Effects of antioxidant supplements on cancer prevention: meta-analysis of randomized controlled trials

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Background: This meta-analysis aimed to investigate the effect of antioxidant supplements on the primary and secondary prevention of cancer as reported by randomized controlled trials.


Results: Among 3327 articles searched, 31 articles on 22 randomized controlled trials, which included 161 045 total subjects, 88 610 in antioxidant supplement groups and 72 435 in placebo or no-intervention groups, were included in the final analyses. In a fixed-effects meta-analysis of all 22 trials, antioxidant supplements were found to have no preventive effect on cancer (relative risk (RR) 0.99; 95% confidence interval (CI) 0.96–1.03). Similar findings were observed in 12 studies on primary prevention trials (RR 1.00; 95% CI 0.97–1.04) and in nine studies on secondary prevention trials (RR 0.97; 95% CI 0.83–1.13). Further, subgroup analyses revealed no preventive effect on cancer according to type of antioxidant, type of cancer, or the methodological quality of the studies. On the other hand, the use of antioxidant supplements significantly increased the risk of bladder cancer (RR 1.52; 95% CI 1.06–2.17) in a subgroup meta-analysis of four trials.

Conclusions: The meta-analysis of randomized controlled trials indicated that there is no clinical evidence to support an overall primary and secondary preventive effect of antioxidant supplements on cancer. The effects of antioxidant supplements on human health, particularly in relation to cancer, should not be overemphasized because the use of those might be harmful for some cancer.

Key words: antioxidants, cancer, meta-analysis, prevention, randomized controlled trials

Introduction

Previous experimental studies using in vivo animal models and in vitro cancer cell lines have reported that antioxidants such as vitamins, beta-carotene, and selenium may reduce oxidative damage and prevent human diseases, including cancer [1–4]. Also, the previous 200 epidemiologic studies have indicated that persons with a low intake of fruits and vegetables that are rich in antioxidant substances are more susceptible to cancer [5].

However, a systematic review of randomized controlled trials published in 2006 reported that the currently available evidence was insufficient to prove whether or not multivitamin supplements were beneficial toward the prevention of cancer and chronic disease [6]. A recently published meta-analysis of 47 low-bias trials involving 180 938 participants revealed that compared with the control group, the antioxidant supplement group exhibited a mortality rate that was significantly higher by at least 5% [7]. A meta-analysis of randomized controlled trials also showed that antioxidant supplements do not exert any significant effects against the development of gastrointestinal cancers and that they increase all-cause mortality [8]. Recently, in a meta-analysis of 12 randomized clinical trials, Bardia et al. [9] reported that antioxidant supplementation did not significantly reduce total cancer incidence or mortality or any site-specific cancer incidence in participants who had neither history of cancer nor precancerous lesions (i.e. primary prevention only). Furthermore, according to the recent report from World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) published in 2007, the strongest evidence, corresponding to judgments of ‘convincing’ or ‘probable’, showed that high-dose beta-carotene supplements in tobacco smokers are a cause of lung cancer and that selenium probably protects against prostate cancer, while there was limited evidence indicating that vitamin A, vitamin E, and selenium protect against squamous cell carcinoma of the skin, prostate cancer, and either lung cancer or colorectal cancer, respectively [10].
This meta-analysis was conducted to investigate the quantitative preventive effects of the consumption of antioxidant supplements such as vitamins A, C, and E; beta-carotene; and selenium on cancer risks determined via randomized controlled trials by type of prevention (primary or secondary), type of antioxidant, and type of cancer.

methods

data sources and keywords

We searched Medline (PubMed) (1968 to October 2007), Excerpta Medica database (1977 to October 2007), and the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (1953 to October 2007) by using select common keywords related to antioxidant supplements and cancer risk in randomized controlled trials. We also searched the bibliographies of relevant articles in order to identify additional studies. We selected the following keywords for the literature search: ‘retinol’, ‘beta-carotene’, ‘carotenoids’, ‘ascorbic acid’, ‘alpha-tocopherol’, ‘selenium’, ‘vitamin’, or ‘antioxidant’; ‘neoplasm’, ‘cancer’, or ‘carcinoma’; and ‘randomized controlled trials’, ’randomized clinical trials’, or ‘randomized placebo-controlled trials’.

selection criteria

We included randomized controlled trials that reported the preventive effects of antioxidant supplements (beta-carotene; vitamins A, C, and E; and selenium) on cancer risk and compared the results of these trials with those in which placebo or no intervention groups were used. The main outcome measure was cancer incidence. We excluded studies that were conducted to investigate the treatment effect, not the preventive effect, of antioxidant supplements.

selection of relevant studies

Two evaluators (S-KM and YK), who are two of the authors of this study, independently evaluated all the studies retrieved from the databases. Disagreements between evaluators concerning the selected studies were resolved by discussion or in consultation with a third author (WJ). In the case of insufficient or missing data, we contacted the authors of the articles and retrieved the relevant data. From the studies included in the final analysis, we extracted the following data: study name (along with the name of the first author and the year of publication), journal name, country and type of prevention, duration of supplement treatment and follow-up period (years), population (project name), study design (content of intervention), type of cancer (outcome measure), relative risk (RR) with 95% confidence intervals (CIs), and number of cancer/number of participants in each intervention group.

main analysis

We estimated the overall effect of antioxidant supplements (beta-carotene, vitamin A, vitamin C, vitamin E, and selenium) administered singly or in combination with other antioxidant supplements on prevention of cancer, compared with placebo administration or no intervention in all 22 trials.

subgroup meta-analyses

We evaluated the effects of antioxidant supplements according to the type of prevention, i.e. primary prevention or secondary prevention. Trials involving the healthy populations or patients with specific disease (nonmalignant or premalignant disease such as dysplasia or skin keratosis) were classified as those on primary prevention, and trials involving patients with cancer were classified as those on secondary prevention. Further, the effects of antioxidant supplements were evaluated according to the type of individual antioxidant administered singly and type of cancer.

