Beta Carotene as a Chemopreventative

Carcinogenesis. 2008 Nov;29(11):2153-61. Epub 2008 Jul 16.

The sensitivity to beta-carotene growth-inhibitory and proapoptotic effects is regulated by caveolin-1 expression in human colon and prostate cancer cells.

Palozza P, **Sestito R**, **Picci N**, **Lanza P**, **Monego G**, **Ranelletti FO**.

Institute of General Pathology, Catholic University School of Medicine, Largo F. Vito 1, Rome 00168, Italy. p.palozza@rm.unicatt.it

Although several mechanisms have been proposed to explain the putative role of beta-carotene in cancer, no studies have investigated a possible influence of beta-carotene on caveolin-1 (cav-1) pathway, an important intracellular signaling deregulated in cancer. Here, different human colon and prostate cancer cell lines, expressing (HCT-116, PC-3 cells) or not (Caco-2, LNCaP cells) cav-1, were treated with varying concentrations of beta-carotene (0.5-30 muM) for different periods of time (3-72 h) and the effects on cell growth were investigated. The results of this study show that (i) beta-carotene acted as a growth-inhibitory agent in cav-1-positive cells, but not in cav-1-negative cells; (ii) in cav-1-positive cells, the carotenoid downregulated in a dose- and time-dependent manner the expression of cav-1 protein and messenger RNA levels and inhibited AKT phosphorylation which, in turn, stimulated apoptosis by increasing the expression of beta-catenin and c-myc and the activity of caspases-3, -7, -8 and -9; when the carotenoid was removed from culture medium, a progressive increase in cell growth was observed with respect to beta-carotene-treated cells and (iii) the transfection of cav-1 in cav-1-negative cells increased cell sensitivity to beta-carotene by inducing apoptosis. This effect was accompanied by a reduction of both cav-1 and AKT phosphorylation and by an increase of c-myc and beta-catenin expression. Silencing of c-Myc attenuated beta-carotene-induced apoptosis and beta-catenin expression. All together, these data suggest that the modulation of cav-1 pathway by beta-carotene could be a novel mechanism by which the carotenoid acts as a potent growth-inhibitory agent in cancer cells.

PMID: 18635524 [PubMed - indexed for MEDLINE]

J Natl Cancer Inst. 2006 Feb 15;98(4):245-54.

Comment in:

- J Natl Cancer Inst. 2006 Feb 15;98(4):225-7.

Supplemental and dietary vitamin E, beta-carotene, and vitamin C intakes and prostate cancer risk.

Kirsh VA, **Hayes RB**, **Mayne ST**, **Chatterjee N**, **Subar AF**, **Dixon LB**, **Albanes D**, **Andriole GL**, **Urban DA**, **Peters U**; **PLCO Trial**.

Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, DHHS, Bethesda, MD 20892, USA.

BACKGROUND: We evaluated the association between intake of these micronutrient antioxidants from foods and supplements and the risk of prostate cancer among men in the screening arm of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. At baseline, trial participants completed a 137-item food frequency questionnaire that included detailed questions on 12 individual supplements. Cox proportional hazards models were used to estimate relative risks (RRs) and 95% confidence intervals (CIs). All statistical tests were two-sided. RESULTS: We identified 1338 cases of prostate cancer among 29 361 men during up to 8 years of follow-up. Overall, there was no association between prostate cancer risk and dietary or supplemental intake of vitamin E, beta-carotene, or vitamin C. However, among current and recent (i.e., within the previous 10 years) smokers, decreasing risks of advanced prostate cancer (i.e., Gleason score > or = 7 or stage III or IV) were associated with increasing dose (RR for > 400 IU/day versus none = 0.29, 95% CI = 0.12 to 0.68; Ptrend = .01) and duration (RR for > or = 10 years of use versus none = 0.30, 95% CI = 0.09 to 0.96; Ptrend = .01) of supplemental vitamin E use. Supplemental beta-carotene intake at a dose level of at least 2000 microg/day was associated with decreased prostate cancer risk in men with low (below the median of 4129 microg/day) dietary beta-carotene intake (RR = 0.52, 95% CI = 0.33 to 0.81). Among smokers, the age-adjusted rate of advanced prostate cancer was 492 per 100,000 person-years in those who did not take supplemental vitamin E, 153 per 100,000 person-years in those who took more than 400 IU/day of supplemental vitamin E, and 157 per 100,000 person-years in those who took supplemental vitamin E for 10 or more years. Among men with low dietary beta-carotene intake, the age-adjusted rate of prostate cancer was 1122 per 100,000 person-years in those who did not take supplemental beta-carotene, and 623 per 100,000 person-years in those who took at least 2000 microg/day of supplemental beta-carotene. CONCLUSIONS: Our results do not provide strong support for population-wide implementation of high-dose antioxidant supplementation for the prevention of prostate cancer. However, vitamin E supplementation in male smokers and beta-carotene supplementation in men with low dietary beta-carotene intakes were associated with reduced risk of this disease.

