Carotenoids and Cancer Prevention

*Cancer Metastasis Rev.* 2002;21(3-4):257-64.

**Carotenoids in cancer chemoprevention.**

**Source**
Department of Biochemistry, Kyoto Prefectural University of Medicine, Kawaramachi-Hirokoji, Kamigyoku, Kyoto, Japan. hnishno@basic.kpu-m.ac.jp

**Abstract**
Various natural carotenoids, besides beta-carotene, were proven to have anticarcinogenic activity, and some of them showed more potent activity than beta-carotene. Thus, these carotenoids (alpha-carotene, lutein, zeaxanthin, lycopene, beta-cryptoxanthin, fucoxanthin, astaxanthin, capsanthin, crocetin and phytoene), as well as beta-carotene, may be useful for cancer prevention. In the case of phytoene, the concept of 'bio-chemoprevention', which means biotechnology-assisted method for cancerchemoprevention, may be applicable. In fact, establishment of mammalian cells producing phytoene was succeeded by the introduction of crtB gene, which encodes phytoene synthase, and these cells were proven to acquire the resistance against carcinogenesis. Antioxidative phytoene-containing animal foods may be classified as a novel type of functional food, which has the preventive activity against carcinogenesis, as well as the ability to reduce the accumulation of oxidative damages, which are hazardous for human health.

**PMID:** 12549764
[PubMed - indexed for MEDLINE]


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**Circulating carotenoids and risk of breast cancer: pooled analysis of eight prospective studies.**

**Source**
Channing Division of Network Medicine, Department of Medicine, Brigham & Women's Hospital and Harvard Medical School, 181 Longwood Ave, Boston, MA 02115, USA. heather.eliassen@channing.harvard.edu

**Abstract**
BACKGROUND:
Carotenoids, micronutrients in fruits and vegetables, may reduce breast cancer risk. Most, but not all, past studies of circulating carotenoids and breast cancer have found an inverse association with at least one carotenoid, although the specific carotenoid has varied across studies.

**METHODS:**
We conducted a pooled analysis of eight cohort studies comprising more than 80% of the world's published prospective data on plasma or serum carotenoids and breast cancer, including 3055 case subjects and 3956 matched control subjects. To account for laboratory differences and examine population differences across studies, we recalibrated participant carotenoid levels to a common standard by reassaying 20 plasma or serum samples from each cohort together at the same laboratory. Using conditional logistic regression, adjusting for several breast cancer risk factors, we calculated relative risks (RRs) and 95% confidence intervals (CIs) using quintiles defined among the control subjects from all studies. All P values are two-sided.

**RESULTS:**
Statistically significant inverse associations with breast cancer were observed for α-carotene (top vs bottom quintile RR = 0.87, 95% CI = 0.71 to 1.05, P(trend) = .04), β-carotene (RR = 0.83, 95% CI = 0.70 to 0.98, P(trend) = .02), lutein+zeaxanthin (RR = 0.84, 95% CI = 0.70 to 1.01, P(trend) = .05),
lycopene (RR = 0.78, 95% CI = 0.62 to 0.99, P(trend) = .02), and total carotenoids (RR = 0.81, 95% CI = 0.68 to 0.96, P(trend) = .01). β-Cryptoxanthin was not statistically significantly associated with risk. Tests for heterogeneity across studies were not statistically significant. For several carotenoids, associations appeared stronger for estrogen receptor negative (ER(-)) than for ER(+) tumors (eg, β-carotene: ER(-): top vs bottom quintile RR = 0.52, 95% CI = 0.36 to 0.77, P(trend) = .001; ER(+): RR = 0.83, 95% CI = 0.66 to 1.04, P(trend) = .06; P(heterogeneity) = .01).

CONCLUSIONS:
This comprehensive prospective analysis suggests women with higher circulating levels of α-carotene, β-carotene, lutein+zeaxanthin, lycopene, and total carotenoids may be at reduced risk of breast cancer.

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[PubMed - indexed for MEDLINE]
PMCID: PMC3525817
[Available on 2013/12/19]


Cancer chemoprevention by carotenoids.
Tanaka T, Shnimizu M, Moriwaki H.
Source
Tohkai Cytopathology Institute, Cancer Research and Prevention-TCI-CaRP, 5-1-2 Minami-Uzura, Gifu 500-8285, Japan. takutt@toukaisaibou.co.jp
Abstract
Carotenoids are natural fat-soluble pigments that provide bright coloration to plants and animals. Dietary intake of carotenoids is inversely associated with the risk of a variety of cancers in different tissues. Preclinical studies have shown that some carotenoids have potent antitumor effects both in vitro and in vivo, suggesting potential preventive and/or therapeutic roles for the compounds. Since chemoprevention is one of the most important strategies in the control of cancer development, molecular mechanism-based cancer chemoprevention using carotenoids seems to be an attractive approach. Various carotenoids, such as β-carotene, a-carotene, lycopene, lutein, zeaxanthin, β-cryptoxanthin, fucoxanthin, canthaxanthin and astaxanthin, have been proven to have anticarcinogenic activity in several tissues, although high doses of β-carotene failed to exhibit chemopreventive activity in clinical trials. In this review, cancer prevention using carotenoids are reviewed and the possible mechanisms of action are described.
PMID: 22418926
[PubMed - indexed for MEDLINE]