We also evaluated the methodological quality of the studies, because studies with low methodological quality tend to overestimate the effect of intervention [8, 11]. Studies with adequate quality components [generation of the allocation sequence (computer-generated random numbers or similar methods), allocation concealment (central independent unit, sealed envelopes, or similar), double-blinding (identical placebo tablets or similar), and follow-up (number of and reasons for dropouts and withdrawals described)] were classified as having high methodological quality [7, 8, 11]. Studies with one or more unclear or inadequate (not described like the adequate ones above) quality components were classified as having low methodological quality [7, 8, 11].

statistical analyses

We estimated the pooled RR with 95% CI on the basis of both the fixed- and random-effects models; the Mantel–Haenszel method was used in the fixed-effects model, and the DerSimonian and Laird method was used in the random-effects model. For the study with a 2 × 2 factorial design, we used the values of the control group and the ones which were calculated by summing up the ones of the remaining antioxidant groups. We estimated heterogeneity (between-studies variability) using the Higgins I² statistic, which measures the percentage of total variation across studies due to heterogeneity rather than chance. I² was calculated as follows:

\[ I^2 = 100\% \times \frac{(Q - df)}{Q}, \]

where Q is Cochran’s heterogeneity statistic and df is the degrees of freedom corresponding to it. Cochran’s Q statistic was calculated as follows:

\[ Q = \sum (\theta_i - \bar{\theta})^2 w_i, \]

where \( \theta_i \) is the RR of each ith study, \( \bar{\theta} \) is the pooled RR of all the studies, and \( w_i \) is the inverse variance of each ith study as a weight. Negative values of I² are set at zero so that I² lies between 0% (no observed heterogeneity) and 100% (maximal heterogeneity). An I² value >50% was considered to indicate substantial heterogeneity. When substantial heterogeneity was not observed, the pooled estimate calculated based on the fixed-effects model was reported. When substantial heterogeneity was observed, the pooled estimate calculated based on the random-effects model was reported.

We estimated publication bias by using Begg’s funnel plot and Egger’s test. Funnel plots are scatter plots of the log odds ratios (ORs) of individual studies on the x-axis against 1/standard error (SE) (or SEs or sample size; as a measure of precision) of each study on the y-axis. If a publication bias exists, the plot is asymmetrical. Egger’s test is a test for linear regression of the normalized effect estimate (log OR/SE against its precision unit/SE). If the P value is found to be <0.05 by Egger’s test, the presence of a publication bias is considered. We used the Stata SE version 10.0 software package (StataCorp, College Station, TX) for statistical analysis.

results

selection of studies

As shown in Figure 1, 3327 articles were obtained after searching databases and relevant bibliographies. After excluding 533 duplicated articles and 2703 articles that did not satisfy the selection criteria, we reviewed the full texts of 91 articles. Among these, 31 articles [12–42] on 22 randomized controlled trials (A trial by Yu [14], shown in Table 1, was classified into two individual randomized controlled trials because it was conducted for two different subpopulations) were included in the final analysis.
We excluded 60 articles [8,43–100] because they lacked sufficient data [43–45], described only the study protocol or rationale [46–49], had identical populations and study results [50–64], included precancerous lesions as outcome measure [65, 66], contained supplements not relevant to the study subject [49,67–73], or did not include randomized clinical trials [8,74–92]. Further, the complete papers were not available for some articles [93, 94], and some did not fulfill the inclusion criteria [95–100].

characteristics of selected studies

The final analysis included 161 045 total subjects, 88 610 in antioxidant supplement groups and 72 435 in placebo or no-intervention groups, from 22 randomized controlled trials reported in 31 articles. In the studies in which the age and sex were reported, the mean (median) age was 58.4 years (age range 15–91 years), and 74.7% of the subjects were male.

Table 1 shows the general characteristics of the 31 articles included in the analysis. The selected articles were published from 1985 through 2007, spanning 22 years. Besides the countries belonging to the European Union (n = 1), the countries in which the studies were conducted were as follows: United States (n = 13), Finland (n = 7), China (n = 4), Canada (n = 3), UK (n = 1), France (n = 1), Italy (n = 1), and India (n = 1). The mean (median) treatment and follow-up periods were 5.3 and 5.8 years, respectively. The following four trials were reported in 14 articles: the Alpha-Tocopherol Beta-Carotene Prevention Study (n = 8), the Nutritional Prevention of Cancer Trial (n = 2), the Women’s Health Study (n = 2), and the Physicians’ Health Study (n = 2). Of the 22 trials, 12 were primary prevention trials, nine were secondary prevention trials, and the remaining one [21] was a mixed one (this study was excluded in the subgroup analysis by type of prevention due to a lack of data by type of prevention). The studies included healthy subjects (among the general population, physicians, and nurses); patients with skin, head and neck cancers; adults with underlying coronary disease, occlusive disease, and diabetes; hepatitis B virus surface antigen carriers; persons at high risk for primary liver cancer; smokers; male asbestos-industry workers; and organ transplant recipients.

Among the 22 trials, 20 had a placebo group as the control and two had a no-intervention group as the control [29, 35]. Further, 19 trials used the parallel design, and three used the 2 × 2 design. In all studies, the antioxidant supplements were administered orally, and the dosage regimens used were as follows: vitamin A (15 mg or 10 000, 15 000, 25 000, 200 000, or 300 000 IU; daily or weekly), vitamin C (120, 180, or 250 mg; daily), vitamin E (30, 50, or 600 mg or 60, 400, or 600 IU; daily or on alternate days), beta-carotene (6, 20, 30, 50, or 75 mg; daily or on alternate days), and selenium (50, 100, or 200 µg; daily).

