Nutritional Interventions and Outcome in Patients With Cancer or Preinvasive Lesions: Systematic Review

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Background: **Dietary modifications and supplements are used widely by patients with cancer and preinvasive lesions as an adjunct to standard treatment. Given the widespread use of nutritional modifications and supplements by such patients and concerns about the lack of benefit and possible harm, we conducted a systematic review of randomized controlled trials to examine the effect of nutritional interventions on patients with cancer or preinvasive lesions.** ***Methods:*** **We searched electronic databases and reference lists to locate all eligible trials and analyzed trial quality. Outcome measures were all-cause and cancer mortality, disease-free survival, cancer recurrence, second primary cancer, recurrence of a preinvasive lesion, or progression to cancer. Results of individual trials were combined by use of random-effects meta-analyses.** ***Results:*** **We identified 59 eligible trials, 25 in patients with cancer and 34 in patients with preinvasive lesions, respectively. Trial quality was generally low; only three trials (two of cancer and one of preinvasive lesions) had adequate methods for generating the allocation sequence, allocation concealment, and masking both outcome assessors and participants. The combined odds ratio (OR) for the effect of a healthy diet—given alone or with dietary supplements, weight loss, or exercise—on all-cause mortality was 0.90 (95% confidence interval [CI] = 0.46 to 1.77). There was no evidence of an association between the use of antioxidant (OR = 1.01, 95% CI = 0.88 to 1.15) or retinol (OR = 0.97, 95% CI = 0.83 to 1.13) supplements and all-cause mortality. Meta-analyses of all other outcomes did not show clear evidence of benefit or harm.** ***Conclusions:*** **The impact of most nutritional interventions cannot be reliably estimated because of the limited number of trials, many of which were of low quality. There is no evidence that dietary modification by cancer patients improves survival and benefits disease prognosis. [J Natl Cancer Inst 2006;98:961–73]**

Food supplements and vitamins are widely used by patients with cancer as an adjunct to conventional treatment. The personal expenditure on dietary supplements and megavitamins by patients with cancer in the United States was estimated to be $60 million per annum in 1990 and is growing *(1)*. Diet was one of the most frequently discussed treatments in a review of 32 Web sites for complementary and alternative medicine likely to be visited by cancer patients *(2)*. These Web sites were selected by use of a predesigned search strategy as follows: from December 2002 to January 2003 eight popular search engines (http://www.about.com, http://www.altavista.com, http://ask.co.uk, http://search.msn.com, http://www.google.com, http://www.lycos.co.uk, http://search.aol.com, and http://www.yahoo.com) were searched for the terms "complementary" or "alternative medicine" and "cancer." Only Web sites in the English language were explored. The first 50 Web sites that appeared on each search engine were included. These were the sites most visited for this specific search query, at that point in time, according to each search engine's ranking system. Only those sites in the top 50 hits of at least three of the eight preselected search engines were included.

Concern about the dose and use of food supplements and vitamins in general has led to the introduction of a European Union Directive to tighten rules on sale of these products *(3)*. Worries about the nature of these remedies and their possible interaction with drug regimens during cancer treatment have also been highlighted *(4)*.

A recent narrative review *(5)* concluded that there was no convincing evidence that nutrition interventions are beneficial for survivors of the four major cancers—breast, colorectal, lung, and prostate. Moreover, the authors found no evidence of harm to cancer survivors. This review, however, was limited in its scope and was not systematic. Recent experience suggests that not all dietary modifications and supplements are harmless. For example, findings from two large-scale randomized controlled trials in subjects at high risk of lung cancer have suggested that β-carotene interventions increase the incidence of lung cancer and overall mortality in smokers *(6,7)*. A recent meta-analysis suggested that high-dose vitamin E supplements may increase all-cause mortality *(8)*.

Given the widespread use of nutritional remedies by patients with cancer and concerns about lack of benefit and possible harm it is important that the use of these diets and supplements is supported by evidence. We therefore conducted a systematic review of randomized controlled trials that examined the effect of nutritional interventions in patients with cancer or preinvasive lesions.

Patients and Methods

Search Strategy

We carried out this review as part of a larger review that was designed to examine the role of both diet and physical activity

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on outcome among patients with cancer or preinvasive lesions. The search strategies and initial inclusion criteria reflect this goal. We searched for literature published through September 30, 2003, by standard systematic review methods *(9,10)*. We searched four online databases: Cochrane Library, MEDLINE, EMBASE, and AMED. We used Medical Subject Headings (MeSH terms) and title and/or abstract words to identify the following: cancer or precancer, survivors, nutrition or physical activity, and randomized controlled trials. The search strategies were adapted for each electronic database (see Supplemental Tables 1–4, available at: http://jncicancerspectrum.oxfordjournals.org/jnci/content/vol98/issue14). We sought to identify additional publications by searching the reference lists of the relevant books, reviews, and publications that we located.

Inclusion Criteria

We considered studies to be eligible for inclusion if they reported on a randomized controlled trial, recruited patients with cancer or preinvasive lesions, and included a nutritional or physical activity intervention. We defined a patient with cancer or a preinvasive lesion as anyone who had been diagnosed with cancer (or preinvasive lesion) from the time of diagnosis through the rest of life *(5)*. We considered a nutritional intervention to be one that altered the intake of foods or dietary constituents either directly (e.g., giving vitamin supplements) or indirectly (e.g., through nutrition education). We defined food as beverages, confectionary, ingredients in preparation of foods, and advertised dietary supplements that contained added vitamins *(11)*. We also included micronutrients in our definition of food. We included trials that reported on one or more of the following outcomes: all-cause mortality, cancer mortality, disease-free survival, cancer recurrence, second primary cancer, number of days in hospital, recurrence of preinvasive lesions, and progression from preinvasive lesions to cancer. There were no restrictions according to language of publication, ethnicity, sex, age of the patients, or type or stage of cancer.

Exclusion Criteria

Our definition of nutritional intervention excluded interventions that were used perioperatively or in combination with chemotherapy or radiotherapy, in which outcomes were related to treatment complications and not cancer survival. We included one study that used a sip feed (a nutritional liquid taken by mouth and used to meet optimal protein and calorie requirements) at the time of radiotherapy and continued use of the feed for 12 months *(12)*. We also excluded studies that used synthetic retinoids, vitamin analogues, herbal supplements, and polysaccharide K (a protein-bound polysaccharide that is extracted from the mycelia of the mushroom *Coriolus versicolor*) because they did not meet our definition of a nutritional intervention.

Trial Quality Assessment

We assessed three aspects of trial quality: generation of the allocation sequence, concealment of allocation, and masking of outcome assessors and participants to treatment allocation during the trial. We considered generation of allocation sequence and concealment of allocation to be adequate if the resulting sequences were random and if participants and enrolling investigators could not predict the assignment *(9)*. We categorized trials stating that subjects were blinded or including an identical placebo as trials that had masked the participant to their treatment allocation. For trials that reported being double blind, we assumed that both the participants and the outcome assessors had been masked to the participant's treatment allocation.

Statistical Methods

We analyzed trials that recruited patients with cancer separately from those that recruited patients with preinvasive lesions. In trials that recruited patients with cancer at more than one anatomic site, site-specific outcome data were extracted whenever possible. The overall lack of data for any particular cancer or preinvasive lesion meant that anatomic sites were combined for all analyses. Additional cancer-specific findings were reported if data were available. When outcomes were reported at more than one time point within a trial, the outcomes nearest the end of the active intervention period were extracted. Odds ratios (ORs) were used to quantify intervention effects.

