevention through adulthood and old age. *Postgrad Med*. 1987;82(1):135-42.

Faw C, Ballentine R, Ballentine L. Unproved cancer remedies: a survey of use in pediatric outpatients. *JAMA*. 1978;238:1536-8.

Feldman EB. Dietary intervention and chemoprevention --1992 perspective. *Prev Med*. 1993;22(5):661-6.

Ferguson LR. Antimutagens as cancer chemopreventive agents in the diet. *Mutat Res*. 1994;307(1):395-410.

Ferguson LR. Micronutrients, dietary questionnaires and cancer. *Biomed Pharmacother*. 1997;51(8):337-44.

Ferguson LR. Prospects for cancer prevention. *Mutat Res*. 1999 ;428 (1-2):329-38.

Ferraroni M, La Vecchia C, D'Avanzo E, et al. Selected micronutrient intake and the risk of colorectal cancer. *Br J Cancer*. 1997;70:1150.

Flagg EW, Coates RJ, Greenberg RS. Epidemiologic studies of antioxidants and cancer in humans. *J Am Coll Nutr*. 1995;14(5):419-27.

Fleshner NE, Kucuk O. Antioxidant dietary supplements: Rationale and current status as chemopreventive agents for prostate cancer. *Urology*. 2001;57(4 suppl 1):90-4.

Fontham ET, Pickle LW, Haenszel W, Correa P, Lin YP, Falk RT. Dietary vitamins A and C and lung cancer risk in Louisiana. *Cancer*. 1988;62(10):2267-73.

Ford ES, Giles WH. Serumvitamins, carotenoids, and angina pectoris: Findings from the National Health and Nutrition Examination Survey III. *Ann Epidemiol*. 2000;10(2):106-116.

Frank E, Bendich A, Denniston M. Use of vitamin-mineral supplements by female physicians in the United States. *Am J Clin Nutr*. 2000;72(4):969-75.

Freedman JE. Antioxidant versus lipid-altering therapy - some answers, more questions. *New Engl J Med*. 2001;345(22):1636-37.

Frei B. Ascorbic acid protects lipids in human plasma and low-density lipoprotein against oxidative damage. *Am J Clin Nutr*. 1991;54(suppl 6):1113S-1118S.

Fryer MJ. Vitamin E supplementation. *Lancet*. 2001;357(9256):633.

Fuller CJ, Grundy SM, Norkus EP, Jialal I. Effect of ascorbate supplementation on low density lipoprotein oxidation in smokers. *Atheroscler*. 1996;119(2):139-50.

Gail MH, Brown LM, You WC. Re: Chemoprevention of gastric dysplasia: randomized trial of antioxidant supplements and anti-helicobacter pylori therapy. *J Natl Cancer Inst*. 2001;93 (7):559-60.

Gail MH, You WC, Chang YS, et al. Factorial trial of three interventions to reduce the progression of precancerous gastric lesions in Shandong, China: design issues and initial data. *Control Clin Trials*. 1998;19(4):352-69.

Gale CR, Martyn CN, Winter PD, Cooper C. Vitamin C and risk of death from stroke and coronary heart disease in cohort of elderly people. *BMJ*. 1995;310:1563-6.

Gale CAH, Powers H, Martyn C. Antioxidant vitamin status and carotid atherosclerosis in the elderly. *Am J Clin Nutr*. 2001;74(3):402-408.

Galley HF, Thornton J, Howdle PD, Walker BE, Webster NR. Combination oral antioxidant supplementation reduces blood pressure. *Clin Sci (Lond)*. 1997;92(4):361-5.

Gamble J, Grewal PS, Gartsides IB. Vitamin C modifies the cardiovascular and microvascular responses to cigarette smoke inhalation in man. *Clin Sci (Lond)*. 2000;98(4):455-460.

Gandini S, Merzenich H, Robertson C, Boyle P. Meta-analysis of studies on breast cancer risk and diet: the role of fruit and vegetable consumption and the intake of associated micronutrients. *Eur J Cancer*. 2000;36(5):636-46.

Garewal H, Meyskens Jr F, Friedman S, Alberts D, Ramsey L. Oral cancer prevention: The case for carotenoids and anti-oxidant nutrients. *Prev Med.* 1993;22(5):701-711.

Garewal HS, Schantz S. Emerging role of beta-carotene and antioxidant nutrients in prevention of oral cancer. *Arch Otolaryngol Head Neck Surg.* 1995;121(2):141-4.

Garg R, Elam M.B, Crouse III J.R, et al. Effective and safe modification of multiple atherosclerotic risk factors in patients with peripheral arterial disease. *Am Heart J.* 2000;140(5):792-803.

Garland M, Willett WC, Manson JE, Hunter DJ. Antioxidant micronutrients and breast cancer. *J Am Coll Nutr.* 1993;12:400-11.

Gaytan RJ, Prisant LM. Oral nutritional supplements and heart disease: a review. *Am J Ther.* 2001;8(4):255-74.

Gaziano JM. Antioxidants in cardiovascular disease: randomized trials. *Nutrition.* 1996;12(9):583-8.

Gaziano JM. Antioxidants in cardiovascular disease: randomized trials (Brief Critical Reviews). *Nutr Rev.* 1996;54(6):175(3).

Gaziano JM, Manson JE, Hennekens CH. Natural antioxidants and cardiovascular disease: Observational epidemiologic studies and randomized trials. In: Frei B, ed. *Natural Antioxidants in Human Health and Disease*. San Diego, CA: Academic Press; 1994:387-409.

Gazis A, Fogarty A.Vitamin E supplemen-tation. *Lancet.* 2001;357(9256):631-2.

Gensini G, Conti AA. NNT and NNH by treatment. *Lancet.* 2001;357(9269):1704.

Gey KF. Vitamins E plus C and interacting conutrients required for optimal health. A critical and constructive review of epidemiology and supplementation data regarding cardiovascular disease and cancer. *Biofactors.* 1998;7(1-2):113-74.

Gey KF. On the antioxidant hypothesis with regard to arteriosclerosis. *Bibl Nutr Dieta.* 1986(37):53-91.

Gey KF. Prospects for the prevention of free radical disease regarding cancer and cardiovascular disease. *Br Med Bull.* 1993;49:679-99.

Gey KF, Moser UK, Jordan P, Stahelin HB, Eichholzer M, Ludin E. Increased risk of cardiovascular disease at suboptimal plasma concentrations of essential antioxidants: an epidemiological update with special attention to carotene and vitamin C. *Am J Clin Nutr.* 1993;57 (suppl 5):S787-97.

Gey KF, Puska P, Jordan P, Moser UK. Inverse correlation between plasma vitamin E and mortality from ischemic heart disease in cross-cultural epidemiology. *Am J Clin Nutr.* 1991;53(suppl 1):S326-34.

Ghosh J, Das S. Evaluation of vitamin-a and vitamin-c status in normal and malignant conditions and their possible role in cancer prevention. *Jpn J Cancer Res.* 1985;76(12):1174-1178.

Ginter E. Decline in coronary mortality in United States and vitamin C. *Am J Clin Nutr.* 1979;32:511-2.

Giugliano D. Dietary antioxidants for cardiovascular prevention. *Nutr Metab Cardiovasc Dis.* 2000;10(1):38-44.

Goldin-Lang P, Kreuser E, Zunft HJ. Basis and consequences of primary and secondary prevention of gastrointestinal tumors. *Recent Results Cancer Res.* 1996;142:163-92.

Gordon D. Can antioxidants enhance chemotherapy? *Gastroenterology.* 1998;114(2):235.

Graham S. Dietary factors in the prevention of cancer. *Transplant Proc.* 1984;16(2):392-400.

Graham S. Toward a dietary prevention of cancer. *Epidemiol Rev.* 1983;5:38-50.

Greco AM, Gentile M, Di Filippo O, Coppola A . Study of blood vitamin C in lung and bladder cancer patients before and after treatment with ascorbic acid. A preliminary report. *Acta Vitaminol Enzymol.* 1982;4(1-2):155-62.

Greenberg ER, Baron JA, Tosteson TD, et al. A clinical trial of antioxidant vitamins to prevent colorectal adenoma. *N Engl J Med.* 1994;331:141-47.

Greenwald P. Cancer risk factors for selecting cohorts for large-scale chemoprevention trials. *J Cell Biochem Suppl.* 1996;25: 29-36.

Greenwald P. Clinical trials of breast and prostate cancer prevention. *J Nutr.* 2001;131(1):176S-178S.

Greenwald P, Malone WF, Cerny ME, Stern HR, Vande WG, Klein G. Cancer prevention research trials. In: Basu N, Temple NJ, Garg M, eds. *Advances in Cancer Research*. Vol 61. 1993:1-23.

Greenwald P, McDonald S. Antioxidants and the prevention of cancer. In: Basu TK, Temple NJ, Garg ML, eds. *Antioxidants in Human Health and Disease*. Wallingford, UK: CAB International Publishing; 1999:217-234.

Gridley G, McLaughlin J, Block G, Blot WJ, Gluch M, Fraumeni JF. Vitamin supplement use and reduced risk of oral and pharyngeal cancer. *Am J Epidemiol*. 1992;135(10):1083-92.

Grundy SM. Antioxidants and heart disease: Overview. *Clin Cardiol*. 1993;16(suppl 4):I1-I2.

Hakama M. Chemoprevention research in Europe. *Int J Cancer*. 1997;10 suppl:30-3.

