Tumeric (Biocurcumin)/black pepper (piperine) combination

Introduction

Biocurcumin has emerged as a potent cancer-preventing agent, with over 240 published studies appearing in the global scientific literature in the past year. Biocurcumin's multimodal effects act to simultaneously counter ten discrete causative factors in cancer development. It intervenes at each stage in the complex sequence of events that must occur in order for a cancer to develop, progress, invade, and ultimately metastasize to healthy tissue. The multi-targeted mechanisms of Biocurcumin have yielded compelling results in combating a broad array of cancers, including those of the breast, uterus, cervix, prostate and gastrointestinal tract. A burgeoning body of research demonstrates Biocurcumin's potential to counter cancers of the blood, brain, lung, and bladder as well. Piperine has been shown to enhance the absorption and effectiveness of Biocurcumin. In addition, piperine may exert anti-inflammatory and anti-tumour activities.

Current Uses & Trials

According to the American Cancer Society, while “Human studies of curcumin in cancer prevention and treatment are in the very early stages,” nonetheless “A number of studies of curcumin have shown promising results. Biocurcumin can kill cancer cells in laboratory dishes and also reduces growth of surviving cells. Curcumin also has been found to reduce development of several forms of cancer in laboratory animals and to shrink animal tumours.” The substance is undergoing further research in universities such as UCLA’s Jonsson’s Comprehensive Cancer Center, which has published promising results regarding head & neck cancers, as well as UCLA’s Center for Integrative Oncology and University of Texas MD Anderson Cancer Center.

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See Full References

Tumeric Biocurcumin - black pepper References

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j. Sehgal A et al; Department of Zoology, Panjab University, Chandigarh, India; Piperine as an adjuvant increases the efficacy of curcumin in mitigating benzo(a)pyrene toxicity; Hum Exp Toxicol. 2011 Oct 25. [Epub ahead of print];
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CURCUMIN SCIENCE REVIEW

1.

Breast Cancer Res Treat. 2010 August; 122(3): 777–785.

Targeting Breast Stem Cells with the Cancer Preventive Compounds Curcumin and Piperine

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Abstract

Background

The cancer stem cell hypothesis asserts that malignancies arise in tissue stem and/or progenitor cells through the dysregulation or acquisition of self-renewal. In order to determine whether the dietary polyphenols, curcumin and piperine, are able to modulate the self-renewal of normal and malignant breast stem cells, we examined the effects of these compounds on mammosphere formation, on expression of the breast stem cell marker aldehyde dehydrogenase (ALDH), and on Wnt signaling.

Design

Mammosphere formation assays were performed after curcumin, piperine and control treatment in unsorted normal breast epithelial cells and normal stem and early progenitor cells, selected by ALDH positivity. Wnt signaling was examined using a Topflash assay.

Results

Both curcumin and piperine inhibited mammosphere formation, serial passaging and percent of ALDH+ cells, by 50% at 5 μM and completely at 10 μM concentration in normal and malignant breast cells. There was no effect on cellular differentiation. Wnt signaling was inhibited by both curcumin and piperine by 50% at 5 μM and completely at 10μM.

Conclusion

Curcumin and piperine separately, and in combination, inhibit breast stem cell self renewal but do not cause toxicity to differentiated cells. These compounds could be potential cancer preventive agents. Mammosphere formation assays may be a quantifiable biomarker to assess cancer preventive agent efficacy and Wnt signaling assessment a mechanistic biomarker for use in human clinical trials.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3039120/

2.

FEBS J. 2010 Aug;277(16):3437-48. Epub 2010 Jul 14.

Curcumin suppresses the dynamic instability of microtubules, activates the mitotic checkpoint and induces apoptosis in MCF-7 cells.

Banerjee M, Singh P, Panda D.

Source

Department of Biosciences & Bioengineering, Indian Institute of Technology Bombay, Mumbai, India.

Abstract

In this study, curcumin, a potential anticancer agent, was found to dampen the dynamic instability of individual microtubules in living MCF-7 cells. It strongly reduced the rate and extent of shortening states,

and modestly reduced the rate and extent of growing states. In addition, curcumin decreased the fraction of time microtubules spent in the growing state and strongly increased the time microtubules spent in the pause state. Brief treatment with curcumin depolymerized mitotic microtubules, perturbed microtubule-kinetochore attachment and disturbed the mitotic spindle structure. Curcumin also perturbed the localization of the kinesin protein Eg5 and induced monopolar spindle formation. Further, curcumin increased the accumulation of Mad2 and BubR1 at the kinetochores, indicating that it activated the mitotic checkpoint. In addition, curcumin treatment increased the metaphase/anaphase ratio, indicating that it can delay mitotic progression from the metaphase to anaphase. We provide evidence suggesting that the affected cells underwent apoptosis via the p53-dependent apoptotic pathway. The results support the idea that kinetic stabilization of microtubule dynamics assists in the nuclear translocation of p53. Curcumin exerted additive effects when combined with vinblastine, a microtubule depolymerizing drug, whereas the combination of curcumin with paclitaxel, a microtubule-stabilizing drug, produced an antagonistic effect on the inhibition of MCF-7 cell proliferation. The results together suggested that curcumin inhibited MCF-7 cell proliferation by inhibiting the assembly dynamics of microtubules.

3.

National Cancer Institute at the National Institutes of Health

NCI Drug Dictionary

Curcumin

A phytopolylphenol pigment isolated from the plant Curcuma longa, commonly known as turmeric, with a variety of pharmacologic properties. Curcumin blocks the formation of reactive-oxygen species, possesses anti-inflammatory properties as a result of inhibition of cyclooxygenases (COX) and other enzymes involved in inflammation; and disrupts cell signal transduction by various mechanisms including inhibition of protein kinase C. These effects may play a role in the agent's observed antineoplastic properties, which include inhibition of tumor cell proliferation and suppression of chemically induced carcinogenesis and tumor growth in animal models of cancer. Check for active clinical trials or closed clinical trials using this agent. (NCI Thesaurus)

http://www.cancer.gov/drugdictionary?cdrid=440023

4.

Mol Nutr Food Res. 2008 Sep;52(9):1010-30.

Multi-targeted therapy by curcumin: how spicy is it?

Goel A, Jhurani S, Aggarwal BB.

Source

Gastrointestinal Cancer Research Laboratory, Department of Internal Medicine, Charles A Sammons Cancer Center and Baylor Research Institute, Baylor University Medical Center, Dallas, TX, USA.

Abstract

Although traditional medicines have been used for thousands of years, for most such medicines neither the active component nor their molecular targets have been very well identified. Curcumin, a yellow component of turmeric or curry powder, however, is an exception. Although inhibitors of cyclooxygenase-2, HER2, tumor necrosis factor, EGFR, Bcr-abl, proteosome, and vascular endothelial cell growth factor have been approved for human use by the United States Food and Drug Administration (FDA), curcumin as a single agent can down-regulate all these targets. Curcumin can also activate apoptosis, down-regulate cell survival gene products, and up-regulate p53, p21, and p27. Although curcumin is poorly absorbed after ingestion, multiple studies have suggested that even low levels of physiologically achievable concentrations of curcumin may be sufficient for its chemopreventive and chemotherapeutic activity. Thus, curcumin regulates multiple targets (multitargeted therapy), which is needed for treatment of most diseases, and it is inexpensive and has been found to be safe in human clinical trials. The present article reviews the key molecular mechanisms of curcumin action and compares this to some of the single-targeted therapies currently available for human cancer.

5.

Asian Pac J Cancer Prev. 2009;10(6):963-7.

Curcumin: from food spice to cancer prevention.

Oyagbemi AA, Saba AB, Ibraheem AO.

Source

Department of Veterinary Physiology, Biochemistry and Pharmacology, Faculty of Veterinary Medicine, University of Ibadan, Oyo State, Nigeria. ademolaoyagbemi@yahoo.com

Abstract

Curcumin [1, 7-bis (4-hydroxy-3-methoxyphenyl)-1, 6 heptadiene-3, 5-dione] is an orange-yellow component of turmeric (Curcuma longa), a spice often found in curry powder. It is known to have a variety of biologic and pharmacologic activities, including anti-inflammatory, anti-oxidant, and anticarcinogenic potential. It is a potent inhibitor of cytochrome P450 with capacity to simultaneously induce detoxifying enzymes such as glutathione S-transferase and as such may find application as a chemopreventive agent. Curcumin is a potent inhibitor of cyclooxygenase-2, lipooxygenase, ornithine decarboxylase (ODC), nuclear factor-kappaB, c-Jun N-terminal kinase and protein kinase C and has also been demonstrated to play a vital role against pathological conditions such as cancer, atherosclerosis, and neurodegenerative diseases.

6.

Front Biosci (Schol Ed). 2010 Jan 1;2:697-717.

Novel aspects for the application of Curcumin in chemoprevention of various cancers.

Bachmeier BE, Killian P, Pfeffer U, Nerlich AG.

Source

Department of Clinical Chemistry and Clinical Biochemistry, Ludwig-Maximilians University Munich, München, Germany. bachmeier@med.uni-muenchen.de

Abstract

Chemoprevention of malignant tumor growth is a novel and potentially powerful approach for tumor therapy. Recent in vitro and in vivo investigations provide increasing evidence that naturally occurring substances may exhibit significant chemopreventive activities. To this regard, the spice Curcumin, widely used in Indian cuisine, has been identified to show considerable anti-tumor effects. Most interestingly, numerous studies have not shown toxic side effects of this substance. Curcumin induces tumor cell apoptosis along with a reduction of tumor cell invasion and metastasis. Recent molecular studies provide evidence that Curcumin acts via a control of the NFkappaB pathway exerting most of the various modulating and moderating effects on malignant cells. Along with these in vitro studies, ex vivo and first clinical investigations confirm the anti-tumor effects of Curcumin, either as an isolated chemoprevention substance or in combination with chemotherapeutic agents as supportive measure reducing pharmaceutical resistance of tumor cells to certain chemotherapeutics. Despite our increasing knowledge on this interesting substance there still remain many unknown effects that deserve intense investigation.