If studies had multiple intervention arms and interventions of different types (e.g., one multivitamin supplement and one dietary counseling intervention), each arm was compared with the usual treatment group (or specific placebo group) and analyzed separately. Consequently, some studies could contribute data to more than one analysis and were thus treated as separate trials when the results were pooled. When multiple interventions within a study were of the same type, data from the intervention arms were treated as one group: this method avoided the control groups being included twice in the same meta-analysis but was performed only after first comparing the results from each arm with the results from the control data arm separately to make sure that they were consistent in size and direction of effect. Factorial trials were analyzed by assuming no interaction between interventions. Random-effects meta-analysis was conducted by the method of der Simonian and Laird *(9)*. We derived tests for heterogeneity by referring the heterogeneity statistic Q to the chi-squared distribution, and we quantified the amount of heterogeneity in each meta-analysis by use of the I^2 statistic *(13)*, which gives the percentage of variance in the meta-analysis from heterogeneity. All analyses were performed in Stata 8 (StataCorp, College Station, TX; http://www.stata.com) and Comprehensive Meta-Analysis (Biostat, Englewood, NJ; http://www.meta-analysis.com).

Results

The numbers of studies that we included or excluded at each stage of the review process are listed in Fig. 1; a total of 47 publications met the full inclusion criteria. Of the 22 publications reporting trials on patients with cancer *(12,14–34)*, three reported outcome data from more than one comparison, so that 25 trials were available for analysis. DeWaard et al. *(18)* reported outcomes from the same trial in two different populations (Dutch and Polish), Evans et al. *(20)* reported outcomes for lung and colorectal cancer patients separately, and van Zandwijk et al. *(34)* reported outcomes for a factorial trial in which the associations of both vitamin A and *N*-acetylcysteine with outcome variables could be independently assessed. Seven of the 25 publications *(35–59)* in patients with preinvasive lesions contained trials with two *(39,41,51,53,57,58)* or three *(46)* different interventions, and one of the 25 publications reported data from two separate trials

Fig. 1. Review process of publications included in this study. Summary of the number of publications included at each stage.

(51), resulting in 34 trials of preinvasive lesions from 25 publications. Data from four trials were reported in more than one publication: Nutritional Prevention of Cancer trial *(16,19)*, Calcium Polyp Prevention Study *(36,37)*, the Linxian Dysplasia Trial *(45,47)*, and a calcium and green tea trial conducted in China *(56,57)*. The general characteristics of the 25 cancer trials and 34 preinvasive lesion trials are summarized separately in Tables 1 and 2, respectively.

General Characteristics of Trials that Evaluated Patients With Cancer

Eighteen of the 25 trials in patients with cancer were cancer site specific [four for skin *(16,19,21,27)*, three for bladder *(15,25,30)*, four for breast *(12,18,33)*, two for head and neck *(22,26)*, two for lung *(23,32)*, one for cervix *(24)*, one for leukemia *(28)*, one for colorectum *(29)*] and seven of the 25 trials included multiple sites *(14,17,20,31,34)*. Cancer stage was described in 19 of the 25 trials, of which six were in advanced disease *(17,20,23,24,29)*. Reported duration of the interventions ranged from 4 weeks *(24)* to five years *(21)*. Of those trials that reported therapeutic treatment at time of intervention *(12,14, 15,18,20,22–28,30–34)*, only one *(28)* began the intervention before treatment had begun.

The interventions among patients with cancer could be broadly categorized into two types: healthy diet and micronutrients. Healthy diet interventions, which were reported in eight trials *(12,14,18,20,31,33)*, were those that advised one or more of the following: a balanced healthy diet, weight loss in overweight women, a general reduction in fat intake (as a percentage of total calories), increased intake of fiber or of fruit and vegetables, or an optimal calorie or protein diet. Micronutrient trials were predominately of antioxidants [two selenium *(16,19)*, two β-carotene *(21,26)*, two vitamin C *(17,29)*, one multivitamin that included an antioxidant *(25)*, and one *N*-acetylcysteine *(34)*] or retinol *(22–24,27,28,32,34)*, with a few vitamin B6 trials *(15,30)*.

General Characteristics of Trials that Evaluated Patients With Preinvasive Lesions

All 34 interventions in people with preinvasive lesions were site specific: 19 colorectal *(35–37,39,41,43,44,46,48–51,54)*, five esophageal *(45,47,56,57)*, three mouth *(53,55)*, three stomach *(58,59)*, two cervical *(40,52)*, one lung *(42)*, and one skin *(38)*. The duration of the interventions in trials evaluating effects associated with preinvasive lesions ranged from 4 months *(42)* to 6 years *(45,47)*. The trials included the following numbers of interventions: six healthy diet *(35,39,46,49,54)*, 14 antioxidant [seven multivitamin *(41,43,45,47,48,51)*, six β-carotene, *(38,41,46,52,53,58)*, and one *N*-acetylcysteine *(51)*], five calcium *(36,37,39,56,57)*, five folate *(40,42,44,50,58)*, two retinol *(53,55)*, one green tea *(57)*, and one vitamin C *(59)*. Most trials compared the nutritional intervention with placebo. However, two trials of fiber also used low-fiber supplements in the comparison groups *(35,49)*, and seven trials used general dietary guidelines *(54)* or usual treatment *(46,51,59)*, as the comparison group.

Quality of Trials

We assessed three aspects of trial quality: generation of allocation sequence, concealment of allocation, and masking of outcome assessors and participants to treatment allocation during the trial (Table 3). In 12 (48%) of 25 cancer trials and 30 (88%) of 34 preinvasive lesion trials, methods used to conceal allocation were not reported. Three trials [two cancer *(21,26)* and one preinvasive lesion *(42)*] had adequate methods for generating the allocation sequence, allocation concealment, and masking both outcome assessors and participants. In most trials, the methods used to generate the allocation sequence and conceal allocation were not reported.

Outcomes

The following outcomes were reported in nutritional trials: 26 reported all-cause mortality [19 cancer *(12,14,16–18,20,21, 23,25–29,31,32,34)* and seven preinvasive lesion *(35,36,39, 45,48,54)*], 15 reported disease-free survival [six cancer *(20,27, 28,34)* and nine preinvasive lesion *(40,42,47,52,53,56,57,59)*], and 11 reported cancer mortality [nine cancer *(12,15,18,19, 24,26,27,32)* and two preinvasive lesion *(38,45)*]. Thirteen nutritional trials also reported cancer recurrence *(12,15,16, 18,22,24–27,30,32,33)*, and seven reported second primary cancer *(18,19,21,22,26,32)* in patients with cancer. Recurrence of preinvasive lesions and development of cancer from preinvasive lesions was reported in 19 *(35,36,39,41,43,44,46,48–51,54,55)*, and seven preinvasive lesion trials *(35,37,45,54,57,58)*. No trials reported the number of days in hospital. Supplemental Tables 5 and 6, detailing the odds ratios (95% confidence intervals [CIs]) for the effect of interventions on individual outcomes, are available at http://jncicancerspectrum.oxfordjournals.org/jnci/content/vol98/issue14.