Halliwell B. The antioxidant paradox. *Lancet*. 2000;355(9210):1179-80.

Halliwell B. Antioxidants in human health and disease. *Annu Rev Nutr*. 1996;16:p.33-50.

Halliwell B. Lipid peroxidation, antioxidants and cardiovascular disease: How should we move forward? *Cardiovasc Res*. 2000;47(3):410-418.

Halperin EC, Gaspar L, George S, Darr D, Pinnell S. A double-blind, randomized, prospective trial to evaluate topical vitamin C solution for the prevention of radiation dermatitis. CNS Cancer Consortium. *Int J Radiat Oncol Biol Phys*. 1993;26(3):413-6.

Hamabe A, Takase B, Uehata A, Kurita A, Ohsuzu F, Tamai S. Impaired endothelium-dependent vasodilation in the brachial artery in variant angina pectoris and the effect of intravenous administration of vitamin C. *Am J Cardio*. 2001;87(10):1154-1159.

Harats D, Ben-Naim M, Dabach Y, Hollander G, Havivi E, Stein O/Stein Y. Effect of vitamin C and E supplementation on susceptibility of plasma lipproteins to peroxidation induced by acute smoking. *Atheroscler*. 1990;85:47-54.

Hathcock JN. Vitamins and minerals: efficacy and safety. *Am J Clin Nutr*. 1997;66(2):427-37.

Hatta A, Frei B. Oxidative modification and antioxidant protection of human low-density lipoprotein at high and low oxygen partial pressures. *J Lipid Res*. 1995;36:2383-93.

Hawk ET, Lippman S.M. Primary cancer prevention trials. *Hematol Oncol Clin North Am*. 2000;14(4):809-30.

Hennekens CH. Antioxidant vitamins and cardiovascular disease: Current perspectives and future directions. *Eur Heart J*. 1997;18(2):177-9.

Hennekens CH. Platelet inhibitors and antioxidant vitamins in cardiovascular disease. *Am Heart J*. 1994;128(suppl 6 II):1333-6.

Hennekens CH, Buring JE, Peto R. Antioxidant vitamins—benefits not yet proved. *N Engl J Med*. 1994;330(15):1080-1.

Henning S, Ingles S, Mahmoud M, et al. Multivitamin and mineral supplement did not alter the antioxidant capacity in plasma of healthy young men and women. *Nutr Res*. 2000;20(2):167-76.

Herbaczynska-Cedro K, Klosiewicz-Wasek B, Cedro K, Wasek W, Panczenko-Kresowska B, Wartanowicz M. Supplementation with vitamins C and E suppresses leukocyte oxygen free radical production in patients with myocardial infarction. *Eur Heart J*. 1995;16(8): 1044-9.

Hercberg S, Preziosi P, Briancon S, et al. A primary prevention trial using nutritional doses of antioxidant vitamins and minerals in cardiovascular diseases and cancers in a general population: the SU.VI.MAX study--design, methods, and participant characteristics. Supplementation en VItamines et Mineraux AntioXydants. *Control Clin Trials*. 1998;19(4):336-51.

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.

Hidvegi M, Raso E, Tomoskozi-Farkas R, Paku S, Lapis K, Szende B. Effect of Avemar and Avemar + vitamin C on tumor growth and metastasis in experimental animals. *Anticancer Res*. 1998;18 (4A):2353-8.

Hinds MW, Kolonel LN, Hankin JH, et al. Dietary vitamin A, carotene, vitamin C, and risk of lung cancer in Hawaii. *Am J Epidemiol*. 1984;119:227-37.

Ho EE, Lee FC, Meyskens FLJ. An exploratory study of attitudes, beliefs and practices related to the interim dietary guidelines for reducing cancer in the elderly. *J Nutr Elder.* 1991;10 (4):31-49.

Hodis HN, Mack WJ, LaBree L, et al. Serial coronary angiographic evidence that antioxidant vitamin intake reduces progression of coronary artery atherosclerosis. *JAMA.* 1995;273(23):1849-54 .

Hoffer A. Antioxidant nutrients and cancer. *J Orthomol Med.* 2000;15(4):193-200.

Hoffer A. Clinical procedures in treating terminally ill cancer patients with vitamin C. *J Orthomol Med.* 1991;6(3-4):155-60.

Hoffer A, Pauling L. Hardin Jones biostatistical analysis of mortality data for cohorts of cancer patients with a large fraction surviving at the termination of the study and a comparison of survival times of cancer patients receiving large regular oral doses of vitamin C and other nutrients with similar patients not receiving those doses. *J Orthomol Med.* 1990;5(3): 143-54.

Hofstad B, Almendingen K, Vatn M, et al. Growth and recurrence of colorectal polyps: a double-blind, three-year intervention with calcium and antioxidants. *Digestion.* 1998;59:148-56.

Hooper L, Ness AR, Smith GD. Antioxidant strategy for cardiovascular diseases. *Lancet.* 2001;357(9269):1705-6.

Horn-Ross PL, Morrow M, Ljung BM. Diet and the risk of salivary gland cancer. *Am J Epidemiol.* 1997;146(2):171-6.

Hornig B, Landmesser U, Kohler C, et al. Comparative effect of ACE inhibition and angiotensin II type 1 receptor antagonism on bioavailability of nitric oxide in patients with coronary artery disease: Role of superoxide dismutase. *Circulation.* 2001;103(6):799-805.

Houser HB. Re: "Dietary vitamin A, carotene, vitamin C and risk of lung cancer in Hawaii". *Am J Epidemiol.* 1985;121(4):623-4.

Howe GR, Hirohata T, Hislop TG, et al. Dietary factors and risk of breast cancer: combined analysis of 12 case-control studies. *J Natl Cancer Inst.* 1990;82(7):561-9.

Huang HY, Helzlsouer KJ, Appel LJ. The effects of vitamin C and vitamin E on oxidative DNA damage: results from a randomized controlled trial. *Cancer Epidemiol Biomarkers Prev.* 2000;9(7):647-52.

Huber MH, Hong WK. Biology and chemoprevention of head and neck cancer. *Curr Probl Cancer.* 1994;18(2):81-140.

Huber MH, Lee J.S, Hong W.K. Chemoprevention of lung cancer. *Semin Oncol.* 1993;20(2):128-141.

Human JA, Ubbink JB, Jerling JJ, et al. The effect of Simvastatin on the plasma antioxidant concentrations in patients with hypercholesterolaemia. *Clin Chim Acta*. 1997;263(1):67-77.

Hunter DJ, Manson JE, Colditz GA, et al. A prospective study of the intake of vitamins C, E, and A and the risk of breast cancer. *N Engl J Med.* 1993;329(4):234-40.

Hunter, D. J., Stampfer, M. J., and Colditz, G. A. A prospective study of consumption of vitamins A, C, and E and breast cancer. [abstract]. Am J Epidemiol. 91;134:715.

IOM (Institute of Medicine); Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids. Washington, DC: National Academy Press; 2000.

Jaakkola K, Lahteenmaki P, Laakso J, Hrju E, Tykka H, Mahlberg K. Treatment with antioxidant and other nutrients in combination with chemotherapy and irradiation in patients with small-cell lung cancer. *Anticancer Res.* 1992;12:599-606.

Jackson RL. Anti-oxidants for the treatment and the prevention of atherosclerosis. *Biochem Soc Trans.* 1993;21(3):650-651.

Jacob RA, Burri BJ. Oxidative damage and defense. *Am J Clin Nutr.* 1996;63(6):985S-990S.

Jacobson JS, Begg MD, Wang LW, et al. Effects of a 6-month vitamin intervention on DNA damage in heavy smokers. *Cancer Epidemiol Biomarkers Prev.* 2000;9(12):1303-11.

Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials.* 1996;17(1):1-12.

Jha P, Flather M, Lonn E, et al. The antioxidant vitamins and cariovascular disease: a critical review of epidemiologic and clinical trial data. *Ann Intern Med*. 1995;123:860-72.

Jialal I, Fuller CJ. Effect of vitamin E, vitamin C and beta-carotene on LDL oxidation and atherosclerosis. *Can J Cardiol*. 1995;11(suppl G):97G-103G.

Jialal I, Grundy SM. Effect of combined supplementation with alpha-tocopherol, ascorbate, and beta carotene on low-density lipoprotein oxidation. *Circulation*. 1993;88(6):2780-6.

Johnson KA, Brawley OW, Perlman JA, Ford LG. Re: Chemoprevention studies in the community clinical oncology program. *J Natl Cancer Inst*. 1993;85(10):832-3.

Jonas CR, Puckett AB, Jones DP, et al. Plasma antioxidant status after high-dose chemotherapy: a randomized trial of parenteral nutrition in bone marrow transplantation patients. *Am J Clin Nutr*. 2000;72(1):181-9.

Joshipura KJ, Hu F.B, Manson J.E, et al. The effect of fruit and vegetable intake on risk for coronary heart disease. *Annals of Internal Medicine.* 2001;134(12):1106-1114+I-28.

Kamat AM, Lamm DL. Chemoprevention of urological cancer. *J Urol*. 1999;161(6):1748-60.

Kaugars GE, Silverman SJ, Lovas JG, et al. A clinical trial of antioxidant supplements in the treatment of oral leukoplakia. *Oral Surg Oral Med Oral Pathol*. 1994;78(4):462-8.