7.

Mol Nutr Food Res. 2008 Sep;52(9):1010-30.

Multi-targeted therapy by curcumin: how spicy is it?

Goel A, Jhurani S, Aggarwal BB.

Source

Gastrointestinal Cancer Research Laboratory, Department of Internal Medicine, Charles A Sammons Cancer Center and Baylor Research Institute, Baylor University Medical Center, Dallas, TX, USA.

Abstract

Although traditional medicines have been used for thousands of years, for most such medicines neither the active component nor their molecular targets have been very well identified. Curcumin, a yellow component of turmeric or curry powder, however, is an exception. Although inhibitors of cyclooxygenase-2, HER2, tumor necrosis factor, EGFR, Bcr-abl, proteosome, and vascular endothelial cell growth factor have been approved for human use by the United States Food and Drug Administration (FDA), curcumin as a single agent can down-regulate all these targets. Curcumin can also activate apoptosis, down-regulate cell survival gene products, and up-regulate p53, p21, and p27. Although curcumin is poorly absorbed after ingestion, multiple studies have suggested that even low levels of physiologically achievable concentrations of curcumin may be sufficient for its chemopreventive and chemotherapeutic activity. Thus, curcumin regulates multiple targets (multitargeted therapy), which is needed for treatment of most diseases, and it is inexpensive and has been found to be safe in human clinical trials. The present article reviews the key molecular mechanisms of curcumin action and compares this to some of the single-targeted therapies currently available for human cancer.

8.

Nutr Cancer. 2010;62(7):919-30.

Curcumin, the golden spice from Indian saffron, is a chemosensitizer and radiosensitizer for tumors and chemoprotector and radioprotector for normal organs.

Goel A, Aggarwal BB.

Source

Department of Internal Medicine, Baylor University Medical Center, Dallas, Texas, USA.

Abstract

Curcumin (diferuloylmethane), the yellow pigment in Indian saffron (Curcuma longa; also called turmeric, haldi, or haridara in the East and curry powder in the West), has been consumed by people for centuries as a dietary component and for a variety of proinflammatory ailments. Extensive research within the last decade in cell culture and in rodents has revealed that curcumin can sensitize tumors to different chemotherapeutic agents including doxorubicin, 5-FU, paclitaxel, vincristine, melphalan, butyrate, cisplatin, celecoxib, vinorelbine, gemcitabine, oxaliplatin, etoposide, sulfinosine, thalidomide, and bortezomib. Chemosensitization has been observed in cancers of the breast, colon, pancreas, gastric, liver, blood, lung, prostate, bladder, cervix, ovary, head and neck, and brain and in multiple myeloma, leukemia, and lymphoma. Similar studies have also revealed that this agent can sensitize a variety of tumors to gamma radiation including glioma, neuroblastoma, cervical carcinoma, epidermal carcinoma, prostate cancer, and colon cancer. How curcumin acts as a chemosensitizer and radiosensitizer has also been studied extensively. For example, it downregulates various growth regulatory pathways and specific genetic targets including genes for NF-κB, STAT3, COX2, Akt, antiapoptotic proteins, growth factor receptors, and multidrug-resistance proteins. Although it acts as a chemosensitizer and radiosensitizer for tumors in some cases, curcumin has also been shown to protect normal organs such as liver, kidney, oral mucosa, and heart from chemotherapy and radiotherapy-induced toxicity. The protective effects of curcumin appear to be mediated through its ability to induce the activation of NRF2 and induce the expression of antioxidant enzymes (e.g., hemeoxygenase-1, glutathione peroxidase, modulatory subunit of gamma-glutamyl-cysteine ligase, and NAD(P)H:quinone oxidoreductase 1, increase glutathione (a product of the modulatory subunit of gamma-glutamyl-cysteine ligase), directly quench free radicals, and inhibit p300 HAT activity. These preclinical studies are expected to lead to clinical trials to prove the potential of this age-old golden spice for treating cancer patients.

9.

Cancer Lett. 2005 Jun 8;223(2):181-90. Epub 2004 Nov 11.

Chemopreventive and therapeutic effects of curcumin.

Duvoix A, Blasius R, Delhalle S, Schnekenburger M, Morceau F, Henry E, Dicato M, Diederich M.

Source

Laboratoire de Biologie Moléculaire et Cellulaire du Cancer, Hôpital Kirchberg, 9, rue Edward Steichen, L-2540 Luxembourg, Luxembourg.

Abstract

Chemoprevention is a promising anti-cancer approach with reduced secondary effects in comparison to classical chemotherapy. Curcumin, one of the most studied chemopreventive agents, is a natural compound extracted from Curcuma longa L. that allows suppression, retardation or inversion of carcinogenesis. Curcumin is also described as an anti-tumoral, anti-oxidant and anti-inflammatory agent capable of inducing apoptosis in numerous cellular systems. In this review, we describe both properties and mode of action of curcumin on carcinogenesis, gene expression mechanisms and drug metabolism.

10.

Curr Drug Discov Technol. 2009 Sep;6(3):192-9. Epub 2009 Sep 1.

Systemic delivery of curcumin: 21st century solutions for an ancient conundrum.

Bisht S, Maitra A.

Source

Department of Pathology, The Sol Goldman Pancreatic Cancer Research Center, Johns Hopkins University School of Medicine, Baltimore, MD 21231, USA.

Abstract

Curcumin, a polyphenolic compound derived from the dietary spice turmeric, possesses diverse pharmacologic effects including anti-inflammatory, anti-oxidant, anti-proliferative and anti-angiogenic activities. Accumulating experimental evidence suggests that curcumin interferes with a variety of molecular targets and processes involved in cancer. Further, data obtained in multiple preclinical models, as well as in preliminary clinical trials, have documented minimal toxicity of curcumin, even at relatively high doses. However, the clinical advancement of this promising molecule has been hindered by its poor water solubility, short biological half-life, and low bioavailability after oral administration. A variety of approaches are being pursued to overcome these limitations, which include synthesis of curcumin analogues, the use of adjuvants (e.g. piperine), and the development of improved delivery platforms for the parental compound, including liposomal, nanoparticulated and phospholipid complex formulations of curcumin. This review is intended to provide the reader an update on the bioavailability and pharmacokinetic pitfalls of free curcumin, and a comprehensive cataloging of ongoing approaches that have been undertaken to resolve these issues, with the goal of harnessing the true potential of this anti-cancer agent in the clinical arena.

11.

Mol Pharmacol. 2006 Jan;69(1):195-206. Epub 2005 Oct 11.

Curcumin (diferuloylmethane) down-regulates expression of cell proliferation and antiapoptotic and metastatic gene products through suppression of IkappaBalpha kinase and Akt activation.

Aggarwal S, Ichikawa H, Takada Y, Sandur SK, Shishodia S, Aggarwal BB.

Source

Cytokine Research Laboratory, Department of Experimental Therapeutics, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030-4009, USA.

Abstract

Curcumin (diferuloylmethane), an anti-inflammatory agent used in traditional medicine, has been shown to suppress cellular transformation, proliferation, invasion, angiogenesis, and metastasis through a mechanism not fully understood. Because several genes that mediate these processes are regulated by nuclear factor-kappaB (NF-kappaB), we have postulated that curcumin mediates its activity by modulating NF-kappaB activation. Indeed, our laboratory has shown previously that curcumin can suppress NF-kappaB activation induced by a variety of agents (J Biol Chem 270:24995-50000, 1995). In the present study, we investigated the mechanism by which curcumin manifests its effect on NF-kappaB and NF-kappaB-regulated gene expression. Screening of 20 different analogs of curcumin showed that curcumin was the most potent analog in suppressing the tumor necrosis factor (TNF)-induced NF-kappaB activation. Curcumin inhibited TNF-induced NF-kappaB-dependent reporter gene expression in a dose-dependent manner. Curcumin also suppressed NF-kappaB reporter activity induced by tumor necrosis factor receptor (TNFR)1, TNFR2, NF-kappaB-inducing kinase, IkappaB kinase complex (IKK), and the p65 subunit of NF-kappaB. Such TNF-induced NF-kappaB-regulated gene products involved in cellular proliferation [cyclooxygenase-2 (COX-2), cyclin D1, and c-myc], antiapoptosis [inhibitor of apoptosis protein (IAP)1, IAP2, X-chromosome-linked IAP, Bcl-2, Bcl-x(L), Bfl-1/A1, TNF receptor-associated factor 1, and cellular Fas-associated death domain protein-like interleukin-1beta-converting enzyme inhibitory protein-like inhibitory protein], and metastasis (vascular endothelial growth factor, matrix metalloproteinase-9, and intercellular adhesion molecule-1) were also down-regulated by curcumin. COX-2 promoter activity induced by TNF was abrogated by curcumin. We found that curcumin suppressed TNF-induced nuclear translocation of p65, which corresponded with the sequential suppression of IkappaBalpha kinase activity, IkappaBalpha phosphorylation, IkappaBalpha degradation, p65 phosphorylation, p65 nuclear translocation, and p65 acetylation. Curcumin also inhibited TNF-induced Akt activation and its association with IKK. Glutathione and dithiothreitol reversed the effect of curcumin on TNF-induced NF-kappaB activation. Overall, our results indicated that curcumin inhibits NF-kappaB activation and NF-kappaB-regulated gene expression through inhibition of IKK and Akt activation.

12.

Clin Cancer Res. 2007 Jun 1;13(11):3423-30.

Curcumin inhibits tumor growth and angiogenesis in ovarian carcinoma by targeting the nuclear factor-kappaB pathway.

Lin YG, Kunnumakkara AB, Nair A, Merritt WM, Han LY, Armaiz-Pena GN, Kamat AA, Spannuth WA, Gershenson DM, Lutgendorf SK, Aggarwal BB, Sood AK.

Source

Department of Gynecologic Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX 77030, USA.

Abstract

PURPOSE:

Curcumin, a component of turmeric, has been shown to suppress inflammation and angiogenesis largely by inhibiting the transcription factor nuclear factor-kappaB (NF-kappaB). This study evaluates the effects of curcumin on ovarian cancer growth using an orthotopic murine model of ovarian cancer.