Publication Types:

- Multicenter Study
- Research Support, N.I.H., Extramural

Braz J Med Biol Res. 2006 Feb;39(2):203-10. Epub 2006 Feb 2.

Lycopene and beta-carotene protect in vivo iron-induced oxidative stress damage in rat prostate.

Matos HR, **Marques SA**, **Gomes OF**, **Silva AA**, **Heimann JC**, **Di Mascio P**, **Medeiros MH**.

Departamento de Fisiologia, Universidade Federal de Sergipe, São Cristóvão, SE, Brazil.

It has been suggested that iron overload may be carcinogenic. In the present study, we evaluated the effect of plasma and prostate carotenoid concentration on oxidative DNA damage in 12-week-old Wistar rats treated with intraperitoneal (ip) ferric nitrilotriacetate (Fe-NTA) (10 mg Fe/kg). Plasma beta-carotene and lycopene concentrations were measured as a function of time after ip injection of carotenoids (10 mg kg(-1) day(-1) beta-carotene or lycopene) in rats. The highest total plasma concentration was reached 3 and 6 h after ip injection of lycopene or beta-carotene, respectively. After 5 days of carotenoid treatment, lycopene and beta-carotene were present in the 0.10-0.51 nmol/g wet tissue range in the prostate. Using a sensitive method to detected 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodGuo) by HPLC/EC, the level of 8-oxodGuo in rat prostate DNA was significantly higher (6.3 +/- 0.6 residues/10(6) dGuo) 3 h after Fe-NTA injection compared with control rats (1.7 +/- 0.3 residues/10(6) dGuo). Rats supplemented with lycopene or beta-carotene for 5 days prior to Fe-NTA treatment showed a reduction of about 70% in 8-oxodGuo levels to almost control levels. Compared with control rats, the prostate of Fe-NTA-treated animals showed a 78% increase in malondialdehyde accumulation. Lycopene or beta-carotene pre-treatment almost completely prevented lipid damage. Epidemiological studies have suggested a lower risk of prostate cancer in men reporting a higher consumption of tomato products. However, before associating this effect with tomato sauce constituents, more information is required. The results described here may contribute to the understanding of the protective effects of carotenoids against iron-induced oxidative stress.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 16470307 [PubMed - indexed for MEDLINE]

Carcinogenesis. 2006 Jul;27(7):1410-9. Epub 2006 Jan 9.

Combined antioxidant (beta-carotene, alpha-tocopherol and ascorbic acid) supplementation increases the levels of lung retinoic acid and inhibits the activation of mitogen-activated protein kinase in the ferret lung cancer model.

Kim Y, **Chongviriyaphan N**, **Liu C**, **Russell RM**, **Wang XD**.

Nutrition and Cancer Biology Laboratory, Jean Mayer United States Department of Agriculture Human Nutrition Research Center on Aging at Tufts University, Boston, MA 02111, USA.

Interactions among beta-carotene (BC), alpha-tocopherol (AT) and ascorbic acid (AA) led to the hypothesis that using a combination of these antioxidants could be more beneficial than using a single antioxidant alone, particularly against smoke-related lung cancer. In this investigation, we have conducted an animal study to determine whether combined BC, AT and AA supplementation (AOX) protects against 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)-induced lung carcinogenesis in smoke-exposed (SM) ferrets. Ferrets were treated for 6 months in the following four groups: (i) control, (ii) SM + NNK, (iii) AOX and (iv) SM + NNK + AOX. Results showed that the combined AOX supplementation (i) prevented the SM + NNK-decreased lung concentrations of retinoic acid (RA) and BC; (ii) inhibited the SM + NNK-induced phosphorylation of Jun N-terminal kinase (JNK), extracellular-signal-regulated protein kinase (ERK) and proliferating cellular nuclear antigen proteins in the lungs of ferrets; and (iii) blocked the SM + NNK-induced up-regulation of total p53 and Bax proteins, as well as phosphorylated p53 in the lungs of ferrets. In addition, there were no lesions observed in the lung tissue of ferrets in the control and/or the AOX groups after 6 months of intervention, but combined AOX supplementation resulted in a trend toward lower incidence of both preneoplastic lung lesions and lung tumor formation in SM + NNK + AOX group of ferrets, as compared with the SM + NNK group alone. These data indicate that combined AOX supplementation could be a useful chemopreventive strategy against lung carcinogenesis through maintaining normal tissue levels of RA and inhibiting the activation of mitogen-activated protein kinase pathways, cell proliferation and phosphorylation of p53.

Publication Types:

- Research Support, N.I.H., Extramural
- Research Support, U.S. Gov't, Non-P.H.S.

PMID: 16401635 [PubMed - indexed for MEDLINE]

Beta Carotene as a Chemopreventative

Am J Clin Nutr. 2006 Jan;83(1):163-9.

Modification of lymphocyte DNA damage by carotenoid supplementation in postmenopausal women.

Zhao X, **Aldini G**, **Johnson EJ**, **Rasmussen H**, **Kraemer K**, **Woolf H**, **Musaeus N**, **Krinsky NI**, **Russell RM**, **Yeum KJ**.

