Antioxidant supplements for prevention of gastrointestinal cancers: a systematic review and meta-analysis

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Summary

Background Oxidative stress can cause cancer. Our aim was to establish whether antioxidant supplements reduce the incidence of gastrointestinal cancer and mortality.

Methods With the Cochrane Collaboration methodology, we reviewed all randomised trials comparing antioxidant supplements with placebo for prevention of gastrointestinal cancers. We searched electronic databases and reference lists (February, 2003). Outcome measures were incidence of gastrointestinal cancers, overall mortality, and adverse effects. Outcomes were analysed with fixed-effect and random-effects model meta-analyses and were reported as relative risk with 95% CIs.

Findings We identified 14 randomised trials (n=170 525). Trial quality was generally high. Heterogeneity of results was low to moderate. Neither the fixed-effect (relative risk 0·96, 95% CI 0·88–1·04) nor random-effects meta-analyses (0·90, 0·77–1·05) showed significant effects of supplementation with β-carotene, vitamins A, C, E, and selenium (alone or in combination) versus placebo on oesophageal, gastric, colorectal, pancreatic, and liver cancer incidences. In seven high-quality trials (n=131 727), the fixed-effect model showed that antioxidant significantly increased mortality (1·06, 1·02–1·10), unlike the random-effects meta-analysis (1·06, 0·98–1·15). Low-quality trials showed no significant effect of antioxidant supplementation on mortality. The difference between the mortality estimates in high-quality and low-quality trials was significant (Z=2·10, p=0·04 by test of interaction). β-carotene and vitamin A (1·29, 1·14–1·45) and β-carotene and vitamin E (1·10, 1·01–1·20) significantly increased mortality, whereas β-carotene alone only tended to increase mortality (1·05, 0·99–1·11). In four trials (three with unclear or inadequate methodology), selenium showed significant beneficial effect on the incidence of gastrointestinal cancer.

Interpretation We could not find evidence that antioxidant supplements can prevent gastrointestinal cancers; on the contrary, they seem to increase overall mortality. The potential preventive effect of selenium should be studied in adequate randomised trials.

Introduction

Oxidative stress can cause cancer.[1,2] The human diet is a complex mixture of oxidants and antioxidants. The gastrointestinal tract is thought to be the major site of antioxidant action.[3] The question of whether antioxidant supplements might protect against cancer has drawn much attention.[4,5]

Oxidative injury might induce gene mutation and promote carcinogenesis.[6] In addition to the deleterious effects of reactive oxygen species on human cells, oxidative injury can lead to cell death (apoptosis).[7] Dysregulation of apoptosis has a role in gastrointestinal diseases, including cancer.[8] Oxidative stress can modulate the apoptotic programme[9,10] and could cause gastro-intestinal cancer.[11,12] Many observational epidemiological studies have shown that a high intake of fruit and vegetables (rich in antioxidants) is associated with a lower cancer incidence.[13,14] However, results of randomised trials looking at the possible preventive effects of dietary supplementation with one or more selected antioxidants have been contradictory.[15–18] In this systematic review, including meta-analyses, we assess the beneficial and harmful effects of such antioxidant supplementation in the prevention of gastrointestinal cancers.

Methods

We did this review by following the Cochrane Collaboration methodology[19] on the basis of our predefined, peer-reviewed, published Cochrane Hepato-Biliary Group protocol.[20] We included all trials that randomised participants to supplementation with antioxidants (β-carotene, vitamins A, C, E, and selenium, as different combinations or separately) versus placebo, and reported the incidence of gastrointestinal cancers.[20] We included participants from the general population, mainly with non-gastrointestinal diseases, and at high risk of developing gastrointestinal cancers.[20]

We identified trials from controlled-trial registers of the four Cochrane groups on gastrointestinal diseases (upper gastrointestinal and pancreatic diseases group; inflammatory bowel diseases group; colorectal cancer group; hepato-biliary group; February, 2003). We used the Cochrane Central Register of Controlled Trials (CENTRAL) on *The Cochrane Library* (Issue 1, 2003; http://www.cochrane.org), MEDLINE (1966 to February, 2003), EMBASE (1985 to February, 2003), LILACS (1982 to February, 2003), Science Citation Index Expanded (1945 to February, 2003), and the Chinese Biomedical Database (from inception to

