What Can Randomized Controlled Trials Tell Us About Nutrition and Cancer Prevention?

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Abstract

Randomized controlled trials are regarded as the most definitive of study designs. The randomized controlled trials that have tested nutritional factors for cancer prevention are reviewed. Trials that have tested the effects of nutrients given as high-dose supplements have been largely disappointing, typically showing either no or harmful effects. Possible benefits of vitamin E for prostate cancer prevention and selenium for prostate, colorectal, and lung cancer prevention have emerged only as secondary endpoints in trials conducted for other purposes; confirmatory new trials for these nutrients are now underway or are planned.

The limitations of both past and current randomized controlled trials for studying diet-cancer relationships are discussed. The disappointing findings that have emerged from short-term studies of high-dose supplements cannot be interpreted as direct tests of the diet-cancer relationship because high-dose supplements cannot fully simulate the effects of whole foods on cancer risk.

As we await findings from current and future trials, we should not forget that the ample evidence from observational epidemiologic research—suggesting that diets rich in fruits and vegetables can reduce the risk of many of the most common cancers—can provide a sound basis for nutritional recommendations aimed at reducing cancer risk. (CA Cancer J Clin 1999;49:353-361.)

Randomized Controlled Trials

Randomized controlled trials are commonly regarded as the definitive study design for proving causality. Relationships between nutrients and cancer risk, previously postulated only on the basis of observation, have now been studied in a number of completed randomized controlled trials; many others are still ongoing.

This is a good time, therefore, to reflect on the lessons we have learned from randomized controlled trials of nutrients and cancer, and on the question of what such trials can tell us about nutrition and cancer prevention. This article will review findings from the randomized controlled trials conducted to date on the relationship between nutrients and cancer prevention, and will discuss the question of how clinicians might best interpret these findings when counseling patients about nutrition and cancer risk reduction.

Findings from Observational Studies

Current dietary recommendations intended to reduce cancer risk are based on extensive data from observational studies of the relationship between diet and cancer incidence. The most informative observational studies have used case-control or cohort designs. In brief, findings from observational epidemiologic studies support the notion that diets high in fruits and vegetables are associated with lower risk for cancer at many sites, especially in the gastrointestinal...
tract (oral, esophageal, gastric, and colorectal cancers), and in the respiratory tract (lung and laryngeal cancers).1,2 In 1981, Doll and Peto estimated that about 35% of all cancers in the US might be attributable to dietary factors.3 Similar estimates were made by the European School of Oncology Task Force on Diet, Nutrition, and Cancer in 1994,4 and by the World Cancer Research Fund and the American Institute for Cancer Research in 1997.2 Many of these estimates are imprecise, of course, both because diet consists of a complex set of factors, and because observational nutritional research is plagued by uncertainties about dietary assessment methodology.

Observational studies generally reveal weaker relationships between cancer and measures of nutrients taken as supplements than for measures of nutrients absorbed from eating fruits and vegetables.1,2 This may mean that nutrients taken in the broad combinations found in whole foods are more effective against cancer than are nutrients taken in supplements. We must be careful about such conclusions, however, as there are many problems with observational studies of vitamin supplements, such as variability in the reporting of supplement doses and in supplement use patterns over time.5

The effects of both diet and nutritional supplement use are often complicated by behaviors, such as physical activity, smoking, food choices, and illness symptoms, all of which can seriously confound any associations that may be noted between diet, supplement use, and cancer risk.6 Whole-diet interventions are difficult to test in randomized controlled trials, but nutritional supplements are well-suited for testing in trials.

Findings from Randomized Controlled Trials

A Medline search of the National Library of Medicine’s PubMed system (www.pubmed.gov) was conducted to examine published studies of nutrition and cancer that used a randomized controlled design. Included in this review are all papers or abstracts published in English that reported study designs featuring a random assignment of foods or nutrients to at least 200 people (to eliminate underpowered studies) and that examined cancer or colorectal adenomatous polyps as the study endpoint. Not included were studies of non-nutritive synthetic compounds or of various intermediate biomarkers of neoplasia risk (e.g., proliferation, dysplasia, or cytologic atypia).

Disappointingly, findings from randomized controlled trials have often not confirmed the relationships between nutrients and cancer risk that have been suggested by observational studies of diet and cancer. In some cases, trials have even demonstrated that high doses of nutrients previously believed to be beneficial could have unexpected harmful effects. In addition to these disappointing findings, though, there have also been some pleasant surprises. Two trials, for instance, uncovered beneficial effects of nutrients on cancers that were not hypothesized a priori as the primary endpoints.7,8 The findings are summarized in the Table, and are also briefly described by cancer site here.