Jean Mayer USDA-Human Nutrition Research Center on Aging, Tufts University, Boston, MA 02111, USA.

BACKGROUND: Oxidative stress has been implicated in the pathogenesis of chronic diseases related to aging such as cancer and cardiovascular disease. Carotenoids could be a part of a protective strategy to minimize oxidative damage in vulnerable populations, such as the elderly. OBJECTIVE: Our aim was to determine the protective effect of carotenoids against DNA damage. DESIGN: A randomized, double-blind, placebo-controlled intervention study was conducted. Thirty-seven healthy, nonsmoking postmenopausal women aged 50-70 y were randomly assigned to 1 of 5 groups and were instructed to consume a daily dose of mixed carotenoids (beta-carotene, lutein, and lycopene; 4 mg each), 12 mg of a single carotenoid (beta-carotene, lutein, or lycopene), or placebo for 56 d. Plasma carotenoid concentrations were analyzed by using HPLC, and lymphocyte DNA damage was measured by using a single-cell gel electrophoresis (comet) assay. RESULTS: At day 57, all carotenoid-supplemented groups showed significantly lower endogenous DNA damage than at baseline ($P < 0.01$), whereas the placebo group did not show any significant change. Significantly less ($P < 0.05$) endogenous DNA damage was found as early as day 15 in the mixed carotenoid ($P < 0.01$) and beta-carotene ($P < 0.05$) groups. CONCLUSIONS: The results indicate that carotenoid supplementation decreases DNA damage and that a combination of carotenoids (4 mg each of lutein, beta-carotene, and lycopene), an intake that can be achieved by diet, or a larger dose (12 mg) of individual carotenoids exerts protection against DNA damage.

Publication Types:

- Randomized Controlled Trial
- Research Support, Non-U.S. Gov't
- Research Support, U.S. Gov't, Non-P.H.S.

PMID: 16400064 [PubMed - indexed for MEDLINE]

Mol Aspects Med. 2005 Dec;26(6):459-516. Epub 2005 Nov 23.

Carotenoid actions and their relation to health and disease.

Krinsky NI, **Johnson EJ**.

Department of Biochemistry, School of Medicine, Tufts University, 136 Harrison Avenue, Boston, MA 02111-1837, USA. norman.krinsky@tufts.edu

Based on extensive epidemiological observation, fruits and vegetables that are a rich source of carotenoids are thought to provide health benefits by decreasing the risk of various diseases, particularly certain cancers and eye diseases. The carotenoids that have been most studied in this regard are beta-carotene, lycopene, lutein and zeaxanthin. In part, the beneficial effects of carotenoids are thought to be due to their role as antioxidants. beta-Carotene may have added benefits due its ability to be converted to vitamin A. Additionally, lutein and zeaxanthin may be protective in eye disease because they absorb damaging blue light that enters the eye. Food sources of these compounds include a variety of fruits and vegetables, although the primary sources of lycopene are tomato and tomato products. Additionally, egg yolk is a highly bioavailable source of lutein and zeaxanthin. These carotenoids are available in supplement form. However, intervention trials with large doses of beta-carotene found an adverse effect on the incidence of lung cancer in smokers and workers exposed to asbestos. Until the efficacy and safety of taking supplements containing these nutrients can be determined, current dietary recommendations of diets high in fruits and vegetables are advised.

Publication Types:

- Review

PMID: 16309738 [PubMed - indexed for MEDLINE]

Oncol Rep. 2005 Nov;14(5):1385-92.

Identification of carotenoids in ovarian tissue in women.

Czeczuga-Semeniuk E, **Wolczynski S**.

Department of Gynaecological Endocrinology, Medical University of Bialystok, M. Sklodowskiej-Curie 24A, 15-267 Bialystok, Poland. czeczuga@wp.pl

Epidemiological and clinical studies have revealed that vitamin A and its derivatives (carotenoids and retinoids) can reduce the risk of ovarian tumours and may have a role in the metabolism of patients with ovarian cancer. The aim of the study was identification and quantitative assessment of carotenoids found in nature, mainly of provitamin A group, in the tissue material obtained from patients with different lesions of the ovaries. Material for analysis was obtained from 100 women, aged 16-74, operated on for ovarian tumours in the Department of Gynaecology. Carotenoid pigments were separated using column chromatography, thin-layer chromatography and high-performance liquid chromatography. In the tissue material subjected to analysis, 14 carotenoids were identified, including provitamin A carotenoids; beta-carotene, beta-cryptoxanthin, echinenone and hydroxyechinenone. alpha-carotene was not found. In the whole group of pathological lesions, the total carotenoid content was relatively low (mean 1.717 microg/g tissue) and the mean content of provitamin A carotenoids was 17.28%. These results are similar to results obtained in the group of normal ovarian tissue. In the group of benign mucinous tumours (1.042 microg/g tissue) and tumours in the thecoma-fibroma group (1.328 microg/g tissue) and dysgerminoma group (1.279 microg/g tissue), the total carotenoid content was lower. Only in the endometriosis group was this value higher (2.185 microg/g tissue). Epoxy carotenoids; lutein epoxide, violaxanthin and mutatoxanthin were predominant (in %). Irrespective of histological classification, beta-carotene, beta-cryptoxanthin, lutein, lutein epoxide, violaxanthin and mutatoxanthin were identified in all tissue examined. Antheraxanthin was isolated in all tissue except for normal ovarian tissue, serous malignant and mucinous benign and malignant tumours, endometrioid malignant tumours, dermoid cysts, corpus luteum cysts and simple cysts. Hydroxyechinenone was isolated sporadically. Only in one case was capsanthin isolated. Carotenoids act as chemopreventive agents, irrespective of whether they are finally transformed into vitamin A, and may represent a potentially powerful alternative to present chemotherapeutic approaches to the treatment of ovarian cancer.