The main outcome measure was the incidence of cancer, and the types of cancer were as follows: esophageal cancer, nonmelanoma skin cancer, primary liver cancer, stomach cancer, lung cancer, locoregionally recurrent and second primary cancer in head and neck cancer patients, prostate cancer, pancreatic cancer, colorectal cancer, urinary tract cancer, head and neck cancer, and upper aerodigestive tract cancer.

effect of antioxidant supplements on prevention of cancer in all 22 trials

Overall, in a fixed-effects model meta-analysis of all 22 trials, administration of antioxidant supplements had no significant influence on the incidence of cancer compared with placebo administration or no intervention (RR 0.99; 95% CI 0.96–1.03) (Figure 2). Heterogeneity was not found across the selected
Table 1. Characteristics of the studies of antioxidant supplements and cancer risk included in the final analysis (n = 31)

<table>
<thead>
<tr>
<th>Study name (No. of reference)</th>
<th>Journal</th>
<th>Country; type of prevention</th>
<th>Population (project name)</th>
<th>Design; interventions</th>
<th>Type of cancer; outcome measure</th>
<th>RR (95% CI)</th>
<th>No. of cancer/no. of participants in each group</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Munoz, 1985 [12]</td>
<td>Lancet</td>
<td>China; primary</td>
<td>610 subjects</td>
<td>Parallel; 15 mg of retinol (vitamin A), 200 mg of riboflavin (vitamin B2), and 50 mg of zinc versus placebo per day</td>
<td>Esophageal cancer; incidence</td>
<td>Not stated</td>
<td>Placebo: 3/305; vitamin A (plus vitamin B2 and zinc): 4/305</td>
</tr>
<tr>
<td>3 Yu, 1991 [14]</td>
<td>Biological trace element research</td>
<td>China; primary</td>
<td>2474 members of families with high risk of primary liver cancer and 226 hepatitis B virus surface antigen carriers</td>
<td>Parallel; 200 μg of selenium versus placebo per day</td>
<td>Primary liver cancer; incidence</td>
<td>Yu, 1991 (1): members of families with high risk of cancer: placebo: 1.26%; selenium: 0.69% (P &lt; 0.05)</td>
<td>Yu, 1991 (1): placebo: 13/1030; selenium: 10/1444</td>
</tr>
<tr>
<td>4 NIT, 1993 [15]</td>
<td></td>
<td>China; primary</td>
<td>3318 persons with cytologic evidence of esophageal dysplasia (the dysplasia trial, NITs in Linxian, China)</td>
<td>Parallel; 15 mg of beta-carotene and a combination of 10 000 IU of vitamin A, 180 mg of vitamin C, 60 IU of vitamin E, 50 μg of selenium, etc. placebo per day</td>
<td>Esophagus, stomach, and other sites; incidence</td>
<td>1.01 (0.84–1.22)</td>
<td>Placebo: 221/1661; antioxidants (beta-carotene and the combination of vitamin A, vitamin C, vitamin E, selenium, etc.): 227/1657</td>
</tr>
<tr>
<td>5 ATBC, 1994 [16]</td>
<td>The New England Journal of Medicine</td>
<td>Finland; primary</td>
<td>29 133 male smokers (ATBC)</td>
<td>2 × 2; 50 mg of alpha-tocopherol (vitamin E), 20 mg of beta-carotene, and placebo per day</td>
<td>Lung cancer; incidence</td>
<td>Alpha-tocopherol: 2% (−14% to 12%); beta-carotene: 18% (3%–36%)</td>
<td>Placebo: 209/7287; antioxidants (vitamin E and/or beta-carotene): 686/21 846</td>
</tr>
<tr>
<td>6 NPCT, 1996 [17]</td>
<td></td>
<td>United States; secondary</td>
<td>1312 patients with a history of basal cell or squamous cell carcinomas of the skin (NPCT)</td>
<td>Parallel; 200 μg of selenium placebo per day</td>
<td>Skin cancers (basal cell and squamous cell carcinomas) and other cancers; incidence</td>
<td>NPCT, 1996 (1): basal cell carcinoma: 1.10 (0.93–1.28) squamous cell carcinoma: 1.14 (0.93–1.39)</td>
<td>Placebo: 540/659; selenium: 595/633</td>
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</table>