GASTRIC AND ESOPHAGEAL CANCER

Case-control and cohort studies have clearly shown that diets high in fruits and vegetables are associated with lower risk for cancers of all the gastrointestinal tract sites, including the oral cavity, esophagus, stomach, colon, and rectum.9 Consequently, there has been intense interest in developing a better understanding of the specific constituents of plant foods that might account for the protective association. Although nutrient indices are often computed from food intake estimates in observational studies (e.g., fiber, ascorbate, folate), it is difficult to confidently distinguish the effects of various nutrients in food-based studies. Experimental de-
## Table
Randomized Controlled Trials of Various Nutrients and the Incidence of Cancers and Adenomatous Polyps

| Cancer         | Study or Investigator | Nutrients Tested, Daily Dose | Years on Study | Relative Risk (agent vs placebo) |
|---------------|-----------------------|-----------------------------|----------------|----------------------------------|
| **Gastric**   | Linxian, China¹⁰      | Vitamin C 120 mg, Mb 30 mcg | 5              | 1.10                             |
|               | Linxian, China¹⁰      | Retinol 5000 IU, Zn 22.5 mg | 5              | 0.96                             |
|               | Linxian, China¹⁰      | Riboflavin 3.2 mg, Niacin 40 mg | 5              | 1.04                             |
|               | Linxian, China¹⁰      | Beta carotene 15 mg, Vitamin E 30 mg, Se 50 mcg | 5              | 0.85                             |
|               | ATBC*⁷                | Beta carotene 20 mg          | 6              | 1.26                             |
|               | ATBC*⁷                | Vitamin E 50 mg              | 6              | 1.26                             |
| **Skin**      | Greenberg³¹           | Beta carotene 50 mg          | 5              | 1.05                             |
|               | NPSC*⁸               | Selenium 200 mcg            | 5              | 1.12                             |
|               | SWSCPS³² (high risk)  | Vitamin A 25,000 IU          | 3              | 1.00                             |
|               | SWSCPS³³ (average risk) | Vitamin A 25,000 IU        | 4              | 1.06                             |
| **Prostate**  | ATBC*,⁷²⁷             | Beta carotene 20 mg          | 6              | 1.23                             |
|               | ATBC*,⁷²⁷             | Vitamin E 50 IU              | 6              | 0.66                             |
|               | NPSC*,²⁸              | Selenium 200 mcg            | 5              | 0.37                             |
| **Lung**      | ATBC⁷                | Beta carotene 20 mg          | 6              | 1.18                             |
|               | ATBC⁷                | Vitamin E 50 IU              | 6              | 0.98                             |
|               | CARET¹⁹              | Beta carotene 30 mg + Vitamin A 25,000 IU | 4              | 1.28                             |
|               | PHS²⁰                | Beta carotene 25 mg          | 11             | 0.95                             |
|               | NPSC*,⁸              | Selenium 200 mcg            | 5              | 0.54                             |
| **Colorectal**| NPSC*,⁸              | Selenium 200 mcg            | 5              | 0.42                             |
| **Colorectal adenomas** | ATBC*⁷              | Beta carotene 20 mg          | 6              | 1.05                             |
|               | ATBC*⁷              | Vitamin E 50 IU              | 6              | 0.83                             |
|               | McKeown-Eyssen¹²     | Cereal fiber 20 g            | 2              | 1.2                              |
|               | MacLennan¹³          | Cereal fiber 25 g            | 4              | 1.2                              |
|               | MacLennan¹³          | Beta carotene 20 mg          | 4              | 1.5                              |
|               | Greenberg¹⁴          | Beta carotene 25 mg          | 4              | 1.01                             |
|               | Greenberg¹⁴          | Vitamin E 400 IU + Vitamin C 1 gm | 4              | 1.08                             |
|               | Baron¹⁵              | Calcium 1.2 gm               | 4              | 0.83                             |
|               | Bonelli¹⁶            | Selenium 200 mcg             | 4              | 0.56                             |

*Sites reported only as secondary endpoints in trials designed to test nutrient effects on other cancers.

ATBC=Alpha Tocopherol Beta Carotene study; NPSC=Nutritional Prevention of Skin Cancer Study; SWSCPS=Southwest Skin Cancer Prevention Study; CARET=Carotene and Retinol Efficacy Trial; PHS=Physicians Health Study.