PMID: 16211314 [PubMed - indexed for MEDLINE]

Biochim Biophys Acta. 2005 May 30;1740(2):206-14. Epub 2005 Feb 5.

The effect of beta-carotene and its derivatives on cytotoxicity, differentiation, proliferative potential and apoptosis on the three human acute leukemia cell lines: U-937, HL-60 and TF-1.

Sacha T, **Zawada M**, **Hartwich J**, **Lach Z**, **Polus A**, **Szostek M**, **Zdzi Owska E**, **Libura M**, **Bodzioch M**, **Dembińska-Kieć A**, **Skotnicki AB**, **Góralczyk R**, **Wertz K**, **Riss G**, **Moele C**, **Langmann T**, **Schmitz G**.

Chair and Department of Haematology, Jagiellonian University Medical College, ul. Kopernika 17, 31-501 Cracow, Poland. mmsacha@cyf-kr.edu.pl

The influence of beta-carotene (BC) and its derivatives on differentiation, proliferation and apoptosis in three human acute leukemia cell lines was studied. We investigated: (i) the cellular uptake of BC, (ii) the cytotoxicity, (iii) the effect on cell cycle progression and/or apoptosis. The dose- and time-dependent pattern of cellular BC uptake in all studied cell lines was seen. We did not observe any cytotoxic effect of BC and ATRA in the chosen concentrations. There was only limited effect of BC on gene expression. The microarrray analysis of U-937 cell line exposed to BC for 72 h showed an increased expression of BAX gene. This finding was confirmed by real-time Q-PCR analysis, and supported by a flow cytometry apoptosis tests. We did not observe any influence of studied components on cellular proliferation. The induction of differentiation after incubation with ATRA in HL-60 cells was noted. The induction of cellular apoptosis by BC was seen in all studied cell lines. We demonstrated that BC used in the concentrations achievable in vivo does not affect the proliferation and differentiation process of the studied leukemic cell lines, but can influence and enhance the apoptosis by modulating the expression of the regulatory genes.

Publication Types:

- Comparative Study
- Research Support, Non-U.S. Gov't

PMID: 15949688 [PubMed - indexed for MEDLINE]

Eur J Cancer. 2007 Nov;43(17):2590-601. Epub 2007 Oct 1.

beta-Carotene induces apoptosis and up-regulates peroxisome proliferator-activated receptor gamma expression and reactive oxygen species production in MCF-7 cancer cells.

Cui Y, **Lu Z**, **Bai L**, **Shi Z**, **Zhao WE**, **Zhao B**.

Chemical Engineering College, Zhengzhou University, No. 100 Science Road, Zhengzhou, 450001, People's Republic of China.

Although the pharmacological role of beta-carotene in the prevention and treatment of many cancer cells has received increasing attention, the molecular mechanisms underlying such chemopreventive activity are not clear. Since peroxisome proliferator-activated receptor gamma (PPAR-gamma) has been implicated in regulating breast cancer cell differentiation and apoptosis, the effects of beta-carotene on the PPAR-gamma-mediated pathway and its association with reactive oxygen species production in MCF-7 cells were investigated in the present study. The results demonstrated that beta-carotene significantly increased PPAR-gamma mRNA and protein levels in time-dependent manner. In addition, beta-carotene increased the cyclin-dependent kinase inhibitor p21(WAF1/CIP1) expression and decreased the prostanoid synthesis rate-limiting enzyme cyclooxygenase-2 expression. 2-chloro-5-nitro-N-phenylbenzamide (GW9662), an irreversible PPAR-gamma antagonist, partly attenuated the cell death caused by beta-carotene. Further, reactive oxygen species (ROS) production was induced by beta-carotene, resulting in mitochondrial dysfunction and cytochrome C release. Reduced glutathione (GSH) treatment decreases the intracellular ROS and prevents cytochrome C release and cell apoptosis induced by beta-carotene. In total, these observations suggest that the synergistic effect of PPAR-gamma expression and ROS production may account for beta-carotene-mediated anticancer activities.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 17911009 [PubMed - indexed for MEDLINE]

J Nutr Biochem. 2007 Oct;18(10):667-75. Epub 2007 Mar 21.