Table 1. General characteristics of the 25 nutrition intervention trials in patients with cancer

Trial reference, y	Site	Stage	Treatment at time of intervention*	Intervention (daily, unless stated)	Comparison	Length of intervention, (mo, unless stated)†
Berglund et al. *(14)*, 1994	Breast, ovary, urological, and other	Unclear	After	Eleven 2-hour sessions: 4 sessions of physical training, 4 sessions of information (including dietary advice toward a balanced healthy diet), and 3 sessions of coping training over a 7-week period	One-third offered one information session; two-thirds received usual treatment	7 weeks
Byar et al. *(15)*, 1977	Bladder	Stage I	During	25 mg of vitamin B6	Placebo	24
Clark et al. *(16)*, 1996	Skin	Early	Unclear	200 μg of selenium	Placebo	54 (mean)
Creagan et al. *(17)*, 1979	Colorectal, GI, lung, and other	Advanced	Unclear	10 g of vitamin C	Placebo	Until unable to feed or death
de Waard et al. *(18)*, 1993‡	Breast	Unclear	After	Dietary advice and psychologic support to achieve a 10-kg weight loss (or more if initial degree of overweight warranted)	Usual treatment	36
de Waard et al. *(18)*, 1993‡	Breast	Unclear	After	Dietary advice and psychologic support to achieve a 10-kg weight loss (or more if initial degree of overweight warranted)	Usual treatment	12
Duffield-Lillico et al. *(19)*, 2002	Skin	Early	Unclear	200 μg of selenium	Placebo	54 (mean)
Elkort et al. *(12)*, 1981	Breast	Unclear	During	500 mL of LDS daily + intensive nutritional support to meet optimal protein and calorie requirements	Usual treatment	12
Evans et al. *(20)*, 1987§	Colorectal	Advanced	During	Counseling to ensure optimal calorie intake + LDS	General dietary guidelines	12 weeks
Evans et al. *(20)*, 1987§	Lung	Advanced	During	Counseling to ensure optimal calorie intake + LDS	General dietary guidelines	12 weeks
Greenberg et al. *(21)*, 1990	Skin	Early	Unclear	50 mg of β-carotene	Placebo	60
Jyothirmayi et al. *(22)*, 1996	Head and neck	Unclear	After	2×10^5 IU of vitamin A weekly	Placebo	12
Kokron et al. *(23)*, 1982	Lung	Advanced	During	1.5×10^6 IU of vitamin A	Usual treatment	35 days
Kucera et al. *(24)*, 1980	Cervix	Advanced	During	1.5×10^6 IU of vitamin A	Usual treatment	4 weeks
Lamm et al. *(25)*, 1994	Bladder	Early	During	Multivitamins RDA + 4×10^4 IU of vitamin A + 100 mg vitamin B6 + 2000 mg of vitamin C + 400 IU of vitamin E + 90 mg of zinc	Multivitamins RDA	49 (mean)
Mayne et al. *(26)*, 2001	Head and neck	Stage I or II	After	50 mg of β-carotene	Placebo	50.9 (median)
Meyskens et al. *(27)*, 1994	Skin	Stage I	After	1×10^5 IU of vitamin A	Usual treatment	18
Meyskens et al. *(28)*, 1995	Leukemia	Unclear	Before	5×10^4 IU of vitamin A	Usual treatment	51 (median)
Moertel et al. *(29)*, 1985	Colorectal	Advanced	Unclear	10 g of vitamin C	Placebo	2.5 (median)
Newling et al. *(30)*, 1995	Bladder	Stage I	After	20 mg of vitamin B6	Placebo	38.5 (mean)
Ovesen et al. *(31)*, 1993	Breast, lung, and ovary	Unclear	During	Individual counseling aimed at a diet to meet or exceed protein and energy requirements + supplements if needed	Ad lib diet and nutritional support at the discretion of the physician	5
Pastorino et al. *(32)*, 1993	Lung	Stage I	After	3×10^5 IU of vitamin A	Usual treatment	24
Sopotsinskaya et al. *(33)*, 1992	Breast	Unclear	During	Diet aimed at a 15% decrease in total caloricity (daily norms for healthy people based on standard BMI of a 58-kg female requiring 2400 cal/day) achieved by a 30% reduction in fat and a 9% reduction in carbohydrates	Usual treatment	36
van Zandwijk et al. *(34)*, 2000‖	Head and neck and lung	Stage I, II, or III	During	3×10^5 IU of vitamin A for 1st year, followed by 1.5×10^5 IU for the 2nd year	Usual treatment	24
van Zandwijk et al. *(34)*, 2000‖	Head and neck and lung	Stage I, II, or III	During	600 mg of NAC	Usual treatment	24

*Treatment at the time of the intervention is defined as radio-, immuno- or chemo- therapy or surgery, with the intervention taking place during, before, or after treatment. LDS = liquid dietary supplement; RDA = recommended daily allowance; GI = gastrointestinal; NAC = *N*-acetylcysteine.

†When length is different for intervention and comparison groups, the length of the intervention arm is reported.

‡De Waard et al. *(18)* reported outcomes from the same trial in two different populations (Dutch and Polish).

§Evans et al. *(20)* reported outcomes for lung and colorectal cancer patients separately.

‖Van Zankwijk et al. *(34)* reported data from a 2 × 2 factorial design trial from which the independent effects of both NAC and vitamin A could be measured.

Table 2. General characteristics of the 34 nutrition intervention trials in patients with preinvasive lesions

Trial reference, y	Site	Intervention (daily, unless stated)	Comparison	Length of intervention, (mo, unless stated)*
Alberts et al. *(35)*, 2000	Colorectal	13.5 g of fiber	2 g of fiber	34 (median)
Baron et al. *(36)*, 1999	Colorectal	1200 mg of calcium	Placebo	45
Baron et al. *(37)*, 1999	Colorectal	1200 mg of calcium	Placebo	45
Bayerl et al. *(38)*, 2003	Skin	50 mg of β-carotene	Placebo	36
Bonithon-Kopp et al. *(39)*, 2000†	Colorectal	2000 mg of calcium	Placebo	36
Bonithon-Kopp et al. *(39)*, 2000†	Colorectal	3.5 g of fiber	Placebo	36
Childers et al. *(40)*, 1995	Cervix	5 mg of folic acid	Placebo	6
Greenberg et al. *(41)*, 1994‡	Colorectal	25 mg of β-carotene	Placebo	48
Greenberg et al. *(41)*, 1994‡	Colorectal	1 g of vitamin C + 400 mg of vitamin E	Placebo	48
Heimburger et al. *(42)*, 1988	Lung	0.5 mg of vitamin B12 + 10 mg of folic acid	Placebo	4
Hofstad et al. *(43)*, 1998	Colorectal	1.6 g of calcium + 101 μg of selenium + 15 mg of β-carotene + 75 mg of vitamin E + 150 mg of vitamin C	Placebo	36
Kim et al. *(44)*, 2001	Colorectal	5 mg of folate	Placebo	12
Li et al. *(45)*, 1993	Esophagus	Multivitamins and minerals (14 vitamins and 12 minerals); doses typically two- to three-fold higher than the RDA in the United States	Placebo	72
MacLennan et al. *(46)*, 1995§	Colorectal	Dietary counseling to reduce fat intake to 25% of total energy intake	Usual treatment	24
MacLennan et al. *(46)*, 1995§	Colorectal	11 g of fiber supplement	Usual treatment	24
MacLennan et al. *(46)*, 1995§	Colorectal	20 mg of β-carotene	Placebo	24
Mark et al. *(47)*, 1994	Esophagus	Multivitamins and minerals (14 vitamins and 12 minerals); doses typically two- to three-fold higher than the RDA in the United States	Placebo	72
McKeown-Eyssen et al. *(48)*, 1988	Colorectal	400 mg of vitamin C + 400 mg of vitamin E	Placebo	24
McKeown-Eyssen et al. *(49)*, 1994	Colorectal	Monthly nutritional counseling aimed at a diet of 50 g of fat or 20% calories from fat sources (whichever was less) + ≥50 g of dietary fiber (a 20-g fiber supplement was given to help obtain target)	Normal diet + 3 g fiber supplement	24
Paspatis et al. *(50)*, 1994	Colorectal	1 mg of folate	Placebo	24
Ponz de Leon et al. *(51)*, 1997‖	Colorectal	3×10^5 IU of vitamin A + 70 mg of vitamin E + 1 g of vitamin C	Usual treatment	17.8 (mean)
Ponz de Leon et al. *(51)*, 1997‖	Colorectal	3×10^5 IU of vitamin A + 70 mg of vitamin E + 1 g of vitamin C (on alternate days)	Usual treatment	Unclear
Ponz de Leon et al. *(51)*, 1997‖	Colorectal	600 mg of NAC	Usual treatment	Unclear
Romney et al. *(52)*, 1997	Cervix	30 mg of β-carotene	Placebo	9
Sankaranarayanan et al. *(53)*, 1997¶	Mouth	3×10^5 IU of vitamin A weekly	Placebo	12
Sankaranarayanan et al. *(53)*, 1997¶	Mouth	360 mg of β-carotene weekly	Placebo	12
Schatzkin et al. *(54)*, 2000	Colorectal	Nutritional counseling aimed at a diet with 20% of calories from fat, 18 g of dietary fiber per 1000 kcal, and 5-8 servings of fruit and vegetables daily	General dietary guidelines	36.6 (median)
Stich et al. *(55)*, 1988	Mouth	2×10^5 IU of vitamin A weekly	Placebo	6
Wang et al. *(56)*, 1993	Esophagus	1200 mg of calcium	Placebo	11
Wang et al. *(57)*, 2002#	Esophagus	1200 mg of calcium	Placebo	11
Wang et al. *(57)*, 2002#	Esophagus	5 mg of decaffeinated green tea given in two tea bags	Placebo	12
Zhu et al. *(58)*, 2002**	Stomach	20 mg of folate daily + 1 mg of vitamin B12 per mo for 1 y then 20 mg of folate twice weekly + 1 mg of vitamin B12 per 3 months for the next year	Placebo	24
Zhu et al. *(58)*, 2002**	Stomach	1) 30 mg of natural β-carotene daily for 1st year then 30 mg twice weekly for 2nd year 2) synthetic β-carotene (no amount given)	Placebo	24
Zullo et al. *(59)*, 2000	Stomach	500 mg of vitamin C	Usual treatment	6