Trial	Generation of the allocation sequence	Allocation concealment	Masking	Follow-up	Sample size calculation	Intention-to-treat analysis	Methodological quality
Munoz et al, 1985[29]	Not reported	Adequate	Adequate	Adequate	No	No	Low
Yu et al, 1991[30]	Not reported	Not reported	Adequate	Inadequate	No	No	Low
Blot et al, 1993[31]	Not reported	Adequate	Adequate	Inadequate	Yes	Yes	Low
Li et al, 1993[32]	Not reported	Not reported	Adequate	Adequate	Yes	Yes	Low
Anonymous, 1994[15]	Adequate	Adequate	Adequate	Adequate	Yes	Yes	High
Omenn et al, 1996[16]	Adequate	Adequate	Adequate	Adequate	Yes	Yes	High
Clark et al, 1996[33]	Adequate	Adequate	Adequate	Adequate	Yes	No	High
Hennekens et al, 1996[34]	Adequate	Adequate	Adequate	Adequate	Yes	Yes	High
Yu et al, 1997[35]	Not reported	Not reported	Adequate	Adequate	Yes	Yes	Low
Lee et al, 1999[36]	Adequate	Adequate	Adequate	Adequate	Yes	Yes	High
Li et al, 2000[37]	Not reported	Not reported	Adequate	Adequate	No	Yes	Low
Correa et al, 2000[38]	Adequate	Adequate	Adequate	Adequate	No	No	High
Zhu et al, 2002[39]	Not reported	Not reported	Adequate	Adequate	No	Yes	Low
Anonymous, 2002[40]	Adequate	Adequate	Adequate	Adequate	Yes	Yes	High

Table 1: **Methodological quality of randomised clinical trials comparing antioxidant supplements versus placebo**

March, 2003). We scanned reference lists and contacted manufacturers of antioxidant supplements to ask for unpublished randomised trials.

In accordance with empirical evidence,[21–24] we assessed the methodological quality of trials based on their reports and information from authors,[20] by using Cochrane Collaboration software (RevMan version 4.2.3, http//:www.cochrane.org). We did a meta-analysis of the data[20] with both fixed-effect[25] and random-effects models.[26] For dichotomous variables, we calculated the relative risk with 95% CIs. We assessed heterogeneity with I^2, which describes the percentage of total variation across studies due to heterogeneity rather than chance. I^2 can be calculated as: $I^2=100\%\times(Q-df)/Q$ (Q=Cochrane's heterogeneity statistics, df=degrees of freedom).[27] Negative values of I^2 equalled zero, so that I^2 ranged between 0% (ie, no observed heterogeneity) and 100%. High values would show increasing heterogeneity.[27] Further, we compared the estimated treatment effects of trials with high (adequate components) and low (one or more unclear or inadequate components) methodological quality[20–24] with a test of interaction.[28]

Role of the funding source

The funding sources had no role in the collection, analyses, interpretation of data, writing of the report, or decision to publish. The authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We identified 681 references through database searches. After exclusion of duplicate and irrelevant references, we retrieved 116. Additionally, we identified 81 through scanning reference lists. Of these 197 references, we excluded 36 non-randomised trials, 11 describing six continuing trials, and 13 describing five trials that did not contain relevant data. The remaining 137 references, describing 14 trials,[15,16,29–40] fulfilled our inclusion criteria and could provide data for the analyses. A total of 170 525 individuals participated in these randomised trials. The number of participants in individual trials ranged from 226 to 39 876. Two trials did not report data for sex.[30,35] The remaining trials included 97 305 (58%) male participants and 70 520 (42%) female participants. Mean age was 55 years (range 15–84).

All trials gave antioxidant supplements orally. Types, doses, dose regimens, and duration of antioxidant supplementation were as follows: β-carotene (15–50 mg), vitamin A (1·5–15·0 mg), vitamin C (120–2000 mg), and vitamin E (30–600 mg) every day or on alternate days for 1–12 years, selenium (50–228 μg)

Antioxidant supplements	Relative risk (95% CI)			
	Oesophageal cancer	Gastric cancer	Colorectal cancer	Pancreatic cancer
β-carotene[15,34,36,38,39]	0·15 (0·01–3·72)	1·12 (0·77–1·63)	0·98 (0·82–1·16)	0·94 (0·63–1·40)
Vitamin E[15]	n/a	1·33 (0·79–2·26)	0·78 (0·48–1·27)	0·96 (0·56–1·66)
Selenium[30,33,35,37]	0·40 (0·08–2·07)	n/a	0·48 (0·22–1·05)	n/a
Vitamin A, vitamin B2, and zinc[29]	1·33 (0·30–5·91)	n/a	n/a	n/a
β-carotene and vitamin A[16]	1·21 (0·60–2·44)	1·26 (0·44–3·63)	1·00 (0·69–1·44)	1·38 (0·68–2·79)
β-carotene and vitamin C[38]	n/a	2·90 (0·12–70·52)	n/a	n/a
β-carotene and vitamin E[15]	n/a	1·54 (0·92–2·58)	0·81 (0·50–1·31)	1·00 (0·58–1·72)
β-carotene, vitamin C, and vitamin E[40]	1·19 (0·71–2·01)	1·20 (0·74–1·95)	0·84 (0·65–1·07)	1·00 (0·57–1·76)
26 vitamins and minerals[32]	0·96 (0·76–1·22)	1·19 (0·89–1·58)	n/a	n/a

Relative risks are analysed with fixed-effect model. n/a=not available.