Carotenoids and apocarotenoids in cellular signaling related to cancer: a review.
Source
Department of Clinical Biochemistry, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel. yoav@bgu.ac.il
Abstract
The basis for the vivid color of carotenoids and their antioxidant activity is the multiple conjugated double bonds, which are characteristic for these phytonutrients. Moreover, the cleavage of these oxidation-prone double bonds leads to the formation of apocarotenoids. A large number of carbonyl-containing oxidation products are expected to be produced as a result of carotenoid oxidation and these can be further metabolized into the corresponding acids and alcohols. As discussed in this review, many, but not all, of these potential products have been detected and identified in plants as
well as in human and animal plasma and tissues. Some of these compounds were found to be biologically active as anticancer agents. In addition to the inhibition of cancer cell proliferation, several carotenoid metabolites were shown to modulate the activity of various transcription systems. These include ligand-activated nuclear receptors, such as the retinoic acid receptor, retinoid X receptor, peroxisome proliferator-activated receptor and estrogen receptor, as well as other transcription systems that have an important role in cancer, such as the electrophile/antioxidant response element pathway and nuclear factor-κB. Therefore, apocarotenoids can be considered as natural compounds with multifunctional, rather than monofunctional, activity and, thus, can be useful in the prevention of cancer and other degenerative diseases.

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PMID: 22102431
[PubMed - indexed for MEDLINE]


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Animal models in carotenoids research and lung cancer prevention.
Kim J, Kim Y.
Source
Department of Nutritional Science and Food Management, Ewha Womans University, Seoul, South Korea.

Abstract
Numerous epidemiological studies have consistently demonstrated that individuals who eat more fruits and vegetables (which are rich in carotenoids) and who have higher serum β-carotene levels have a lower risk of cancer, especially lung cancer. However, two human intervention trials conducted in Finland and in the United States have reported contrasting results with high doses of β-carotene supplementation increasing the risk of lung cancer among smokers. The failure of these trials to demonstrate actual efficacy has resulted in the initiation of animal studies to reproduce the findings of these two studies and to elucidate the mechanisms responsible for the harmful or protective effects of carotenoids in lung carcinogenesis. Although these studies have been limited by a lack of animal models that appropriately represent human lung cancer induced by cigarette smoke, ferrets and A/J mice are currently the most widely used models for these types of studies. There are several proposed mechanisms for the protective effects of carotenoids on cigarette smoke-induced lung carcinogenesis, and these include antioxidant/prooxidant effects, modulation of retinoic acid signaling pathway and metabolism, induction of cytochrome P450, and molecular signaling involved in cell proliferation and/or apoptosis. The technical challenges associated with animal models include strain-specific and diet-specific effects, differences in the absorption and distribution of carotenoids, and differences in the interactions of carotenoids with other antioxidants. Despite the problems associated with extrapolating from animal models to humans, the understanding and development of various animal models may provide useful information regarding the protective effects of carotenoids against lung carcinogenesis.

PMID: 21966544
[PubMed]
PMCID: PMC3162302


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Carotenoids inhibit proliferation and regulate expression of peroxisome proliferators-activated receptor gamma (PPARγ) in K562 cancer cells.
Zhang X, Zhao WE, Hu L, Zhao L, Huang J.
Source
School of Chemical Engineering and Energy, Zhengzhou University, No. 100 Science Road, Zhengzhou 450001, PR China.

Abstract
As one of the main micronutrients in vegetables and fruit carotenoids are almost daily intaken in significant quantity. Although the pharmacological roles of carotenoids in the prevention and reduction of cancer incidence have received more and more attention, the exact molecular mechanisms underlying anticancer effects of carotenoids remain unclear yet. Activated peroxisome proliferator-activated receptor gamma (PPARγ) plays an inhibitory role in cancer cell proliferation and growth. Involvement of PPARγ in the growth inhibition of leukemia K562 cells by carotenoids was investigated in the present study. The results demonstrated that β-carotene, astaxanthin, capsanthin, and bixin inhibited the proliferation and decreased the viability of leukemia K562 cells in dose- and time-dependent manners, induced cell apoptosis, and interfered with cell cycle progression. Pretreatment with GW9662, a potent antagonist of PPARγ, partly attenuated the inhibition of K562 cell proliferation by the four carotenoids at 8µM. These carotenoids up-regulated the expression of PPARγ and p21 and down-regulated the expression of cyclin D1 in a dose-dependent manner. In addition, β-carotene, astaxanthin, capsanthin and bixin also up-regulated the expression of Nrf2, an important transcription factor in Keap1-Nrf2/EpRE/ARE signaling pathway. It appears to us that PPARγ signaling pathways and Keap1-Nrf2/EpRE/ARE signaling pathway were involved in the inhibition of K562 cell proliferation by carotenoids and the up-regulation of PPARγ expression at least partly contributed to the antiproliferative effects of β-carotene, astaxanthin, capsanthin, and bixin on K562 cells.