Carotenoids suppress proliferating cell nuclear antigen and cyclin D1 expression in oral carcinogenic models.

Cheng HC, **Chien H**, **Liao CH**, **Yang YY**, **Huang SY**.

Orthodontic Department, Taipei Medical University Hospital, Taipei Medical University, Taipei 110, Taiwan.

The purpose of this study was to investigate the chemopreventive effect of carotenoids on proliferating cell nuclear antigen (PCNA) and cyclin D(1) expression in betel (Areca catechu) quid extract (BQE)-induced hamster oral cancer and human KB cell models, respectively. In the in vivo animal study, 41 hamsters were divided into six groups and treated with 0.3 ml of 0.5% 9,10-dimethyl-1,2-benz[a]-anthracene, BQE, alpha-tocopherol, beta-carotene, lycopene, lutein and mixed carotenoids for 12 weeks. After treatment, the pouches were excised and graded using an immunohistochemical assay of PCNA. In the in vitro cell experiment, KB cells were cultured, and the inhibitory effect of carotenoids (beta-carotene, lycopene and lutein) on cell proliferation was evaluated. Cyclin D(1) and PCNA were evaluated in terms of cell differentiation. In the results, most of the animal lesions showed no overexpression of PCNA. However, in dysplastic lesions, PCNA expressions by the beta-carotene, lutein, lycopene, mixed and vitamin E groups were less than that of the control group. In papilloma lesions, PCNA expressions by the beta-carotene, mixed and vitamin E groups were less severe than that of the control group. PCNA expression by the vitamin E-treated group was less severe than that of the control group. No carcinoma was found in the lycopene or mixed groups. In the cell study, all carotenoids exerted a significant inhibitory effect on KB cell proliferation. Although lycopene suppressed KB cell proliferation at the G(0)/G(1) phase with a significant decrease in PCNA expression, beta-carotene and lutein possessed less of an inhibitory effect and even exhibited elevated cell proliferation at the G(2)/M phase. These results indicate that different carotenoids present various suppressive abilities against PCNA and cyclin D(1) expressions in cell proliferation. In conclusion, carotenoids suppressed the carcinogenesis of induced hamster oral cancer and a cancer cell line by acting as a suppressor which inhibited the expressions of PCNA and cyclin D(1).

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 17369034 [PubMed - indexed for MEDLINE]

Int J Cancer. 2009 Jun 15;124(12):2929-37.

Dietary carotenoids and the risk of invasive breast cancer.

Mignone LI, **Giovannucci E**, **Newcomb PA**, **Titus-Ernstoff L**, **Trentham-Dietz A**, **Hampton JM**, **Willett WC**, **Egan KM**.

Department of Epidemiology, Harvard School of Public Health, Boston, MA 02115, USA. lmignone@hsph.harvard.edu

Certain classes of vitamins and nutrients found in fruits and vegetables have been of particular interest in relation to cancer prevention, owing to their potential anticarcinogenic properties. We examined the association between certain fruits, vegetables, carotenoids, and vitamin A and breast cancer risk in a large population-based case-control study of women residing in the states of Massachusetts, New Hampshire and Wisconsin. The study was comprised of 5,707 women with incident invasive breast cancer (2,363 premenopausal women and 3,516 postmenopausal women) and 6,389 population controls (2,594 premenopausal women and 3,516 postmenopausal women). In an interview, women were asked about their intake of carotenoid rich fruits and vegetables 5 years prior to a referent date. An inverse association observed among premenopausal women was for high levels of vitamin A (OR: 0.82, 95% CI: 0.68-0.98, p for trend = 0.01), beta-carotene (OR: 0.81, 95% CI 0.68-0.98, p for trend = 0.009), alpha-carotene (OR: 0.82, 95% CI: 0.68-0.98, p for trend = 0.07) and lutein/zeaxanthin (OR: 0.83, 95% CI 0.68-0.99, p for trend = 0.02). An inverse association was not observed among postmenopausal women. Among premenopausal women who reported ever smoking, these results were stronger than among never smokers, although tests for interaction were not statistically significant. Results from this study are comparable to previous prospective studies, and suggest that a high consumption of carotenoids may reduce the risk of premenopausal but not postmenopausal breast cancer, particularly among smokers. Copyright 2008 UICC.

Publication Types:

- Comparative Study
- Multicenter Study
- Research Support, N.I.H., Extramural

PMID: 19330841 [PubMed - indexed for MEDLINE]

Cancer Causes Control. 2009 Jul;20(5):699-711. Epub 2008 Dec 16.

Antioxidant vitamins and the risk of endometrial cancer: a dose-response meta-analysis.

Bandera EV, **Gifkins DM**, **Moore DF**, **McCullough ML**, **Kushi LH**.