Note: For RR (95% CI), the values represent the risk ratio with a 95% confidence interval.
<table>
<thead>
<tr>
<th>Study name (No. of reference)</th>
<th>Journal</th>
<th>Country; type of prevention</th>
<th>Duration of supplement treatment/follow-up period (years)</th>
<th>Population (project name)</th>
<th>Design; interventions</th>
<th>Type of cancer; outcome measure</th>
<th>RR (95% CI)</th>
<th>No. of cancer/no. of participants in each group</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 Jyothirmayi, 1996 [18]</td>
<td>European journal of cancer. Part B, Oral oncology</td>
<td>India; secondary</td>
<td>1/3</td>
<td>106 head and neck cancer patients who had achieved complete regression of their disease</td>
<td>Parallel; 200 000 IU of retinyl palmitate (vitamin A) versus placebo per week</td>
<td>Locoregional recurrence and second primary cancers; incidence</td>
<td>Not presented</td>
<td>Placebo: 7/50; vitamin A: 11/56</td>
</tr>
<tr>
<td>8 CARET, 1996 [19]</td>
<td>Journal of the National Cancer Institute</td>
<td>United States; primary</td>
<td>4/4</td>
<td>18 314 men and women at high risk of developing lung cancer: 14 254 general smokers and 4060 asbestos-exposed male workers (the Beta-Carotene and Retinol Efficacy Trial: CARET)</td>
<td>Parallel; A combination of 30 mg beta-carotene and 25 000 IU retinyl palmitate (vitamin A) versus placebo per day</td>
<td>Lung cancer; incidence</td>
<td>1.36 (1.07–1.73)</td>
<td>Placebo: 159/8894; antioxidants (A combination of beta-carotene and vitamin A): 229/9420</td>
</tr>
<tr>
<td>9 Levine, 1997 [20]</td>
<td>Cancer epidemiology, biomarkers &amp; prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology</td>
<td>United States; secondary</td>
<td>3/3</td>
<td>525 participants with a history of at least four BCCs and/or cutaneous SCCs</td>
<td>Parallel; 25 000 U retinol (vitamin A) versus placebo per day</td>
<td>BCC or cutaneous SCC; incidence</td>
<td>Presented using the proportion of occurrence; retinol group: 32.8%; placebo group: 32.8%</td>
<td>Placebo: 41/174; vitamin A: 41/173</td>
</tr>
<tr>
<td>10 Skin Cancer Prevention Study, 1997 [21]</td>
<td>Cancer epidemiology, biomarkers &amp; prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology</td>
<td>United States; primary and secondary</td>
<td>5/5</td>
<td>2297 subjects with a history of at least 10 actinic keratoses and at most two prior skin cancers (the SKICAP-AK: Skin Cancer Prevention Studies-Actinic Keratosis)</td>
<td>Parallel; 25 000 IU retinol versus placebo per day</td>
<td>BCC or SCC; incidence</td>
<td>SCC: 0.74 (0.56–0.99); BCC: 1.06 (0.86–1.32)</td>
<td>Placebo: 40/1140; vitamin A: 378/1137</td>
</tr>
<tr>
<td>11 Clark, 1998 [22]</td>
<td>British Journal of Urology</td>
<td>United States; secondary</td>
<td>4.5/6.5</td>
<td>974 men with a history of either a basal cell or a squamous cell carcinoma</td>
<td>Parallel; 200 µg of selenium versus placebo per day</td>
<td>Prostate cancer; incidence</td>
<td>0.37 (P = 0.002)</td>
<td>Placebo: 35/495; selenium: 13/479</td>
</tr>
<tr>
<td>12 ATBC, 1998 [23]</td>
<td>Journal of the National Cancer Institute</td>
<td>Finland; primary</td>
<td>6.1/6.1</td>
<td>29 133 male smokers (ATBC)</td>
<td>2 × 2, 50 mg of alpha-tocopherol (vitamin E), 20 mg of beta-carotene, and placebo per day</td>
<td>Prostate cancer; incidence</td>
<td>Alpha-tocopherol: 32% (~47% to ~12%); beta-carotene: 23% (~4% to 59%)</td>
<td>Placebo: 67/7287; antioxidants (vitamin E and/or beta-carotene): 181/21 846</td>
</tr>
<tr>
<td>Study name</td>
<td>Journal</td>
<td>Country; type of prevention</td>
<td>Duration of supplement treatment/follow-up period (years)</td>
<td>Population (project name)</td>
<td>Design; interventions</td>
<td>Type of cancer; outcome measure</td>
<td>RR (95% CI)</td>
<td>No. of cancer/no. of participants in each group</td>
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<td>13 WHS, 1999 [24]</td>
<td><em>Journal of the National Cancer Institute</em></td>
<td>United States; primary</td>
<td>2.1/4.1</td>
<td>39 876 apparently healthy USA women aged at least 45 years (WHS)</td>
<td>2 × 2; 600 IU of natural-source vitamin E, aspirin, and placebo on alternate days</td>
<td>All cancers; incidence</td>
<td>1.03 (0.89–1.18)</td>
<td>Placebo: 369/19 937; vitamin E: 378/19 939</td>
</tr>
<tr>
<td>14 ATBC, 1999 [25]</td>
<td><em>Cancer</em></td>
<td>Finland; primary</td>
<td>6.1/6.1</td>
<td>29 133 male smokers (ATBC)</td>
<td>2 × 2; 50 mg of alpha-tocopherol (vitamin E), 20 mg of beta-carotene, and placebo per day</td>
<td>Pancreatic carcinoma; incidence</td>
<td>Alpha-tocopherol: 34% (−12% to 105%); beta-carotene: −25% (−51% to 14%)</td>