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PMID: 21620794
[PubMed - indexed for MEDLINE]


Biological activity of carotenoids: its implications in cancer risk and prevention.
Chatterjee M, Roy K, Janarthan M, Das S, Chatterjee M.

Source
Chemical Carcinogenesis and Chemoprevention Laboratory, Division of Biochemistry, Department of Pharmaceutical Technology, Jadavpur University, Kolkata-700032, India.

Abstract
Recently nontoxic natural compounds are getting immense importance for the prevention of diseases of different etiology. Natural product provitamin A "carotenoids", largely a-carotene, β-carotene, and β-cryptoxanthin, are typical constituents of orange/red/yellow colored fruits and green vegetables. Different in vitro and in vivo studies have shown that carotenoids possess the capacity to scavenge DNA damaging free radicals, suppress angiogenesis, inhibit cell proliferation and induce apoptosis. Epidemiological reports of case-control studies, nested case-control studies, and cohort studies support significant association between dietary intake and circulating levels of carotenoids and reduction in cancer risk/carcinoma of various organs. However, randomized trials regarding β-carotene supplementation, alone or in combination with other supplements, have not always well corroborated with this. Of seven trials, one observed a significant benefit on cancer mortality, four reported no significant benefit or harm, while the remaining two trials found an unexpected, but significant increase in lung cancer incidence. This review discusses implications and significance of carotenoids in the field of cancer risk and prevention.

PMID: 21466428
[PubMed - indexed for MEDLINE]

Omega-3 and Cancer Prevention

Omega-3 fatty acids in cancer.
Laviano A, Rianda S, Moffino A, Rossi Fanelli F.
Source
Department of Clinical Medicine, Sapienza University, Rome, Italy.

PURPOSE OF REVIEW:
Significant achievements have been obtained in cancer treatment, but the clinical relevance of drug approach in daily practice remains questionable due to the high costs, limited efficacy, and negligible influence on quality of life. A new concept is emerging which is based on the early combination of chemotherapy and nutrition therapy.

RECENT FINDINGS:
Inflammation dictates tumour initiation, progression and growth. Omega-3 fatty acids exert anti-inflammatory effects, and therefore recent studies investigated their role in cancer prevention, in cancer cachexia treatment and in enhancement of antitumour therapies. Limited evidence suggests a role for omega-3 fatty acid supplementation in cancer prevention, but they have been shown to preserve muscle mass and function in cancer patients even during active treatment. During chemotherapy, omega-3 fatty acids may contribute to a reduced inflammatory response, but whether cancer treatment toxicity can be prevented remains to be assessed. Finally, small studies showed that omega-3 fatty acids increase response rate to chemotherapy.

SUMMARY:
Combination of chemotherapy and omega-3 supplementation appears an effective strategy to enhance the clinical outcome of cancer patients in their curative and palliative clinical trajectory.

PMID: 23299701
[PubMed - in process]


Consumption of n-3 fatty acids and fish reduces risk of hepatocellular carcinoma.
The following togger user interface control may not be accessible. Tab to the next button to revert the control to an accessible version.

Source
Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tsukiji, Chuo-ku Tokyo, Japan. nsawada@ncc.go.jp

Abstract
BACKGROUND & AIMS:
Fish is a rich source of n-3 polyunsaturated fatty acids (PUFAs), such as eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA), and docosahexaenoic acid (DHA). Although consumption of fish and n-3 PUFA has been reported to protect against the development of some types of cancer, little is known about its association with hepatocellular carcinoma (HCC).

**METHODS:**

We investigated the association between fish and n-3 PUFA consumption and HCC incidence (n = 398) in a population-based prospective cohort study of 90,296 Japanese subjects (aged, 45-74 y). Hazard ratios and 95% confidence intervals (CIs) for the highest vs the lowest quintile were estimated from multivariable adjusted Cox proportional hazards regression models. We also conducted subanalyses of subjects with known hepatitis B virus (HBV) or hepatitis C virus (HCV) status, and of subjects who were anti-HCV and/or hepatitis B surface antigen positive. All tests of statistical significance were 2-sided.

**RESULTS:**

Among all subjects, consumption of n-3 PUFA-rich fish and individual n-3 PUFAs was associated inversely with HCC, in a dose-dependent manner. Hazard ratios for the highest vs lowest quintiles were 0.64 (95% CI, 0.42-0.96) for n-3 PUFA-rich fish, 0.56 (95% CI, 0.36-0.85) for EPA, 0.64 (95% CI, 0.41-0.98) for DPA, and 0.56 (95% CI, 0.35-0.87) for DHA. These inverse associations were similar irrespective of HCV or HBV status.

**CONCLUSIONS:**

Consumption of n-3 PUFA-rich fish or n-3 PUFAs, particularly EPA, DPA, and DHA, appears to protect against the development of HCC, even among subjects with HBV and/or HCV infection.


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**Omega-3 polyunsaturated fatty acids: photoprotective macronutrients.**

Pilkington SM, Watson RE, Nicolau A, Rhodes LE.