Table 2: **Intervention effect of different antioxidant supplements versus placebo on incidence of different gastrointestinal cancers**

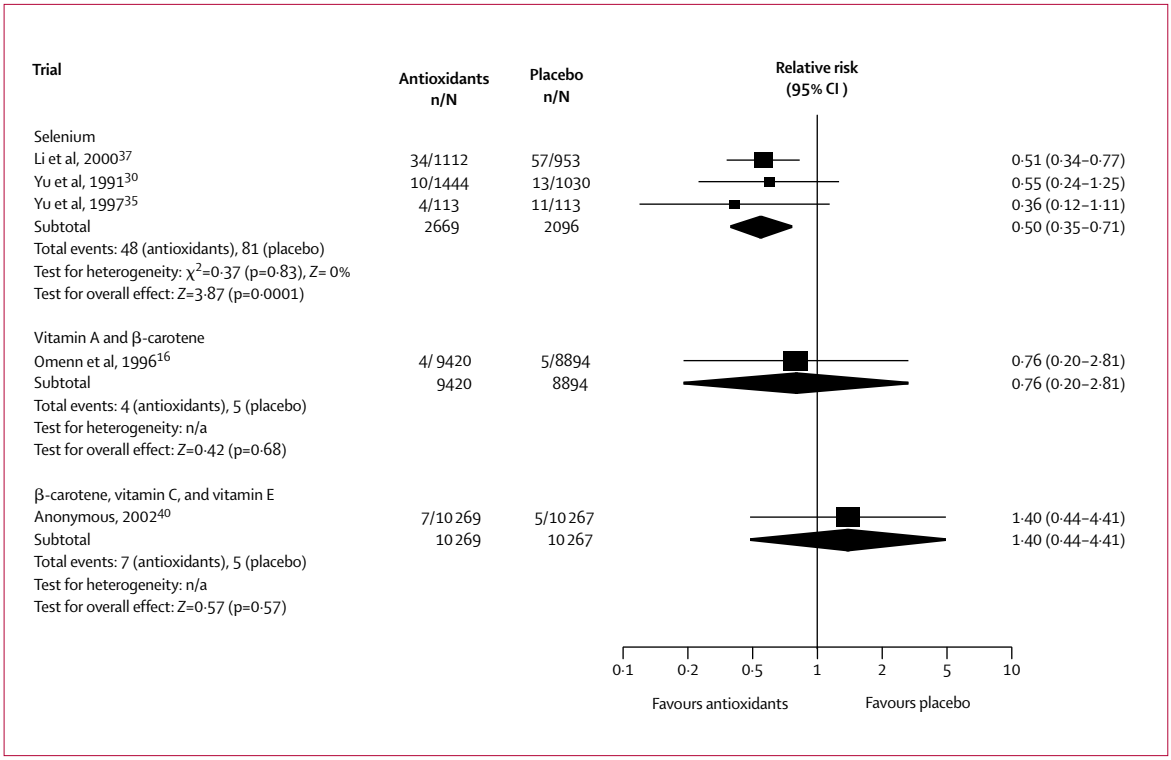

Figure 1: **Intervention effect of different antioxidant supplements versus placebo on incidence of hepatocellular carcinoma**
Relative risks are analysed with fixed-effect model. n/a=not applicable. n=number of patients with outcome; N=number of participants at risk. Black squares=relative risks. Horizontal lines=95% CI. Diamonds=relative risks (95% CI) for particular subtotals.