Kaugars GE, Silverman SJ, Lovas JG, Thompson JS, Brandt RB, Singh VN. Use of antioxidant supplements in the treatment of human oral leukoplakia. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1996;81(1):5-14.

Kelloff GJ, Lieberman R, Steele VE, et al. Agents, biomarkers, and cohorts for chemopreventive agent development in prostate cancer. *Urology*. 2001;57(4 suppl 1):46-51.

Kiningham R. The value of antioxidant vitamin supplements. *Am Fam Physician*. 1999;60(3):742-744.

Knekt P, Jarvinen R, Seppanen R, et al. Dietary antioxidants and the risk of lung cancer. *Am J Epidemiol*. 1991;134(5): 471-9.

Kostis JB, Wilson AC, Lacy CR. Hypertension and ascorbic acid. *Lancet*. 2000;355(9211):1272; discussion 1273-4.

Krishnan K, Ruffin MT, Brenner DE. Cancer chemoprevention. A new way to treat cancer before it happens. *Prim Care*. 1998;25(2):361-79.

Kritchevsky D. Antioxidant vitamins in the prevention of cardiovascular disease. *Nutri Today*. 1992;27(1):30.

Kromhout D. Essential micronutrients in relation to carcinogenesis. *Am J Clin Nutr*. 1987;45:1361-7.

Krzanowski JJ. Oxidants, antioxidants and cardiovascular dis ease. *J Fla Med Assoc*. 1991;78(7):435-438.

Kuklinski B, Weissenbacher E, Fahnrich A. Coenzyme Q10 and antioxidants in acute myocardial infarction. *Mol Aspects Med*. 1994;suppl 15:s143-7.

Kune GA, Kune S, Field B, et al. Oral and pharyngeal cancer, diet, smoking, alcohol, and serum vitamin A and beta-carotene levels: a case-control study in men. *Nutr Cancer*. 1993;20(1):61-70.

Kurbacher CM, Wagner U, Kolster B, Andreotti PE, Krebs D, Bruckner HW. Ascorbic acid (vitamin C) improves the antineoplastic activity of doxorubicin, cisplatin, and paclitaxel in human breast carcinoma cells in vitro. *Cancer Lett*. 1996;103(2):183-9.

Kurowska EM, Spence J.D, Jordan J, et al. HDL-cholesterol-raising effect of orange juice in subjects with hypercholesterolemia. *Am J Clin Nutr*. 2000;72(5):1095-1100.

Kushi LH, Fee RM, Sellers TA, Zheng W, Folsom AR. Intake of vitamins A, C, and E and postmenopausal breast cancer. The Iowa Women's Health Study. *Am J Epidemiol*. 1996;144(2):165-74.

Kushi LH, Folsom AR, Prineas RJ, Mink PJ, Wu Y, Bostick RM. Dietary antioxidant vitamins and death from coronary heart disease in postmenopausal women. *N Engl J Med*. 1996;334:1156-62.

Kyrtopoulos SA. Ascorbic acid and the formation of N-nitroso compounds: possible role of ascorbic acid in cancer prevention. *Am J Clin Nutr.* 1987;45(suppl 5):1344-50.

Lamm D, Riggs DR, Shriver JS, vanGilder PF, Rach JF, DeHaven JI. Megadose vitamins in bladder cancer: a double-blind clinical trial. *J Urol.* 1994;151(1):21-6.

Le Marchand L, Hankin JH, Carter FS, et al. A pilot study on the use of plasma carotenoids and ascorbic acid as markers of compliance to a high fruit and vegetable dietary intervention. *Cancer Epidemiol Biomarkers Prev.* 1994;3(3):245-51.

Lee JJ, Lieberman R, Sloan JA, Piantadosi S, Lippman SM. Design considerations for efficient prostate cancer chemoprevention trials. *Urology.* 2001;57(4 suppl 1): 205-12.

Leonard TK, Mohs M.E., Watson R.R. Nutrient intakes: cancer causation and prevention. *Prog Food Nutr Sci.* 1986;10(3-4):237-77.

Lerner IJ, Kennedy BJ. The prevalence of questionable methods of cancer treatment in the United States. *CA Cancer J Clin.* 1992; 42(3):181-91.

Levin JS, Glass TA, Kushi LH, Schuck JR, Steele L , Jonas WB. Quantitative methods in research on complementary and alternative medicine. A methodological manifesto. NIH Office of Alternative Medicine. *Med Care.* 1997;35(11):1079-94.

Li B, Taylor PR, Li JY, et al. Linxian nutrition intervention trials: design, methods, participant characteristics, and compliance. *Ann Epidemiol.* 1993;3:577-85.

Li J, Li B, Blot W, Taylor P. [Preliminary report on the results of nutrition prevention trials of cancer and other common diseases among residents in Linxian, China]. *Zhonghua Zhong Liu Za Zhi.* 1993;15(3):165-81.

Li J, Taylor P, Li B, et al. Nutrition intervention trials in Linxian, China: multiple vitamin/mineral supplementation, cancer incidence, and disease-specific mortality among adults with esophageal dysplasia. *J Natl Cancer Inst.* 1993;85(18):1492-8.

Lippman SM, Benner SE, Hong WK. Cancer chemoprevention. *J Clin Oncol.* 1994;12(4):851-73.

Lockwood K, Moesgaard S, Hanioka T, Folkers K. Apparent partial remission of breast cancer in 'high risk' patients supplemented with nutritional antioxidants, essential fatty acids and coenzyme Q10. *Mol Aspects Med.* 1994(suppl 15):s231-40.

Loescher LJ, Sauer KA. Vitamin therapy for advanced cancers. *Oncol Nurs Forum.* 1984;11(6):38-45.

Losonczy KG, Harris TB, Havlik RJ. Vitamin E and vitamin C supplement use and risk of all-cause and coronary heart disease mortality in older persons: the Established Populations for Epidemiologic Studies of the Elderly. *Am J Clin Nutr.* 1996;64(2):190-6.

Lupulescu A. The role of hormones, growth factors and vitamins in carcinogenesis. *Crit Rev Oncol Hematol.* 1996;23(2):95-130.

Lupulescu AP. Hormones, vitamins, and growth factors in cancer treatment and prevention: A critical appraisal. *Cancer.* 1996;78(11):2264-2280.

Lush DT. Preventing heart disease and cancer. What randomized, primary-prevention studies show. *Postgrad Med.* 1999;106(5):143-8.

Lyko HC, Hartmann JX. Ascorbate, cyclic nucleotides, citrus and a model for preventing large bowel cancer. *J Theor Biol.* 1980;83(4):675-86.

Mackerras D, Irwig L, Simpson JM, et al. Randomized double-blind trial of beta-carotene and vitamin C in women with minor cervical abnormalities. *Br J Cancer.* 1999;79(9-10):1448-53.

Malone WF. Studies evaluating antioxidants and beta-carotene as chemopreventives. *Am J Clin Nutr.* 1991;53(suppl 1):305S-313S.

Marcus SL, Petrylak DP, Dutcher JP, et al. Hypovitaminosis C in patients treated with high-dose interleukin 2 and lymphokine-activated killer cells. *Am J Clin Nutr.* 1991;54(suppl 6):1292S-1297S.

Mark SD, Wang W, Fraumeni JF, et al. Do nutritional supplements lower the risk of stroke or hypertension? *Epidemiol.* 1998;9:9-15.

Maxwell A, Anderson BE, Cooke JP. Nutritional therapy for peripheral arterial disease: A double-blind, placebo-controlled, randomized trial of HeartBar(R). *Vasc Med.* 2000;5(1):11-19.

Maxwell S. Antioxidant vitamin supplements. Update of their potential benefits and possible risks. *Drug Safety.* 1999;21(4):253-266.

Maxwell SR. Can antioxidants prevent ishaemic heart disease? *J Clin Pharm Ther.* 1993;18:85-95.

McCann J. Alternative remedies for cancer: an update. *J Natl Cancer Inst.* 2000;92(11):872.

McDermott JH. Complementary lipid-lowering therapies. *Am J Health-Syst Pharm.* 1999;56(16):1668-1671.

McGinnis LS. Alternative therapies, 1990. An overview. *Cancer.* 1991;67(suppl 6):1788-92.

McKeown-Eyssen G, Holloway C, Jazmaji V, Bright-See E, Dion P, Bruce WR. A randomized trial of vitamins C and E in the prevention of recurrence of colorectal polyps. *Cancer Res.* 1988;48 (16):4701-5.

Mendelsohn AB, Belle SH, Stoehr GP, et al. Use of antioxidant supplements and its association with cognitive function in a rural elderly cohort. *Am J Epidemiol.* 1998;148:38-44.

Meraji S, Abuja PM, Hayn M, et al. Relationship between classic risk factors, plasma antioxidants and indicators of oxidant stress in angina pectoris (AP) in Tehran. *Atheroscler.* 2000;150(2):403-412.

Meyskens JFL. Coming of age - The chemoprevention of cancer. *New Engl J Med.* 1990;323(12):825-827.

Miyake Y, Shouzu A, Nishikawa M, et al. Effect of treatment with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors on serum coenzyme Q10 in diabetic patients. *Arzneimittelforschung.* 1999;49(4):324-9.

Miyake Y, Shouzu A, Nishikawa M, et al. Effect of treatment with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors on serum coenzyme Q10 in diabetic patients. *Arzneimittelforschung.* 1999;49(4):324-9.