EXPERIMENTAL DESIGN:

In vitro and in vivo experiments of curcumin with and without docetaxel were done using human ovarian cancer cell lines SKOV3ip1, HeyA8, and HeyA8-MDR in athymic mice. NF-kappaB modulation was ascertained using electrophoretic mobility shift assay. Evaluation of angiogenic cytokines, cellular proliferation (proliferating cell nuclear antigen), angiogenesis (CD31), and apoptosis (terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling) was done using immunohistochemical analyses.

RESULTS:

Curcumin inhibited inducible NF-kappaB activation and suppressed proliferation in vitro. In vivo dose-finding experiments revealed that 500 mg/kg orally was the optimal dose needed to suppress NF-kappaB and signal transducers and activators of transcription 3 activation and decrease angiogenic cytokine expression. In the SKOV3ip1 and HeyA8 in vivo models, curcumin alone resulted in 49% ($P = 0.08$) and 55% ($P = 0.01$) reductions in mean tumor growth compared with controls, whereas when combined with docetaxel elicited 96% ($P < 0.001$) and 77% reductions in mean tumor growth compared with controls. In mice with multidrug-resistant HeyA8-MDR tumors, treatment with curcumin alone and combined with docetaxel resulted in significant 47% and 58% reductions in tumor growth, respectively ($P = 0.05$). In SKOV3ip1 and HeyA8 tumors, curcumin alone and with docetaxel decreased both proliferation ($P < 0.001$) and microvessel density ($P < 0.001$) and increased tumor cell apoptosis ($P < 0.05$).

CONCLUSIONS:

Based on significant efficacy in preclinical models, curcumin-based therapies may be attractive in patients with ovarian carcinoma.

13.

Pharmacol Res. 2003 Feb;47(2):133-40.

Anticarcinogenic effect of bis-1,7-(2-hydroxyphenyl)-hepta-1,6-diene-3,5-dione a curcumin analog on DMH-induced colon cancer model.

Devasena T, Rajasekaran KN, Gunasekaran G, Viswanathan P, Menon VP.

Source

Department of Biochemistry, Faculty of Science, Annamalai University, Annamalai Nagar 608 002, Tamil Nadu, India.

Abstract

1,2-Dimethylhydrazine (DMH) is a toxic environmental pollutant which was reported also to be a colon-specific carcinogen. This study was performed to study the effect of bis-1,7-(2-hydroxyphenyl)-hepta-1,6-diene-3,5-dione, a bisdemethoxycurcumin analog (BDMC-A) on DMH-induced colon carcinogenesis in male Wistar rats and effects were compared with that of the reference drug, curcumin. Rats were given a weekly subcutaneous injection of DMH (20mg/kg body weight) in the groin, for 15 weeks. After a total experimental period of 32 weeks (including 2 weeks of acclimatization) tumor incidence was 100% in DMH-treated rats. Tumor was identified histologically as adenocarcinoma. Dysplasia, papillary pattern, cellular pleomorphism and carcinomatous glands were also noticed in DMH-treated rats. However, there was no colonic tumor in DMH+BDMC-A- and DMH+curcumin-treated rats but, lymphocyte infiltrations were observed. The levels of total bile acids and cholesterol in 24h fecal samples were significantly lower in DMH administered rats when compared to control rats, while, the excretion of bile acids and cholesterol were significantly increased and was near normal levels in DMH+BDMC-A- and DMH+curcumin-treated rats. In DMH-induced tumor bearing rats the levels of colonic and intestinal cholesterol was significantly increased whereas, the levels of phospholipid was decreased with a concomitant increase in the activities of phospholipase A (PLA) and phospholipase C (PLC), compared to untreated control rats. Intragastric administration of BDMC-A and curcumin to DMH administered rats significantly lowered the cholesterol content and raised the phospholipid content and lowered the activities of PLA and PLC towards near normal values. Our study shows that the protective effect of BDMC-A during DMH-induced colon carcinogenesis may be due to its modulatory effects on (i). histological changes, (ii). bile acids, (iii). cholesterol, and (iv). phospholipid metabolism in the target organ. Absence of histological changes in the colon of rats treated with BDMC-A, shows that long term administration of BDMC-A is nontoxic to experimental animals. Our study suggest that BDMC-A may emerge as a potent anticarcinogenic agent against colon cancer. As both BDMC-A and curcumin are equipotent in inhibiting the DMH-induced colon tumor incidence and normalizing histological changes, it could be concluded that the terminal phenolic group and the conjugated double bonds in the central seven carbon change may be responsible for the beneficial effects.

14.

Carcinogenesis. 2012 Oct 26. [Epub ahead of print]

Curcumin inhibits prostate cancer metastasis in vivo by targeting the inflammatory cytokines CXCL1 and -2.

Killian PH, Kronski E, Michalik KM, Barbieri O, Astigiano S, Sommerhoff CP, Pfeffer U, Nerlich AG, Bachmeier BE.

Source

Institute of Laboratory Medicine, Ludwig-Maximilians-University, Munich, Germany.

Abstract

In America and Western Europe, prostate cancer is the second leading cause of death in men. Emerging evidence suggests that chronic inflammation is a major risk factor for the development and metastatic progression of prostate cancer. We previously reported that the chemopreventive polyphenol curcumin inhibits the expression of the proinflammatory cytokines CXCL1 and -2 leading to diminished formation of breast cancer metastases. In this study, we analyze the effects of curcumin on prostate carcinoma growth, apoptosis and metastasis. We show that curcumin inhibits translocation of NFκB to the nucleus through the inhibition of the IκB-kinase (IKKβ, leading to stabilization of the inhibitor of NFκB, IκBα, in PC-3 prostate carcinoma cells. Inhibition of NFκB activity reduces expression of CXCL1 and -2 and abolishes the autocrine/paracrine loop that links the two chemokines to NFκB. The combination of curcumin with the synthetic IKKβ inhibitor, SC-541, shows no additive or synergistic effects indicating that the two compounds share the target. Treatment of the cells with curcumin and siRNA-based knockdown of CXCL1 and -2 induce apoptosis, inhibit proliferation and downregulate several important metastasis-promoting factors like COX2, SPARC and EFEMP. In an orthotopic mouse model of hematogenous metastasis, treatment with curcumin inhibits statistically significantly formation of lung metastases. In conclusion, chronic inflammation can induce a metastasis prone phenotype in prostate cancer cells by maintaining a positive proinflammatory and prometastatic feedback loop between NFκB and CXCL1/-2. Curcumin disrupts this feedback loop by the inhibition of NFκB signaling leading to reduced metastasis formation in vivo.

15.

Cancer Epidemiol Biomarkers Prev January 2005 14; 120

Consumption of the Putative Chemopreventive Agent Curcumin by Cancer Patients: Assessment of Curcumin Levels in the Colorectum and their Pharmacodynamic Consequences

1. Giuseppe Garcea1,
2. David P. Berry2,
3. Donald J.L. Jones1,
4. Raj Singh1,
5. Ashley R. Dennison2,
6. Peter B. Farmer1,
7. Ricky A. Sharma1,
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Abstract

Curcumin, a constituent of the spice turmeric, has been shown to reduce the adenoma burden in rodent models of colorectal cancer accompanied by a reduction of levels of the oxidative DNA adduct 3-(2-deoxy-**β**-di-erythro-pentafuranosyl)-pyr[1,2-α]-purin-10(3*H*)one (M_1G) and of expression of the enzyme

cyclooxygenase-2 (COX-2). We tested the hypothesis that pharmacologically active levels of curcumin can be achieved in the colorectum of humans as measured by effects on levels of M_1G and COX-2 protein. Patients with colorectal cancer ingested curcumin capsules (3,600, 1,800, or 450 mg daily) for 7 days. Biopsy samples of normal and malignant colorectal tissue, respectively, were obtained at diagnosis and at 6 to 7 hours after the last dose of curcumin. Blood was taken 1 hour after the last dose of curcumin. Curcumin and its metabolites were detected and quantitated by high-performance liquid chromatography with detection by UV spectrophotometry or mass spectrometry. M_1G levels and COX-2 protein expression were measured by immunoslot blot and Western blotting, respectively. The concentrations of curcumin in normal and malignant colorectal tissue of patients receiving 3,600 mg of curcumin were 12.7 ± 5.7 and 7.7 ± 1.8 nmol/g, respectively. Curcumin sulfate and curcumin glucuronide were identified in the tissue of these patients. Trace levels of curcumin were found in the peripheral circulation. M_1G levels were 2.5-fold higher in malignant tissue as compared with normal tissue ($P < 0.05$ by ANOVA). Administration of curcumin (3,600 mg) decreased M_1G levels from 4.8 ± 2.9 adducts per 107 nucleotides in malignant colorectal tissue to 2.0 ± 1.8 adducts per 107 nucleotides ($P < 0.05$ by ANOVA). COX-2 protein levels in malignant colorectal tissue were not affected by curcumin. The results suggest that a daily dose of 3.6 g curcumin achieves pharmacologically efficacious levels in the colorectum with negligible distribution of curcumin outside the gut.