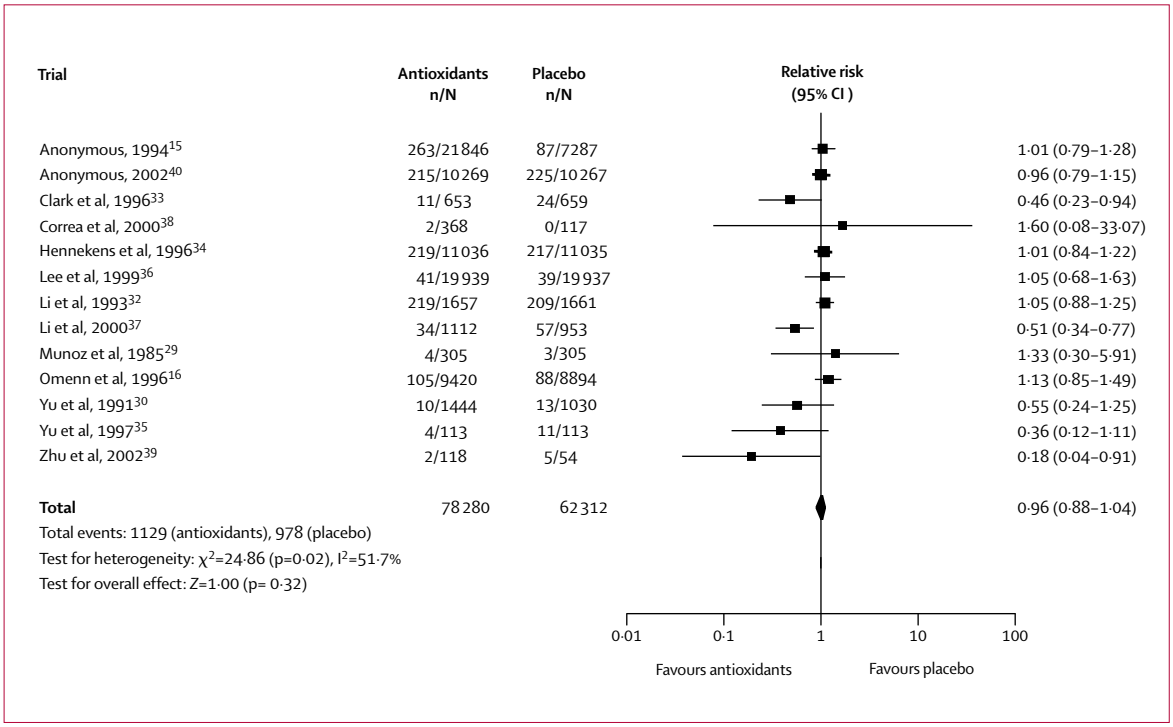

Figure 2: **Intervention effect of all antioxidant supplements versus placebo on incidence of all gastrointestinal cancers combined**
Relative risks analysed with fixed-effect model.

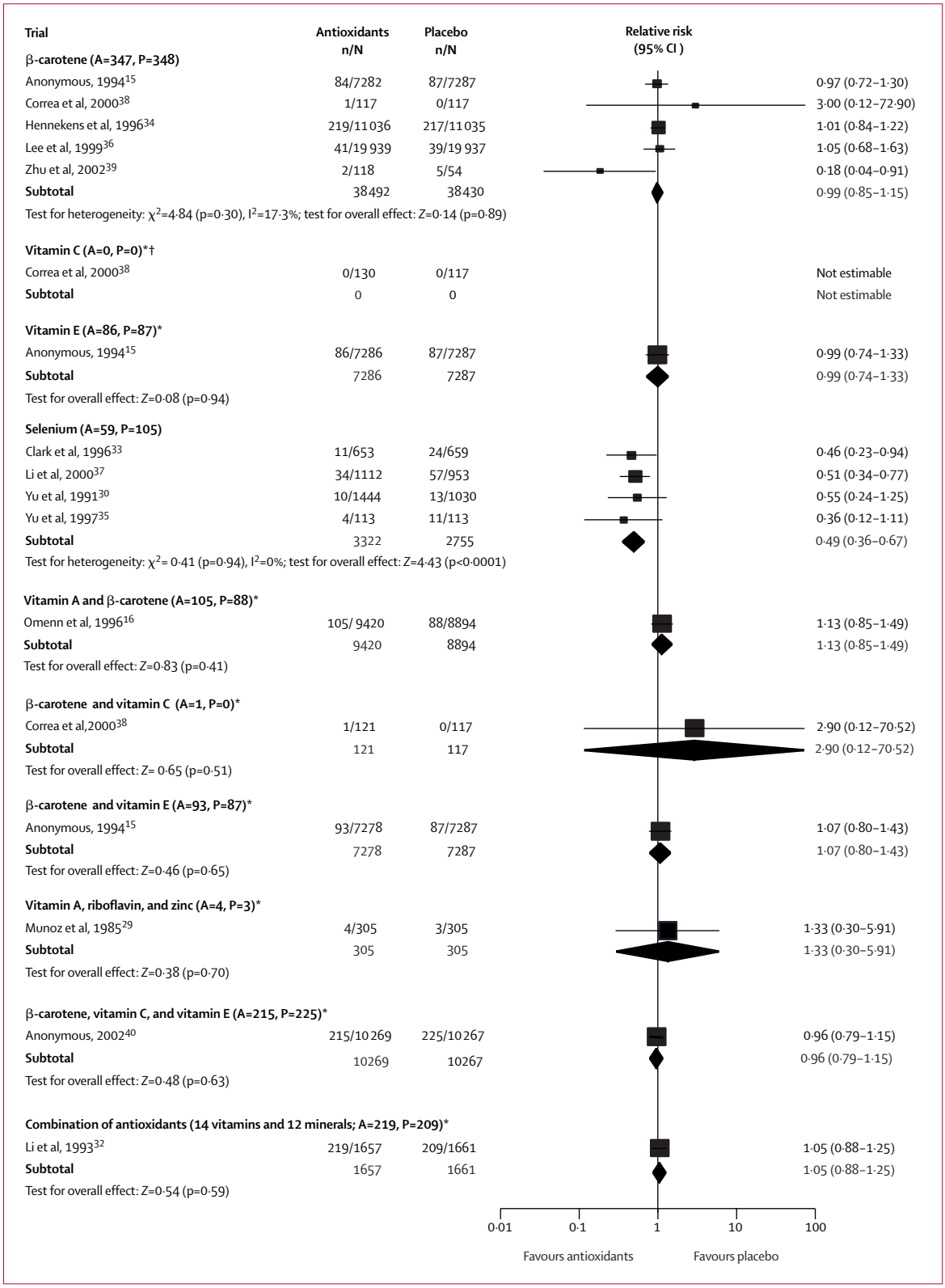

Figure 3: **Intervention effect of different antioxidant supplements versus placebo on incidence of all gastrointestinal cancers combined**
Relative risks analysed with fixed-effect model. A=total events for antioxidants. P=total events for placebo. *Test for heterogeneity=not applicable. †Test for overall effect=not applicable.