The Cancer Institute of New Jersey, Robert Wood Johnson Medical School, 195 Little Albany St, New Brunswick, NJ 08903, USA. elisa.bandera@umdnj.edu

Antioxidant vitamins may reduce cancer risk by limiting oxidative DNA damage. To summarize and quantify the current epidemiologic evidence of an association between antioxidant vitamin intake and endometrial cancer, we conducted a systematic literature review and meta-analysis. One cohort and 12 case-control studies presenting relevant risk estimates were identified by conducting bibliographical searches through June 2008. Dose-response meta-analyses were conducted for beta-carotene, vitamin C, and vitamin E from food sources. Intake from supplements was not considered in the meta-analyses because of the few studies that reported relevant information. Based on case-control data, the random-effects summary odds ratios (OR) were, for beta-carotene: 0.88 (95% CI: 0.79-0.98) per 1,000 mcg/1,000 kcal (I2: 77.7%; $p < 0.01$); for vitamin C: 0.85 (95% CI: 0.73-0.98) per 50 mg/1,000 kcal (I2: 66.1%; $p < 0.01$); and, for vitamin E: 0.91 (95% CI: 0.84-0.99) per 5 mg/1,000 kcal (I2: 0.0%; p: 0.45). In contrast, the only prospective study identified provided little indication of an association. Although the current case-control data suggest an inverse relationship of endometrial cancer risk with dietary intakes of beta-carotene, vitamin C, and vitamin E from food sources, additional studies are needed, particularly cohort studies, to confirm an association.

Publication Types:

- Research Support, N.I.H., Extramural
- Research Support, Non-U.S. Gov't

PMID: 19083131 [PubMed - in process]

Ann Oncol. 2009 Jan;20(1):160-5. Epub 2008 Jul 31.

Dietary intake of selected micronutrients and gastric cancer risk: an Italian case-control study.

Pelucchi C, **Tramacere I**, **Bertuccio P**, **Tavani A**, **Negri E**, **La Vecchia C**.

Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy. pelucchi@marionegri.it

BACKGROUND: A high consumption of non-starchy vegetables and fruits likely decreases the risk of gastric cancer, but no specific constituent of plant foods has been consistently identified to explain this association. PATIENTS AND METHODS: We considered several micronutrients and minerals in an Italian case-control study conducted between 1997 and 2007, including 230 patients with incident, histologically confirmed gastric cancer and 547 matched controls, admitted with acute conditions. Micronutrients computation was based on a validated and reproducible food frequency questionnaire, through an Italian food composition database. We estimated odds ratios (ORs) using conditional logistic regression, adjusted for energy intake and selected covariates. RESULTS: We found decreased ORs for the highest versus lowest quartile of vitamin E (OR=0.50), alpha-carotene (OR=0.52) and beta-carotene (OR=0.42) intake. Gastric cancer was directly associated with sodium, with ORs of 2.22 for the second, 2.56 for the third and 2.46 for the fourth quartile of intake. No significant relation emerged with iron, calcium, potassium, zinc, vitamin C, thiamin, riboflavin, niacin, vitamin B6, folate, vitamin D, retinol, beta-cryptoxanthin, lycopene and lutein plus zeaxanthin. CONCLUSIONS: Our data support a favourable effect on gastric cancer of vitamin E and selected carotenoids and a detrimental effect of sodium even at intermediate levels of intake.

Publication Types:

- Research Support, Non-U.S. Gov't

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PMCID: PMC2638677 [Available on 2010/01/01]

Carcinogenesis. 2008 May;29(5):1042-8. Epub 2008 Mar 13.

Plasma levels of carotenoids, retinol and tocopherol and the risk of gastric cancer in Japan: a nested case-control study.

Persson C, **Sasazuki S**, **Inoue M**, **Kurahashi N**, **Iwasaki M**, **Miura T**, **Ye W**, **Tsugane S**; **JPHC Study Group**.Collaborators (100).

Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, 5-1-1 Tsukiji, Chuo-ku 104-0045, Tokyo, Japan.

Fruits and vegetables have been suggested to confer protection against diseases such as cancer through the effects of antioxidants, often represented by carotenoids. We investigated the impact of carotenoids, retinol and tocopherol on gastric cancer development in a large nested case-control study among Japanese with known Helicobacter pylori infection status. A total of 36 745 subjects aged 40-69 in the Japan Public Health Center-based Prospective Study who responded to the baseline questionnaire and provided blood samples in 1990-1995 were followed until 2004. Plasma levels of carotenoids in 511 gastric cancer cases and 511 matched controls were measured by high-performance liquid chromatography. Odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) were estimated using conditional logistic regression models. Plasma level of beta-carotene was inversely associated with the risk of gastric cancer (compared with the lowest quartile: OR = 0.63, 95% CI = 0.31-0.75; OR = 0.48, 95% CI = 0.31-0.75 and OR = 0.46, 95% CI = 0.28-0.75, for quartile 2, 3 and 4, respectively, P(trend) < 0.01). Inverse associations were evident in men for alpha-carotene (P(trend) = 0.04) and beta-carotene (P(trend) < 0.01), but not in women, who had relatively higher plasma levels compared with men. We found no statistically significant association between plasma levels of lutein/zeaxanthin, lycopene, retinol, alpha- or gamma-tocopherol and gastric cancer risk. Our findings suggest that those who have very low plasma levels of alpha-carotene and beta-carotene are at a higher risk of gastric cancer.
Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 18339681 [PubMed - indexed for MEDLINE]

Urology. 2008 Sep;72(3):633-7. Epub 2008 Feb 15.