Cancer Prev Res March 2011 4; 354

Phase IIa Clinical Trial of Curcumin for the Prevention of Colorectal Neoplasia

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Abstract

Curcumin is derived from the spice tumeric and has antiinflammatory and antineoplastic effects *in vitro* and in animal models, including preventing aberrant crypt foci (ACF) and adenomas in murine models of colorectal carcinogenesis. Inhibiting the production of the procarcinogenic eicosanoids prostaglandin E_2 (PGE_2) and 5-hydroxyeicosatetraenoic acid (5-HETE) can suppress carcinogenesis in rodents. Curcumin reduces mucosal concentrations of PGE_2 (via inhibition of cyclooxygenases 1 and 2) and 5-HETE (via inhibition of 5-lipoxygenase) in rats. Although preclinical data support curcumin activity in many sites, the poor bioavailability reported for this agent supports its use in the colorectum. We assessed the effects of oral curcumin (2 g or 4 g per day for 30 days) on PGE_2 within ACF (primary endpoint), 5-HETE, ACF number, and proliferation in a nonrandomized, open-label clinical trial in 44 eligible smokers with eight or more ACF on screening colonoscopy. We assessed pre- and post treatment concentrations of PGE_2 and 5-HETE by liquid chromatography tandem mass spectroscopy in ACF and normal-tissue biopsies; ACF number via rectal endoscopy; proliferation by Ki-67 immuno-histochemistry; and curcumin concentrations by high-performance liquid chromatography in serum and rectal mucosal samples. Forty-one subjects completed the study. Neither dose of curcumin reduced PGE_2 or 5-HETE within ACF or normal mucosa or reduced Ki-67 in normal mucosa. A significant 40% reduction in ACF number occurred with the 4-g dose ($P < 0.005$), whereas ACF were not reduced in the 2-g group. The ACF reduction in the 4-g group was associated with a significant, five-fold increase in posttreatment plasma curcumin/conjugate levels (versus pretreatment; $P = 0.009$). Curcumin was well tolerated at both 2 g and 4 g. Our data suggest that curcumin can decrease ACF number, and this is potentially mediated by curcumin conjugates delivered systemically.

Ginger

GINGER SCIENCE REVIEW

1.

BMC Complement Altern Med. 2007 Dec 20;7:44.

Ginger inhibits cell growth and modulates angiogenic factors in ovarian cancer cells.

Rhode J, Fogoros S, Zick S, Wahl H, Griffith KA, Huang J, Liu JR.

Source

Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, University of Michigan, Ann Arbor, MI, USA. JnMRhode@aol.com

Abstract

BACKGROUND:

Ginger (Zingiber officinale Rosc) is a natural dietary component with antioxidant and anticarcinogenic properties. The ginger component [6]-gingerol has been shown to exert anti-inflammatory effects through mediation of NF-kappaB. NF-kappaB can be constitutively activated in epithelial ovarian cancer cells and may contribute towards increased transcription and translation of angiogenic factors. In the present study, we investigated the effect of ginger on tumor cell growth and modulation of angiogenic factors in ovarian cancer cells in vitro.

METHODS:

The effect of ginger and the major ginger components on cell growth was determined in a panel of epithelial ovarian cancer cell lines. Activation of NF-kappaB and and production of VEGF and IL-8 was determined in the presence or absence of ginger.

RESULTS:

Ginger treatment of cultured ovarian cancer cells induced profound growth inhibition in all cell lines tested. We found that in vitro, 6-shogaol is the most active of the individual ginger components tested. Ginger treatment resulted in inhibition of NF-kB activation as well as diminished secretion of VEGF and IL-8.

CONCLUSION:

Ginger inhibits growth and modulates secretion of angiogenic factors in ovarian cancer cells. The use of dietary agents such as ginger may have potential in the treatment and prevention of ovarian cancer.

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1 .	Cancer Prev Res (Phila). 2011 Nov;4(11):1929-37. Epub 2011 Oct 11. **Phase II Study of the Effects of Ginger Root Extract on Eicosanoids in Colon Mucosa in People at Normal Risk for Colorectal Cancer.** Zick SM, Turgeon DK, Vareed SK, Ruffin MT, Litzinger AJ, Wright BD, Alrawi S, Normolle DP, Djuric Z, Brenner DE. **Source** 24 Frank Lloyd Wright Drive, Lobby M, P.O. Box 385, University of Michigan Medical Center, Ann Arbor, MI 48105. szick@med.umich.edu. **Abstract** Inhibitors of COX indicate that upregulation of inflammatory eicosanoids produced by COX, and in particular prostaglandin E(2) (PGE(2)), are early events in the development of colorectal cancer (CRC). Ginger has shown downregulation of COX in vitro and decreased incidence/multiplicity of adenomas in rats. This study was conducted to determine if 2.0 g/d of ginger could decrease the levels of PGE(2), 13-hydroxy-octadecadienoic acids, and 5-, 12-, and 15-hydroxyeicosatetraenoic acid (5-, 12-, and 15-HETE), in the colon mucosa of healthy volunteers. To investigate this aim, we randomized 30 subjects to 2.0 g/d ginger or placebo for 28 days. Flexible sigmoidoscopy at baseline and day 28 was used to obtain colon biopsies. A liquid chromatography mass spectrometry method was used to determine eicosanoid levels in the biopsies, and levels were expressed per protein or per free arachidonic acid. There were no significant differences in mean percent change between baseline and day 28 for any of the eicosanoids, when normalized to protein. There was a significant decrease in mean percent change in PGE(2) (P = 0.05) and 5-HETE (P = 0.04), and a trend toward significant decreases in 12-HETE (P = 0.09) and 15-HETE (P = 0.06) normalized to free arachidonic acid. There was no difference

	between the groups in terms of total adverse events P = 0.55). On the basis of these results, it seems that ginger has the potential to decrease eicosanoid levels, perhaps by inhibiting their synthesis from arachidonic acid. Ginger also seemed to be tolerable and safe. Further investigation in people at high risk for CRC seems warranted. Cancer Prev Res; 4(11); 1929-37. ©2011 AACR. PMCID: PMC3208778 [Available on 2012/11/1]
PMID: 21990307 [PubMed - in process]	

Introduction

Research has shown that ginger appears to offer a two-pronged attack on cancer cells: it makes them commit suicide, known as apoptosis, and self-digest, known as autophagy. The anti-carcinogenic properties come from the pungent constituents such as valinoids, gingeroids, and paradols, as well as some of the other components like shogaois and zingerone found in the aromatic rhizome of the herb.

Current Uses & Trials

The University of Michigan has been most aggressive in its testing and publishing of results regarding ginger and colo-rectal cancer prevention. Georgia State University has conducted additional research on the use of ginger in prevention and treatment of prostate cancer. The substance is also in use in the treatment of various malignancies at the University of Texas MD Anderson Cancer Center.

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See Full Document

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j. GINGER SCIENCE REVIEW

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m. Ginger inhibits cell growth and modulates angiogenic factors in ovarian cancer cells.

n. Rhode J, Fogoros S, Zick S, Wahl H, Griffith KA, Huang J, Liu JR.

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p. Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, University of Michigan, Ann Arbor, MI, USA. JnMRhode@aol.com

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r. BACKGROUND:

s. Ginger (Zingiber officinale Rosc) is a natural dietary component with antioxidant and anticarcinogenic properties. The ginger component [6]-gingerol has been shown to exert anti-inflammatory effects through mediation of NF-kappaB. NF-kappaB can be constitutively activated in epithelial ovarian cancer cells and may contribute towards increased transcription and translation of angiogenic factors. In the present study, we investigated the effect of ginger on tumor cell growth and modulation of angiogenic factors in ovarian cancer cells in vitro.

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u. The effect of ginger and the major ginger components on cell growth was determined in a panel of epithelial ovarian cancer cell lines. Activation of NF-kappaB and and production of VEGF and IL-8 was determined in the presence or absence of ginger.

v. *RESULTS:*

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ee. 24 Frank Lloyd Wright Drive, Lobby M, P.O. Box 385, University of Michigan Medical Center, Ann Arbor, MI 48105. szick@med.umich.edu.

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ll. Shukla Y, Singh M.

mm. Source

nn. Environmental Carcinogenesis Division, Industrial Toxicology Research Centre, P.O. Box 80, M.G. Marg, Lucknow 226 001, Uttar Pradesh, India. yogeshwer_shukla@hotmail.com <yogeshwer_shukla@hotmail.com>

oo. Abstract

pp. Ginger, the rhizome of Zingiber officinalis, one of the most widely used species of the ginger family, is a common condiment for various foods and beverages. Ginger has a long history of medicinal use dating back 2500 years. Ginger has been traditionally used from time immemorial for varied human ailments in different parts of the globe, to aid digestion and treat stomach upset, diarrhoea, and nausea. Some pungent constituents present in ginger and other zingiberaceous plants have potent antioxidant and anti-inflammatory activities, and some of them exhibit cancer preventive activity in experimental carcinogenesis. The anticancer properties of ginger are attributed to the presence of certain pungent vallinoids, viz. [6]-gingerol and [6]-paradol, as well as some other constituents like shogaols, zingerone etc. A number of mechanisms that may be involved in the chemopreventive effects of ginger and its components have been reported from the laboratory studies in a wide range of experimental models. 4.

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tt. Source

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vv. Abstract

ww. The rhizomes of Zingiber officinale Roscoe (Zingiberaceae), commonly known as ginger, is one of the most widely used spice and condiment. It is also an integral part of many traditional medicines and has been extensively used in Chinese, Ayurvedic, Tibb-Unani, Srilankan, Arabic, and African traditional medicines, since antiquity, for many unrelated human ailments including common colds, fever, sore throats, vomiting, motion sickness, gastrointestinal complications, indigestion, constipation, arthritis, rheumatism, sprains, muscular aches, pains, cramps, hypertension, dementia, fever, infectious diseases, and helminthiasis. The putative active compounds are nonvolatile pungent principles, namely gingerols, shogaols, paradols, and zingerone. These compounds are some of the extensively studied phytochemicals and account for the antioxidant, anti-inflammatory, antiemetic, and gastroprotective activities. A number of preclinical investigations with a wide variety of assay systems and carcinogens have shown that ginger and its compounds possess chemopreventive and antineoplastic effects. A number of mechanisms have been observed to be involved in the chemopreventive effects of ginger. The cancer preventive activities of ginger are supposed to be mainly due to free radical scavenging, antioxidant pathways, alteration of gene expressions, and induction of apoptosis, all of which contribute towards decrease in tumor initiation, promotion,

and progression. This review provides concise information from preclinical studies with both cell culture models and relevant animal studies by focusing on the mechanisms responsible for the chemopreventive action. The conclusion describes directions for future research to establish its activity and utility as a human cancer preventive and therapeutic drug. The above-mentioned mechanisms of ginger seem to be promising for cancer prevention; however, further clinical studies are warranted to assess the efficacy and safety of ginger.