Source

Dermatological Sciences, Inflammation Sciences Research Group, School of Translational Medicine, University of Manchester, Manchester Academic Health Science Centre, Salford Royal NHS Foundation Hospital, Manchester, UK.

Abstract

Ultraviolet radiation (UVR) in sunlight has deleterious effects on skin, while behavioural changes have resulted in people gaining more sun exposure. The clinical impact includes a year-on-year increase in skin cancer incidence, and topical sunscreens alone provide an inadequate measure to combat overexposure to UVR. Novel methods of photoprotection are being targeted as additional measures, with growing interest in the potential for systemic photoprotection through naturally sourced nutrients. **Omega-3 polyunsaturated fatty acids (n-3 PUFA) are promising candidates, showing potential to protect the skin from UVR injury through a range of mechanisms. In this review, we discuss the biological actions of n-3 PUFA in the context of skin protection from acute and chronic UVR overexposure and describe how emerging new technologies such as nutrigenomics and lipidomics assist our understanding of the contribution of such nutrients to skin health.**


Fish oil prevents breast cancer cell metastasis to bone.

Mandal CC, Ghosh-Choudhury T, Yoneda T, Choudhury GG, Ghosh-Choudhury N.

Source
Department of Pathology, University of Texas Health Science Center at San Antonio, Texas, USA.

Abstract
The data derived from epidemiological and animal models confirm a beneficial effect of fish oil (rich in ω-3 polyunsaturated fatty acids) in the amelioration of tumor growth and progression, including breast cancer. The breast cancer patients often develop bone metastasis evidenced by osteolytic lesions, leading to severe pain and bone fracture. Using a mouse model of MDA-MB-231 human breast cancer cell metastasis to bone, here we show that fish oil diet enriched in DHA (docosahexaenoic acid) and EPA (eicosapentaenoic acid) prevents the formation of osteolytic lesions in bone, indicating suppression of cancer cell metastasis to bone. These results are supported by our data showing both DHA and EPA significantly attenuate the migration/invasion of MDASMBS231 breast cancer cells in culture. The mechanism that limits breast cancer cells to selective metastasis to bone remains hitherto unexplored. Aberrant increased expression of CD44 is associated with generation of cancer stem cells, which contribute to metastasis of breast cancer cells. We demonstrate that DHA and EPA significantly inhibit the expression of CD44 protein and mRNA by a transcriptional mechanism. Furthermore, we show markedly reduced levels of CD44 mRNA and protein in the tumors of mice, which were fed fish oil diet than those in control diet. Our data provide the first evidence for a salutary effect of fish oil on breast cancer metastasis to bone. Our results identify a novel function of the fish oil active components, DHA and EPA, which target the cell-intrinsic pro-metastatic molecule CD44 to inhibit migration/invasion.

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dependent on p27(Kip1) induction, by which δ-tocotrienol can inhibit proliferation in PDCA cells, providing a new rationale for p27(Kip1) as a biomarker for δ-tocotrienol efficacy in pancreatic cancer prevention and therapy.

**PMID:** 23393547
[PubMed - in process]
**PMCID:** PMC3564846

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**Tocotrienols and Cancer Prevention**

_Anticancer Agents Med Chem_, 2012 Dec 11. [Epub ahead of print]

**Tocotrienols Target PI3K/Akt Signaling in Anti-Breast Cancer Therapy.**

_Sylvester PW, Ayoub NM._

**Source**
College of Pharmacy, University of Louisiana at Monroe, 700 University Ave, Monroe, LA 71209-0470, USA. sylvester@ulm.edu.

**Abstract**

The PI3K/Akt signaling pathway mediates mitogen-dependent growth and survival in various types of cancer cells, and inhibition of this pathway results in tumor cell growth arrest and apoptosis. Tocotrienols are natural forms of vitamin E that display potent anticancer activity at treatment doses that had little or no effect on normal cell viability. Mechanistic studies revealed that the anticancer effects of γ-tocotrienol were associated with a suppression in PI3K/Akt signaling. Additional studies showed that cytotoxic LD50 doses of γ-tocotrienol were 3-5-fold higher than growth inhibitory IC50 treatment doses, suggesting that cytotoxic and antiproliferative effects of γ-tocotrienol might be mediated through different mechanisms. However, γ-tocotrienol-induced caspase activation and apoptosis in mammary tumor cells was also found to be associated with suppression in intracellular PI3K/Akt signaling and subsequent down-regulation of FLIP, an endogenous inhibitor of caspase processing and activation. Since breast cancer cells are significantly more sensitive to the inhibitory effects of γ-tocotrienol on PI3K/Akt signaling than normal cells, these findings suggest that γ-tocotrienol may provide significant health benefits in reducing the risk of breast cancer in women. Studies have also shown that combined treatment of γ-tocotrienol with other chemotherapeutic agents can result in a synergistic anticancer response. Combination therapy was most effective when the anticancer mechanism of action of γ-tocotrienol is complimentary to that of the other drug and can provide significant health benefits in the prevention and/or treatment of breast cancer, while at the same time avoiding tumor resistance or toxic effects that are commonly associated with high dose monotherapy.

