Carotenoids and the risk of developing lung cancer: a systematic review
Guallar E, Alberg A J

CRD summary
The authors concluded that β-carotene supplementation was not associated with a reduced risk of developing lung cancer. Dietary or serum carotenoids were associated with a small and generally non-significant reduction in lung cancer risk. The authors' cautious conclusions followed the data presented, however, given the lack of a formal validity assessment, the reliability of the conclusions is unclear.

Authors' objectives
To investigate the association between carotenoid intake and the development of lung cancer as part of a wider project funded by the World Cancer Research Fund (WCRF) (see Publications of related interest).

Searching
PubMed, EMBASE, Pascal, ISI Web of Science, NIAAA (National Institute on Alcohol Abuse and Alcoholism) Alcohol and Alcohol Problems Science, The Cochrane Library Biological Abstracts, CINAHL, Latin American and Caribbean Center on Health Sciences Information, Index Medicus for the WHO Eastern Mediterranean Region and Index Medicus for South East Asian Region were searched for published articles in any language. The search was carried out up to September 2007 for Pubmed and to April 2006 for all other databases. Search terms were reported. The bibliographies of selected studies and of studies included in an earlier WCRF report (see Publications of related interest) were handsearched.

Study selection
Randomised controlled trials (RCT) investigating carotenoid supplements or prospective studies investigating carotenoids in the development of lung cancer were eligible for inclusion. Studies that did not measure association or variability or that did not provide data enabling this calculation were excluded. Only studies that adjusted for cigarette smoking status were eligible for inclusion. Case-series and case reports were excluded.

RCTs included in the review investigated the association between supplementation with β-carotene monotherapy or in combination with retinol or selenium plus α-tocopherol (doses ranging from 20 mg/d to 30 mg/d) and a diagnosis of lung cancer in both high-risk only patients (smokers, asbestos workers) or general populations (healthy adults, health professionals) over a period of 2.1 to 15 years. Prospective cohort studies included in the review investigated the association between dietary carotenoid intake, as measured by food-frequency questionnaire, dietary history questionnaire, interview or dietary recall or serum carotenoid levels (as measured by high performance liquid chromatography), and incidence of or mortality from lung cancer over a period ranging from four years to 25 years. The populations for the prospective studies were not described. Where stated, included studies were mixed and single sex; a large number were male only. Participants’ mean age ranged from 49 years to 75 years. Studies were conducted in 10 different countries, most in the USA.

Studies were independently selected for review by two reviewers.

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

Data extraction
Relative risks (RR) and their 95% confidence intervals (CI) were extracted from each study or calculated from available data. Where more than one RR was available, the RR adjusted for the most covariates was abstracted. Two reviewers independently extracted the data and entered them into an electronic database designed by the World Cancer Research Fund. Disagreements were resolved by consensus.

Methods of synthesis
Pooled relative risks were calculated using the DerSimonian and Laird random-effects model weighted by inverse variance. Heterogeneity was assessed using the Q and the $I^2$ statistic. The meta-analysis of RCTs was based on intention-to-treat principles. For prospective studies of dietary intake or serum concentrations, the highest and lowest categories were compared. For prospective studies of dietary intake, subgroup analyses were conducted for specific types of carotenoids and for smoking status. Sensitivity analyses were conducted excluding each study in turn. Publication bias was assessed using funnel plots. Where studies reported three or more exposure categories, dose response RRs were calculated using the method of Greenland and Longnecker.

**Results of the review**

Thirty-seven studies were included for review (n=1,119,519): six RCTs (n=103,316); 18 prospective cohort studies (n=420,834); one case cohort (n=56,837); and 12 nested case-control studies (n=538,532).

**RCTs (six studies, n=103, 316)**

β-carotene was not associated with a significant change in the risk of developing lung cancer compared to placebo (three studies, n=83,080). In placebo-controlled studies in high risk populations, β-carotene was associated with a significantly greater risk of developing lung cancer in smokers compared to placebo (RR 1.17, 95% CI: 1.02, 1.34; one study, n=29,133) and β-carotene plus retinol was associated with a significantly greater risk of developing lung cancer in asbestos exposed workers and heavy smokers compared to placebo (RR 1.36, 95% CI: 1.07, 1.72; one study n=18,314).

**Prospective studies**

Increased dietary carotenoid intake was associated with a reduced risk of developing or dying from lung cancer (RR 0.79, 95% CI: 0.72, 0.87; eight studies, n=247,706), with a two per cent reduction in risk for an increase of 1000 μg/d intake (RR 0.98, 95% CI: 0.97, 0.99; four studies n=153,272). Dietary intake of β-cryptoxanthin (RR 0.80, 95% CI: 0.72, 0.89; eight studies, n=350,378) and lycopene (RR 0.86, 95% CI: 0.77, 0.97; nine studies n=392,215) were associated with a significant reduction in the risk of developing lung cancer.

There was no significant association between dietary intake of other specific carotenoids and lung cancer risk. When serum carotenoid levels were measured, only lycopene was associated with a significant reduction in risk of lung cancer (RR 0.71, 95% CI 0.51, 0.98; four studies, n=78,982), with an 18 per cent reduction in risk for an increase of 0.05 mmol/L (RR 0.82, 95% CI 0.68, 0.98; one study, n=39,242). There was no evidence of statistical heterogeneity for any of the above outcomes.

**Authors' conclusions**

β-carotene supplementation was not associated with a reduced risk of developing lung cancer. Prospective studies of dietary or serum carotenoids show an inverse relationship between carotenoid and lung cancer risk. However, these associations are small, generally non-significant and may be an artefact of the carotenoids' marker of a healthier lifestyle.

**CRD commentary**

The review addressed a clear question. Inclusion criteria for studies were well defined. However, inclusion criteria for intervention and outcomes were broad and were not defined for participants. Several relevant databases were searched for articles in any language, thereby reducing the risk of language bias. The search was restricted to published articles, so the possibility of publication bias could not be ruled out. Appropriate steps were taken in the study selection and data extraction processes to minimise the risk of reviewer error and bias. However, a validity assessment did not appear to have been carried out, so it was not possible to ascertain the quality of the included studies and, therefore, the reliability of the data. Appropriate methods were used to pool the studies. Statistical heterogeneity was assessed. However, studies measuring incidence and mortality of lung cancer may have been better treated separately. The authors' cautious conclusions followed the data presented, but given the lack of a formal validity assessment, the reliability of the conclusions is unclear.

**Implications of the review for practice and research**
Practice: The authors did not state any implications for practice.

Research: The authors did not state any implications for research.

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