<td>Placebo: 26/7287; antioxidants (vitamin E and/or beta-carotene): 63/21 846</td>
</tr>
<tr>
<td>15 ATBC, 2000 [26]</td>
<td><em>Cancer causes &amp; control: CCC</em></td>
<td>Finland; primary</td>
<td>6.1/6.1</td>
<td>29 133 male smokers (ATBC)</td>
<td>2 × 2; 50 mg of alpha-tocopherol (vitamin E), 20 mg of beta-carotene, and placebo per day</td>
<td>Colorectal cancer; incidence</td>
<td>Alpha-tocopherol: 0.78 (0.55–1.09); beta-carotene: 1.05 (0.75–1.47)</td>
<td>Placebo: 37/7287; antioxidants (vitamin E and/or beta-carotene): 98/21 846</td>
</tr>
<tr>
<td>16 PHS, 2000 [27]</td>
<td><em>Archives of dermatology</em></td>
<td>United States; primary</td>
<td>12/12</td>
<td>22 071 male physicians (PHS)</td>
<td>Parallel; 50 mg of beta-carotene versus placebo on alternate days</td>
<td>Nonmelanoma skin cancer; incidence</td>
<td>0.98 (0.92–1.05)</td>
<td>Placebo: 1821/10 945; beta-carotene: 1786/10 941</td>
</tr>
<tr>
<td>17 PHS, 2000 [28]</td>
<td><em>Cancer causes &amp; control: CCC</em></td>
<td>United States; primary</td>
<td>12.9/12.9</td>
<td>22 071 male physicians (PHS)</td>
<td>Parallel; 50 mg of beta-carotene versus placebo on alternate days</td>
<td>Malignant neoplasm excluding nonmelanoma skin cancer; incidence</td>
<td>1.00 (0.9–1.0)</td>
<td>Placebo: 1535/11 035; beta-carotene: 1314/11 036</td>
</tr>
<tr>
<td>18 EUROSCAN, 2000 [29]</td>
<td><em>Journal of the National Cancer Institute</em></td>
<td>European Union; secondary</td>
<td>2/4.1</td>
<td>2592 patients with head and neck cancer (The EUROSCAN study)</td>
<td>2 × 2; 300 000 IU for 1 year followed by 150 000 IU for a second year of retinyl palmitate (vitamin A), 600 mg of NAC, and placebo per day</td>
<td>Recurrence, distant metastasis, and second primary tumor; incidence</td>
<td>No statistically significant difference observed</td>
<td>Control (no drugs): 183/641; antioxidant (vitamin A and/or NAC): 401/1290</td>
</tr>
<tr>
<td>Study name</td>
<td>Journal</td>
<td>Country; type of prevention</td>
<td>Duration of supplement treatment/follow-up period (years)</td>
<td>Population (project name)</td>
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<tr>
<td>19 ATBC, 2000 [30]</td>
<td>Cancer causes &amp; control: CCC</td>
<td>Finland; primary</td>
<td>6.1/6.1</td>
<td>29 133 male smokers (ATBC)</td>
<td>2 × 2; 50 mg of alpha-tocopherol (vitamin E), 20 mg of beta-carotene, and placebo per day</td>
<td>Urinary tract cancer; incidence</td>
<td>Urothelial cancer (bladder, renal pelvis, and ureter); alpha-tocopherol group: 1.1 (0.8–1.5); beta-carotene group: 1.0 (0.7–1.3); Renal cell cancer: alpha-tocopherol group: 1.1 (0.7–1.6); beta-carotene: 0.8 (0.6–1.3)</td>
<td>Placebo: 64/7287; antioxidants (vitamin E and/or beta-carotene): 207/21 846</td>
</tr>
<tr>
<td>20 Mayne, 2001 [31]</td>
<td>Cancer research</td>
<td>United States; secondary</td>
<td>4.3/4.3</td>
<td>264 patients who had been curatively treated for a recent early-stage squamous cell carcinoma of the head and neck</td>
<td>Parallel; 50 mg of beta-carotene versus placebo per day</td>
<td>Head and neck cancer; incidence</td>
<td>0.90 (0.56–1.45)</td>
<td>Placebo: 34/129; beta-carotene: 33/135</td>
</tr>
<tr>
<td>21 HPSCG, 2002 [32]</td>
<td>Cancer</td>
<td>UK; primary</td>
<td>5/5</td>
<td>20 536 adults with coronary disease, other occlusive arterial disease, or diabetes</td>
<td>Parallel; A combination of 600 mg vitamin E, 250 mg vitamin C, and 20 mg beta-carotene versus placebo per day</td>
<td>All cancers; incidence</td>
<td>Any cancer except nonmelanoma skin: 0.98 (0.89–1.08); nonmelanoma skin cancer: vitamin group (2.156); placebo group (2.2%)</td>
<td>Placebo: 1045/10 267; antioxidants (vitamin E, vitamin C, and beta-carotene): 1017/10 269</td>
</tr>
<tr>
<td>22 NPCT, 2002 [33]</td>
<td>Cancer epidemiology, biomarkers &amp; prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology</td>
<td>United States; secondary</td>
<td>7/7 (about)</td>
<td>1312 patients with a history of basal cell or squamous cell carcinomas of the skin (NPCT)</td>
<td>Parallel; 200 μg of selenium versus placebo per day</td>
<td>All cancers; incidence</td>
<td>0.75 (0.56–0.97) (adjusted for age, gender, and smoking at randomization)</td>
<td>Placebo: 137/621; selenium: 105/629</td>
</tr>
<tr>
<td>23 ATBC, 2002 [34]</td>
<td>Cancer causes &amp; control: CCC</td>
<td>Finland; primary</td>
<td>6.1/6.1</td>
<td>29 133 male smokers (ATBC)</td>
<td>2 × 2; 50 mg of alpha-tocopherol (vitamin E), 20 mg of beta-carotene, and placebo per day</td>
<td>Gastric cancer; incidence</td>
<td>Alpha-tocopherol: 1.21 (0.85–1.74); beta-carotene: 1.26 (0.88–1.80)</td>
<td>Placebo: 24/7287; antioxidants (vitamin E and/or beta-carotene): 102/21 846</td>
</tr>
</tbody>
</table>
Table 1. (Continued)