Mb=molybdenum; Zn=Zinc; Se=Selenium.
signs have therefore been used to study the preventive effects of single nutrients by administering them as supplements in blinded randomized controlled trials.

In Linxian, China, where the micronutrient-deficient population has unusually high rates of gastric and esophageal cancers, four different combinations of micronutrient supplements were given as part of a randomized controlled trial to approximately 30,000 volunteers for about seven years. None of the nutrient combinations reduced gastric cancer risk except for the beta carotene-selenium-vitamin E combination, which was associated with a modest 16% risk reduction in the incidence of gastric cancer. This same combination had no effect on the incidence of esophageal cancer, however, and a parallel trial of a much smaller number of subjects with esophageal dysplasia showed no benefit from a combination of 14 vitamins and minerals.

COLORECTAL CANCER ADENOMAS

Two trials of nutritional supplementation have reported colorectal cancer endpoints, but neither included colorectal cancer as one of the a priori primary endpoints. Neither beta carotene nor vitamin E appeared to affect colorectal cancer risk in the Alpha Tocopherol Beta Carotene study, but in the Nutritional Prevention of Skin Cancer study, colorectal cancer was seen less frequently in the intervention group.

Several studies have used a convenient clinical model to examine the impact of nutritional supplements on the formation of adenomatous polyps in the colon and rectum. In this model, patients undergoing a polypectomy with a cleansing colonoscopy are randomized to intervention versus placebo groups. The efficacy of the nutritional supplement is then estimated by the relative rates of new adenomas detected in the two groups at the time of their repeat colonoscopy three years later.

New polyp growth was not affected by wheat bran fiber supplements in two studies, or in studies testing antioxidant nutrients, singly or in combination. A trial of calcium supplementation was associated with a 17% reduction in the rate of new polyp formation. This effect is hypothesized to be due to the binding of calcium to bile acids, making them insoluble and less likely to stimulate growth in the colonic mucosa. To test the observation (albeit as a secondary endpoint) that selenium appeared to lower colorectal cancer incidence in the Nutritional Prevention of Skin Cancer trial, Italian investigators used the polyp prevention trial design, and found a 44% reduction in the incidence of new polyp growth in the selenium arm of the study.

LUNG CANCER

There has been a remarkable consistency among findings from observational studies that suggest that diets high in fruits and vegetables are associated with lower risk for cancers of the lung and larynx, even after adjusting for the fact that smokers tend to eat less healthy diets than do non-smokers. Nevertheless, observational epidemiology can not satisfactorily separate the independent contributions and effects of the various nutrients contained in fruits and vegetables.

In 1981, Peto proposed an interesting question: Can dietary beta carotene materially reduce human cancer rates? The beta carotene hypothesis was based on the notion that lower cancer risk for those who ate more fruits and vegetables might be due to both the antioxidant and pro-vitamin A functions of beta carotene. In both the Alpha Tocopherol Beta Carotene study and the Carotene and Retinol Efficacy Trial, however, lung cancer risk was found to be increased by taking high-dose beta carotene, and in the Physicians Health Study, beta carotene did not alter lung cancer risk in either direction. The reason for the unanticipated adverse effects of beta carotene remains unknown but it is clear...
that 15 years after Peto’s question, three failed experimental trials using beta carotene supplements have led to the conclusion that the answer appears to be ‘no.’ 7,19,20

In view of these disappointing results, researchers have sought other nutritional strategies to prevent lung cancer. A randomized clinical trial of high-dose vitamin A (300,000 IU per day) for lung cancer prevention has recently been completed in Europe, for instance, although the findings have not yet been reported,21 and the possibility of benefit from selenium supplements on lung cancer is now being assessed in new trials.

BREAST CANCER

Breast cancer is perhaps the most intensively studied human neoplasm with respect to its possible nutritional causes. Most epidemiologic studies have not found a relationship between dietary fats and breast cancer, yet the hypothesis is currently being tested as part of the Women’s Health Initiative, a large trial in which thousands of women have been randomly assigned to a mixed dietary intervention that features, among other things, a diet that derives between 20% and 25% of calories from fat.23 The results of that trial will not be known for several more years. A stronger relationship than that with dietary fat has been seen between breast cancer and alcohol,22 yet the effects of alcohol cannot easily be tested in a randomized controlled trial, both because alcohol has adverse effects in excess and in lower doses and because alcohol is also associated with cardiovascular benefits.