**PMID:** 23272909
[PubMed - as supplied by publisher]


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**γ-Tocotrienol attenuates TNF-α-induced changes in secretion and gene expression of MCP-1, IL-6 and adiponectin in 3T3-L1 adipocytes.**


**Source**
Ajinomoto Integrative Research for Advanced Dieting, Graduate School of Agriculture, Kyoto University, Kyoto, Japan.

**Abstract**

Tocotrienols, members of the vitamin E family, have been shown to possess anti-inflammatory properties and display activity against a variety of chronic diseases, such as cancer, cardiovascular and neurological diseases. However, whether tocotrienols contribute to the prevention of inflammatory responses in adipose tissue remains to be elucidated. In this study, we examined the effects of γ-
tocotrienol, the most common tocotrienol isomer, on tumor necrosis factor-α (TNF-α)-induced inflammatory responses by measuring the expression of the adipokines, monocyte chemoattractant protein-1 (MCP-1), interleukin-6 (IL-6) and adiponectin in 3T3-L1 adipocytes. Exposure to TNF-α (10 ng/ml) for 24 h increased MCP-1 and IL-6 secretion, and decreased adiponectin secretion and peroxisome proliferator-activated receptor-γ (PPARγ) mRNA expression. γ-tocotrienol effectively improved the TNF-α-induced adverse changes in MCP-1, IL-6 and adiponectin secretion, and in MCP-1, IL-6, adiponectin and PPARγ mRNA expression. Furthermore, TNF-α-mediated IκB-α phosphorylation and nuclear factor-κB (NF-κB) activation were significantly suppressed by the γ-tocotrienol treatment. Our results suggest that γ-tocotrienol may improve obesity-related functional abnormalities in adipocytes by attenuating NF-κB activation and the expression of inflammatory adipokines.

PMID: 22293775
[PubMed - indexed for MEDLINE]


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Chemopreventive activity of vitamin E in breast cancer: a focus on γ- and δ-tocopherol.
Smolarek AK, Suh N.
Source
Department of Chemical Biology, Ernest Mario School of Pharmacy, Rutgers, The State University of New Jersey, Piscataway, NJ 08854, USA smoaman@eden.rutgers.edu

Abstract
Vitamin E consists of eight different variants: α-, β-, γ-, and δ-tocopherols (saturated phytyl tail) and α-, β-, γ-, and δ-tocotrienols (unsaturated phytyl tail). Cancer prevention studies with vitamin E have primarily utilized the variant α-tocopherol. To no avail, a majority of these studies focused on variant α-tocopherol with inconsistent results. However, γ-tocopherol, and more recently δ-tocopherol, have shown greater ability to reduce inflammation, cell proliferation, and tumor burden. Recent results have shown that γ-enriched mixed tocopherols inhibit the development of mammary hyperplasia and tumorigenesis in animal models. In this review, we discuss the possible differences between the variant forms, molecular targets, and cancer-preventive effects of tocopherols. We recommend that a γ-enriched mixture, γ- and δ-tocopherol, but not α-tocopherol, are promising agents for breast cancer prevention and warrant further investigation.

PMID: 22254089
[PubMed - indexed for MEDLINE]

PMCID: PMC3257724


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Tocotrienol as a potential anticancer agent.
Ling MT, Luk SU, Al-Ejeh F, Khanna KK.
Source
Australian Prostate Cancer Research Centre-Queensland, Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, Queensland, Qld 4102, Australia. mingtat.ling@qut.edu.au

Abstract
Vitamin E is composed of two structurally similar compounds: tocopherols (TPs) and tocotrienols (T3). Despite being overshadowed by TP over the past few decades, T3 is now considered to be a promising anticancer agent due to its potent effects against a wide range of cancers. A growing body of evidence suggests that in addition to its antioxidative and pro-apoptotic functions, T3 possesses a number of anticancer properties that make it superior to TP. These include the inhibition of epithelial-to-mesenchymal transitions, the suppression of vascular endothelial growth factor tumor angiogenic pathway and the induction of antitumor immunity. More recently, T3, but not TP, has been shown to have chemosensitization and anti-cancer stem cell effects, further demonstrating the potential of T3
as an effective anticancer therapeutic agent. With most of the previous clinical studies on TP producing disappointing results, research has now focused on testing T3 as the next generation vitamin E for chemoprevention and cancer treatment. This review will summarize recent developments in the understanding of the anticancer effects of T3. We will also discuss current progress in clinical trials involving T3 as an adjuvant to conventional cancer therapy.