Mobarhan S. Micronutrient supplementation trials and the reduction of cancer and cerebrovascular incidence and mortality. *Nutr Rev.* 1994;52(3):102-5.

Mobarhan S. Micronutrient supplementation trials and the reduction of cancer and cerebrovascular incidence and mortality. *Nutr Rev.* 1994;52(3):102-5.

Moertel CG, Fleming TR, Creagan ET, Rubin J, O'Connell MJ, Ames MM. High-dose vitamin C versus placebo in the treatment of patients with advanced cancer who have had no prior chemotherapy. A randomized double-blind comparison. *N Engl J Med.* 1985;312(3):137-41.

Moriarty M, Mulgrew S, Mothersill C, Malone JF, Hatch M. Some effects of administration of large doses of vitamin C in patients with skin carcinoma. *Ir J Med Sci.* 1978;147(5):166-70.

Mosca L, Rubenfire M, Mandel C, et al. Antioxidant nutrient supplementation reduces the susceptibility of low density lipoprotein to oxidation in patients with coronary artery disease. *J Am Coll Cardiol .* 1997;30(2):392-9.

Mosca L, Rubenfire M, Mandel C, et al. Antioxidant supplementation reduces the susceptibility of low density lipoprotein (LDL) to oxidation in patients with coronary artery disease. *J Am Coll Cardiol.* 1996;27(suppl 2 A):275A.

MRC/BHF Heart Protection Study Collaborative group. MRC/BHF Heart Protection Study of antioxidant vitamin supplementation in 20536 high-risk individuals: a randomised placebo-controlled trial. *Lancet.* 2002;360:23-33.

MRC/BHF Heart Protection Study Collaborative group. MRC/BHF Heart Protection Study of cholesterol-lowering therapy and of antioxidant vitamin supplementation in a wide range of patients at increased risk of coronary heart disease death: early safety and efficacy experience. *Eur Heart J.* 1999;20(10):725-41.

Munoz N, Vivas J, Buiatti E, Kato I, Oliver W. Chemoprevention trial on precancerous lesions of the stomach in Venezuela: summary of study design and baseline data. *IARC Sci Publ.* 1996;139:125-33.

Nappo F, De Rosa N, Marfella R, et al. Impairment of endothelial functions by acute hyperhomocysteinemia and reversal by antioxidant vitamins. *JAMA.* 1999;281(22):2113-8.

Negri E, La Vecchia C, Franceschi S, Levi F, Parazzini F. Intake of selected micronutrients and the risk of endometrial carcinoma. *Cancer.* 1996;77(5):917-23.

Neogi T, Oza AM. Use of alternative medicine: are we failing in our communication with patients? A study assessing psychosocial impact of alternative medicine on cancer patients. *Proc Am Soc Clin Oncol*. 1998;17:416.

Ness A, Sterne J, Rolla G, et al. Hypertension and ascorbic acid (multiple letters). *Lancet*. 2000;355(9211):1271-1274.

Neugut A, Horvath K, Whelan RL, et al. The effect of calcium and vitamin supplements on the incidence and recurrence of colorectal adenomatous polyps. *Cancer*. 1996;78(4):723-8.

Newberne PM, Suphakarn V. Nutrition and cancer: a review, with emphasis on the role of vitamins C and E and selenium. *Nutr Cancer*. 1983;5(2):107-19.

Nierenberg DW, Stukel TA, Mott LA, Greenberg ER. Steady-state serum concentration of alpha tocopherol not altered by supplementation with oral beta carotene. The Polyp Prevention Study 1 Group. *J Natl Cancer Inst*. 1994;86(2):117-20.

Niki E. Action of ascorbic acid as a scavenger of active and stable oxygen radicals. *Am J Clin Nutr*. 1991;54:S1119-24.

Nyyssonen K, Poulsen HE, Hayn M, et al. Effect of supplementation of smoking men with plain or slow release ascorbic acid on lipoprotein oxidation. *Eur J Clin Nutr*. 1997;51:154-63.

Nyyssonen K/Porkkala E, .Salonen R, Korpela H, Salonen JT. Increase in oxidation resistance of atherogenic serum lipoproteins following antioxidant supplementation: a randomized double-blind placebo-controlled trial. *Eur J Clin Nutr*. 1997;48:633-42.

O'Toole P, Lombard M. Vitamin C and gastric cancer: supplements for some or fruit for all? *Gut*. 1996;39(3):345-7.

Ocke MC, Kromhout D, Menotti A, et al. Average intake of anti-oxidant (pro)vitamins and subsequent cancer mortality in the 16 cohorts of the Seven Countries Study. *Int J Cancer*. 1995;61 (4):480-4.

Olmedilla B, Granado F, Southon S, et al. Serum concentrations of carotenoids and vitamins A, E, and C in control subjects from five European countries. *Br J Nutr*. 2001;85(2):227-38.

Olsen SJ, Love RR. A new direction in preventive oncology: chemoprevention. *Semin Oncol Nurs*. 1986;2(3):211-21.

Omenn GS. Research on antioxidants to prevent cancer or heart disease. *Am J Health Promot*. 1992;6(5):334.

Osaki T, Ueta E, Yoneda K, Hirota J, Yamamoto T. Prophylaxis of oral mucositis associated with chemoradiotherapy for oral carcinoma by Azelastine hydrochloride (Azelastine) with other antioxidants. *Head Neck*. 1994;16(4):331-9.

Osborne M, Boyle P, Lipkin M. Cancer prevention. *Lancet*. 1997;349(suppl 9063):27-30.

Overvad OK, Diamant B, Holm L, Holmer G, Mortensen SA, Stender S. [Efficacy and safety of dietary supplementation containing Q10]. *Ugeskr Laeger*. 1997;159(49):7309-15.

Paajanen H, Harmoinen A, Sisto T, et al. Effect of antioxidants on postoperative hyperamylasemia in coronary bypass surgery. *Pancreas*. 1996;13(3):236-40.

Padayatty SJ, Levine M. Reevaluation of ascorbate in cancer treatment: emerging evidence, open minds and serendipity. *J Am Coll Nutr*. 2000;19(4):423-5.

Paganelli GM, Biasco G, Brandi G, et al. Effect of vitamin A, C, and E supplementation on rectal cell proliferation in patients with colorectal adenomas. *J Natl Cancer Inst*. 1992;84 (1):47-51.

Palan PR, Mikhail MS, Goldberg GL, Basu J, Runowicz CD, Romney SL. Plasma levels of beta-carotene, lycopene, canthaxanthin, retinol, and alpha- and tau-tocopherol in cervical intraepithelial neoplasia and cancer. *Clin Cancer Res*. 1996;2(1):181-5.

Paleologos M, Cummings RG, Lazarus R. Cohort study of vitamin C intake and cognitive impairment. *Am J Epidemiol*. 1998;148:45-50.

Paltiel O, Avitzour M, Peretz T, et al. Determinants of the use of complementary therapies by patients with cancer. *J Clin Oncol*. 2001;19(9):2439-48.

Pandey DK, Shekelle R, Selwyn BJ, Tangney C, Stamler J. Dietary vitamin C and beta-carotene and risk of death in middle-aged men. The Western Electric Study. *Am J Epidemiol*. 1995;142(12):1269-78.

Paolini M, Luigi Biagi G, Cantelli-Forti G, Bauer C. Plasma ascorbic acid in heart disease [4]. *Lancet.* 2001;358(9275):71-72.

Paolisso G, Esposito R, D'Alessio MA, Barbieri M. Primary and secondary prevention of atherosclerosis: Is there a role for antioxidants? *Diabetes Metab.* 1999;25(4):298-306.

Paolisso G, Gambardella A, Galzerano D, Varricchio M, D'Onofrio F. Antioxidants in adipose tissue and risk of myocardial infarction. *Lancet.* 1994;343(8897):596.

Papoz L. [Prevention of cardiovascular disease - a literature review]. *Ann Endocrinol (Paris).* 2001;62(N4):274-279.

Pappalardo G, Guadalaxara A, Maiani G, et al. Antioxidant agents and colorectal carcinogenesis: role of beta-carotene, vitamin E and vitamin C. *Tumori.* 1996;82(1):6-11.

Pardo B, Mena MA, Fahn S, Garcia de Yebenes J. Ascorbic acid protects against levodopa-induced neurotoxicity on a catecholamine-rich human neuroblastoma cell line . *Mov Disord.* 1993;8(3):278-84.

Patterson RE, White E, Kristal AR, Neuhouser ML, Potter JD. Vitamin supplements and cancer risk: the epidemiologic evidence. *Cancer Causes Control.* 1997;8(5):786-802.

Pauling L. Vitamin C therapy of advanced cancer. *N Engl J Med.* 1980;302:694.

Pauling L, Moertel C. A proposition: megadoses of vitamin C are valuable in the treatment of cancer. *Nutr Rev.* 1986;44(1):28-32.

Perticone F, Ceravolo R, Maio R, et al. Effects of atorvastatin and vitamin C on endothelial function of hypercholesterolemic patients. *Atheroscler.* 2000;152(2):511-518.

Plevova P. Prevention and treatment of chemotherapy- and radiotherapy-induced oral mucositis: a review. *Oral Oncol.* 1999;35(5):453-70.

Polakoff PL. Can chemointervention impede cancer growth? *Occup Health Saf.* 1983;52(6):23-4.

Ponz de Leon M, Roncucci L. Chemoprevention of colorectal tumors: role of lactulose and of other agents. *Scand J Gastroenterol Suppl.* 1997;222:72-5.