*When length is different for intervention and comparison groups, the length of the intervention arm is reported. RDA = recommended daily allowance.

†In Bonithon-Kopp et al. *(39)*, randomization was balanced every six patients: two to the calcium treatment, two to the fiber treatment, one to the calcium placebo, and one to the fiber placebo. From this trial, the independent effects of both fiber and calcium could be measured.

‡Greenberg et al. *(41)* was a 2 × 2 factorial design trial from which the independent effects of β-carotene and vitamins C + E could be measured.

§MacLennan et al. *(46)* was a 2 × 2 × 2 factorial design trial from which the independent effects of fat reduction, bran supplementation, and β-carotene could be measured.

‖Ponz de Leon et al. *(51)* reported outcomes for two trials. The first compared vitamins A + C + E with usual treatment. The second trial included two intervention arms from which the independent effects of vitamins A + C + E and N-acetylcysteine (NAC), compared with usual treatment, could be measured.

¶In Sankaranarayanan et al. *(53)*, participants were allocated to two interventions, 1) vitamin A or 2) β-carotene, which could be independently compared with the placebo.

#In Wang et al. *(57)*, participants were allocated to two interventions, 1) calcium or 2) decaffeinated green tea, which could be independently compared with a calcium placebo and decaffeinated green tea placebo, respectively.

**In Zhu et al. *(58)*, participants were allocated to three interventions: 1) folate + vitamin B12, 2) natural β-carotene, or 3) synthetic β-carotene, which could be independently compared with the placebo. The natural and synthetic β-carotene groups were combined for all analysis.

Table 3. Design quality of the 47 trials (22 of cancer and 25 of preinvasive lesions) that met inclusion criteria for this systematic review*

Trial reference, y	Generation of allocation sequence	Allocation concealment	Assessors blinded	Participants blinded
Cancer trials				
Berglund et al. *(14)*, 1994	Adequate	NR	NR	No
Byar et al. *(15)*, 1977	NR	NR	NR	NR
Clark et al. *(16)*, 1996	NR	Adequate	Yes	Yes
Creagan et al. *(17)*, 1979	NR	NR	Yes	Yes
de Waard et al. *(18)*, 1993†	NR	NR	NR	No
Duffield-Lillico et al. *(19)*, 2002	NR	Adequate	Yes	Yes
Elkort et al. *(12)*, 1980	NR	NR	NR	No
Evans et al. *(20)*, 1987†	NR	Adequate	NR	No
Greenberg et al. *(21)*, 1990‡	Adequate	Adequate	Yes	Yes
Jyothirmayi et al. *(22)*, 1996	NR	NR	Yes	NR
Kokron et al. *(23)*, 1982	NR	NR	NR	No
Kucera et al. *(24)*, 1980	NR	NR	NR	NR
Lamm et al. *(25)*, 1994	NR	Adequate	Yes	Yes
Mayne et al. *(26)*, 2001	Adequate	Adequate	Yes	Yes
Meyskens et al. *(27)*, 1994	NR	NR	NR	NR
Meyskens et al. *(28)*, 1995	NR	NR	NR	NR
Moertel et al. *(29)*, 1985	NR	Adequate	Yes	Yes
Newling et al. *(30)*, 1995	NR	Adequate	Yes	Yes
Ovesen et al. *(31)*, 1993	Adequate	Adequate	NR	No
Pastorino et al. *(32)*, 1993	NR	Adequate	NR	NR
Sopotsinskaya et al. *(33)*, 1992	NR	NR	NR	No
van Zandwijk et al. *(34)*, 2000†	Adequate	Adequate	NR	No
Preinvasive lesion trials				
Alberts et al. *(35)*, 2000‡	NR	NR	Yes	Yes
Baron et al. *(36)*, 1999	Adequate	NR	Yes	Yes
Baron et al. *(37)*, 1999	Adequate	NR	Yes	Yes
Bayrel et al. *(38)*, 2003	Adequate	NR	Yes	Yes
Bonithon-Kopp et al. *(39)*, 2000†	NR	Adequate	Yes	Yes
Childers et al. *(40)*, 1995	NR	NR	Yes	NR
Greenberg et al. *(41)*, 1994†	NR	NR	Yes	Yes
Heimburger et al. *(42)*, 1988	Adequate	Adequate	Yes	Yes
Hofstad et al. *(43)*, 1998	NR	NR	Yes	Yes
Kim et al. *(44)*, 2001	Adequate	NR	Yes	Yes
Li et al. *(45)*, 1993	NR	NR	Yes	NR
MacLennan et al. *(46)*, 1995§	NR	NR	Yes	No
Mark et al. *(47)*, 1994	NR	NR	Yes	NR
McKeown-Eyssen et al. *(48)*, 1988	NR	NR	Yes	NR
McKeown-Eyssen et al. *(49)*, 1994	NR	NR	Yes	No
Paspatis et al. *(50)*, 1994	NR	NR	Yes	Yes
Ponz de Leon et al. *(51)*, 1997§	NR	NR	NR	NR
Romney et al. *(52)*, 1997	NR	NR	Yes	NR
Sankaranarayanan et al. *(53)*, 1997†	NR	NR	Yes	Yes
Schatzkin et al. *(54)*, 2000‡	Adequate	Adequate	Yes	No
Stich et al. *(55)*, 1988	NR	NR	Yes	NR
Wang et al. *(56)*, 1993	NR	NR	Yes	Yes
Wang et al. *(57)*, 2002†	NR	NR	Yes	Yes
Zhu et al. *(58)*, 2002†	NR	NR	Yes	Yes
Zullo et al. *(59)*, 2000	NR	NR	Yes	NR

*NR = not reported.

†Both nutritional trials reported in this publication had identical design quality.