Although fruits and vegetables have been associated with lower breast cancer risk in many observational studies, the degree of that association is less than that for colon or lung cancers. Moreover, individuals who report eating few fruits and vegetables also report other health-related risk factors, including greater levels of body weight, higher alcohol use, and less physical activity—factors that could together confound the weak relationship with fruits and vegetables.6

Some have proposed that breast cancer risk may be modified by the phytoestrogenic compounds found in certain fruits and vegetables. According to that hypothesis, the beneficial endocrine effects of these compounds, together with essential vitamins and minerals, might account for reduced breast cancer risk. Recent findings regarding tamoxifen and reduced breast cancer risk24 have further fuelled interest in any natural antiestrogens that can be obtained from foods.25 Soybean products that contain high levels of phytoestrogens have been of particular interest. Although it is possible that these plant foods could reduce breast cancer risk because they act as antiestrogens, it is equally possible that soy, when taken in high doses, exerts pro-estrogenic effects, especially among postmenopausal women, resulting in increased cancer incidence among women carrying estrogen-receptor positive breast tumors.26 Hopefully, the uncontrolled experimentation that is now underway among breast cancer survivors taking high-dose soy will not result in the same sort of disturbing surprise found by the randomized clinical trials of high-dose beta carotene.

PROSTATE CANCER

In the Alpha Tocopherol Beta Carotene study, although vitamin E had no effect on lung cancer risk, the incidence of prostate cancer among men receiving 50 IU per day of alpha tocopherol was only 66% that of those on placebo.7,27 Likewise, in the Nutritional Prevention of Skin Cancer trial, although selenium had no effect on skin cancer risk, the incidence of prostate cancer among men given 200 mcg selenium per day was only 37% that of those given placebo.8,28 These surprising findings for prostate cancer as a secondary endpoint in two randomized clinical trials provide new leads for further studies, which are now underway,
but are insufficient evidence on which to base general nutritional recommendations. Despite considerable publicity about a possible link between high lycopene intake and lower prostate cancer risk that was observed in one study, there is little evidence of such an association when all studies are analyzed.

SKIN CANCER
Four randomized clinical trials have tested the effects of nutrients on the formation of basal cell and squamous cell skin cancers in patients with a history of skin cancer. Neither selenium, vitamin A, or beta carotene reduced the rate of new skin cancer formation in those studies. Because the genetic mutations (e.g., p53 alterations) that lead to skin cancer may occur many years before the appearance of a lesion, randomized controlled trials of only a few years' duration may be too short and too late in the process of carcinogenesis to demonstrate any protective effects of nutrients.

Comment
Randomized controlled trials are commonly regarded as much more definitive than are observational studies with respect to causality. In controlled trials, the random assignment of subjects to the intervention eliminates the problems of dietary recall and controls the effects of both known and unknown confounding factors. Nevertheless, randomized controlled trials of nutrition are rare compared with observational studies because they are justified only after considerable evidence has accumulated from animal, in vitro, and observational studies suggesting that a particular compound or set of nutrients is associated with reduced cancer risk. Despite their strengths, however, the randomized controlled trials of nutrition and cancer that have been completed to date have largely followed the investigational paradigm of pharmacology—testing single nutrients in super-nutritional doses.

Whole foods or whole-diet interventions cannot easily be incorporated into randomized controlled trial designs, certainly not in a blinded way. Typically, for reasons of economy, such trials study only individuals at high risk of neoplasia for short periods of time. Although randomized controlled trials can usually answer only narrowly defined questions, and cannot easily assess the effects of long-term dietary patterns, a few such trials designed to test the effects of foods on cancer risk are currently underway.

As if we were searching for a new therapeutic compound, we have expected high doses of a single nutrient to reproduce the beneficial effects of the complex nutrient mixtures found in whole foods. Perhaps this basic assumption is wrong. The first generation of randomized controlled trials of antioxidant nutrients has not shown any substantial benefit thus far with most of the nutritional supplements tested. There are only a few exceptions: A modest reduction in gastric cancer risk with a combination of beta carotene, vitamin E, and selenium in China; a modest reduction of colorectal adenomatous polyp growth with calcium supplementation; and surprising effects of vitamin E on the secondary endpoint of prostate cancer, and of selenium on colorectal, lung, and prostate cancers. If selenium becomes the first widely recommended nutritional supplement for cancer risk reduction, that recommendation will need to be based on findings from other larger trials designed specifically to test its effects in the general population.

