Beta-carotene supplementation and cancer risk: a systematic review and metaanalysis of randomized controlled trials

CRD summary
The review found that beta-carotene supplementation was not protective against primary cancer and may increase risk of lung and stomach cancers in smokers and asbestos workers and at higher doses. The lack of assessment of study validity and potential confounding from use of multiple antioxidants in the primary studies mean that the authors’ conclusions require cautious interpretation.

Authors' objectives
To evaluate the relationship between beta-carotene supplementation and cancer risk.

Searching
PubMed was searched to April 2009. Search terms were reported. Reference lists of relevant articles were checked. There were no language restrictions.

Study selection
Randomised controlled trials (RCTs) of supplementation with beta-carotene (alone or with other antioxidants) were eligible for inclusion. Studies were required to report the incidence of primary cancer at the end of the intervention (with an exception made for one study that reported data after a further two years’ follow-up)

The mean age of participants in the included studies ranged from 47 to 60 years (where stated). Some studies were limited to smokers and asbestos workers; in most studies 30% to 76% of participants were former or current smokers. The proportion of female participants varied widely across studies (range zero to 100%). Beta-carotene was most commonly given at a daily dose of 20mg to 30mg and usually in combination with other antioxidants (such as vitamins A, E and C). Outcomes reported in the review included total and site-specific cancer incidence. Follow-up ranged from two to 13 years.

Two reviewers independently selected the studies. Disagreements were resolved by discussion.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
The relative risk (RR) with 95% confidence interval (CI) of cancer was extracted or calculated for each study. Weighted data were used where appropriate.

Two reviewers independently extracted data and contacted primary study authors for more information as required.

Methods of synthesis
Studies were combined to calculate pooled relative risks and 95% CIs. Heterogeneity was assessed using the Q test. Fixed-effect models were used unless there was significant heterogeneity, in which case random-effects models were used.

Subgroup analyses investigated the impact of beta-carotene dose (low was 6mg to 15mg and high was 20mg to 30mg), participant characteristics and of combining beta-carotene with other antioxidants.

Results of the review
Nine RCTs (13 articles) were included (n=182,323, range 1,621 to 39,876).

There was no statistically significant difference between the beta-carotene group and the placebo group in the incidence of all-site cancer (eight RCTs) and of stomach (seven RCTs), pancreas (four RCTs), colon-rectum (seven RCTs), prostate (five RCTs), breast (four RCTs) and skin (six RCTs) cancers. The risk of lung cancer was significantly higher in the beta-carotene than the placebo group (RR 1.13, 95% CI 1.04 to 1.24; eight RCTs). There was no statistically significant heterogeneity for any of these analyses.

In subgroup analyses, among smokers and asbestos workers beta-carotene significantly increased the risk of all-site cancer (RR 1.08, 95% CI 1.01 to 1.15; two RCTs), lung cancer (RR 1.20, 95% CI 1.07 to 1.34; two RCTs) and stomach cancer (RR 1.54, 95% CI 1.08 to 2.19; one RCT). Beta-carotene at high doses significantly increased the risk of lung cancer (RR 1.16, 95% CI 1.06 to 1.27; six RCTs) and stomach cancer (RR 1.54, 95% CI 1.08 to 2.19; four RCTs) cancer. At low doses beta-carotene significantly decreased the risk of stomach cancer (RR 0.84, 95% CI 0.71 to 1.00; two RCTs).

Other findings were reported in the review.

**Authors’ conclusions**

Beta-carotene supplementation was not protective against primary cancer and may increase the risk of lung and stomach cancers in smokers and asbestos workers and at higher doses.

**CRD commentary**

The objectives and inclusion criteria of the review were clear. The search was not limited by language, but was restricted to a single database and no apparent specific efforts were made to retrieve unpublished studies; therefore, it was possible that some studies were missed. It appeared that publication bias was not formally assessed. Steps were taken to minimise risks of reviewer bias and error by having more than one reviewer independently select studies and extract data. It appeared that study validity was not assessed. This made it difficult to determine the reliability of the results.

Appropriate statistical techniques were used to combine the studies and assess statistical heterogeneity. Findings for most analyses were relatively homogeneous. The authors noted a number of possible sources of bias. These included the use in most studies of other antioxidants in addition to beta-carotene, the small number of RCTs for some analyses and problems determining the significance of subgroup analyses.

The lack of assessment of study validity and potential confounding from use of multiple antioxidants in the primary studies mean that the authors’ conclusions require cautious interpretation.

**Implications of the review for practice and research**

**Practice:** The authors stated that regular use of beta-carotene supplements should not be recommended for cancer prevention.

**Research:** The authors stated that studies were required to clarify the effects of beta-carotene on risk of melanoma and prostate cancer in different populations.

**Funding**

Not stated.

**Bibliographic details**

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.