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ddd. Department of Biology, Georgia State University, Atlanta, GA 30303, USA.

eee. Abstract

fff. It is appreciated far and wide that increased and regular consumption of fruits and vegetables is linked with noteworthy anticancer benefits. Extensively consumed as a spice in foods and beverages worldwide, ginger (Zingiber officinale Roscoe) is an excellent source of several bioactive phenolics, including non-volatile pungent compounds such as gingerols, paradols, shogaols and gingerones. Ginger has been known to display anti-inflammatory, antioxidant and antiproliferative activities, indicating its promising role as a chemopreventive agent. Here, we show that whole ginger extract (GE) exerts significant growth-inhibitory and death-inductory effects in a spectrum of prostate cancer cells. Comprehensive studies have confirmed that GE perturbed cell-cycle progression, impaired reproductive capacity, modulated cell-cycle and apoptosis regulatory molecules and induced a caspase-driven, mitochondrially mediated apoptosis in human prostate cancer cells. Remarkably, daily oral feeding of 100 mg/kg body weight of GE inhibited growth and progression of PC-3 xenografts by approximately 56 % in nude mice, as shown by measurements of tumour volume. Tumour tissue from GE-treated mice showed reduced proliferation index and widespread apoptosis compared with controls, as determined by immunoblotting and immunohistochemical methods. Most importantly, GE did not exert any detectable toxicity in normal, rapidly dividing tissues such as gut and bone marrow. To the best of our knowledge, this is the first report to demonstrate the in vitro and in vivo anticancer activity of whole GE for the management of prostate cancer.

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ppp. Biomedical Research Center, Ulsan University Hospital, College of Medicine, University of Ulsan, Ulsan, Republic of Korea.

qqq. Abstract

rrr. Tumor-infiltrating lymphocytes (TILs) play critical roles in host anti-tumor immune responses. It is known that cancer patients with tumor-reactive lymphocyte infiltration in their tumors have better prognoses, while patients with tumors infiltrated by immunosuppressive cells have worse prognoses. We found that administration of 6-gingerol, which is a component of ginger, inhibited tumor growth in several types of murine tumors, such as B16F1 melanomas, Renca renal cell carcinomas and CT26 colon carcinomas, which were established by inoculating tumor cells on the flanks of mice. However, administration of 6-gingerol did not lead to complete eradication of the tumors. 6-Gingerol treatment of tumor-bearing mice caused massive infiltration of CD4 and CD8 T-cells and B220(+) B-cells, but reduced the number of CD4(+) Foxp3(+) regulatory T-cells. The CD8 tumor-infiltrating T lymphocytes in 6-gingerol-treated mice strongly expressed IFN-γ, a marker of activation of CTL CD107a, and chemokine receptors that are expressed on T(H) 1 cells, such as CXCR3 and CCR5. To test whether 6-gingerol could promote infiltration of tumor antigen-specific CD8 T-cells into tumors, we adoptively transferred CFSE-labeled OT-I CD8 T-cells into EG7 tumor-bearing mice. We found that CD8 T cells isolated from 6-gingerol pre-treated OT-I mice, but not from control OT-I mice, massively infiltrated tumors and tumor draining lymph nodes and divided several times. Our results strongly suggest that 6-gingerol can be used in tumor immunotherapy to increase the number of TILs.

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xxx. Source

yyy. Institute of Biomedical Sciences and School of Life Sciences, East China Normal University, 500 Dongchuan Road, Shanghai 200241, China. xfpang@bio.ecnu.edu.cn

zzz. Abstract

aaaa. Cancer therapeutic agents that are safe, effective and affordable are urgently needed. We describe that 1'-acetoxychavicol acetate (ACA), a component of Siamese ginger (Languas galanga), can suppress prostate tumor growth by largely abrogating angiogenesis. ACA suppressed vascular endothelial growth factor (VEGF)-induced proliferation, migration, adhesion and tubulogenesis of primary cultured human umbilical vascular endothelial cells (HUVECs) in a dose-dependent manner. ACA also inhibited VEGF-induced microvessel sprouting from aortic rings ex vivo and suppressed new vasculature formation in Matrigel plugs in vivo. We further demonstrated that the mechanisms of this chavicol were to block the activation of VEGF-mediated Src kinase, focal adhesion kinase (FAK) and Rho family of small guanosine

triphosphatases (GTPases) (Rac1 and Cdc42 but not RhoA) in HUVECs. Furthermore, treatment of human prostate cancer cells (PC-3) with ACA resulted in decreased cell viability and suppression of angiogenic factor production by interference with dual Src/FAK kinases. After subcutaneous administration to mice bearing human prostate cancer PC-3 xenografts, ACA (6 mg/kg/day) remarkably inhibited tumor volume and tumor weight and decreased levels of Src, CD31, VEGF and Ki-67. As indicated by immunohistochemistry and TUNEL analysis, microvessel density and cell proliferation were also dramatically suppressed in tumors from ACA-treated mice. Taken together, our findings suggest that ACA targets the Src-FAK-Rho GTPase pathway, leading to the suppression of prostate tumor angiogenesis and growth.

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eeee. **Pharmacokinetic profiles of anticancer herbal medicines in humans and the clinical implications.**

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hhhh. Department of General Surgery, Shunde First People's Hospital Affiliated to Southern Medical University, Foshan, Guangdong, China.

iiii. **Abstract**

jjjj. A number of herbal medicines are increasingly used by cancer patients worldwide, despite the fact that the clinical evidence that supports their use to fight cancer is weak or lacking. Pharmacokinetic studies have been integrated into modern drug development, but they are generally not needed for herbal remedies. To update our knowledge in this field, this paper highlights the pharmacokinetic properties of anticancer herbal medicines and the clinical relevance. To retrieve relevant data, the authors have searched through computer-based literatures by full text search in Medline (via Pubmed), ScienceDirect, Current Contents Connect (ISI), Cochrance Library, CINAHL (EBSCO), CrossRef Search and Embase ((all from inception to May 2011). An extensive literature search indicatesthat there are limited data on the pharmacokinetic properties of anticancer herbal medicines in humans. There are increasing pharmacokinetic studies of anticancer herbal remedies, but these studies are mainly focused on a small number of herbal medicines including curcumin, ginseng, ginkgo, ginger and milk thistle. For an anticancer herbal medicine, the pharmacological activity is gained when the active agents or the active metabolites reach and sustain proper levels at their sites of action. Both the dose levels and pharmacokinetic processes of active herbal components in the body determine their target-site concentrations and thus the anticancer effect. In this regard, a safe and optimal use of anticancer herbal medicines requires a full understanding of their pharmacokinetic profiles. To optimize the use of anticancer herbal remedies, further studies to explore their pharmacokinetic properties and the relevance to pharmacodynamics and toxicity in humans are certainly warranted.

Vitamin D3

Introduction

A vitamin D receptor (VDR), a protein encoded by the VDR gene plays a role in the vitamin D pathway such that higher levels are associated with significantly higher risks of dying from cancer. These receptors are associated with low vitamin D levels. Vitamin D has been shown to decrease cell proliferation and boost apoptosis. Dozens of studies suggest an association between low vitamin D levels and increased many types of prevalent cancers. Strong research suggests that sufficient levels of Vitamin D could prevent at least two-thirds of breast cancer, colorectal cancer and skin cancer, and more than a fifth of pancreatic cancer.

Current Uses & Trials

Vitamin D has been the most studied and documented of the natural cancer preventatives. It is being used and researched in many clinical settings as a preventative and treatment. Most promising results have been published with respect to prevention of breast, prostate, colo-rectal, lung and ovarian cancers.

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See Full Document

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Secrets Revealed: The Powerful Health Benefits of the Pomegranate

One of the oldest known fruits, found in writings and artifacts of many cultures and religions, the pomegranate (punica granatum) is an original native of Persia. This nutrient dense, antioxidant rich fruit has been revered as a symbol of health, fertility and eternal life. If you're not familiar with the pomegranate, it is a red fruit with a tough outer layer; only the juice and the seeds inside are edible. Pomegranate juice is available year round, but you can purchase fresh pomegranates in most grocery stores from September through January. When refrigerated in a plastic bag, pomegranates keep for up to 2 months. Try tossing the seeds on a salad for a brilliantly colorful, crunchy, and nutritious addition.

Seeding a pomegranate may seem like a lot of work for just a piece of fruit but think again. getting at those seeds may be well worth it. The pomegranate is a nutrient dense food source rich in phytochemical compounds. Pomegranates contain high levels of flavonoids and polyphenols, potent antioxidants offering protection against heart disease and cancer. A glass of pomegranate juice has more antioxidants than red wine, green tea, blueberries, and cranberries.

Amazing Clinical Results
This fantastic little fruit recently made its way back into the news after some spectacular clinical results. Here's what you need to know:

Compounds found only in pomegranates called punicalagins are shown to benefit the heart and blood vessels. Punicalagins are the major component responsible for pomegranate's antioxidant and health benefits. They not only lower cholesterol, but also lower blood pressure and increase the speed at which heart blockages (atherosclerosis) melt away.

Recent medical research studied heart patients with severe carotid artery blockages. They were given an ounce of pomegranate juice each day for a year. Not only did study participants' blood pressure lower by over 12 percent, but there was a 30 percent reduction in atherosclerotic plaque. Just as astounding, participants who did not take the pomegranate juice saw their atherosclerotic plaque increase by 9 percent.[1]

In other studies, potent antioxidant compounds found in pomegranates have shown to reduce platelet aggregation and naturally lower blood pressure, factors that prevent both heart attacks and strokes.[2]

Not only are pomegranates good for your heart and blood vessels but they have been shown to inhibit breast cancer, prostate cancer, colon cancer, leukemia and to prevent vascular changes that promote tumour growth in lab animals.[3] Several in vitro studies have shown this remarkable anti-cancer effect. Additional studies and clinical trials currently taking place are hopeful to reveal this fascinating effect on humans.