every day for 2–4 years. β-carotene, vitamin A, C, E, or selenium were given separately or in different combinations: β-carotene and vitamin A; β-carotene and vitamin E; β-carotene and vitamin C; β-carotene, vitamin C, and vitamin E; β-carotene, vitamin C, vitamin E, and selenium; or vitamin A, riboflavin, and zinc. In two trials, participants were given six vitamins and three minerals[31] or 14 vitamins and 12 minerals.[32] All trials used placebo capsules or tablets as control intervention.

All trials reported the separate or combined incidence of oesophageal, gastric, colorectal, pancreatic, or liver cancers. None reported on small intestinal or biliary tract cancers. We were not able to extract relevant data for the incidence of gastrointestinal cancers in one trial;[31] consequently, this trial only provided data for overall mortality. Seven[15,16,33,34,36,38,40] (50%) of 14 trials were of high methodological quality, having adequate generation of allocation sequence, allocation concealment, masking, and follow-up[21–24] (table 1).

In the nine trials reporting mortality,[15,16,31–34,36,38,40] seven were of high methodological quality[15,16,33,34,36,38,40] and two of low methodological quality.[31,32] We could not obtain mortality data from the remaining five trials, either because overall mortality was not an outcome measure because of the short follow-up or we could not obtain data from the publications or authors.[29,30,35,37,38,39]

Antioxidant supplements given separately or in specific combinations versus placebo for 1–12 years did not significantly affect the incidence of oesophageal, gastric, colorectal, or pancreatic cancers (table 2). There was no significant heterogeneity in these cancers (ie, I^2=0%). In three low-quality trials, selenium versus placebo given for 2–4 years significantly decreased the incidence of hepatocellular carcinoma in high-risk patients, such as hepatitis B surface antigen carriers or members of families with high incidence of liver cancer (figure 1). Combinations of β-carotene and vitamin A or β-carotene, vitamin C, and vitamin E did not significantly change the incidence of hepatocellular carcinoma (figure 1).

Analysed with a fixed-effect model, high-quality trials[15,16,33,34,36,38,40] did not show a significant effect of antioxidant supplements on the incidence of gastrointestinal cancers (relative risk 0·99, 95% CI 0·90–1·10, I^2=0%). In low-quality trials,[29,30,32,35,37,39] antioxidant supplements also did not have a significant effect (0·88, 0·75–1·02), but heterogeneity was significant (I^2=72·3%). In the random-effects model, neither high-quality (0·99, 0·90–1·10) nor low-quality trials (0·61, 0·37–1·03) showed significant effects of antioxidant supplements on the incidence of gastrointestinal cancers. The difference between estimates obtained in high-quality and low-quality trials was not significant (Z=1·26, p=0·21 by test of interaction).[28]

Antioxidants (irrespective of type) versus placebo did not significantly affect the incidence of gastrointestinal cancers (0·96, 0·88–1·04, fixed; 0·90, 0·77–1·05, random; figure 2). 1129 (1·4%) of 78 280 participants in the antioxidant group compared with 978 (1·6%) of 62 312 in the placebo group developed gastrointestinal cancer.