‡Design publications were used to extract data on trial design quality.

§All three nutritional trials reported in this publication had identical design quality.

All-Cause Mortality and Cancer-Specific Mortality in Patients With Cancer

The 19 trials reporting analyzable data on all-cause mortality included the following interventions: seven healthy diet *(12,14,18,20,31)*, four retinol *(27,28,32,34)* [one retinol trial was not analyzable because all participants died *(23)*], two β-carotene *(21,26)*, two vitamin C *(17,29)*, one multivitamin *(25)*, one *N*-acetylcysteine *(34)*, and one selenium *(16)*. Eight trials reported data on cancer-specific mortality and included the following interventions: three healthy diet *(12,18)*, one β-carotene *(26)*, one selenium *(19)*; three retinol *(24,27,32)*, and one vitamin B6 *(15)*.

As shown in Fig. 2, there was little evidence that a healthy diet, given as dietary advice separately or in specific combinations with supplements, weight loss, or exercise *(12, 14,18,20,31)*, was associated with a reduction in all-cause mortality (pooled OR = 0.90, 95% CI = 0.46 to 1.77). When we combined results from the three breast cancer trials only *(12,18)* (results not shown in figure), the pooled odds ratio was 0.70 (95% CI = 0.26 to 1.87). Data from these three small breast cancer studies also suggested a reduction in cancer-specific mortality (pooled OR = 0.53) with healthy diet interventions, although the confidence interval was wide (95% CI = 0.16 to 1.79). There was little evidence of between-trial heterogeneity. The seven interventions *(16,17,21,25,26,29,34)*

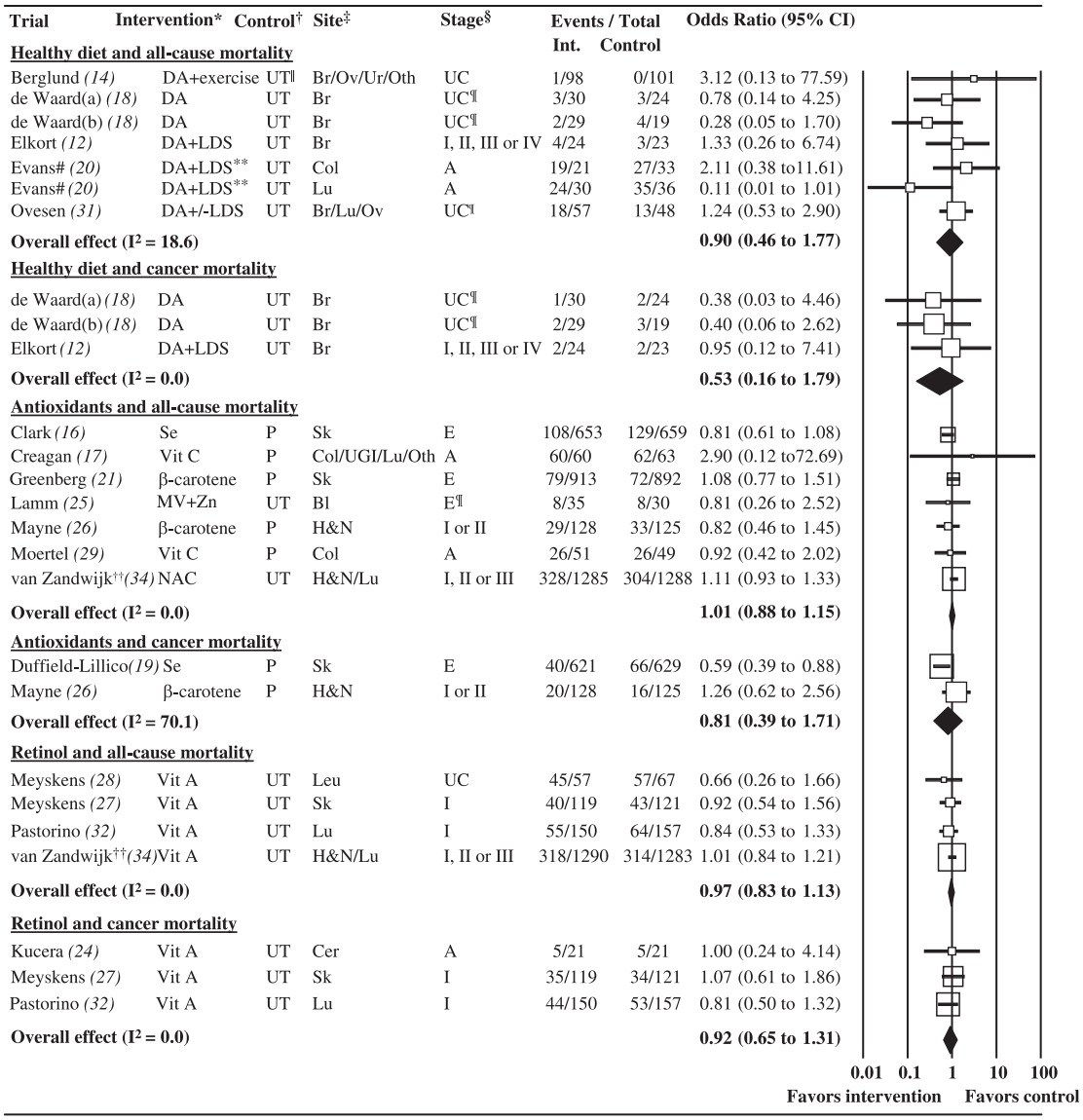

Fig. 2. Meta-analyses examining the effect of dietary interventions on all-cause and cancer mortality in trials of patients with cancer. Int. = intervention; CI = confidence interval. *DA = dietary advice toward a healthier optimal diet; LDS = liquid diet supplement; MV = multivitamins; NAC = *N*-acetylcysteine; Se = selenium; Zn = zinc. †P = placebo; UT = usual treatment. ‡Bl = bladder; Br = breast; Cer = cervix; Col = colorectal; H&N = head and neck; Leu = leukemia; Lu = lung; Oth = other (not specified in text); Ov = ovary; Sk = skin; UGI = upper gastrointestinal; Ur = urological. §A = advanced; E = early; UC = unclear. ‖One-third of control subjects were offered dietary advice, and two-thirds of control subjects were offered usual treatment. ¶In De Waard et al. (a) *(18)*, locoregional disease was present in 28% of the study population. Numbers were not reported separately for intervention arms. In De Waard et al. (b) *(18)*, locoregional disease was present in 94% of the study population. Numbers were not reported separately for intervention arms. In Lamm et al. *(25)*, the percentages of participants with Ta, T1, and T2 disease were 66%, 23%, 11% (intervention arm) and 67%, 20%, 13% (control arm), respectively. In Ovesen et al. *(31)*, the percentage ratio of local/extensive cancer was 56 : 44 (intervention arm) and 63 : 37 (control arm). #This trial contained the following two intervention arms: 1) dietary advice + liquid diet supplement + zinc + magnesium and 2) dietary advice + liquid diet supplement. To get the most accurate estimate of the effect of dietary advice on all-cause mortality, only intervention arm 2 was compared with usual treatment. **Depending on the calorie intake and patient tolerance, the liquid dietary supplement was administered enterally or parenterally. ††A factorial trial included the following arms: 1) vitamin A, 2) *N*-acetylcysteine (NAC), 3) vitamin A + NAC, and 4) usual treatment. The effect of vitamin A was assessed by comparing arms 1 and 3 versus arms 2 and 4, and the effect of NAC was assessed by comparing arms 2 and 3 versus arms 1 and 4.

that included an antioxidant supplement found no evidence of an association between this intervention and all-cause mortality, compared with placebo or usual treatment (OR = 1.01, 95% CI = 0.88 to 1.15), with no heterogeneity ($I^2 = 0\%$). When we combined data from only the two skin cancer trials *(16,21)* (data not shown), we also obtained a similar result (pooled OR = 0.92, 95% CI = 0.70 to 1.22). Although a large selenium trial in skin cancer patients *(19)* showed a 41% (95% CI = 61% to 12%) reduction in cancer mortality in the intervention group, the only other trial *(26)* reporting the effect of antioxidants on cancer mortality found no evidence of a protective effect of β-carotene on head and neck cancer mortality (OR = 1.26, 95% CI = 0.62 to 2.56). Retinol showed no evidence of effect on all-cause mortality [four trials *(27,28,32,34)*: OR = 0.97, 95% CI = 0.83 to 1.13], cancer mortality [three trials *(24,27,32)*], or disease-free survival [three trials *(27,28,34)*; data not shown in Fig. 2], compared with usual treatment.