<table>
<thead>
<tr>
<th>Study name</th>
<th>Journal</th>
<th>Country; type of prevention</th>
<th>Duration of supplement treatment/follow-up period (years)</th>
<th>Population (project name)</th>
<th>Design; interventions</th>
<th>Type of cancer; outcome measure</th>
<th>RR (95% CI)</th>
<th>No. of cancer/no. of participants in each group</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 IHNCSG, 2003 [35]</td>
<td>Oncology reports</td>
<td>Italy; secondary</td>
<td>3/5.1</td>
<td>214 patients with a radically treated stage I-II squamous head and neck tumors (IHNCSG)</td>
<td>Parallel, 75 mg of beta-carotene for 3-month cycles within 1-month intercycle intervals versus placebo per day</td>
<td>Relapse of the primary or second primary tumors; incidence</td>
<td>1.49 (0.58–4.66)</td>
<td>Control: 141/100; beta-carotene: 15/104</td>
</tr>
<tr>
<td>25 ATBC, 2003 [36]</td>
<td>JAMA the journal of the American Medical Association</td>
<td>Finland; primary</td>
<td>6.1/6.1</td>
<td>29 133 male smokers (ATBC)</td>
<td>Parallel, 400 IU of alpha-tocopherol (vitamin E) and 30 mg of beta-carotene versus placebo per day</td>
<td>Second primary cancer; incidence</td>
<td>0.88 (0.74–1.05)</td>
<td>Placebo: 551/7287; antioxidants (vitamin E and/or beta-carotene): 1719/21 846</td>
</tr>
<tr>
<td>26 Bairati, 2005 [37]</td>
<td>Journal of the National Cancer Institute</td>
<td>Canada; secondary</td>
<td>4.3/4.3</td>
<td>540 patients with stage I or II head and neck cancer treated by radiation therapy</td>
<td>Parallel, 2 x 2; 600 IU of natural-source vitamin E, aspirin, and placebo on alternate days</td>
<td>Total invasive cancer; incidence</td>
<td>1.01 (0.94–1.08)</td>
<td>Placebo: 1428/19 937; vitamin E: 1437/19 937</td>
</tr>
<tr>
<td>27 WHS, 2005 [38]</td>
<td>JAMA the journal of the American Medical Association</td>
<td>United States; primary</td>
<td>10.1/10.1</td>
<td>39 876 apparently healthy USA women aged at least 45 years (WHS)</td>
<td>Parallel, 400 IU of natural-source vitamin E versus placebo per day</td>
<td>All cancers; incidence</td>
<td>0.94 (0.84–1.06)</td>
<td>Placebo: 586/4780; vitamin E: 552/4761</td>
</tr>
<tr>
<td>28 HOPE, 2005 [39]</td>
<td>JAMA the journal of the American Medical Association</td>
<td>Canada; primary</td>
<td>7/7</td>
<td>9541 patients at least 55 years with vascular disease or diabetes (the initial HOPE trial)</td>
<td>Parallel; 400 IU of natural-source vitamin E versus placebo per day</td>
<td>Alpha-tocopherol: 0.88 (0.60–1.29)</td>
<td>Placebo: 54/2512; antioxidants (vitamin C, vitamin E, beta-carotene, and selenium): 49/2522</td>
<td></td>
</tr>
<tr>
<td>29 SUVIMAX, 2005 [40]</td>
<td>International journal of cancer: Journal international du cancer</td>
<td>Canada; primary</td>
<td>8/9</td>
<td>5141 men; 107 men among 5141 were withdrawn early (supplementation en vitamines et minéraux antioxydants: The SUVIMAX trial)</td>
<td>Parallel; A combination of 120 mg vitamin C, 30 mg alpha-tocopherol, 6 mg beta-carotene, 100 µg selenium, and 20 mg zinc versus placebo per day</td>
<td>Prostate cancer; incidence</td>
<td>0.88 (0.60–1.29)</td>
<td>Placebo: 54/2512; antioxidants (vitamin C, vitamin E, beta-carotene, and selenium): 49/2522</td>
</tr>
<tr>
<td>30 ATBC, 2007 [41]</td>
<td>Cancer</td>
<td>Finland; primary</td>
<td>6.1/6.1</td>
<td>29 133 male smokers (ATBC)</td>
<td>Parallel; 2 x 2; 50 mg of alpha-tocopherol (vitamin E), 20 mg of beta-carotene, and placebo per day</td>
<td>Upper aerodigestive tract cancer; incidence</td>
<td>0.81 (0.67–1.00)</td>
<td>Placebo: 42/2787; antioxidants (vitamin E and/or beta-carotene): 103/21 846</td>
</tr>
<tr>
<td>31 Dreno, 2007 [42]</td>
<td>European journal of dermatology: EJD</td>
<td>France; primary</td>
<td>3/5</td>
<td>184 recent organ transplant recipients</td>
<td>Parallel; 200 µg of selenium versus placebo per day</td>
<td>Skin cancer; incidence</td>
<td>3.08 (P = 0.15)</td>
<td>Placebo: 239; selenium: 6/91</td>
</tr>
</tbody>
</table>