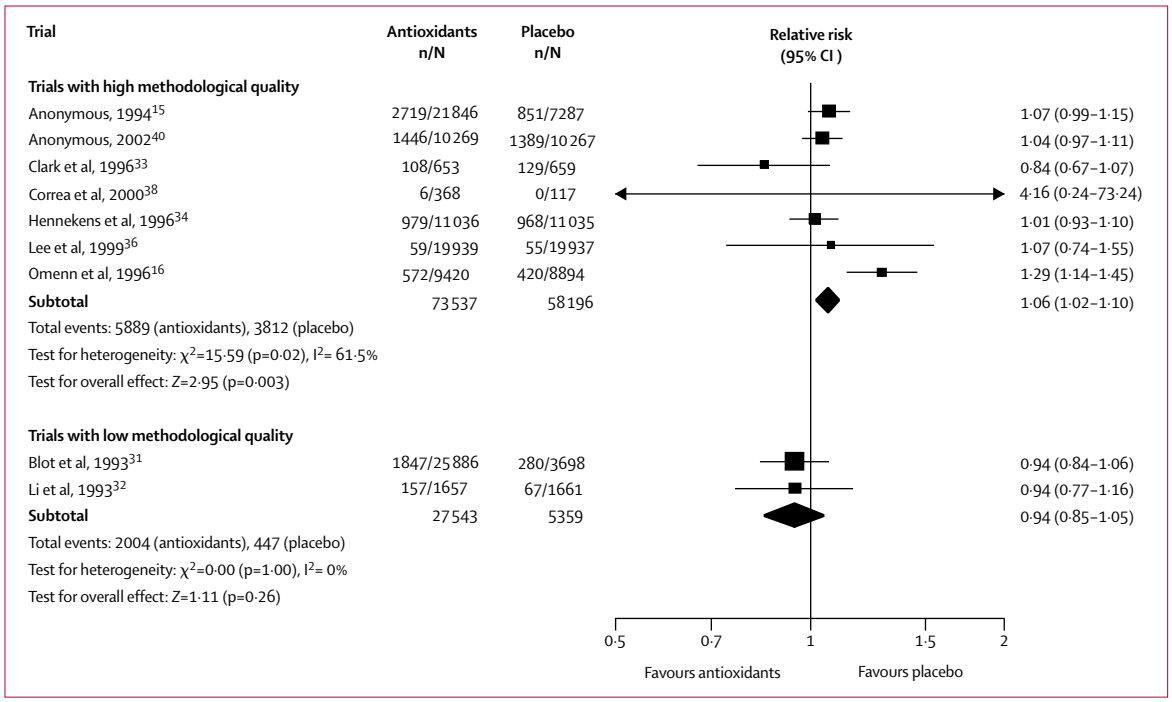

Figure 4: **Effect of antioxidant supplements versus placebo on mortality stratifying trials according to methodological quality**
Relative risks analysed with fixed-effect model.

In four trials (three of low quality), selenium versus placebo significantly reduced the incidence of gastrointestinal cancers. This incidence did not differ significantly by supplement of β-carotene; vitamin C; vitamin E; β-carotene and vitamin A; β-carotene and vitamin C; β-carotene and vitamin E; vitamin A, riboflavin, and zinc; β-carotene, vitamin C, and vitamin E; or combinations of 26 vitamins and minerals versus placebo (figure 3).

Analysed with the fixed-effect model, high-quality trials[15,16,33,34,36,38,40] showed significantly higher mortality in the antioxidant group than in the placebo group (1·06, 1·02–1·10; I^2=66·0%), but not with the random-effects model (1·06, 0·98–1·15). Both low-quality trials[31,32] did not show significant effects of antioxidant supplements on mortality with either model (both 0·94, 0·85–1·05, I^2=0%). The difference between estimates of antioxidant effect on mortality in high-quality and low-quality trials was significant (Z=2·10, p=0·04 by test of interaction;[28] figure 4).

In a heterogeneous set of trials similar to our high-quality trials, the effect of smaller trials was given more weight in the random-effects model than in the fixed-effect meta-analysis. Therefore, we removed the smallest trial, which assessed selenium versus placebo in 1312 patients.[33] The remaining high-quality trials now showed a significantly increased mortality in antioxidant supplemented participants in both models (1·07, 1·03–1·11, fixed; 1·08, 1·01–1·17, random). However, heterogeneity (I^2=66.0%) remained significant because of the strong effect of the Omenn 1996 trial.[16]

Some single antioxidant or combinations of antioxidant supplements (ie, β-carotene [1·05, 0·99–1·11]; vitamin E [1·02, 0·93–1·11]; β-carotene, vitamin C, and vitamin E [1·04, 0·97–1·11]; combination of 26 vitamins and minerals [0·94, 0·85–1·05]; or selenium [0·84, 0·67–1·07]) versus placebo given for 2·1 to 12 years did not significantly affect mortality. However, mortality was significantly increased by β-carotene in combination with vitamin A (1·29, 1·14–1·45) and β-carotene in combination with vitamin E (1·10, 1·01–1·20).

Several adverse effects were recorded in the anti-oxidant group. Patients given β-carotene had a significant increase in belching (2·22, 1·80–2·74) and yellowing of the skin, which was transient (1·96, 1·90–2·03) or persistent (29·1, 21·6–39·3).

Discussion

Our systematic review contains several major findings. β-carotene, vitamin A, vitamin C, and vitamin E supplements given alone or in combinations do not seem to have much effect in the prevention of gastrointestinal cancers. Further, these antioxidant supplements seem to increase overall mortality. Selenium might be an exception, potentially leading to reduction of gastrointestinal cancers, but this result might be biased because of low methodological quality in three of four trials. Compared with other medical specialties,[21–24] the trials assessing antioxidants were of high methodological quality.

We were aware of the risk of comparing the intervention effects of different types of antioxidants on gastrointestinal cancers with different causes, biology, and epidemiology. However, we found no significant heterogeneity in the trials with adequate methodology with respect to the effects of a single antioxidant on incidence of all gastrointestinal cancers, all antioxidants on incidence of individual gastrointestinal cancers, or all antioxidants on incidence of all gastrointestinal cancers. The assessed antioxidants (apart from selenium) do not seem to prevent gastrointestinal cancers. However, 95% CIs were large in the analysis of single cancer types and could be compatible with either beneficial or harmful effects.