The Men's Eating and Living (MEAL) study: a Cancer and Leukemia Group B pilot trial of dietary intervention for the treatment of prostate cancer.

Parsons JK, **Newman V**, **Mohler JL**, **Pierce JP**, **Paskett E**, **Marshall J**; **Cancer and Leukemia Group B**.

Moores Cancer Center, University of California-San Diego, La Jolla, California, USA. jkparsons@ucsd.edu

OBJECTIVES: To evaluate the feasibility of implementing a diet-based intervention in men with prostate cancer. METHODS: Seventy-four men aged 50 to 80 years with biopsy-proven adenocarcinoma of the prostate were randomized to receive either telephone-based dietary counseling or standardized, written nutritional information. Telephone dietary counseling targets included increased intakes of vegetables (particularly cruciferous vegetables and tomato products), whole grains, and beans/legumes. Dietary intakes and plasma carotenoid levels were assessed at baseline and at 6 months' follow-up. RESULTS: In the intervention arm, mean daily intakes of total vegetables, crucifers, tomato products, and beans/legumes increased by 76%, 143%, 292%, and 95%, respectively, whereas fat intake decreased by 12% (P = 0.02). In the control arm, there were no significant changes in mean intakes of total vegetables, tomato products, crucifers, beans/legumes, or fat. Similarly, in the intervention arm, mean plasma levels of alpha-carotene, beta-carotene, lutein, lycopene, and total carotenoids increased by 33%, 36%, 19%, 30%, and 26%, respectively (P <0.05). In the control arm, there were no significant changes in plasma levels of alpha- or beta-carotene, lutein, lycopene, or total carotenoids. CONCLUSIONS: Telephone-based dietary counseling increases vegetable intake, decreases fat intake, and significantly increases plasma levels of potentially anticarcinogenic carotenoids in men with prostate cancer. These data support the feasibility of implementing clinical trials of dietary intervention in men with prostate cancer.

Publication Types:

- Research Support, Non-U.S. Gov't

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Cell cycle regulation and induction of apoptosis by beta-carotene in U937 and HL-60 leukemia cells.

Upadhyaya KR, **Radha KS**, **Madhyastha HK**.

Department of Applied Physiology, Faculty of Medicine, University of Miyazaki, Miyazaki, Japan.

In this communication, we report the efficacy of beta-carotene towards differentiation and apoptosis of leukemia cells. Dose (20 microM) and time dependence (12 h) tests of beta- carotene showed a higher magnitude of decrease (significance $p < 0.05$) in cell numbers and cell viability in HL-60 cells than U937 cells but not normal cell like Peripheral blood mononuclear cell (PBMC). Microscopical observation of beta-carotene treated cells showed a distinct pattern of morphological abnormalities with inclusion of apoptotic bodies in both leukemia cell lines. When cells were treated with 20 microM of beta-carotene, total genomic DNA showed a fragmentation pattern and this pattern was clear in HL-60 than U937 cells. Both the cell lines, on treatment with beta- carotene, showed a clear shift in G(1) phase of the cell cycle. In addition the study also revealed anti-oxidant properties of beta-carotene since there was reduction in relative fluorescent when treated than the control at lower concentration. Collectively this study shows the dual phenomenon of apoptosis and differentiation of leukemia cells on treatment with beta-carotene.

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Nutrition and immunity in cancer.

Valdés-Ramos R, **Benítez-Arciniega AD**.

Facultad de Medicina, Universidad Autónoma del Estado de México, Jesús Carranza esq. Paseo Tollocan, Col. Moderna de la Cruz, Toluca, Estado de México, 50180, Mexico. rycramos@uaemex.mx

The purpose of this article is to give a general overview of the effects of nutrition on the development of cancer as well as part of a therapeutic approach. There is much evidence that diet and lifestyle can alter the risk of cancer development as is the case for many other chronic diseases. This may be through a direct action on the immune system, either by enhancing or suppressing it, as well as on the development of the tumour itself, by modulating gene expression or by antioxidant activity. Protective effects can be achieved by adequate intakes of vitamins A and C, beta-carotene, selenium and n-3 fatty acids among others, while negative effects are found mainly with high intakes of n-6 and saturated fatty acids. Weight gain, obesity and lack of regular physical activity have also been associated with an increased risk of cancer. The protective effects are best observed when adequate diet and lifestyle are present together. With respect to the therapeutic role of nutrition in cancer, it has been observed that the use of pre- or post-operative enteral or parenteral nutrition may improve patients' survival rates and quality of life; however, more research is needed in this particular area. Breast, colon, rectum, prostate, stomach and lung are the types of cancer most commonly associated with diet or dietary components.

Publication Types:

- Review

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J Cancer Res Ther. 2006 Jan-Mar;2(1):24-7.

Brain tumor and role of beta-carotene, a-tocopherol, superoxide dismutase and glutathione peroxidase.