RR, relative risk; CI, confidence interval; HBV Ag, hepatitis B virus antigen; NIT, nutrition intervention trial; ATBC, Alpha-Tocopherol Beta-carotene Cancer Prevention Study; BCCs, basal cell carcinomas; SCMs, squamous cell carcinomas; WHS, Women’s Health Study; PHS, Physicians’ Health Study; NAC, N-acetylcysteine; HPSCG, Heart Protection Study Collaborative Group; IHNCSG, Italian Head and Neck Chemoprevention Study Group; HOPE, Heart Outcomes Prevention Evaluation; CARET, beta-carotene and retinol efficacy trial; EUROSCAN; European study on chemoprevention with vitamin A and N-acetylcysteine; SUVIMAX, supplementation en vitamines et minéraux antioxydants.
studies ($I^2 = 46.6\%$). There was no evidence of publication bias in the selected studies (Egger’s test, $P$ for bias $= 0.98$; Begg’s funnel plot was symmetrical).

**subgroup analyses by type of prevention**

In the 12 studies on primary prevention trials, administration of antioxidant supplements had no significant effect on cancer prevention (RR 1.00; 95% CI 0.97–1.04; fixed-effects model) (Figure 3). Even in the nine studies on secondary prevention trials, no significant effect was observed (RR 0.97; 95% CI 0.83–1.13; random-effects model) (Figure 3).

**subgroup analyses by type of antioxidant administered singly**

None of the antioxidant supplements had any significant influence on cancer prevention: beta-carotene (RR 1.01; 95% CI 0.96–1.07; $n = 5$; fixed-effects model), vitamin A (RR 0.98; 95% CI 0.90–1.08; $n = 4$; fixed-effects model), vitamin E (RR 0.97; 95% CI 0.90–1.07; $n = 5$; fixed-effects model), vitamin C (RR 0.99; 95% CI 0.96–1.02; $n = 4$; fixed-effects model), and selenium (RR 0.98; 95% CI 0.90–1.08; $n = 4$; fixed-effects model).

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**Figure 3.** Effects of antioxidant supplements versus placebo or no intervention on cancer incidence by type of prevention. *fixed-effects model; RR, relative risk; CI, confidence interval.
1.02; 95% CI 0.90–1.16; n = 4; random-effects model), and selenium (RR 0.62; 95% CI 0.36–1.08; n = 5; random-effects model) (Figure 4).

**subgroup analyses by type of cancer**

Table 2 shows the results of the subgroup analyses by type of cancer. Antioxidant supplements had no preventive effect on the following 11 of the 13 types of cancers included in this analysis: skin cancer, colorectal cancer, head and neck cancer, lung cancer, prostate cancer, esophageal cancer, breast cancer, stomach cancer, lymphoma and leukemia, renal cancer, and brain tumor. However, the use of antioxidant supplements significantly increased the risk of bladder cancer (RR 1.52; 95% CI 1.06–2.17; n = 4; fixed-effects model) (Figure 4).

**subgroup analyses by methodological quality**

After referring to previously published reports [7, 8], 12 studies [13, 15, 19, 21, 27, 32, 33, 36–40] of the 22 were classified as having a high methodological quality. The remaining 10 studies had one or more inadequate components. No significant preventive effects of the antioxidant supplements were found in studies of either high (RR 1.00; 95% CI 0.96–1.03; fixed-effects model) or low (RR 0.92; 95% CI 0.70–1.20; random-effects model) methodological quality.

Meanwhile, when we assessed the methodological quality of the studies on the basis of what is stated in those articles without getting additional information on the study method by direct contact with those authors, only three studies [13, 37, 39] were classified as having a high methodological quality.

Likewise, no significant effects were found in studies of either high (OR 0.99; 95% CI 0.92–1.07; n = 3; fixed-effects model) or low (OR 0.99; 95% CI 0.93–1.06; n = 19; random-effects model) methodological quality.

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**Table 2. Effects of antioxidant supplements versus placebo or no intervention on cancer incidence by type of cancer**

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>No. of studies</th>
<th>Summary RR (95% CI)</th>
<th>Heterogeneity, I² (%)</th>
<th>Model used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin cancer</td>
<td>9</td>
<td>0.98 (0.91–1.05)</td>
<td>0.0</td>
<td>Fixed effects</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>7</td>
<td>0.97 (0.84–1.12)</td>
<td>21.7</td>
<td>Fixed effects</td>
</tr>
<tr>
<td>Head and neck cancer</td>
<td>7</td>
<td>0.87 (0.68–1.13)</td>
<td>0.0</td>
<td>Fixed effects</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>7</td>
<td>1.00 (0.83–1.20)</td>
<td>62.9</td>
<td>Random effects</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>7</td>
<td>0.84 (0.69–1.02)</td>
<td>57.8</td>
<td>Random effects</td>
</tr>
<tr>
<td>Esophageal cancer</td>
<td>5</td>
<td>1.01 (0.81–1.26)</td>
<td>0.0</td>
<td>Fixed effects</td>
</tr>
<tr>
<td>Bladder cancer²</td>
<td>4</td>
<td>1.52 (1.06–2.17)</td>
<td>0.0</td>
<td>Fixed effects</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>4</td>
<td>1.00 (0.90–1.11)</td>
<td>0.0</td>
<td>Fixed effects</td>
</tr>
<tr>
<td>Stomach cancer</td>
<td>3</td>
<td>0.99 (0.79–1.24)</td>
<td>43.5</td>
<td>Fixed effects</td>
</tr>
<tr>
<td>Lymphoma and leukemia</td>
<td>3</td>
<td>0.98 (0.81–1.20)</td>
<td>0.0</td>
<td>Fixed effects</td>
</tr>
<tr>
<td>Renal cancer</td>
<td>2</td>
<td>0.95 (0.62–1.46)</td>
<td>0.0</td>
<td>Fixed effects</td>
</tr>
<tr>
<td>Brain tumor</td>
<td>1</td>
<td>0.76 (0.45–1.27)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Thyroid cancer</td>
<td>1</td>
<td>9.50 (2.21–40.77)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

²Statistically significant.
RR, relative risk; CI, confidence interval.

**Figure 4.** Effects of antioxidant supplements versus placebo or no intervention on cancer incidence by type of antioxidant. *fixed-effects model; brandom-effects model; RR, relative risk; CI, confidence interval.
In our meta-analysis of randomized controlled trials published over >20 years, we found that there was no overall association between the consumption of antioxidant supplements and cancer risk. Further, subgroup analyses according to the type of prevention, type of antioxidant, and methodological quality of the studies also showed no preventive effect of antioxidant supplements on cancer. Our findings were consistent with those of previously published meta-analyses that evaluated the effect of antioxidant supplements on the prevention of lung cancer [101] and gastrointestinal cancers [8] and on the prevention of cancers and chronic diseases [6] in randomized controlled trials.