We also draw attention to the fact that in many different types of natural or synthetic antioxidants, only a few have been tested in the included randomised trials. Most of the trials have neither taken into account the recommended daily allowances of antioxidant vitamins nor the recommended amounts in the case of combinations of two or more antioxidants.[41,42] Indeed, most trials have investigated the effects of antioxidant vitamins given at substantially higher doses than those usually found in a balanced diet, and some trials used dosages well above the recommended tolerable upper intake levels.[41,42] This excess of supplement given might be a cause for the absence of the expected protective effects and for the increase in mortality of antioxidant supplements recorded.

β-carotene is the most widely tested antioxidant for cancer prevention. Our results show that β-carotene does not have substantial anticarcinogenic properties in gastrointestinal cancers. β-carotene alone only tended to increase mortality. However, β-carotene combined with vitamin A and vitamin E significantly increased mortality.[15,16] A recent study has suggested that β-carotene might act as a co-carcinogen.[18] Our results accord with those reported by Caraballoso and colleagues[43] (no significant effect of antioxidant supplements on lung cancer incidence or mortality) and Vivekananthan and co-workers[44] (significant mortality increase in patients given β-carotene to prevent cardiovascular disease), including data from almost 110 000 participants from four of the trials in our review.[15,16,34,36] With respect to other adverse effects, significant differences between antioxidant and placebo groups were seen only in trials assessing β-carotene supplementation.

We could not identify trials assessing vitamin A alone in the prevention of gastrointestinal cancers. The combination of vitamin A and β-carotene was assessed in a high-quality, large-scale randomised trial with lung cancer prevention as the primary outcome.[16] Cancer incidence and overall mortality were significantly higher in the antioxidant group than placebo.[16] Cochrane Reviews on vitamin A for pregnant women[45] and for very low birthweight infants[46] and a meta-

analysis on vitamin A for infected children in low-income countries[47] suggests beneficial effects of the vitamin on mortality. Therefore, vitamin A per se probably does not present a threat to survival, but additional evidence might be needed.[45–47] Effects of vitamin A could depend on factors such as age, dietary needs, oxidative stress, or supply of other antioxidants.

Trials in which vitamin C was given separately or in different combinations with β-carotene, vitamin A, vitamin E, and selenium showed no significant effect on the incidence of gastrointestinal cancers or on overall mortality. Recent studies have shown that vitamin C could act as both a pro-oxidant and as an antioxidant in vivo.[48] Vitamin E did not significantly affect the incidence of gastric, pancreatic, and colorectal cancer or mortality. Before any use of vitamin C and vitamin E supplements is considered, results of large randomised clinical trials should be awaited.[49,50]

Our results show that selenium might have beneficial effects on the incidence of gastrointestinal cancers. However, only one of the trials investigating selenium had high methodological quality.[33] The Nutrition Prevention of Cancer trial in the USA,[33] the first randomised trial in a western population designed to investigate whether selenium could reduce the risk of cancer, reported significantly lower total cancer incidence and total cancer mortality in patients given selenium than those who were not. These results are similar to those of three Chinese trials.[30,35,37]

We identified seven randomised trials that assessed antioxidant supplements in the primary or secondary prevention of colorectal adenomas,[51–57] which represent an intermediate step towards colorectal carcinogenesis.[58] These trials assessed different combinations of β-carotene, vitamin A, vitamin C, and vitamin E. The pooled effect of all trials on colorectal adenomas was not statistically significant (Bjelakovic G, Nagorni A, Nikolova D, Simonetti R, Bjelakovic M, Gluud C, unpublished data). Thus, no trial data currently indicate that antioxidants are protective against the development of colorectal adenomas or colorectal cancer.

Our results for the detrimental effect of antioxidant supplements on mortality were unexpected. In the high-quality trials, we noted a substantially higher mortality in the antioxidant group than in placebo with the fixed-effect meta-analysis, but not with the random-effects meta-analysis. This difference was solved by exclusion of the smallest trial, which assessed selenium.[33] After exclusion of this trial, both the fixed-effect and random-effects meta-analyses showed significantly increased mortality in the antioxidant-supplemented group. Mortality was also significantly higher in the antioxidant group in high-quality trials compared with no significant effect in low-quality trials. Similar results were seen in two large-scale, randomised double-blind trials[15,16] testing the efficacy of β-carotene and vitamin A or β-carotene and vitamin E. Mortality was significantly higher in antioxidant groups than in controls. However, a third large-scale randomised trial[36] recorded neither benefit nor harm from β-carotene. A possible explanation might be that participants in the two trials showing harmful effects of β-carotene[15,16] were at higher risk for cardiovascular disease and lung cancer because they were smokers or exposed to asbestos. In the third trial, participants were physicians with a low number of smokers.[34]