PMID: 22095072
[PubMed - indexed for MEDLINE]

DHA and Cancer Prevention

Docosahexaenoic fatty acid (DHA) in the regulation of colon cell growth and cell death: a review.
Skender B, Vaculova AH, Hofmanova J.
Source
Department of Cytokinetics, Institute of Biophysics, Academy of Sciences of the Czech Republic, v.v.i. Brno, Czech Republic.
Abstract
BACKGROUND:
Experimental, epidemiological and clinical data substantiate the beneficial role of n-3 polyunsaturated fatty acids (PUFAs) in preventing inflammation and cancer of the colon. This review covers the unsaturated docosahexaenoic fatty acid (DHA), describes some of its important cellular and molecular mechanisms, its interaction with another dietary lipid, butyrate and with endogenous apoptotic regulators of the tumour necrosis factor (TNF) family. We also discuss the clinical impact of this knowledge and the use of these lipids in colon cancer prevention and treatment.
RESULTS:
From the literature, DHA has been shown to suppress the growth, induce apoptosis in colon cancer cells in vitro and decrease the incidence and growth of experimental tumours in vivo. Based on these data and our own experimental results, we describe and discuss the possible mechanisms of DHA anticancer effects at various levels of cell organization. We show that DHA can sensitize colon cancer cells to other chemotherapeutic/chemopreventive agents and affect the action of physiological apoptotic regulators of the TNF family.
CONCLUSION:
Use of n-3 PUFAs could be a relatively non-toxic form of supportive therapy for improving colon cancer treatment and slowing down or preventing its recurrence. However, it is necessary to use them with caution, based on solid scientific evidence of their mechanisms of action from the molecular to the cellular and organism levels.
PMID: 23069883
[PubMed - in process]


Docosahexaenoic acid sensitizes colon cancer cells to sulindac sulfide-induced apoptosis.
Source
Department of Bioscience and Biotechnology, Sejong University, Seoul, Republic of Korea.
Abstract
Sulindac analogs represent one of the most efficacious groups of NSAIDs reducing the risk of colon cancer. Recent studies have shown that sulindac sulfide, a sulindac analog effective at lower doses compared to its parent compound, triggers the death receptor (DR)5-dependent extrinsic apoptotic
pathway. Induction of apoptosis via activation of the DR-mediated pathway would be an ideal therapeutic strategy to eliminate cancer cells. In this study, we investigated the possibility that colon cancer cells are sensitized to sulindac sulfide-induced apoptosis by docosahexaenoic acid (DHA), via activation of the DR/extrinsic apoptotic pathway. Our data demonstrated that DHA combination sensitized colon cancer cells to sulindac sulfide-induced apoptosis, leading to enhanced growth suppression of human colon cancer xenografts. The combination effect was primarily attributed to increased cleavage of poly(ADP-ribose) polymerase (PARP) and caspase-8 activation. Moreover, pretreatment with z-IETD-FMK (caspase-8 inhibitor) or stable expression of dominant negative caspase-8 genes blocked DHA/sulindac sulfide cotreatment-induced apoptosis. In view of the finding that DR5 silencing abrogated the combination-stimulated apoptosis, we propose that apoptotic synergy induced by sulindac sulfide plus DHA is mediated via DR5. Our findings collectively support the utility of a combination of sulindac sulfide and DHA in the effective prevention and treatment of colon cancer.

PMID: 22395735
[PubMed indexed for MEDLINE]  

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Docosahexaenoic acid induces autophagy through p53/AMPK/mTOR signaling and promotes apoptosis in human cancer cells harboring wild-type p53.


Source
Department of Biochemistry, College of Medicine, Chungnam National University, Daejeon, Korea.

Abstract
Docosahexaenoic acid (DHA) has been reported to induce tumor cell death by apoptosis. However, little is known about the effects of DHA on autophagy, another complex well-programmed process characterized by the sequestration of cytoplasmic material within autophagosomes. Here, we show that DHA increased both the level of microtubule-associated protein light-chain 3 and the number of autophagic vacuoles without impairing autophagic vesicle turnover, indicating that DHA induces not only apoptosis but also autophagy. We also observed that DHA-induced autophagy was accompanied by p53 loss. Inhibition of p53 increased DHA-induced autophagy and prevention of p53 degradation significantly led to the attenuation of DHA-induced autophagy, suggesting that DHA-induced autophagy is mediated by p53. Further experiments showed that the mechanism of DHA-induced autophagy associated with p53 attenuation involved an increase in the active form of AMP-activated protein kinase and a decrease in the activity of mammalian target of rapamycin. In addition, compelling evidence for the interplay between autophagy and apoptosis induced by DHA is supported by the findings that autophagy inhibition suppressed apoptosis and further autophagy induction enhanced apoptosis in response to DHA treatment. Overall, our results demonstrate that autophagy contributes to the cytotoxicity of DHA in cancer cells harboring wild-type p53.

PMID: 21811093  
[PubMed indexed for MEDLINE]  
PMCID: PMC3242799

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EPA and Cancer Prevention


Eicosapentaenoic acid (EPA) efficacy for colorectal aberrant crypt foci (ACF): a double-blind randomized controlled trial.