Porkkala-Sarataho E, Salonen J.T, Nyyssonen K, et al. Long-term effects of vitamin E, vitamin C, and combined supplementation on urinary 7-hydro-8-oxo-2'-deoxyguanosine, serum cholesterol oxidation products, and oxidation resistance of lipids in nondepleted men. *Arterioscler Thromb Vasc Biol.* 2000;20(9):2087-2093.

Poulter JM, White WF, Dickerson JW. Ascorbic acid supplementation and five year survival rates in women with early breast cancer. *Acta Vitaminol Enzymol.* 1984;6(3):175-82.

Prasad KN, Cole WC, Kumar B, Prasad KC. Scientific rationale for using high-dose multiple micronutrients as an adjunct to standard and experimental cancer therapies. *J Am Coll Nutr.* 2001;20(suppl 5):450S-463S; discussion 473S-475S.

Prasad KN, Kumar A, Kochupillai V, Cole WC. High doses of multiple antioxidant vitamins: essential ingredients in improving the efficacy of standard cancer therapy. *J Am Coll Nutr.* 1999;18 (1):13-25.

Preston-Martin S, Pogoda JM, Mueller BA, et al. Prenatal vitamin supplementation and pediatric brain tumors: huge international variation in use and possible reduction in risk. *Childs Nerv Syst.* 1998;14(10):551-7.

Raineri R, Weisburger JH. Reduction of gastric carcinogens with ascorbic acid. *Ann N Y Acad Sci.* 1975;258:181-9.

Raitakari O, Adams MR, McCredie RJ, Griffiths KA, Stocker R, Celermajer DS. Oral vitamin C and endothelial function in smokers: Short-term improvement, but no sustained beneficial effect. *J Am Coll Cardiol.* 2000;35(6):1616-1621.

Rath M. How vitamin C and other nutrients can help nip heart disease in the bud. *Exec Health's Good Health Rprt.* 1993;30(1):1.

Rautalahti M, Huttunen J. Antioxidants and carcinogenesis. *Ann Med.* 1994;26(6):435-41.

Rawson RW. Future perspectives for studies on the inhibition of carcinogenesis and their relationship to the prevention of human cancer. *Prev Med.* 1980;9(3):368-70.

Reaven PD, Khouw A, Beltz W.F, Parthasarathy S, Witztum J.L. Effect of dietary antioxidant combinations in humans: Protection of LDL by vitamin E but not by beta-carotene. *Arterioscler Thromb*. 1993;13(4):590-600.

Reed PI, Johnston B.J. [Primary prevention of gastric cancer - the ECP-IM intervention study.]. *Acta Endoscopica*. 1995;25(1):45-54.

Reynolds T. Antioxidants and cancer: what is the evidence? *J Natl Cancer Inst*. 2000;92(13):1033-4.

Rich-Edwards JW, Manson J.E., Hennekens C.H., Buring J.E. Medical Progress: The primary prevention of coronary heart disease in women. *New Engl J Med*. 1995;332(26):1758-1766.

Richardson MA, Ramirez T, Nanney K. Alternative/complementary medicine: implications for patient-provider communication. *Proc Am Soc Clin Concol*. 1999;18:590a.

Richardson MA, Sanders T, Palmer JL, Greisinger A, Singletary SE. Complementary/alternative medicine use in a comprehensive cancer center and the implications for oncology. *J Clin Oncol*. 2000;18(13):2505-14.

Riemersma RA, Oliver M, Elton RA, et al. Plasma antioxidants and coronary heart disease: Vitamins C and E, and selenium. *Eur J Clin Nutr*. 1990;44:143-50.

Riemersma RA, Wood DA, Macintyre CCA, Elton RA, Gey KF, Oliver MF. Risk of angina pectoris and plasma concentrations of vitamins A, C, and E and carotene. *Lancet*. 1991;337:1-5.

Rimm EB, Stampfer MJ, Ascherio A, et al. Vitamin E consumption and the risk of coronary heart disease in men. *N Engl J Med*. 1993;328:1450-56.

Riordan H, Jackson JA, Schultz M. Case study: high-dose intravenous vitamin C in the treatment of a patient with adenocarcinoma of the kidney. *J Orthomol Med*. 1990;5(1):5-7.

Riordan M, Jackson JA, Riordan NH, Schultz M. High-dose intravenous vitamin C in the treatment of a patient with renal cell carcinoma of the kidney. *J Orthomol Med*. 1998;13(2):72-3.

Rodriguez JR, Gonzalez M.J. Treatment of hypercholesterolemia with vitamins E, C and lecithin: A case report. *J Orthomol Med*. 1991;6(2):78-80.

Rohan TE, Howe GR, Friedenreich CM, Jain M, Miller AB. Dietary fiber, vitamins A, C, and E, and risk of breast cancer: a cohort study. *Cancer Causes Control*. 1993;4(1):29-37.

Rokkas T, Papatheodorou G, Karameris A, Mavrogeorgis A, Kalogeropoulos N, Giannikos N. Helicobacter pylori infection and gastric juice vitamin C levels. Impact of eradication. *Dig Dis Sci*. 1995;40(3):615-21.

Romney SL, Palan PR, Duttagupta C, et al. Retinoids and the prevention of cervical dysplasias. *Am J Obstet Gynecol*. 1981;141(8):890-4.

Romney S, Palan PR, Basu J, Mikhail M. Nutrient antioxidants in the pathogenesis and prevention of cervical dysplasias and cancer. *J Cell Biochem Suppl*. 1995;23//: 96-103.

Ronco A, De Stefani E, Boffetta P, Deneo-Pellegrini H, Mendilaharsu M, Leborgne F. Vegetables, fruits, and related nutrients and risk of breast cancer: a case-control study in Uruguay. *Nutr Cancer*. 1999;35(2):111-9.

Roncucci L, Di Donato P, Carati L, et al. Antioxidant vitamins or lactulose for the prevention of the recurrence of colorectal adenomas. Colorectal Cancer Study Group of the University of Modena and the Health Care District 16. *Dis Colon Rectum*. 1993;36(3):227-34.

Roncucci L, Ponz de Leon M. Antioxidant vitamins or lactulose as chemopreventive agents for colorectal cancer. In: Waldron K, Johnson I, Fenwick G, eds. *Food and Cancer Prevention: Chemical and Biological Aspects*. Cambridge, UK: Royal Society of Cambridge; 1993:p.147-150.

Rosenberg IH. Effect of wheat fiber and vitamins C and E supplements on rectal polyps in patients at high risk for colon cancer. (Brief Critical Reviews). *Nutr Rev*. 1990;48(5):218(3).

Rustin P, von Kleist-Retzow JC, Chantrel-Groussard K, Sidi D, Munnich A, Rotig A. Effect of idebenone on cardiomyopathy in Friedreich's ataxia: a preliminary study. *Lancet*. 1999;354(9177):477-9.

Salonen JT, Nyyssonen K, Salonen R, et al. Antioxidant Supplementation in Atherosclerosis Prevention (ASAP) study: A randomized trial of the effect of vitamins E and C on 3-year progression of carotid atherosclerosis. *J Intern Med*. 2000;248(5):377-386.

Sandler RS, Halabi S, Kaplan EB, Baron JA, Paskett E, Petrelli NJ. Use of vitamins, minerals, and nutritional supplements by participants in a chemoprevention trial. *Cancer.* 2001;91(5):1040-5.

Sasaki S, Tsubono Y, Okubo S, Hayashi M, Kakizoe T, Tsugane S. Effects of three-month oral supplementation of beta-carotene and vitamin C on serum concentrations of carotenoids and vitamins in middle-aged subjects: a pilot study for a randomized controlled trial to prevent gastric cancer in high-risk Japanese population. *Jpn J Cancer Res.* 2000;91 (5):464-70.

Scheen AJ. [Antioxidant vitamins in the prevention of cardiovascular diseases. 2nd part: results of clinical trials]. *Rev Med Liege.* 2000;55(2):105-9.

Schlegel JU. Proposed uses of ascorbic acid in prevention of bladder carcinoma. *Ann N Y Acad Sci.* 1975;258:432-7.

Schlegel JU, Pipkin GE, Nishimura R, Duke GA . Studies in the etiology and prevention of bladder carcinoma. *J Urol.* 1969;101(3):317-24.

Schlegel JU, Pipkin GE, Nishimura R, Shultz GN. The role of ascorbic acid in the prevention of bladder tumor formation. *J Urol.* 1970;103(2):155-9.

Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA.* 1995;273(5):408-12.

Schwartz LH, Urban T, Hercberg S. [Antioxidant minerals and vitamins. Role in cancer prevention]. *Presse Med.* 1994;23(39):1826-30.

Shaw S, Jayatilleke E, Herbert V. Evidence against antioxidant-prooxidant vitamin c supplements protecting against cancer. *Clin Res.* 1994;42(2):172A.

Shibata A, Paganini-Hill A, Ross R, Henderson BE. Intake of vegetables, fruits, beta-carotene, vitamin C and vitamin supplements and cancer incidence among the elderly: a prospective study. *Br J Cancer.* 1992;66(4):673-9.

Shimpo K, Nagatsu T, Yamada K, et al. Ascorbic acid and adriamycin toxic ity. *Am J Clin Nutr.* 1991;54 (suppl 6):1298S-1301S.