Formation of colorectal adenomatous polyps can be conveniently studied with randomized clinical trials, as they utilize a standard clinical protocol to assess discrete neoplastic endpoints that are part of the causal chain of cancer development. However, the possible role of nutrients as protective factors in the later phases of the transition of adenomas to cancer cannot be easily studied in these trials.
polyp trial designs, as they focus only on the first one to three years of new polyp growth following the removal of a metachronous polyp. Studying the earlier phases of polyp development among individuals found to be polyp-free at baseline would require much larger numbers of subjects over longer periods of time. Even more problematic, though, and probably more important, is our inability to study later phases of colorectal cancer development when large adenomatous polyps devolve to cancer. Trials in which adenomas are left in place are ethically difficult, although one such small trial was recently reported.37

Other polyp prevention trials of aspirin, folate, and wheat bran fiber are still underway and the effects of a whole-diet intervention on adenoma formation are also being tested by the Polyp Prevention Trial, a randomized controlled trial looking at the effects on polyp formation of a low-fat diet that includes seven daily servings of fruits and vegetables.34 That study, although strengthened by featuring a whole-diet intervention, is nonetheless also weakened by the fact that, like other polyp trials, it is being conducted only during the three-year period between initial polypectomy and repeat colonoscopic exam. Consequently, as in other polyp prevention trials, the Polyp Prevention Trial does not test the effects of fruits and vegetables on later stages of cancer development.

Despite their limitations, large randomized controlled trials have featured prominently in research on nutrition and cancer prevention over the past decade, and results from such studies have substantial influence on our judgments about the role of nutrition in cancer prevention. Although largely unsuccessful in supporting their research hypotheses, even these early nutrition trials have taught us important lessons about cancer. From the beta carotene trials, for instance, we learned quickly that high-dose, single-agent nutrients can have unexpected adverse effects.7,19 Perhaps when we explain the biologic mechanism whereby high-dose beta carotene dramatically affected cancer risk in such a short period of time, we will better understand how to reverse the process to prevent lung cancer.

The beta carotene trials should also remind us that it is only within the context of such large controlled trials that completely unexpected adverse effects of high-dose supplements will be discovered. This is increasingly important because of the nutritional supplement industry that sells high-dose products to the public.

The second generation of randomized controlled trials will need to incorporate lessons learned in early trials. In addition to the large and expensive whole-diet trials underway,23,34 it would seem wise to test the effects of nutritional supplements given in broader combinations, and in more modest doses, thereby simulating the micronutrient combinations in the matrix of whole foods. Trials should also be designed to be long-term, testing nutrients over many years among people at average risk. It may be that individuals who are at high risk because of factors such as specific carcinogen exposure, familial history, or the existence of a premalignant lesion, may be generally less susceptible to nutrient effects than

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are those at average risk. Consequently, it may be unwise to study only those at high risk.

In view of confusing and even conflicting nutritional messages reported by the media, clinicians have a more important role than ever in helping patients understand and interpret information about the complex relationship of nutrition and cancer. We are at an important juncture in our understanding of the relationships between diet and cancer. Hypotheses based on observational studies seem to be in conflict with many of the “early returns” from randomized controlled trials. It is not surprising, therefore, that many feel a renewed skepticism about the scientific basis for nutritional advice to the public. As researchers struggle with the science of this difficult area of inquiry, the general public, increasingly eager for answers about nutritional means to reduce cancer risk, is turning in ever larger numbers to unproven diets and nutritional supplements.

Disappointing results from randomized controlled trials designed to answer only narrow questions about the biology of carcinogenesis should not distract us from counseling patients on the basis of the extensive database that already exists from observational studies. We already know a great deal about the epidemiology of nutrition and cancer. Should future randomized controlled trials replicate and thereby prove some of the preventive effects hypothesized for certain supplements (eg, vitamin E, calcium, or selenium), then these agents can be more broadly recommended. Likewise, should future randomized controlled trials not support the compelling body of evidence from observational studies, we should critically appraise the observational methodology, as well as the limitations of the randomized controlled trial design, when applied to diet-cancer relationships.

There remains compelling evidence that eating five or more servings of fruits and vegetables per day can substantially reduce the risk of some of the most commonly occurring cancers in the US. The combined effects of nutrients as contained in the mixtures commonly known as whole foods seem to be more effective in reducing cancer risk than are nutrients contained in supplements. This simple conclusion can be a sound basis for broad nutritional advice to the population, as well as for clinical counseling of individual patients.

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