Also of note, pomegranate juice contains phytochemical compounds that stimulate serotonin and oestrogen receptors, improving symptoms of depression and increasing bone mass in lab animals. [4]

Many studies show that the pomegranate is one of the most powerful, nutrient dense foods for overall good health. These clinical findings clearly show a correlation between pomegranate compounds and their positive effect on both human and animal cardiovascular, nervous, and skeletal health. This is one fruit that you can't afford to exclude from your diet!

Features of the Pomegranate

- Most powerful anti-oxidant of all fruits
- Potent anti-cancer and immune supporting effects
- Inhibits abnormal platelet aggregation that could cause heart attacks, strokes and embolic disease
- Lowers cholesterol and other cardiac risk factors
- Lowers blood pressure
- Shown to promote reversal of atherosclerotic plaque in human studies
- May have benefits to relieve or protect against depression and osteoporosis

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TEA

A Member of the University of Maryland Medical System in Partnership with the University of Maryland School of Medicine

Tea has been cultivated for centuries, beginning in India and China. Today, tea is the most widely consumed beverage in the world, second only to water. Hundreds of millions of people drink tea, and studies suggest that green tea (Camellia sinesis) in particular has many health benefits.

There are three main varieties of tea -- green, black, and oolong. The difference is in how the teas are processed. Green tea is made from unfermented leaves and reportedly contains the highest concentration of powerful antioxidants called polyphenols. Antioxidants are substances that fight free radicals -- damaging compounds in the body that change cells, damage DNA, and even cause cell death. Many scientists believe that free radicals contribute to the aging process as well as the development of a number of health problems, including cancer and heart disease. Antioxidants such as polyphenols in green tea can neutralize free radicals and may reduce or even help prevent some of the damage they cause.

In traditional Chinese and Indian medicine, practitioners used green tea as a stimulant, a diuretic (to help rid the body of excess fluid), an astringent (to control bleeding and help heal wounds), and to improve heart health. Other traditional uses of green tea include treating gas, regulating body temperature and blood sugar, promoting digestion, and improving mental processes.

Green tea has been extensively studied in people, animals, and laboratory experiments. Results from these studies suggest that green tea may help treat the following health conditions:

Atherosclerosis

Clinical studies that look at populations of people indicate that the antioxidant properties of green tea may help prevent atherosclerosis, particularly coronary artery disease. Population-based studies are studies that follow large groups of people over time or studies that compare groups of people living in different cultures or with different diets.

Researchers aren't sure why green tea reduces the risk of heart disease by lowering cholesterol and triglyceride levels. Studies show that black tea has similar effects. In fact, researchers estimate that the rate of heart attack decreases by 11% with consumption of 3 cups of tea per day.

In May 2006, however, the U.S. Food and Drug Administration (FDA) rejected a petition from teamakers to allow tea labels to claim that green tea reduces the risk of heart disease. The FDA concluded that there is no credible evidence to support that claim.

High cholesterol

Research shows that green tea lowers total cholesterol and raises HDL ("good") cholesterol in both animals and people. One population-based clinical study found that men who drink green tea are more likely to have lower total cholesterol than those who do not drink green tea.

Results from one animal study suggest that polyphenols in green tea may block cholesterol from being absorbed in the intestine and also help the body get rid of cholesterol. In another small study of male smokers, researchers found that green tea significantly reduced blood levels of harmful LDL cholesterol.

Cancer

Several population-based clinical studies have shown that both green and black teas may help protect against cancer. For example, cancer rates tend to be low in countries such as Japan where people regularly consume green tea. However, it is not possible to know for sure from these population-based studies whether green tea actually prevents cancer in people.

Early clinical studies suggest that the polyphenols in tea, especially green tea, may play an important role in the prevention of cancer. Researchers also believe that polyphenols help kill cancerous cells and stop them from growing.

Bladder cancer. Only a few clinical studies have examined the relationship between bladder cancer and drinking tea. In one study that compared people with and without bladder cancer, researchers found that women who drank black tea and powdered green tea were less likely to develop bladder cancer. A follow-up clinical study by the same group of researchers revealed that people with bladder cancer -- particularly men -- who drank green tea had a better 5-year survival rate than those who did not.

Breast cancer. Clinical studies in animals and test tubes suggest that polyphenols in green tea inhibit the growth of breast cancer cells. In one study of 472 women with various stages of breast cancer, researchers found that women who drank the most green tea had the least spread of cancer. It was especially true in premenopausal women in the early stages of breast cancer. They also found that women with early stages of the disease who drank at least 5 cups of tea every day before being diagnosed with cancer were less likely to have the cancer come back after they finished treatment. However, women with late stages of breast cancer had little or no improvement from drinking green tea.

There is no clear evidence one way or the other about green tea and breast cancer prevention. In one very large study, researchers found that drinking tea, green or any other type, was not associated with a reduced risk of breast cancer. However, when the researchers broke down the sample by age, they found that women under the age of 50 who consumed 3 or more cups of tea per day were 37% less likely to develop breast cancer compared to women who didn't drink tea.

Ovarian cancer. In a clinical study done with ovarian cancer patients in China, researchers found that women who drank at least one cup of green tea per day lived longer with the disease than those who didn’t drink green tea. In fact, those who drank the most tea, lived the longest. But other studies found no beneficial effects.

Colorectal cancer. Clinical studies on the effects of green tea on colon or rectal cancer have showed conflicting results. Some studies show decreased risk in those who drink the tea, while others show increased risk. In one study, women who drank 5 or more cups of green tea per day had a lower risk of colorectal cancer compared to non-tea-drinkers. There was no protective effect for men, however. Other studies show that drinking tea regularly may reduce the risk of colorectal cancer in women. More research is needed before researchers can recommend green tea for the prevention of colorectal cancer.

Esophageal cancer. Studies in laboratory animals have found that green tea polyphenols inhibit the growth of esophageal cancer cells. However, studies in people have produced conflicting findings. For example, one large-scale population-based clinical study found that green tea offered protection against the development of esophageal cancer, particularly among women. Another population-based clinical study found just the opposite -- green tea consumption was associated with an increased risk of esophageal cancer. In fact, the stronger and hotter the tea, the greater the risk. Given these conflicting results, more research is needed before scientists can recommend green tea for the prevention of esophageal cancer.

Lung cancer. While green tea polyphenols have been shown to inhibit the growth of human lung cancer cells in test tubes, few clinical studies have looked at the link between drinking green tea and lung cancer in people. And even these studies have been conflicting. One population-based study found that Okinawan tea -- similar to green tea but partially fermented -- was associated with lower lung cancer risk, particularly among women. But a second clinical study found that green tea and black tea increased the risk of lung cancer. More studies are needed before researchers can draw any conclusions about green tea and lung cancer.

Pancreatic cancer. In one large-scale clinical study researchers compared green tea drinkers with non-drinkers and found that those who drank the most tea were less likely to develop pancreatic cancer. This was particularly true for women -- those who drank the most green tea were half as likely to develop pancreatic cancer as those who drank less tea. Men who drank the most tea were 37% less likely to develop pancreatic cancer.

However, it is not clear from this population-based study whether green tea is solely responsible for lowering pancreatic cancer risk. More studies in animals and people are needed before researchers can recommend green tea for the prevention of pancreatic cancer.

Prostate cancer. Laboratory studies have found that green tea extracts prevent the growth of prostate cancer cells in test tubes. In a large clinical study in Southeast China researchers found that the risk of prostate cancer went down with increasing frequency, duration and quantity of green tea consumption. However, both green and black tea extracts also stimulated genes that cause cells to be less sensitive to chemotherapy drugs. People who are undergoing chemotherapy should ask their doctors before drinking green or black tea, or taking tea supplements.

Skin cancer. The main polyphenol in green tea is epigallocatechin gallate (EGCG). Scientific studies suggest that EGCG and green tea polyphenols have anti-inflammatory and anticancer properties that may help prevent the development and growth of skin tumors.

Stomach cancer. Laboratory studies have found that green tea polyphenols inhibit the growth of stomach cancer cells in test tubes, but studies in people have been less conclusive. In two studies that compared green tea drinkers with non-drinkers, researchers found that people who drank tea were about half as likely to develop stomach cancer and stomach inflammation as those who did not drink green tea. However, a clinical study with more than 26,000 men and women in Japan found no association between green tea and stomach cancer risk. Some studies even suggest that green tea may increase the risk of stomach cancer.

More clinical studies are underway to see whether green tea helps reduce the risk of stomach cancer.

Inflammatory Bowel Disease (IBD)

Green tea may help reduce inflammation associated with Crohn's disease and ulcerative colitis, the two types of IBD. If green tea proves to help prevent colon cancer, it would also help those with IBD because they are at higher risk for colon cancer.

Diabetes

Green tea has been used traditionally to control blood sugar levels. Animal studies suggest that green tea may help prevent the development of type 1 diabetes and slow the progression once it has developed. In people with type 1 diabetes, their bodies make little or no insulin, which helps convert glucose or sugar into energy. Green tea may help regulate glucose in the body.

A few small clinical studies have found that taking a green tea extract daily lowered the hemoglobin A1c level in people with borderline diabetes.

Liver disease

Population-based clinical studies have shown that men who drink more than 10 cups of green tea per day are less likely to develop liver problems. Green tea also seems to protect the liver from the damaging effects of toxic substances such as alcohol. Animal studies have shown that green tea helps protect against liver tumors in mice.

Results from several animal and human studies suggest that one of the polyphenols in green tea, known as catechin, may help treat viral hepatitis, an inflammation of the liver. In these studies, catechin was

used by itself in very high amounts. It is not clear whether green tea, which has a lower concentration of catechins, would have the same benefits.

10 cups of green tea a day could cause problems because of the high level of caffeine consumed. Ask your doctor about the best way to include green tea in your treatment.

Weight loss

Clinical studies suggest that green tea extract may boost metabolism and help burn fat. One study found that the combination of green tea and caffeine improved weight loss and maintenance in people who were overweight and moderately obese. Some researchers think that substances in green tea known as catechins are responsible for the herb's fat-burning effect.