Source
Division of Gastroenterology, Yokohama City University School of Medicine, 3-9 Fuku-ura, Kanazawa-ku, Yokohama 236-0004, Japan.
Abstract

BACKGROUND:
Colorectal cancer (CRC) is one of the most commonly occurring neoplasms and a leading cause of cancer death worldwide, and new preventive strategies are needed to lower the burden of this disease. Eicosapentaenoic acid (EPA), the omega-3 polyunsaturated fatty acid that is widely used in the treatment of hyperlipidemia and prevention of cardiovascular disease, has recently been suggested to have a suppressive effect on tumorigenesis and cancer cell growth. In CRC chemoprevention trials, in general, the incidence of polyps or of the cancer itself is set as the study endpoint. Although the incidence rate of CRC would be the most reliable endpoint, use of this endpoint would be unsuitable for chemoprevention trials, because of the relatively low occurrence rate of CRC in the general population and the long-term observation period that it would necessitate. Moreover, there is an ethical problem in conducting long-term trials to determine whether a test drug might be effective or harmful. Aberrant crypt foci (ACF), defined as lesions containing crypts that are larger in diameter and stain more darkly with methylene blue than normal crypts, are considered as a reliable surrogate biomarker of CRC. Thus, we devised a prospective randomized controlled trial as a preliminary study prior to a CRC chemoprevention trial to evaluate the chemopreventive effect of EPA against colorectal ACF formation and the safety of this drug, in patients scheduled for polypectomy.

METHODS:
This study is a multicenter, double-blind, placebo-controlled, randomized controlled trial to be conducted in patients with both colorectal ACF and colorectal polyps scheduled for polypectomy. Eligible patients shall be recruited for the study and the number of ACF in the rectum counted at the baseline colonoscopy. Then, the participants shall be allocated randomly to either one of two groups, the EPA group and the placebo group. Patients in the EPA group shall receive oral 900 mg EPA capsules thrice daily (total daily dose, 2.7 g per day), and those in the placebo group shall receive oral placebo capsules thrice daily. After one month's treatment with EPA/placebo, colonoscopic examination and polypectomy will be performed to evaluate the formation of ACF, and the cell-proliferative activity and cell-apoptotic activity in normal colorectal mucosa and colorectal polyps.

DISCUSSION:
This is the first study proposed to explore the effect of EPA against colorectal ACF formation in humans. This trial has been registered in the University hospital Medical Information Network (UMIN) Clinical Trials Registry as UMIN000008172.

PMID:
22992267
[PubMed - in process]
PMCID:
PMCS3515435

Fatty acids from fish: the anti-inflammatory potential of long-chain omega-3 fatty acids.
Wall R, Ross RP, Fitzgerald GF, Stanton C.
Source
Alimentary Pharmabiotic Centre (APC), County Cork, Ireland.
Abstract
Omega-6 (n-6) and omega-3 (n-3) polyunsaturated fatty acids (PUFA) are precursors of potent lipid mediators, termed eicosanoids, which play an important role in the regulation of inflammation. Eicosanoids derived from n-6 PUFAs (e.g., arachidonic acid) have proinflammatory and immunoactive functions, whereas eicosanoids derived from n-3 PUFA s [e.g., eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)] have anti-inflammatory properties, traditionally attributed to their ability to inhibit the formation of n-6 PUFA-derived eicosanoids. While the typical Western diet has a much greater ratio of n-6 PUFAs compared with n-3 PUFAs, research has shown that by increasing the ratio of n-3 to n-6 fatty acids in the diet, and consequently favoring the production of EPA in the body, or by increasing the dietary intake of EPA and DHA through consumption of fatty fish or fish-oil supplements, reductions may be achieved in the incidence of many chronic diseases that involve inflammatory processes; most notably, these include cardiovascular diseases, inflammatory bowel disease (IBD), cancer, and rheumatoid arthritis, but psychiatric and neurodegenerative illnesses are other examples.
PMID:
20500789
Eicosapentaenoic acid reduces rectal polyp number and size in familial adenomatous polyposis.

**West NJ, Clark SK, Phillips RK, Hutchinson JM, Leicester RJ, Belluzzi A, Hull MA.**

**Source**
Section of Molecular Gastroenterology, Leeds Institute of Molecular Medicine, St James's University Hospital, Leeds, UK.

**Abstract**

**OBJECTIVE:** The omega-3 polyunsaturated fatty acid eicosapentaenoic acid (EPA) has anticolorectal cancer activity in vitro and in preclinical models. The present study tested whether a novel, enteric-coated formulation of EPA, as the free fatty acid (EPA-FFA), has chemopreventative efficacy in patients with familial adenomatous polyposis (FAP), in a randomised, double-blind, placebo-controlled trial.

**METHODS:** Patients undergoing endoscopic surveillance of their retained rectum postcolectomy were randomised to EPA-FFA (SLA Pharma) 2 g daily or placebo for 6 months. The number and size of polyps in an area of mucosa defined by a tattoo were determined before and after intervention. Global rectal polyp burden was scored (-1, 0, +1) by examination of video endoscopy records. Mucosal fatty acid content was measured by gas chromatography-mass spectrometry.