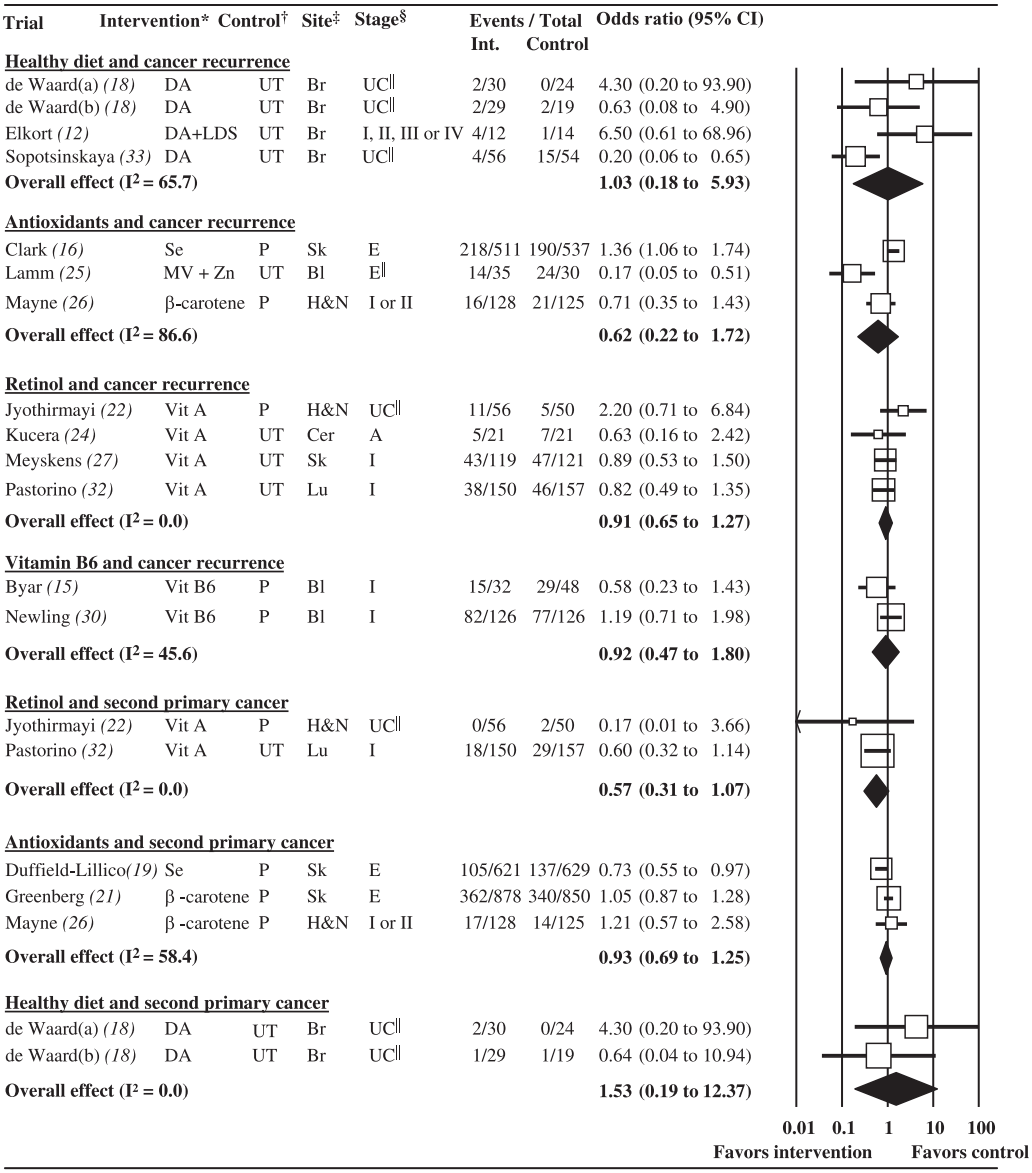

Fig. 3. Meta-analyses examining the effect of dietary interventions on cancer recurrence and second primary cancer occurrence in trials of patients with cancer. Int. = intervention; CI = confidence interval. *DA = dietary advice toward a healthier optimal diet; LDS = liquid diet supplement; MV = multivitamins; Se = selenium; Zn = zinc. †UT = usual treatment; P = placebo. ‡Bl = bladder; Br = breast; Cer = cervix; H&N = head & neck; Lu = lung; Sk = skin. §A = advanced; E = early; UC = unclear. ‖In De Waard et al. (a) *(18)*, locoregional disease was present in 28% of the study population. Numbers were not reported separately for intervention arms. In De Waard et al. (b) *(18)*, locoregional disease was present in 94% of the study population. Numbers were not reported separately for intervention arms. In Jyothirmayi et al. *(22)*, participants were already treated and in complete remission of lesions. In Lamm et al. *(25)*, the percentages of participants with Ta, T1, and T2 disease were 66%, 23%, 11% (intervention arm) and 67%, 20%, 13% (control arm), respectively. In Sopotsinskaya et al. *(33)*, participants had to have sufficiently high levels of blood leukocytes to suggest that they had successfully recovered from six months of chemotherapy.

Cancer Recurrence and Second Primary Cancers in Patients With Cancer

Thirteen trials reported data on cancer recurrence and included the following interventions: four healthy diet *(12,18,33)*, four retinol *(22,24,27,32)*, two vitamin B6 *(15,30)*, one β-carotene *(26)*, one selenium *(16)*, and one multivitamin *(25)*. Seven trials reported data on second primary cancer occurrence and included the following interventions: two healthy diet *(18)*, two β-carotene *(21,26)*, two retinol *(22,32)*, and one selenium *(19)*. As indicated in Fig. 3, there was considerable heterogeneity in the results of four trials, all of which included breast cancer survivors only, that examined the effect of healthy diet compared with usual treatment on cancer recurrence. Although all these trials were small, there was evidence of a protective effect (OR = 0.20, 95% CI = 0.06 to 0.65) in the largest (110 patients, 19 events) *(33)*. There was little overall evidence of an effect of antioxidant, retinol, or vitamin B6 interventions on cancer recurrence; however, the trials estimating antioxidant effects included a diverse range of cancer sites and had widely varying results (I^2 = 86.6). Results from two trials *(22,32)* of the effect of retinol on second primary cancers also suggested a reduction in the risk of second primary cancers (summary OR = 0.57), although the confidence interval was wide (95% CI = 0.31 to 1.07), and a meta-analysis of three trials [one of selenium *(19)* and two of β-carotene *(21,26)*]—including two of the largest interventions in the review *(19,21)*—provided little evidence of a reduced risk with antioxidant supplementation,

compared with placebo (OR = 0.93, 95% CI = 0.69 to 1.25). When we combined data from the two large skin cancer trials *(19,21)* only (data not shown), we found some evidence of a small reduction in the risk of second primary cancer associated with the antioxidant intervention (pooled OR = 0.89, 95% CI = 0.62 to 1.27), although there was also evidence of between-trial heterogeneity (I^2 = 77.1 %). We found no consistent effect of healthy diet interventions on second primary cancer occurrence.