Other uses

One small study found that drinking green tea helped prevent dental cavities. More studies need to be done. Green tea may also be useful in inflammatory diseases, such as arthritis. Research suggests that green tea may help arthritis by reducing inflammation and slowing the breakdown of cartilage. Chemicals in green tea may also be help treat genital warts and prevent symptoms of colds and flu. Studies also show that drinking green tea is associated with reduced risk of dying from any cause.

Plant Description

Green, black, and oolong tea are all derived from the leaves of the Camellia sinensis plant. Originally cultivated in East Asia, this plant grows as large as a shrub or tree. Today, Camellia sinensis grows throughout Asia and parts of the Middle East and Africa.

People in Asian countries more commonly consume green and oolong tea while black tea is most popular in the United States. Green tea is prepared from unfermented leaves, the leaves of oolong tea are partially fermented, and black tea is fully fermented. The more the leaves are fermented, the lower the polyphenol content (See: "What's It Made Of?") and the higher the caffeine content. Green tea has the highest polyphenol content while black tea has roughly 2 - 3 times the caffeine content of green tea.

What's It Made Of?

Researchers think the health-giving properties of green tea are mostly due to polyphenols, chemicals with potent antioxidant properties. In fact, the antioxidant effects of polyphenols seem to be greater than vitamin C. The polyphenols in green tea also give it a somewhat bitter flavor.

Polyphenols contained in teas are classified as catechins. Green tea contains six primary catechin compounds: catechin, gallaogatechin, epicatechin, epigallocatechin, epicatechin gallate, and apigallocatechin gallate (also known as EGCG). EGCG is the most studied polyphenol component in green tea and the most active.

Green tea also contains alkaloids including caffeine, theobromine, and theophylline. They provide green tea's stimulant effects. L-theanine, an amino acid compound found in green tea, has been studied for its calming effects on the nervous system.

Available Forms

Most green tea dietary supplements are sold as dried leaf tea in capsule form. Look for standardized extracts of green tea. There are also liquid extracts made from the leaves and leaf buds. The average cup of green tea contains 50 - 150 mg polyphenols (antioxidants). Decaffeinated green tea products contain concentrated polyphenols. Caffeine-free supplements are available.

How to Take It

Paediatric

Green tea has not been studied in children, so it is not recommended for paediatric use.

Adult

Depending on the brand, 2 - 3 cups of green tea per day (for a total of 240 - 320 mg polyphenols) or 100 - 750 mg per day of standardized green tea extract is recommended. Caffeine-free products are available and recommended.

Precautions

The use of herbs is a time-honoured approach to strengthening the body and treating disease. However, herbs contain active substances that can trigger side effects and interact with other herbs, supplements, or medications. For these reasons, people should take herbs with care, under the supervision of a practitioner knowledgeable in the field of botanical medicine.

People with heart problems or high blood pressure, kidney problems, liver problems, stomach ulcers, and psychological disorders, particularly anxiety, should not take green tea. Pregnant and breastfeeding women should also avoid green tea.

People with anaemia, diabetes, glaucoma, or osteoporosis should ask their health care provider before drinking green tea or taking an extract.

People who drink large amounts of caffeine, including caffeine from green tea, for long periods of time may experience irritability, insomnia, heart palpitations, and dizziness. Caffeine overdose can cause nausea, vomiting, diarrhoea, headaches, and loss of appetite. If you are drinking a lot of tea and start to vomit or have abdominal spasms, you may have caffeine poisoning. If your symptoms are severe, lower your caffeine intake and see your health care provider.

Possible Interactions

If you are being treated with any of the following medications, you should not drink green tea or take green tea extract without first talking to your health care provider:

Adenosine -- Green tea may inhibit the actions of adenosine, a medication given in the hospital for an irregular and usually unstable heart rhythm.

Beta-lactam -- Green tea may increase the effectiveness of beta-lactam antibiotics by making bacteria less resistant to treatment.

Benzodiazepines -- Caffeine, including caffeine from green tea, may reduce the sedative effects of these medications commonly used to treat anxiety, such as diazepam (Valium) and lorazepam (Ativan).

Beta-blockers, Propranolol, and Metoprolol -- Caffeine, including caffeine from green tea, may increase blood pressure in people taking propranolol (Inderal) and metoprolol (Lopressor, Toprol XL). These medications are used to treat high blood pressure and heart disease.

Blood Thinning Medications -- People who take warfarin (Coudamin) should not drink green tea. Since green tea contains vitamin K, it can make this medication ineffective. You should not mix green tea and aspirin because they both prevent blood from clotting. Using the two together may increase your risk of bleeding.

Chemotherapy -- The combination of green tea and chemotherapy medications, specifically doxorubicin and tamoxifen, increased the effectiveness of these medications in laboratory tests. However, the same results have not been found in studies on people. On the other hand, there have been reports of both green and black tea extracts affecting a gene in prostate cancer cells that may make them less sensitive to chemotherapy drugs. For that reason, people should talk to their doctors before drinking black and green tea or taking tea extracts while undergoing chemotherapy.

Clozapine (Clozaril) -- The effects of the clozapine may be reduced if taken within 40 minutes after drinking green tea.

Ephedrine -- When taken with ephedrine, green tea may cause agitation, tremors, insomnia, and weight loss.

Lithium -- Green tea has been shown to reduce blood levels of lithium, a medication used to treat bipolar disorder. That can make lithium less effective.

Monoamine Oxidase Inhibitors (MAOIs) -- Green tea may cause a severe increase in blood pressure, called a "hypertensive crisis," when taken together with these drugs used to treat depression. Examples of MAOIs include:

Isocarboxazid (Marplan)

Moclobemide (Manerix)

Phenelzine (Nardil)

Tranylcypromine (Parnate)

Birth control pills -- Oral contraceptives can prolong the amount of time caffeine stays in the body, which may increase its stimulating effects.

Phenylpropanolamine -- A combination of caffeine, including caffeine from green tea, and phenylpropanolamine, used in many over-the-counter and prescription cough and cold medications and weight loss products, may cause mania and a severe increase in blood pressure. The FDA issued a public health advisory in November 2000 to warn people of the risk of bleeding in the brain from use of this medication and urged all manufacturers of this drug to remove it from the market. Most drugs that contained phenylpropanolamine have been reformulated without it.

Quinolone antibiotics -- Green tea may makes these medications more effective and also increase the risk of side effects. These medications include:

Ciprofloxacin (Cipro)

Enoxacin (Penetrex)

Grepafloxacin (Raxar)

Norfloxacin (Chibroxin, Noroxin)

Sparfloxacin (Zagam)

Trovafloxacin (Trovan)

Other medications -- Green tea, especially caffeinated green tea, may interact with a number for medications, including:

Acetaminophen (Tylenol)

Carbamazepine (Tegretol)

Dipyridamole (Persatine)

Estrogen

Fluvoxamine (Luvox)

Methotrexate

Mexiletine (Mexitil)

Phenobarbital

Theophylline

Verapamil (Bosoptin, Calan, Covera- HS, Verelan, Verelan PM)

To be safe, check with your health care provider before drinking or taking green tea if you also take other medications.

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Alternative Names

Camellia sinensis

[1] These statements have not been approved by the FDA. This product is not intended to diagnose, treat, cure, or prevent any disease

[1] National Cancer Institute, NCI Drug Dictionary
[1] This statement has not been approved by the FDA

Library

This section is intended to provide a central resource for the latest research, information and scientific insight on the subject of cancer prevention. We hope it will help you understand the issues more clearly and make it easier for you to come to discuss the subject with your health care provider and come to informed decisions.

- Vitamin D3 articles
- Biocurcumin (Tumeric)
- Additional Biocurcumin articles
- Ginger articles
- Pomegranate articles
- Green Tea Leaf articles

Cancer Prevention Facts

Cancer is a leading cause of death worldwide and deaths from cancer continue to rise.

- The latest research shows that about 65% of all cancer deaths can be prevented!

- Cancer – like most chronic diseases – involves a breakdown in the body's immune system due to environmental pollution, smoking, exposure to second hand smoke, alcohol consumption, poor or inadequate nutrition, lack of sufficient exercise and obesity, stress and genetic factors.

- Cancer prevention is an essential component of all cancer control plans and immuno-therapy is a cornerstone of this holistic approach.

- Building a stronger immune system is one of the keys to prevention. By invigorating the immune system, the body can maintain and rebuild its defences against the abnormal cell function that lies at the heart of the disease.

- It is nearly impossible to get total prevention from healthy foods alone since it would take ingestion of large quantities of often unavailable or expensive foods to achieve therapeutic levels.

- Taking single component nutrients do not add up to a viable nutrient-based prevention program since it is hard to know what works, which mixtures are complementary and which products are of suitable quality and potency.

- While growing consumer awareness, healthier diets and increased exercise have improved the success rate for preventive protocols today, the easiest and by far most effective part of a cancer prevention regimen is to implement a science-based immune-protective program.

That is precisely what RECNAC is all about.

Recnac LLC. has created RECNAC, an over-the counter formula that selectively combines a group of safe and promising natural ingredients, based upon the research of independent scientists and academic clinicians around the globe. Each ingredient has been and/or is currently being researched for effectiveness in prevention of some of the most widely diagnosed types of cancers – breast, prostate, colo-rectal, and pancreatic -- as the following science sections of this website will show. The formula represents a rich and powerful array of bioactive compounds, including phenolics, flavonoids, catechins and anthocyanins, some of which have antioxidant activity[1]. Four of the RECNAC ingredients are currently in active or closed clinical trials[2].

[1] These statements have not been approved by the FDA. This product is not intended to diagnose, treat, cure, or prevent any disease

[2] National Cancer Institute, NCI Drug Dictionary

For optimal results, the formula is meant to be combined with a cancer-prevention regime that includes diet and a vigorous exercise program, reduction of tobacco and alcohol use and exposure to toxins, and regular screening under the supervision of a competent health care practitioner**.**

[1] These statements have not been approved by the FDA. This product is not intended to diagnose, treat, cure, or prevent any disease

[2] National Cancer Institute, NCI Drug Dictionary

This scientific review is provided to doctors and health care practitioners only; it is for informational purposes only

THE SCIENCE BEHIND RECNAC

THE RECNAC FORMULAS

Mens & Womens

"RECNAC [Formulas Inc.] has put forward a combination of agents derived from plants and natural products which can probably help us increase further our chance of not getting cancer … It works on various mechanisms, including the immune system, which is very important and usually protects us against cancer... We can improve the immune system with these agents, and we can also bring about cell arrest and apoptosis, which are mechanisms that will prevent the cancer from spreading further."