Shklar G. Mechanisms of cancer inhibition by anti-oxidant nutrients. *Oral Oncol.* 1998;34(1):24-9.

Shklar G, Schwartz J, Trickler D, Cheverie SR. The effectiveness of a mixture of beta -carotene, alpha -tocopherol, glutathione, and ascorbic acid for cancer prevention. *Nutr Cancer.* 1993;20:p.145-151.

Silverman J. Nutritional aspects of cancer prevention: an overview. *J Am Vet Med Assoc.* 1981;179(12):1404-9.

Simon JA. Vitamin C and cardiovascular disease: A review. *J Am Coll Nutr.* 1992;11:107-25.

Simonenko VB. [Antioxidants in the comprehensive therapy of myocardial infarction]. *Klin Med (Mosk).* 1998;76 (11):20-5.

Singal PK, Siveski-Iliskovic N, Hill M, Thomas T.P, Li T. Combination therapy with probucol prevents adriamycin-induced cardiomyopathy. *J Mol Cell Cardiol.* 1995;27(4):1055-1063.

Singh DK, Lippman SM. Cancer chemoprevention. Part 1: Retinoids and carotenoids and other classic antioxidants. *Oncology (Huntingt).* 1998;12(11):1643-53, 1657-8.

Singh DK, Lippman SM. Cancer chemoprevention. Part 2: Hormones, nonclassic antioxidant natural agents, NSAIDs, and other agents. *Oncology (Huntingt).* 1998;12(12):1787-800; discussion 1802, 1805.

Singh RB, Niaz MA, Rastogi SS, Rastogi S. Usefulness of antioxi dant vitamins in suspected acute myocardial infarction (the Indian experiment of infarct survival-3). *Am J Cardiol.* 1996;77 (4):232-6.

Singh RB, Gosh S, Niaz MA, et al. Dietary intake, plasma levels of antioxidant vitamins, and oxidative stress in relation to coronary artery disease in elderly subjects. *Am J Cardiol.* 1995;76:1233-38.

Singh VN, Gaby SK. Premalignant lesions: role of antioxidant vitamins and beta-carotene in risk reduction and prevention of malignant transformation. *Am J Clin Nutr.* 1991;53(suppl 1):386S-390S.

Singhal S, Gupta R, Goyle A. Comparison of antioxidant efficacy of vitamin E, vitamin C, vitamin A and fruits in coronary heart disease: a controlled trial. *J Assoc Physicians India.* 2001;49:327-31.

Sirtori C. [Importance of active and passive prevention of cancer, arteriosclerosis and senility]. *Minerva Med.* 1982;73(41):2867-72.

Sisto T, Paajanen H, Metsa-Ketela T, Harmoinen A, Nordback I, Tarkka M. Pretreatment with antioxidants and allopurinol diminishes cardiac onset events in coronary artery bypass grafting. *Ann Thorac Surg.* 1995;59(6):1519-23.

Slaga TJ. Multistage skin carcinogenesis: a useful model for the study of the chemoprevention of cancer. *Acta Pharmacol Toxicol (Copenh).* 1984;55 suppl 2:107-24.

Smigel K. Dietary supplements reduce cancer deaths in China. *J Natl Cancer Inst.* 1993;85(18):1448-50.

Smythies J. Recent advances in oxidative stress and antioxidants in medicine. *J Orthomol Med.* 1998;13(1):11-18.

Soloway MS, Cohen SM, Dekernion JB, Persky L . Failure of ascorbic acid to inhibit FANFT-induced bladder cancer. *J Urol.* 1975;113(4):483-6.

Solzbach U, Hornig B, Jeserich M, Just H. Vitamin C improves endothelial dysfunction of epicardial coronary arteries in hypertensive patients. *Circulation.* 1997;96:1513-9.

Sparber A, Bauer L, Curt G, et al. Use of complementary medicine by adult patients participating in cancer clinical trials. *Oncol Nurs Forum.* 2000;27(4):623-30.

Stahelin HB, Gey KF, Eichholzer M, Ludin E. Beta-carotene and cancer prevention: the Basel Study. *Am J Clin Nutr.* 1991;53(suppl 1):265S-269S.

Stahl P. The antioxidant conundrum: two recent studies point in different directions. *J Am Diet Assoc.* 2000;100(5):510.

Steinberg D. Antioxidant vitamins and coronary heart disease. *N Engl J Med.* 1993;328(20):1487-9.

Steinberg D. Antioxidants in the prevention of human atherosclerosis: Summary of the proceedings of a National Heart, Lung, and Blood Institute Workshop: September 5-6, 1991, Bethesda, Maryland. *Circulation.* 1992;85(6):2338-44.

Steinberg D. Clinical trials of antioxidants in artherosclerosis: Are we doing the right thing? *Lancet.* 1995;346(8966):36-38.

Steinmetz K, Potter JD. Vegetables, fruit, and cancer prevention: a review. *J Am Diet Assoc.* 1996;96(10):1027-39.

Stephens N. Anti-oxidant therapy for ischaemic heart disease: where do we stand? *Lancet.* 1997;349(9067):1710-1.

Subar AF, Block G. Use of vitamin and mineral supplements: demographics and amounts of nutrients consumed: The 1987 Health Interview Survey. *Am J Epidemiol.* 1990;132:1091-101.

Sullivan JL. Antioxidants and coronary heart disease. *Lancet.* 1991;337(8738):432-433.

Szarka CE, Grana G, Engstrom PF. Chemoprevention of cancer. *Curr Probl Cancer.* 1994;18(1):6-79.

Taddei S, Virdis A, Ghiadoni L, Magagna A, Salvetti A. Vitamin C improves endothelium-dependent vasodilation by restoring nitric oxide activity in essential hypertension. *Circulation.* 1998;97:2222-9.

Tanaka T. Chemoprevention of human cancer: biology and therapy. *Crit Rev Oncol Hematol.* 1997;25(3):139-74.

Taper HS, Jamison JM, Gilloteaux J, Gwin CA, Gordon T, Summers JL. In vivo reactivation of DNases in implanted human prostate tumors after administration of a vitamin C/K(3) combination. *J Histochem Cytochem.* 2001;49(1):109-20.

Tardif JC, Cote G, Lesperance J, et al. Probucol and multivitamins in the prevention of restenosis after coronary angioplasty. Multivitamins and Probucol Study Group . *N Engl J Med.* 1997;337(6):365-72.

Taylor PR, Li B, Dawsey SM, et al. Prevention of esophageal cancer: the nutrition intervention trials in Linxian, China. Linxian Nutrition Intervention Trials Study Group. *Cancer Res.* 1994;54(suppl 7):2029s-2031s.

Thangaraju M, Vijayalakshmi T, Sachdanandam P. Effect of tamoxifen on lipid peroxide and antioxidative system in postmenopausal women with breast cancer. *Cancer.* 1994;74(1):78-82.

Thompson IM, Coltman CA, Brawley OW, Ryan A. Chemoprevention of prostate cancer. *Semin Urol.* 1995;13(2):122-9.

Todd S, Woodward M, Tunstall-Pedoe H, Bolton-Smith C. Dietary antioxidant vitamins and fiber in the etiology of cardiovascular disease and all-causes mortality: Results from the Scottish Heart Health Study. *Am J Epidemiol*. 1999;150(10):1073-1080.

Tribble DL, Frank E. Dietary antioxidants, cancer, and atherosclerotic heart disease. *West J Med.* 1994;161(6):605-612.

Trizna Z, Schantz SP, Hsu TC. Effects of N-acetyl-L-cysteine and ascorbic acid on mutagen-induced chromosomal sensitivity in patients with head and neck cancers. *Am J Surg*. 1991;162(4):294-8.

Trout DL. Vitamin C and cardiovascular risk factors. *Am J Clin Nutr.* 1991;53:322S-5S.

Tseng M, Murray S, Kupper LL, Sandler RS. Micronutrients and the risk of colorectal adenomas. *Am J Epidemiol*. 1996;144(11):1005-14.

Tsubono Y, Okubo S, Hayashi M, Kakizoe T, Tsugane S. A randomized controlled trial for chemoprevention of gastric cancer in high-risk Japanese population; study design, feasibility and protocol modification. *Jpn J Cancer Res.* 1997;88(4):344-9.

Tsugane S, Tsubono Y, Okubo S, Hayashi M, Kakizoe T. A pilot study for a randomized controlled trial to prevent gastric cancer in high-risk Japanese population: study design and feasibility evaluation. *Jpn J Cancer Res.* 1996;87:676-9.

Uddin S, Ahmad S. Antioxidants protection against cancer and other human diseases. *Compr Ther.* 1995;21(1):41-5.

Upritchard JE, Sutherland WH, Mann JI. Effect of supplementation with tomato juice, vitamin E, and vitamin C on LDL oxidation and products of inflammatory activity in type 2 diabetes. *Diabetes Care.* 2000;23(6):733-8.

van het Hof KH, de Boer H, Wiseman S, Lien N, Westrate J, Tijburg L. Consumption of green or black tea does not increase resistance of low- density lipoprotein to oxidation in humans. *Am J ClinNutr.* 1997;66(5):1125-1132.

van Poppel G, van den Berg H. Vitamins and cancer. *Cancer Lett.* 1997;114(1-2):195-202.

van Zandwijk N, Pastorino U, de Vries N. Chemoprevention of cancer. *Eur Respir J.* 1993;6(3):322-4.