However, our findings were inconsistent with those of previous experimental studies and previous epidemiological studies regarding the association between the intake of fruits and vegetables rich in antioxidant substances or the dietary intake of antioxidant substances and the risk of cancer [1–5]. This implies that there is a discrepancy in findings between experimental studies on animal or cancer cell lines and clinical trials for human studies with regard to the association between antioxidant substances (antioxidant supplements or fruits and vegetables rich in antioxidant substances) and the risk of cancer. The findings of experimental studies on the effects or actions of antioxidant substances should not be directly applied to humans because these substances might promote toxic effects or enhance carcinogenesis under clinical circumstances. For example, even though experimental studies showed that beta-carotene is anticarcinogenic and might play a potential protective role against cancer initiation [102], it may act as a prooxidant in the presence of chronic oxidative stress such as that resulting from smoking; this may induce the oxidation of beta-carotene and DNA oxidative damage and eventually lead to lung cancer [103, 104]. Such discrepancy is also observed between the results of observational epidemiologic studies and randomized controlled trials. Retrospective case–control studies, which investigate the relationship between diet and the risk of cancer, are susceptible to two potential biases, i.e. recall and selection: cancer patients might recall their diet differently from healthy controls, and healthy controls tend to report a healthy diet [105, 106]. Although cohort studies are less biased than case–control studies and indicate a relationship between antioxidant supplements and the risk of cancer, they are unable to confirm the causality [5]. The causality can be confirmed by repetitive, larger intervention trials (i.e. randomized controlled trials). Further, it should be noted that the consumption of antioxidant supplements in the randomized controlled trials differs from the intake of fruits and vegetables or the dietary intake of antioxidants in epidemiological studies in that the combination of several antioxidants and other micronutrients in foods or vegetables could cause unexpected consequences, and the assessment of the dietary intake for antioxidant substances could suffer from a lack of precision due to information bias or lack of validity of the questionnaire [5].

In our study, we report that the use of antioxidant supplements increased the risk of bladder cancer. We are unable to confirm this relationship because the number of trials published is not sufficient to form a conclusion. In particular, further primary prevention trials are required to study the effect of antioxidant supplements on bladder cancer because three of the four studies on cancer included in this analysis were secondary prevention trials.

Our study indicated that antioxidant supplements had no effects on either primary or secondary prevention of cancer, i.e. there was no specific difference in the effects of antioxidants between them. We are unable to evaluate the effect of vitamin C on the risk of cancer because there was no published study on vitamin C administered alone, although there were three studies [15, 32, 40] on vitamin C administered in combination with other antioxidants.

With regard to the assessment of the methodological quality of the studies, there was a remarkable discrepancy between our classification of the studies as having high or low methodological quality and that in other published reports [7, 8]. For example, the other published reports classified nine studies as studies with high methodological quality, while we classified these studies as having low methodological quality because they did not adequately report the generation of the allocation sequence (computer-generated random numbers or similar methods) and merely stated that the sequences were ‘randomly assigned’ or that ‘randomization was carried out.’ The authors of previously published meta-analyses stated that they obtained additional information on the actual design, including the randomization methods, from the authors of the individual study included in their analyses. We insist that the methodological quality of studies should be assessed on the basis of what is stated in those articles without getting additional information on the study method by direct contact with those authors.

There are several possible limitations of our study. First, as described earlier, we are unable to clearly explain why, unlike the findings of experimental and epidemiologic studies, our study revealed that antioxidant supplements had no preventive effect on cancer. However, our findings at least imply that those of the experimental and epidemiologic studies should be interpreted cautiously and evaluated clinically.

Secondly, our study included only synthetic antioxidants. Therefore, our findings are not applicable to the effects of fruits and vegetables. In addition, this might be a possible explanation for the discrepancy in the findings between randomized trials using synthetic antioxidants and epidemiologic studies such as case–control or cohort studies using fruits and vegetables. In other words, we think that there might be a difference between the biological activities of a synthetic antioxidant and those of an individual constituent in fruits or vegetables or whole fruits or vegetables. Even though the protective role of the individual constituent against the development of cancer was not identified in the randomized clinical trials, it is possible that the interactions and complex biological mechanisms of multiple constituents of fruits and vegetables, including antioxidants and various phytochemicals, result in the preventive effects on cancer.

In summary, we found no overall preventive effect of antioxidant supplements on cancer in our meta-analysis of randomized controlled trials published over the past 20 years.
Our findings are consistent with the other published meta-analyses and systematic reviews [6–10]. There is no clinical evidence to support the use of antioxidant supplements for primary and secondary prevention of cancer. Furthermore, even though the current study did not investigate the association between each type of antioxidant supplement and each type of cancer, the recent report from WCRF/AICR indicated that the evidence that beta-carotene supplements cause lung cancer in current smokers is convincing: that is, the use of some antioxidant supplements might be harmful. Considering that many people consume antioxidant supplements in order to improve their health and prevent cancer, we think that these findings may play a certain role in modifying these health behaviors. The potential effects (either beneficial or detrimental) of antioxidant supplements on human health, particularly in relation to cancer risk, should not be overemphasized. Our findings and explanations should be explored in future research.

acknowledgements
Contributorship statement and guarantor: S-KM was responsible for the initial plan, study design, and statistical analysis and for conducting the study. S-KM and YK were responsible for data collection, data extraction, data analysis and for conducting the study. S-KM and YK were responsible for the initial plan, study design, and statistical analysis. WKB was responsible for data interpretation and manuscript drafting. S-KM is the guarantor for this paper and has full responsibility for this study.

Group name: The Korean Meta-analysis Study Group.

references