Aggarwal S, **Subberwal M**, **Kumar S**, **Sharma M**.

Department of Biochemistry, Maulana Azad Medical College, New Delhi, India.

The erythrocyte levels of the antioxidant enzymes SOD and GPx, and serum levels of antioxidants vitamins beta-carotene and beta-tocopherol were estimated in various types of brain tumors, and were compared with the levels in controls. Statistically significant (P<.001) diminished levels of beta-carotene, beta-tocopherol, SOD and GPx, were observed in all the brain tumor patients as compared to controls. Malignant tumor also showed a relative decrease in antioxidant levels as compared to benign tumors. Comparison of histopathological sections of brain tumors also suggested a inverse relationship between antioxidant level and grades of malignancy. Marked decrease in antioxidant levels may have a role in genesis of considerable oxidative stress in brain tumors. Furthermore, the degree of decline in antioxidant levels may indicate severity of malignancy in brain tumors.

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Eur J Cancer. 2007 Nov;43(17):2590-601. Epub 2007 Oct 1.

beta-Carotene induces apoptosis and up-regulates peroxisome proliferator-activated receptor gamma expression and reactive oxygen species production in MCF-7 cancer cells.

Cui Y, **Lu Z**, **Bai L**, **Shi Z**, **Zhao WE**, **Zhao B**.

Chemical Engineering College, Zhengzhou University, No. 100 Science Road, Zhengzhou, 450001, People's Republic of China.

Although the pharmacological role of beta-carotene in the prevention and treatment of many cancer cells has received increasing attention, the molecular mechanisms underlying such chemopreventive activity are not clear. Since peroxisome proliferator-activated receptor gamma (PPAR-gamma) has been implicated in regulating breast cancer cell differentiation and apoptosis, the effects of beta-carotene on the PPAR-gamma-mediated pathway and its association with reactive oxygen species production in MCF-7 cells were investigated in the present study. The results demonstrated that beta-carotene significantly increased PPAR-gamma mRNA and protein levels in time-dependent manner. In addition, beta-carotene increased the cyclin-dependent kinase inhibitor p21(WAF1/CIP1) expression and decreased the prostanoid synthesis rate-limiting enzyme cyclooxygenase-2 expression. 2-chloro-5-nitro-N-phenylbenzamide (GW9662), an irreversible PPAR-gamma antagonist, partly attenuated the cell death caused by beta-carotene. Further, reactive oxygen species (ROS) production was induced by beta-carotene, resulting in mitochondrial dysfunction and cytochrome C release. Reduced glutathione (GSH) treatment decreases the intracellular ROS and prevents cytochrome C release and cell apoptosis induced by beta-carotene. In total, these observations suggest that the synergistic effect of PPAR-gamma expression and ROS production may account for beta-carotene-mediated anticancer activities.

Publication Types:

- Research Support, Non-U.S. Gov't

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Integr Cancer Ther. 2007 Sep;6(3):258-70.

Beta-carotene inhibits tumor-specific angiogenesis by altering the cytokine profile and inhibits the nuclear translocation of transcription factors in B16F-10 melanoma cells.

Guruvayoorappan C, **Kuttan G**.

Department of Immunology, Amala Cancer Research Centre, Amala Nagar, Kerala State, India.

Angiogenesis is the formation of new blood vessels out of the preexisting vascular network and involves a sequence of events that are of key importance in a broad array of physiological and pathological processes. The growth of tumor and metastasis are dependent on the formation of new blood vessels. The present study therefore aims at evaluating the antiangiogenic effect of beta-carotene using in vivo and in vitro models. Male C57BL/6 mice as well as B16F-10 cells were used for the experimental study. The in vivo study includes the inhibitory effect of beta-carotene on the formation of tumor-directed capillaries. Rat aortic ring assay, human umbilical vein endothelial cell proliferation, migration, and tube formation are used for assessing the in vitro antiangiogenic effect of beta-carotene. The differential regulation of proinflammatory cytokines as well as the inhibitory effect of beta-carotene on the activation and nuclear translocation of transcription factors are also assessed. Beta-carotene treatment significantly reduces the number of tumor-directed capillaries accompanied by altered serum cytokine levels. Beta-carotene is able to inhibit proliferation, migration, and tube formation of endothelial cells. Beta-carotene treatment downregulates the expression of matrix metalloproteinase (MMP)-2, MMP-9, prolyl hydroxylase, and lysyl oxidase gene expression and upregulates the expression of tissue inhibitor of metalloproteinase (TIMP)-1 and TIMP-2. The study reveals that beta-carotene treatment could alter proinflammatory cytokine production and could inhibit the activation and nuclear translocation of p65, p50, c-Rel subunits of nuclear factor-kappa B, and other transcription factors such as c-fos, activated transcription factor-2, and cyclic adenosine monophosphate response element-binding protein in B16F-10 melanoma cells. These observations show that beta -carotene exerts its antiangiogenic effect by altering the cytokine profile and could inhibit the activation and nuclear translocation of transcription factors.

Publication Types:

- In Vitro

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