Vazquez Martinez C, Galan P, Preziosi P, Ribas L, Serra LL, Hercberg S. The SUVIMAX (France) study: the role of antioxidants in the prevention of cancer and cardiovascular disorders. *Rev Esp Salud Publica.* 1998;72(3):173-83.

Verhoeven DT, Assen N, Goldbohm RA, et al. Vitamins C and E, retinol, beta-carotene and dietary fibre in relation to breast cancer risk: a prospective cohort study. *Br J Cancer.* 1997;75 (1):149-55.

Vermeer IT, Moonen EJ, Dallinga JW, Kleinjans JC, van Maanen JM. Effect of ascorbic acid and green tea on endogenous formation of N-nitrosodimethylamine and N-nitrosopiperidine in humans. *Mutat Res.* 1999;428(1-2):353-61.

Violi F, Micheletta F, Iuliano L. Vitamin E supplementation. *Lancet.* 2001;357(9256):632-3.

Violi F, Micheletta F, Luliano L. Antioxidant strategy for cardiovascular disease. *Lancet.* 2001;357(9269):1704.

Vogel R. Cholesterol lowering and endothelial function. *Am J Med.* 1999;107(5):479-487.

Von Eggers Doering W, Pietrzik K, DeGrand D, et al. Antioxidant vitamins, cancer, and cardiovascular disease (2). *New Engl J Med.* 1996;335(14):1065-1069.

Voorrips LE, Goldbohm RA, Brants HA, et al. A prospective cohort study on antioxidant and folate intake and male lung cancer risk. *Cancer Epidemiol Biomarkers Prev.* 2000;9(4):357-65.

Waddell WR, Gerner RE. Indomethacin and ascorbate inhibit desmoid tumors. *J Surg Oncol.* 1980;15(1):85-90.

Wagdi P, Fluri M, Aeschbacher B, Fikrle A, Meier B. Cardioprotection in patients undergoing chemo - and/or radiotherapy for neoplastic disease. A pilot study. *Jpn Heart J.* 1996;37 (3):353-9.

Wang GQ, Dawsey SM, Li JY, et al. Effects of vitamin/mineral supplementation on the prevalence of histological dysplasia and early cancer of the esophagus and stomach: results from the General Population Trial in Linxian, China. *Cancer Epidemiol Biomarkers Prev.* 1994;3(2):161-6.

Wardman P, Folkes LK, Bentzen SM, et al. Influence of plasma glutathione levels on radiation mucositis. *Int J Radiat Oncol Biol Phys.* 2001;51(2):460-4.

Watanabe H, Kakihana M, Ohtsuka S, Sugishita Y. Randomized, double-blind, placebo-controlled study of ascorbate on the preventive effect of nitrate tolerance in patients with congestive heart failure. *Circulation.* 1998;97(9):886-91.

Watson RR, Leonard TK. Selenium and vitamins A, E, and C: nutrients with cancer prevention properties. *J Am Diet Assoc.* 1986;86(4):505-10.

Weijl NI, Cleton FJ, Osanto S. Free radicals and antioxidants in chemotherapy-induced toxicity. *Cancer Treat Rev.* 1997;23(4):209-40.

Weijl NI, Hopman GD, Wipkink-Bakker A, et al. Cisplatin combination chemotherapy induces a fall in plasma antioxidants of cancer patients. *Ann Oncol.* 1998;9(12):1331-7.

Weisburger JH. Nutritional approach to cancer prevention with emphasis on vitamins, antioxidants, and carotenoids. *Am J Clin Nutr.* 1991;53(suppl 1):226S-237S.

Weisburger JH. Vitamin C and disease prevention. *J Am Coll Nutr.* 1995;14(2):109-111.

Weisburger JH. Vitamin C and prevention of nitrosamine formation. *Lancet.* 1977;2(8038):607.

Weisburger J, Horn CL. Human and laboratory studies on the causes and prevention of gastrointestinal cancer. *Scand J Gastroenterol Suppl.* 1984;104:15-26.

Westhuyzen J, Cochrane AD, Tesar PJ, et al. Effect of preoperative supplementation with alpha-tocopherol and ascorbic acid on myocardial injury in patients undergoing cardiac operations. *J Thorac Cardiovasc Surg.* 1997;113(5):942-8.

Whelan RL, Horvath KD, Gleason NR, et al. Vitamin and calcium supplement use is associated with decreased adenoma recurrence in patients with a previous history of neoplasia. *Dis Colon Rectum.* 1999;42(2):212-7.

White E, Shannon JS, Patterson RE. Relationship between vitamin and calcium supplement use and colon cancer. *Cancer Epidemiol Biomarkers Prev.* 1997;6:769-74.

Willett W, Sampson L, Bain C, et al. Vitamin supplement use among registered nurses. *Am J Clin Nutr.* 1981;34 (6):1121-1125.

Willett WC, MacMahon B. Diet and cancer--an overview. *N Engl J Med.* 1984;310(10):633-8.

Wilson CW. Clinical pharmacological aspects of ascorbic acid. *Ann N Y Acad Sci.* 1975;258:355-76.

Wilson TS, Datta SB, Murrell JS, Andrews CT. Relation of vitamin C levels to mortality in a geriatric hospital: a study of the effect of vitamin C administration. *Age Aging.* 1973 ;2(3):163-71.

Witte KK, Clark AL, Cleland JG. Chronic heart failure and micronutrients. *J Am Coll Cardiol.* 2001;37 (7):1765-74.

Woodside JV, Yarnell JW, McMaster D, et al. Effect of B-group vitamins and antioxidant vitamins on hyperhomocysteinemia: a double-blind, randomized, factorial-design, controlled trial. *Am J Clin Nutr.* 1998;67(5):858-66.

Woodside JV, Young IS, Yarnell JW, et al. Antioxidants, but not B-group vitamins increase the resistance of low-density lipoprotein to oxidation: a randomized, factorial design, placebo-controlled trial. *Atheroscler.* 1999;144(2):419-27.

Wyatt GK, Friedman LL, Given CW, Given BA, Beckrow KC. Complementary therapy use among older cancer patients. *Cancer Pract.* 1999;7(3):136-44.

Yamanaka WK. Vitamins and cancer prevention. How much do we know? *Postgrad Med.* 1987;82(3):149-51, 153.

Yang CS, Miao J, Yang W, et al. Diet and vitamin nutrition of the high esophageal cancer risk population in Linxian, China. *Nutr Cancer.* 1982;4:154-64.

Yong LC, Brown CC, Schatzkin A, et al. Intake of vitamins E, C, and A and risk of lung cancer. The NHANES I epidemiologic followup study. First National Health and Nutrition Examination Survey. *Am J Epidemiol.* 1997;146(3):231-43.

Youn HS, Ko GH, Chung MH, Lee WK, Cho MJ, Rhee KH. Pathogenesis and prevention of stomach cancer. *J Korean Med Sci.* 1996;11(5):373-85.

Young VR, Newberne PM. Vitamins and cancer prevention: issues and dilemmas. *Cancer*. 1981;47(suppl 5):1226-40.

Young VR, Richardson D.P. Nutrients, vitamins and minerals in cancer prevention. Facts and fallacies. *Cancer*. 1979;43(suppl 5):2125-2136.

Yun TK. Update from Asia. Asian studies on cancer chemoprevention. *Ann N Y Acad Sci*. 1999;889:157-92.

Yusuf S, Lessem J, Jha P, Lonn E. Primary and secondary prevention of myocardial infarction and strokes: An update of randomly allocated, controlled trials. *J Hypertens*. 1993;11(suppl 4):S61-S73.

Zhang S, Hunter DJ, Forman MR, et al. Dietary carotenoids and vitamins A, C, and E and risk of breast cancer. *J Natl Cancer Inst*. 1999;91(6):547-56.

Zheng W, Anderson KE, Kushi LH, et al. A prospective cohort study of intake of calcium, vitamin D, and other micronutrients in relation to incidence of rectal cancer among postmenopausal women. *Cancer Epidemiol Biomarkers Prev*. 1998;7(3):221-5.

Zheng W, Sellers T, Doyle TJ, Kushi LH, Potter JD , Folsom AR. Retinol, antioxidant vitamins, and cancers of the upper digestive tract in a prospective cohort study of postmenopausal women. *Am J Epidemiol*. 1995;142(9):955-60.

Zullo A, Rinaldi V, Hassan C, et al. Ascorbic acid and intestinal metaplasia in the stomach: a prospective, randomized study. *Aliment Pharmacol Ther*. 2000;14(10):1303-9.

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.