**RESULTS:** 55 patients with FAP were evaluated by an intention-to-treat analysis (EPA-FFA 28, placebo 27). Treatment with EPA-FFA for 6 months was associated with a mean 22.4% (95% CI 5.1% to 39.6%) reduction in polyp number (p=0.012) and a 29.8% (3.6% to 56.1%) decrease in the sum of polyp diameters (p=0.027). Global polyp burden worsened over 6 months in the placebo group (-0.34) unlike the EPA-FFA group (+0.09, difference 0.42 (0.10-0.75), p=0.011). EPA-FFA treatment led to a mean 2.6-fold increase in mucosal EPA levels (p=0.018 compared with placebo). EPA-FFA was well tolerated with an incidence of adverse events similar to placebo.

**CONCLUSIONS:** EPA-FFA has chemopreventative efficacy in FAP, to a degree similar to that previously observed with selective cyclo-oxygenase-2 inhibitors. EPA holds promise as a colorectal cancer chemoprevention agent with a favourable safety profile.

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[PubMed - indexed for MEDLINE]
DHA and EPA significantly attenuate the migration/invasion of MDA-MB-231 breast cancer cells in culture. The mechanism that limits breast cancer cells to selective metastasis to bone remains hitherto unexplored. Aberrant increased expression of CD44 is associated with generation of cancer stem cells, which contribute to metastasis of breast cancer cells. We demonstrate that DHA and EPA significantly inhibit the expression of CD44 protein and mRNA by a transcriptional mechanism. Furthermore, we show markedly reduced levels of CD44 mRNA and protein in the tumors of mice, which were fed fish oil diet than those in control diet. Our data provide the first evidence for a salutary effect of fish oil on breast cancer metastasis to bone. Our results identify a novel function of the fish oil active components, DHA and EPA, which target the cell-intrinsic pro-metastatic molecule CD44 to inhibit migration/invasion.

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Fatty fish and fish omega-3 fatty acid intakes decrease the breast cancer risk: a case-control study.


Source
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Abstract
BACKGROUND:
Although it is believed that fish omega-3 fatty acids may decrease breast cancer risk, epidemiological evidence has been inconclusive. This study examined the association between fish and fish omega-3 fatty acids intake with the risk of breast cancer in a case-control study of Korean women.

METHODS:
We recruited 358 incident breast cancer patients and 360 controls with no history of malignant neoplasm from the National Cancer Center Hospital between July 2007 and April 2008. The study participants were given a 103-item food intake frequency questionnaire to determine their dietary consumption of fish (fatty and lean fish) and omega-3 fatty acids derived from fish (eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA)).

RESULTS:
Using a multivariate logistic regression model, high intake of fatty fish was associated with a reduced risk for breast cancer in both pre- and postmenopausal women (OR [95% CI] for highest vs. lowest intake quartiles, p for trend: 0.19 [0.08 to 0.45], p < 0.001 for premenopausal women, 0.27 [0.11 to 0.66], p = 0.005 for postmenopausal women). Similarly, reductions in breast cancer risk were observed among postmenopausal subjects who consumed more than 0.101 g of EPA (OR [95% CI]: 0.38 [0.15 to 0.96]) and 0.213 g of DHA (OR [95% CI]: 0.32 [0.13 to 0.82]) from fish per day compared to the reference group who consumed less than 0.014 g of EPA and 0.037 g of DHA per day. Among premenopausal women, there was a significant reduction in breast cancer risk for the highest intake quartiles of omega-3 fatty acids (ORs [95% CI]: 0.46 [0.22 to 0.96]), compared to the reference group who consumed the lowest quartile of intake.

CONCLUSION:
These results suggest that high consumption of fatty fish is associated with a reduced risk for breast cancer, and that the intake of omega-3 fatty acids from fish is inversely associated with postmenopausal breast cancer risk.

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Fatty acid facts, part II: role in the prevention of carcinogenesis, or, more fish on the dish?

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Abstract
Many laboratory studies suggest that n-3 fatty acids, especially the long-chain polyunsaturated fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have antitumor effects. The mechanisms involved in their anticarcinogenic action include the suppression of the biosynthesis of proinflammatory molecules, the influence on transcription factor activity and gene expression, the influence on signal transduction, the alteration of hormone-stimulated cell growth and the suppression of the production of free radicals and reactive oxygen species. In general, n-6 fatty acids and their derivatives promote the production of proinflammatory eicosanoids, whereas n-3 fatty acids suppress this action. The encouraging preclinical results are only scarcely confirmed in reviews and meta-analysis of epidemiological data roughly published before 2005. However, around 2005, the first reports on epidemiological studies based on the assessment of the concentration of EPA and DHA in the erythrocyte cell membrane in individual study participants started to appear. Without exception, these publications demonstrate that higher EPA (and possibly DHA) concentrations in the cell membrane, a validated measure for plasma fatty acids, is associated with lower cancer risk. These intriguing results are confirmed by the recently published huge European Prospective Investigation into cancer and nutrition (N = 478,040 men and women) and U.S.-based Physicians Health Study (N = 22,071 men). These studies have unequivocally confirmed that fish intake has a favorable effect on cancer risk. This review aims to elucidate the various mechanisms by which n-3 fatty acids may affect the process of carcinogenesis. For this summary of knowledge, we focus on the effects of n-3 intake on the risk of breast cancer, prostate cancer and colorectal cancer.

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