Development of Cancer in Patients With Preinvasive Lesions

The following seven trials reported data on the development of invasive cancer from preinvasive lesions: two healthy diet *(35,54)*, two calcium *(37,57)*, one β-carotene *(58)*, one folate *(58)*, and one multivitamin *(45)*. Both healthy diet interventions included a fiber component, and the combined effect estimate suggested an increased risk of progression from colorectal adenomas to malignancy (OR = 2.64, 95% CI = 1.04 to 6.73). We combined data from the multivitamin and β-carotene trials to investigate the effect of antioxidants on the development of invasive cancer from preinvasive lesions and found little evidence of reduced risk of malignant change in the esophagus or stomach (OR = 0.76, 95% CI = 0.30 to 1.92). Two trials in patients with colorectal and esophageal preinvasive lesions evaluating the effect of calcium versus placebo on the risk of developing cancer also found little evidence of effect.

Recurrence of Preinvasive Lesions

Nineteen trials reported data on the recurrence of preinvasive lesions: six healthy diet *(35,39,46,49,54)*, two β-carotene *(41,46)*, two calcium *(36,39)*, two folate *(44,50)*, five multivitamin *(41,43,48,51)*, one retinol *(55)*, and one *N*-acetylcysteine *(51)* (Fig. 4). Three trials *(41,46,51)* included multiple interventions that were combined for all analyses. These were healthy diet interventions [dietary counseling to reduce fat intake and fiber supplementation *(46)*], and antioxidant interventions [vitamins C + E and β-carotene *(41)* and vitamins A + C + E and *N*-acetylcysteine *(51)*]. Five healthy diet interventions *(35,39,46,49,54)* (all included participants with colorectal preinvasive lesions and aimed to increase fiber intake) showed little evidence of an effect on the risk of recurrence of colorectal polyps (OR = 1.03, 95% CI = 0.85 to 1.26) (I^2 = 40.1%). After combining data from the two β-carotene trials *(41,46)*, four multivitamin trials *(41,43,48,51)*, and the trial *(51)* containing a multivitamin arm and a *N*-acetylcysteine arm, there was weak evidence of a reduction in risk of colorectal polyps with these antioxidant interventions (OR = 0.63, 95% CI = 0.36 to 1.12) (I^2 = 78.2%), and smaller studies reported extreme effects. Two calcium interventions *(36,39)* showed some evidence of a reduced risk of recurrence of colorectal polyps (OR = 0.74, 95% CI = 0.59 to 0.94). The two folate trials *(44,50)* were too small to allow treatment effects to be estimated with precision (OR = 0.58, 95% CI = 0.19 to 1.81).

Discussion

Several trials have investigated the effects of a diverse range of nutritional interventions in patients with a previous diagnosis of cancer or preinvasive lesions. These trials provide little evidence that specific interventions, or groups of interventions, have any effect, either beneficial or harmful. The impact of most nutritional interventions cannot be estimated reliably because of the limited number of trials, many of which are small and/or of low quality. However, there were enough data to exclude substantial effects of antioxidants or retinol on all-cause mortality in patients with cancer. Two trials reported an adverse effect of healthy diet on development of colorectal cancer from preinvasive lesions, although the number of events detected in the trials was small. We were able to exclude any substantial protective association between fiber interventions and recurrence of colorectal adenomas, but two trials *(36,39)* suggested a possible protective association between calcium and recurrence.

Our study had several limitations. Although our review was systematic and used extensive searches of several databases and inclusive search terms, it did not include unpublished results. We think it is implausible, however, that there are large unpublished trials that demonstrate a protective association between nutritional interventions and cancer. Inclusion of unpublished results in systematic reviews typically has only a modest impact on intervention effect estimates, which tend to move toward the null. We did not exclude trials on the basis of methodologic quality, but exclusion of poor-quality trials would also tend to move effect estimates toward the null *(60,61)*. The major limitations of our review related to the limitations of the relevant literature. The diversity of the interventions and the cancers that have been studied mean that decisions on when it is appropriate to use meta-analysis to combine results are difficult. Although most of the meta-analyses that we included were cancer specific, the limited trial data on any specific nutritional intervention forced some grouping of trials from different cancer sites. However, different dietary interventions may not have equal effects, or even effects in the same direction, for different cancer types with different causes and biology. Cancer stage, timing of the intervention in relation to treatment, and the duration of the intervention varied between trials. It may be difficult to detect any effects on cancer incidence—beneficial or harmful—in trials conducted at a late stage of disease. The interventions included in our meta-analysis lasted between 4 weeks and 6 years, and the study period of many, therefore, may not have been long enough for effects to develop.

Most trials had methodologic limitations. The aspects of trial quality that have been demonstrated consistently to be associated with treatment effect estimates in randomized controlled trials are concealment of the allocation sequence and double blinding *(60,61)*. We found that only a few trials reported the methods used to conceal allocation in sufficient detail to allow us to assess their adequacy by use of standard criteria *(9)*. Even when allocation concealment was assessed as adequate, there is no guarantee that bias was prevented, because most concealment processes can be subverted *(62)*. Similarly, we assumed that a trial that was reported as double-blind successfully blinded both patients and outcome assessors. In most trials reported as double-blind, no further detail on methods of blinding was given.

Although previous reviews examining the role of dietary modification and supplements in patients with cancer have been nonsystematic, they reached broadly similar conclusions to those in our study. Norman et al. *(63)* concluded that patients with cancer should take only moderate doses of supplements because evidence of their safety or benefit is limited. Brown et al. *(5)* concluded that there was no convincing evidence that nutrition interventions were beneficial among survivors of four major

Trial	Intervention*	Control†	Site‡	Events / Total Int.	Control	Odds ratio (95% CI)	
Healthy diet and cancer development							
Alberts *(35)*	High fiber	Low fiber	Col	7/719	2/584	2.86	(0.59 to13.82)
Schatzkin *(54)*	DA	UT	Col	10/1037	4/1042	2.53	(0.79 to 8.08)
Overall effect (I^2 = 0.0)						**2.64**	**(1.04 to 6.73)**
Antioxidants and cancer development							
Li *(45)*	MV	P	Es	123/1657	128/1661	0.96	(0.74 to 1.24)
Zhu *(58)*	β-carotene	P	Sto	2/118	3/54	0.29	(0.05 to 1.81)
Overall effect (I^2 = 37.6)						**0.76**	**(0.30 to 1.92)**
Calcium and cancer development							
Baron *(37)*	Ca	P	Col	3/454	5/459	0.60	(0.14 to 2.54)
Wang *(57)*	Ca	P	Es	8/82	8/88	1.08	(0.39 to 3.03)
Overall effect (I^2 = 0.0)						**0.89**	**0.38 to 2.05)**
Healthy diet and recurrence of preinvasive lesions							
Alberts *(35)*	High fiber	Low fiber	Col	338/719	299/584	0.85	(0.68 to 1.05)
Bonithon-Kopp *(39)*	Fiber	P	Col	58/198	36/178	1.63	(1.01 to 2.63)
MacLennan§ *(46)*	DA and/or fiber	UT	Col	65/291	21/99	1.07	(0.61 to 1.86)
McKeown-Eyssen *(49)*	DA+high fiber	UT+low fiber	Col	17/78	16/87	1.24	(0.58 to 2.65)
Schatzkin *(54)*	DA	UT	Col	380/958	374/947	1.01	(0.84 to 1.21)
Overall effect (I^2 = 40.1)						**1.03**	**(0.85 to 1.26)**
Antioxidants and recurrence of preinvasive lesions							
Greenberg ‖ *(41)*	Vit C, E and/or β-carotene	P	Col	211/564	68/187	1.05	(0.74 to 1.47)
Hofstad *(43)*	MV + minerals	P	Col	21/42	36/51	0.42	(0.18 to 0.98)
MacLennan *(46)*	β-carotene	P	Col	50/198	36/192	1.46	(0.90 to 2.38)
McKeown-Eyssen *(48)*	Vit C, E	P	Col	29/70	34/67	0.69	(0.35 to 1.35)
Ponz de Leon *(51)*	Vit A,C,E	UT	Col	4/70	28/78	0.11	(0.04 to 0.33)
Ponz de Leon¶ *(51)*	Vit A,C,E or NAC	UT	Col	14/69	10/34	0.61	(0.24 to 1.57)
Overall effect (I^2 = 78.2)						**0.63**	**(0.36 to 1.12)**
Calcium and recurrence of preinvasive lesions							
Baron *(36)*	Ca	P	Col	196/454	232/459	0.74	(0.57 to 0.96)
Bonithon-Kopp *(39)*	Ca	P	Col	28/176	36/178	0.75	(0.43 to 1.29)
Overall effect (I^2 = 0.0)						**0.74**	**(0.59 to 0.94)**
Folate and recurrence of preinvasive lesions							
Kim *(44)*	Folate	P	Col	5/8	5/9	1.33	(0.19 to 9.31)
Paspatis *(50)*	Folate	P	Col	4/31	8/29	0.39	(0.10 to 1.47)
Overall effect (I^2 = 5.0)						**0.58**	**(0.19 to 1.81)**