On the basis of data from postmenopausal women entering the Women's Health Initiative in the USA,[59] use of antioxidant supplementation has increased substantially. More than half the women took antioxidant supplements in some form.[59] 26% took vitamin C, 30% vitamin E, and 4·4% β-carotene as separate supplements, at maximum doses for a substantial length of time.[59] If our mortality findings are correct, they could be expressed as the number needed to treat to harm one patient of about 112, based on a mortality risk of 6·7% in the control group and a relative risk of mortality of 1·06. For every million people exposed to toxic combinations or amounts of antioxidant supplements, about 9000 premature deaths could have occurred. The most frequently recorded non-serious adverse effect of antioxidant supplements was yellowing of the skin in patients supplemented with β-carotene, and it was reported as one of the reasons for lower compliance with the treatment.

Our review had several potential limitations. We analysed a group of trials, which by nature of the topic—ie, preventive efforts for years—could have inherent weaknesses. We saw several inconsistencies in the different reports of the individual trials. Although we tried in all cases to obtain reconfirmation from the authors, we could not always do so. In several trials, the dropout rate was high, and this rate might have affected the results of individual trials and thereby our meta-analyses. Diagnostic criteria and timing of screening differed between trials or were not always well defined. Moreover, the examined populations varied. Generally, the risk of cancer was less than one in 100, which could make it difficult to detect any effects—beneficial or harmful. In nine trials, the effect of antioxidant supplements was assessed in people with a high risk of cancer (ie, smokers, patients with oesophageal dysplasia, patients with previous history of skin cancer, hepatitis B surface antigen carriers, or relatives of patients with liver cancer), whereas three trials investigated healthy participants. One trial assessed the incidence of cancer as a secondary outcome in patients at high risk for cardiovascular disease. This variable risk to develop cancer could have affected our results. Likewise, the fact that occurrence of gastrointestinal cancers was not the primary objective of some of the trials might have affected the detection rate, but this factor would probably have affected both arms of the trials equally.

The methodological quality of some of the trials could only be assessed by use of published reports, which might

not have indicated the actual design of the trials. Not all authors responded to our requests for further information. Because we had to rely mainly on the published reports, the association between reported methodological quality and overestimation of intervention effect was very important.[23] Our data for the effect of antioxidant supplements on mortality were based on a select sample of trials assessing antioxidants for gastrointestinal cancers. We are in the process of identifying all trials investigating mortality after exposure to antioxidants. Finally, supplementation only lasted 1–12 years, which could be thought too short a period (compared with the length of time needed for cancers to develop) to draw definitive conclusions. In this respect, the fact that selenium seemed to be effective after only 2–4 years is noteworthy.

We emphasise that our review analysed only the effect of certain antioxidant supplements. Therefore, the results should not be translated to the potential effects of vegetables and fruits, which are rich in antioxidants and other substances. Many substances in fruits and vegetables have been postulated to have anticarcinogenic properties. The most extensively investigated constituents of fruits and vegetables (acting as antioxidants) are micronutrients, dietary fibre, and various phytochemicals.[60–63] Some of these constituents, acting independently or in combination, might have protective effects. Fruits and vegetables typically contain safe levels of vitamins, but high-level antioxidant supplements could be hazardous.[64] Amounts of protective antioxidants are not known and probably differ between individuals. People exposed to increased oxidative stress might have raised antioxidant requirements.[65]

Although most observational studies have reported that adequate intake of fruits and vegetables is associated with a low incidence of cancer, some of them showed no significant effect.[66,67] Furthermore, recent clinical trials showed no significant association between fruit and vegetable consumption and cancer at several sites.[68,69]

Salganik[7] provided an interesting explanation about the harmful effects of antioxidants on the basis of the heterogeneity of people with respect to baseline levels of reactive oxygen species. Antioxidants could be beneficial in people with innate or acquired high baseline levels of reactive oxygen species, but harmful in people with low innate levels of reactive oxygen species, by inhibiting apoptosis and promoting carcinogenesis. According to our results, poorly controlled application of antioxidants can lead to unwanted consequences to our health.

Our results accord with those of other published meta-analyses or systematic reviews assessing the role of antioxidant supplements for the prevention of lung cancer[43] and cardiovascular diseases,[44] as well as the US Preventive Services Task Force recommendations for the use of vitamin supplementation to prevent cancer.[70,71] These studies collectively suggest that antioxidant supplements might not be beneficial for cancer prevention.

Contributors

G Bjelakovic conceived the idea for and drafted the manuscript. D Nikolova developed the search strategy and revised the manuscript. R Simonetti revised the manuscript. C Gluud provided strategy for data analyses and interpretation and revised the manuscript. All co-authors contributed to data extraction and data verification.

Conflict of interest statement

We have no conflict of interest to declare.

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This review will be published as a Cochrane Review in *The Cochrane Library*. Cochrane Reviews are regularly updated as new evidence emerges and in response to comments and criticisms; *The Cochrane Library* should be consulted for the most recent version of this review.

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