Jeffrey Blumberg, PhD, FACN, CNS
Nutrition Research Center on Aging
Tufts University
Boston, MA

Julie Buring, ScD
Brigham and Women's Hospital
Harvard Medical School
Boston, MA

Rebecca Costello, PhD
Office of Dietary Supplements
National Institutes of Health
Bethesda, MD

David Golde, MD
Memorial Sloan-Kettering Cancer Center
New York, NY

Michael Hawkins, MD
Washington Cancer Institute
Washington, DC

Ishwarlal Jialal, MD, PhD
UCD Medical Center
University of California, Davis
Sacramento, CA

Martin Kendall, MD, FRCP
Department of Medicine
Queen Elizabeth Hospital
Birmingham, United Kingdom

David Leaf, MD
Department of Medicine
VA Greater Los Angeles Medical Center
Los Angeles, CA

Ralph Moss, PhD
The Moss Reports
State College, PA

Alex Sevanian, MD
Department of Molecular Pharmacology and Toxicology
University of Southern California
Los Angeles, CA

Technical Expert Panel

We wish to acknowledge the work of our technical expert panel:

Betty L. Chang, DNSc, FNP-C, FAAN
Professor, School of Nursing
University of California, Los Angeles
Los Angeles, CA

Seigward-Markus Elsas, MD
Clinical Fellow in Neurophysiology
University of California, Los Angeles
Los Angeles, CA

Glenn Clark, DDS
School of Dentistry
University of California, Los Angeles
Los Angeles, CA

Deborah Glik, Ph.D.
Associate Professor, School of Public Health
University of California, Los Angeles
Los Angeles, CA

Michael Goldstein, PhD
Professor, School of Public Health
University of California, Los Angeles
Los Angeles, CA

Eric Hurwitz, DC, PhD
Assistant Professor, Department of Epidemiology,
School of Public Health, University of California
Los Angeles, CA

Ka Kit Hui, MD, FACP
Director, UCLA Center for East-West Medicine
University of California
Los Angeles, CA

Simon Mills, MA, MCPP, FNIMH
Director for the Center of Complementary Medicine
University of Exeter
Exeter, England

Lakshmi C. Mishra, BIMS, M Pharm, PhD
Professor of Research
Southern California University of Health Science
Whittier, CA

Shri K. Mishra, MD, MS, Doctor of Ayurveda
Professor of Neurology and Coordinator Integrative Medicine
USC School of Medicine
USC Keck School of Medicine
Los Angeles, CA

Lucy Postolov, LAc
Postolova Acupuncture Group
Los Angeles, CA

David Riley, MD
Clinical Associate Professor
University of North West Medical School,
Director, Integrative Medicine Research
Santa Fe, NM

Betsy B. Singh, PhD
Dean of Research
Southern California University of Health Sciences
Whittier, CA

George Solomon, MD
Professor Emeritus, UCLA School of Medicine,
Dept. of Psychiatry and Biobehavioral Medicine
University of California
Los Angeles, CA

Hitoshi Tomizawa, MD
Director, Japanese Executive Medical Services,
Cedars-Sinai Medical Center
Los Angeles, CA

Xiao-Ping Xu, LAc
Burns and Allen Research Institute
Cedars Sinai Medical Center
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:

MEDLINE	1966-2001/Dec W2
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 W1
Biosis Previews	1969-2001/Nov W2
EMBASE	1974-2001/Nov W2
Social SciSearch	1972-2001/Nov W3
SciSearch Cited Ref Sci	1990-2001/Nov W3
SciSearch Cited Ref Sci	1974-1989/Dec
ELSEVIER BIOBASE	1994-2001/Nov W2

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
SciSearch Cited Ref Sci	1990-2001/Nov W4
SciSearch Cited Ref Sci	1974-1989/Dec
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
Social SciSearch	1972-2001/Dec W3
SciSearch Cited Ref Sci	1990-2001/Dec W3
SciSearch Cited Ref Sci	1974-1989/Dec
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:

MEDLINE	1966-2002/JAN W3
MANTIS	1880-2001/Oct
Allied & Complementary Medicine	1984-2001/Feb
CancerLit	1975-2001/Oct
CAB HEALTH	1983-2001/Dec
TGG Health&Wellness DB	1976-2002/Dec W5
Biosis Previews	1969-2002/Jan W2
EMBASE	1974-2002/Jan W2
Social SciSearch(R)	1972-2002/Jan W3
SciSearch Cited Ref Sci	1990-2002/Jan W3
SciSearch Cited Ref Sci	1974-1989/Dec
ELSEVIER BIOBASE	1994-2002/Jan W2

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

Article# **Antioxidant Screener** **RAND EPC Alternative Medicine**

Reviewers: _____ mm/dd/yy
_____ mm/dd/yy

Assigned on:

[article author, title, journal, date, vol, pages]

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

2. What topic does the article study: **Check all that apply**
   - 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: **Check all that apply**
   - Cancer ..... π
   - Cardiovascular Disease ..... π
   - No condition/disease ..... π (STOP)
   - Other (Specify_____) .... π (STOP)
   - Unclear ..... π

4. Subject Population: **Check all that apply**
   - Human ..... π
   - In vitro / In vivo ..... π (STOP)
   - Animal ..... π (STOP)
   - Other (Specify_____) .... π (STOP)
   - Unclear ..... π

5. Article Type: **Check all that apply**
   - 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? **Circle One**
   - Treatment 1
   - Primary prevention 2
   - Secondary prevention 3
   - Adjunct to conventional treatment 4
   - Other (Specify_____) .. 5
   - Unclear 6

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

NOTES:

Abstract:

RAND EPC, CAM Project

Quality Review Form, Topic = ANTIOXIDANT

Article ID:_____ Reviewer:_____

First Author: _____
(Last Name Only)

Study Number: ___of____Description:_____
(Enter '1of 1' if only one) (if more than one study)

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)**

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

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

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

5. Is the study described as: (circle one)
   - Double blind....1
   - Single blind, patient....2
   - Single blind, outcome assessment....3
   - Open....4
   - Blinding 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.....π (01)
CVA/TIA .....ρ (02)
PVD .....ρ (03)
CHF.....ρ (04)
Angina.....ρ (05)

Code: ____ ____

____ ____

____ ____

____ ____

Not Applicable .....ρ (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.....ρ (01)
Lung.....ρ (02)
Prostate.....ρ (03)
Oral.....ρ (04)
Cervix.....ρ (05)
Gastric .....ρ (06)
Colon .....ρ (07)

Code: ____ ____

____ ____

____ ____

____ ____

Not Applicable 99

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

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

Other code: ____ ____

Not Applicable 99

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

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 1 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:

	Intervention	Daily Dose	Units		Route of administration	Duration	Units
1	_____	_____	_____	taken	_____	_____	_____
2	_____	_____	_____	taken	_____	_____	_____
3	_____	_____	_____	taken	_____	_____	_____
4	_____	_____	_____	taken	_____	_____	_____
	Enter code	Enter a number	1. µg 2. mg 3. gm 4. IU 8. ND 9. NA		1. PO 2. IV 8. ND 9. NA	Enter a number 998. ND 999. NA	1. Hour 2. Day 3. Week 4. Month 5. Year 6. Mean Month 7. Median Month 8. Mean Year 9. Median Year 10. Maximum Month 11. Minimum Month 12. Maximum Year 13. Minimum Year 98. ND 99. NA

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

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:

Intervention	Daily Dose	Units		Route of administration	Duration	Units
1 _____	_____	_____	taken	_____	_____	_____
2 _____	_____	_____	taken	_____	_____	_____
3 _____	_____	_____	taken	_____	_____	_____
4 _____	_____	_____	taken	_____	_____	_____
Enter code	Enter a number	1. µg 2. mg 3. gm 4. IU 8. ND 9. NA		1. PO 2. IV 8. ND 9. NA	Enter a number 998. ND 999. NA	1. Hour 2. Day 3. Week 4. Month 5. Year 6. Mean Month 7. Median Month 8. Mean Year 9. Median Year 10. Maximum Month 11. Minimum Month 12. Maximum Year 13. Minimum Year 98. ND 99. NA

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

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?

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

(Enter 999,999 if not reported.)

---

20. Intervention:

Intervention	Daily Dose	Units		Route of administration	Duration	Units
1 _____	_____	_____	taken	_____	_____	_____
2 _____	_____	_____	taken	_____	_____	_____
3 _____	_____	_____	taken	_____	_____	_____
4 _____	_____	_____	taken	_____	_____	_____
Enter code	Enter a number	1. µg 2. mg 3. gm 4. IU 8. ND 9. NA		1. PO 2. IV 8. ND 9. NA	Enter a number 998. ND 999. NA	1. Hour 2. Day 3. Week 4. Month 5. Year 6. Mean Month 7. Median Month 8. Mean Year 9. Median Year 10. Maximum Month 11. Minimum Month 12. Maximum Year 13. Minimum Year 98. ND 99. NA

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

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 4 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:

Intervention	Daily Dose	Units		Route of administration	Duration	Units
1 _____	_____	_____	taken	_____	_____	_____
2 _____	_____	_____	taken	_____	_____	_____
3 _____	_____	_____	taken	_____	_____	_____
4 _____	_____	_____	taken	_____	_____	_____
Enter code	Enter a number	1. µg 2. mg 3. gm 4. IU 8. ND 9. NA		1. PO 2. IV 8. ND 9. NA	Enter a number 998. ND 999. NA	1. Hour 2. Day 3. Week 4. Month 5. Year 6. Mean Month 7. Median Month 8. Mean Year 9. Median Year 10. Maximum Month 11. Minimum Month 12. Maximum Year 13. Minimum Year 98. ND 99. NA

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

Outcomes

21. Type of outcomes measured:

Enter the code for each outcome measured.
_____ _____
_____ _____
_____ _____
_____ _____
_____ _____
_____ _____
_____ _____
_____ _____
_____ _____
_____ _____
_____ _____
_____ _____

Evaluation

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

Enter the number and letters in the appropriate box

	Number	**Unit**
1st follow-up		
2nd follow-up		
3rd follow-up		
4th follow-up		
5th follow-up		
6th follow-up		
Additional follow-ups:		

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
YRMX	maximum 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

_____ _____ _____ _____
_____ _____ _____ _____
_____ _____ _____ _____