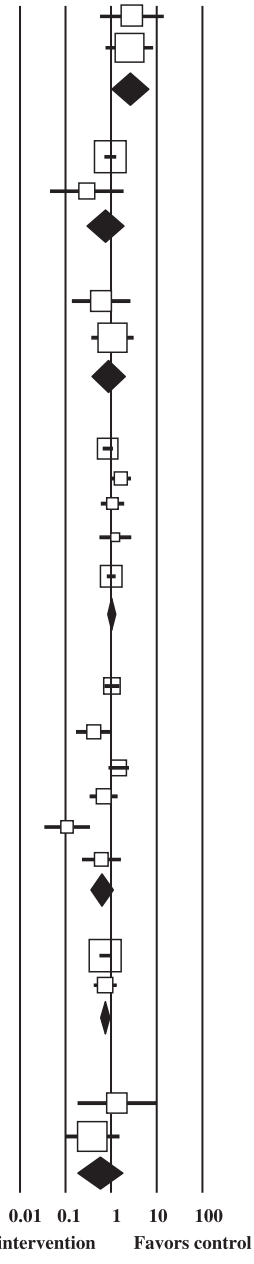

Fig. 4. Meta-analyses examining the effect of dietary interventions on recurrence of preinvasive lesions and development from preinvasive lesions to cancer in trials of patients with preinvasive lesions. Int. = intervention; CI = confidence interval. *DA = Dietary advice toward a healthier optimal diet; Ca = calcium; MV = multivitamins; NAC = *N*-acetylcysteine. †P = placebo; UT = usual treatment. ‡Col = colorectal; Es = esophagus; Sto = stomach. §A 2 × 2 × 2 factorial trial of β-carotene, dietary advice, and high fiber. In this comparison, arms including dietary advice or high fiber or both were combined and compared with those receiving neither. ‖A 2 × 2 factorial trial of vitamin C + E and β-carotene. We combined the three active interventions arms and compared with placebo. ¶This trial contained the following two antioxidant intervention arms: 1) vitamin A+ C + E; 2) *N*-acetylcysteine, which were combined and compared with usual treatment.

cancers—breast, colorectal, lung, and prostate cancer. Two previous meta-analyses *(64,65)* have investigated the specific role of dietary fiber and calcium on cancer incidence in people with colorectal polyps. In their review, Asano et al. *(64)* concluded that the apparent increased risk of colorectal cancer observed in dietary fiber trials may be due to chance because 11 of the 23 cases of colorectal cancer were diagnosed within the first year of the study, suggesting that they may have been missed by the baseline colonoscopy. The meta-analysis of calcium supplementation *(65)*, which used the same trials and reached the same conclusions as we did in this systematic review, suggested that trial efficiency might be improved by identifying subgroups with increased susceptibility to colorectal cancer who may benefit most from calcium supplements *(65)*.

Thus, those planning future studies face challenges. A priority should be given to large-scale, high-quality trials evaluating the most promising interventions. Unfortunately, there is little evidence from the randomized controlled trials that we have

reviewed to guide the choice of either the intervention or the patient groups. The available evidence suggests that large trials of calorie and fat restriction in breast cancer and calcium in colorectal preinvasive lesions are most likely to be successful. Recent results from the Women's Intervention Nutrition Study *(66)*—a large-scale randomized controlled trial investigating the role of dietary fat reduction on relapse-free survival in postmenopausal women with early-stage resected breast cancer—found that women on the reduced-fat diet had a lower risk of recurrence (hazard ratio [HR] = 0.76, 95% CI = 0.60 to 0.98) than women on the standard diet; the risk was reduced further (HR = 0.58, 95% CI = 0.37 to 0.91) in those women whose cancers were estrogen receptor negative *(67)*. A further large-scale trial that was aimed primarily at increasing vegetable intake in women diagnosed with breast cancer is currently ongoing *(68)*. More information from a range of study types could be used to provide information for the design of randomized controlled trials: epidemiologic studies remain important for identifying potential diets associated with mortality, although studies in animal models and genetics are also critical for improving our understanding of the mechanisms of cancer biology, and, therefore, the potential relevance of interventions. Finally, identification of reliable biomarkers would improve trial efficiency.

Nutritional interventions should not be assumed to be benign. Such interventions, notably antioxidant supplementation in the primary prevention setting, have yielded unexpected adverse effects, particularly with respect to β-carotene supplementation and lung cancer in smokers *(6,7)*. As previously noted, fiber interventions with colorectal polyps have also produced a worrying, if imprecisely estimated, adverse effect. Therefore, we should not maintain the notion that nutritional interventions can be promoted because at least they will do no harm.

There is little current evidence that specific dietary interventions work, and thus we cannot recommend the widespread use of dietary modifications and supplements in cancer management. Encouraging a healthy diet is certainly important because many patients with cancer and preinvasive lesions will live a long time and may die of other diseases related to diet. Until there is more evidence that nutritional interventions improve cancer survival, clinicians should counsel their patients to consume a healthy diet but should not state that it is a priority in management of cancer itself. Clinicians need to be clear about the lack of evidence and give reliable advice, in particular on Internet sites from which many patients with cancer, and their companions, may seek information *(69,70)*.

Evidence is lacking to support the hypothesis that dietary modification by cancer patients improves survival and benefits disease prognosis. The large personal expenditure on supplements and dietary modifications by patients with cancer demonstrates an urgent need to understand their effects on cancer outcomes. This vulnerable group of people needs to be better informed, as diet is one of the few areas of their lives where they may feel that they have some control.

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A. A. Davies and S. Thomas designed the review, extracted the data, interpreted the results, and drafted the article for publication. J. A. C. Sterne drafted the article for publication, advised on the study protocol, and interpreted the results. G. Davey Smith advised on the study protocol, interpreted the results, and commented on manuscript drafts. R. Harbord analyzed and interpreted the results, G. E. Bekkering assisted in data extraction, and R. Beynon retrieved the review publications and entered the extracted data. All authors commented on the final draft.

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