-- ***Michael Burke, MD, Immunologist -- former Director, Clinical Immunology Unit, Tel Aviv Sourasky Medical Center (Ichilov), former faculty member, Harvard Medical School, Children's Hospital***

- ***RECNAC'S MEN'S AND WOMEN'S FORMULAS SHARE 4 BASIC INGREDIENTS THAT HAVE SHOWN PROMISE IN CANCER PREVENTION RESEARCH WITH RESPECT TO SOME OF THE MOST COMMONLY DIAGNOSED CANCERS, INCLUDING BREAST AND COLO-RECTAL[3]***
  - **BCM-95 Bio-Curcumin®**
  - **Ginger Extract**
  - **Green Tea Extract**
  - **Vitamin D3**

[3] This statement has not been approved by the FDA

- ***RECNAC MEN'S FORMULA IS FURTHER ENHANCED BY INGREDIENTS THAT HAVE BEEN CITED BY THE NATIONAL CANCER INSTITUTE AS HOLDING PROMISE IN THE AREA OF PROSTATE CANCER PREVENTION***[4]
  - **Pomegranate Extract**
  - **Additional Green Tea Extract**

- ***FOUR OF THE NEGDA INGREDIENTS ARE UNDERGOING CURRENT CLINICAL TRIALS***[5]

- ***WE HAVE SELECTED ONLY THE HIGHEST QUALITY INGREDIENTS AND EXTRACTS***

- ***BCM-95 BIO-CURCUMIN® is a patent pending curcuminoids complex from turmeric with enhanced*** *bioavailability* ***and sustained retention time in the body. The superior efficacy of BCM-95® is confirmed by*** *human clinical trials****.***
  - **100%** natural **turmeric extract.**
  - **4-8 times lower recommended dosage than with normal curcumin.**
  - **Clinical studies with BCM-95® have shown that the extract is 7-8 times more bioavailable than existing extracts from turmeric.**
  - **Powerful antioxidant with higher** ORAC **value (= 4000) than regular curcumin.**
  - **Superior anti-inflammatory activity.**

- ***GINGER EXTRACT that is neither treated nor irradiated***

- ***GREEN TEA EXTRACT containing:***
  - **98 polyphenols**
  - **EDCG: over 45%**
  - **Catechins: over 75%**

- ***POMEGRANATE EXTRACT containing 40% ellagic acid (men's formula)***

- ***VITAMIN D3 – 400iu/capsule***

- ***RECNAC IS VEGETARIAN, HALAAL AND KOSHER AND ALL INGREDIENTS ARE GRAS ("GENERALLY REGARDED AS SAFE") UNDER FDA GUIDELINES***

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[4] National Cancer Institute: Prostate Cancer, Nutrition, and Dietary Supplements (PDQ®); http://www.cancer.gov/cancertopics/pdq/cam/prostatesupplements/healthprofessional/page2

[5] NCI Drug Dictionary; http://www.cancer.gov/drugdictionary

RESEARCH HIGHLIGHTS BY INGREDIENT

CURCUMIN

GINGER EXTRACT

GREEN TEA EXTRACT

POMEGRANATE EXTRACT (men's formula only)

VITAMIN D3

(view the full library of research references and abstracts by clicking here)

CURCUMIN

"…multiple studies have suggested that even low levels of physiologically achievable concentrations of curcumin may be sufficient for its chemopreventive and chemotherapeutic activity"… **Gastrointestinal Cancer Research Laboratory, Baylor University Medical Center**

"…ex vivo and first clinical investigations confirm the anti-tumor effects of Curcumin, either as an isolated chemoprevention substance or in combination with chemotherapeutic agents as supportive measure reducing pharmaceutical resistance of tumor cells to certain chemotherapeutics"… **Department of Clinical Chemistry and Clinical Biochemistry, Ludwig-Maximilians University Munich**

"Curcumin, one of the most studied chemopreventive agents, is a natural compound extracted from Curcuma longa L. that allows suppression, retardation or inversion of carcinogenesis. Curcumin is also described as an anti-tumoral, anti-oxidant and anti-inflammatory agent capable of inducing apoptosis in numerous cellular systems"… **Laboratoire de Biologie Moléculaire et Cellulaire du Cancer, Hôpital Kirchberg, Luxembourg**

"Accumulating experimental evidence suggests that curcumin interferes with a variety of molecular targets and processes involved in cancer"… **Department of Pathology, The Sol Goldman Pancreatic Cancer Research Center, Johns Hopkins University School of Medicine**

"Curcumin (diferuloylmethane), an anti-inflammatory agent used in traditional medicine, has been shown to suppress cellular transformation, proliferation, invasion, angiogenesis, and metastasis"… **Cytokine Research Laboratory, The University of Texas MD Anderson Cancer Center**

"Based on significant efficacy in preclinical models, curcumin-based therapies may be attractive in patients with ovarian carcinoma"… **Department of Gynecologic Oncology, The University of Texas M. D. Anderson Cancer**

"Curcumin inhibits prostate cancer metastasis in vivo"… **Institute of Laboratory Medicine, Ludwig-Maximilians-University, Munich, Germany**

(click here to return to top of page)

GINGER

"Ginger inhibits cell growth and modulates angiogenic factors in ovarian cancer cells"… **Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, University of Michigan**

"…it seems that ginger has the potential to decrease eicosanoid levels, perhaps by inhibiting their synthesis from arachidonic acid. Ginger also seemed to be tolerable and safe"…. **University of Michigan Medical Center**

"Here, we show that whole ginger extract (GE) exerts significant growth-inhibitory and death-inductory effects in a spectrum of prostate cancer cells"… **Department of Biology, Georgia State University**

"Administration of 6-gingerol greatly enhances the number of tumor-infiltrating lymphocytes in murine tumors"… **College of Medicine, University of Ulsan, Ulsan, Republic of Korea**

(click here to return to top of page)

GREEN TEA

In a double-blind placebo-controlled study of 60 volunteers: "After 1 year, only one tumor was diagnosed among the 30 GTCs-treated men (incidence, approximately 3%), whereas nine cancers were found among the 30 placebo-treated men (incidence, 30%)… GTCs-treated men showed values constantly lower with respect to placebo-treated ones. International Prostate Symptom Score and quality of life scores of GTCs-treated men with coexistent benign prostate hyperplasia improved, reaching statistical significance in the case of International Prostate Symptom Scores. No significant side effects or adverse effects were documented" … **Department of Medicina Sperimentale, Sezione di Biochimica, University of Parma**

“In 2008, follow-up results to [THE PRECEEDING] study were published, indicating that the inhibitory effects of green tea catechins on prostate cancer progression were long-lasting” … **National Cancer Institute at NIH**

“These results provide strong evidence of both anti-mutagenic, anti-proliferative and anti-neoplastic activities for both black and green tea extracts. Such anticancer mechanisms may well be responsible for the cancer preventive efficacies seen in both experimental and human studies”… **Chemoprevention Branch, Division of Cancer Prevention, National Cancer Institute, NIH**

“The inhibition of tumorigenesis by green or black tea preparations has been demonstrated in animal models on different organ sites such as skin, lung, oral cavity, esophagus, forestomach, stomach, small intestine, colon, pancreas, and mammary gland”… **Laboratory for Cancer Research, Rutgers, The State University of New Jersey**

“We conclude that regular consumption of green tea can protect against breast cancer”… **The School of Population Health, The University of Western Australia**

“This study suggests that regular consumption of green tea may reduce CRC risk in women”… **Department of Medicine, Vanderbilt University School of Medicine**

“Green tea may be associated with a decreased risk of advanced prostate cancer”… **Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, Japan**

“These data suggest that the chemopreventive effects of green tea polyphenols may involve a p57 mediated survival pathway in normal epithelial cells, while oral carcinoma cells undergo an apoptotic pathway. Therefore, regular consumption of green tea could be beneficial in the prevention of oral cancer”… **Department of Oral Biology and Maxillofacial Pathology, School of Dentistry, Medical College of Georgia**

“All the results suggest that consumption of green tea is a practical and effective cancer preventive both before cancer onset and after cancer treatment”…. **Saitama Cancer Center Research Institute, Japan**

"Inhibition of VEGF transcription appeared to be one of the molecular mechanism(s) involved in the antiangiogenic effects of green tea"… **Department of Surgery, Division of Oncology and Center for Human Nutrition, University of California, Los Angeles**

"Epidemiologic and preclinical data support the oral cancer prevention potential of green tea extract (GTE)"… **Department of Thoracic/Head and Neck Medical Oncology, The University of Texas M. D. Anderson Cancer Center**

"The present study provides direct evidence that tea polyphenols may act as chemopreventive agents against gastric and esophageal cancer development"… **USC/Norris Comprehensive Cancer Center, University of Southern California Keck School of Medicine**

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POMEGRANATE EXTRACXT (MEN'S FORMULA ONLY)

"We report the first clinical trial of pomegranate juice in patients with prostate cancer. The statistically significant prolongation of PSA doubling time, coupled with corresponding laboratory effects on prostate cancer in vitro cell proliferation and apoptosis as well as oxidative stress, warrant further testing in a placebo-controlled study." … **Dept. of Urology, UCLA**

"Overall, this study demonstrates significant antitumor activity of pomegranate-derived materials against human prostate cancer." … **Institute of Anatomy and Cell Biology, Philipps University, Marburg, Germany**

"In conclusion, punicic acid, the main constituent of pomegranate seed (70-80%), exhibited potent growth inhibitory activities in androgen-dependent LNCaP cells, which appear to be mediated by both antiandrogenic and pro-apoptotic mechanisms." … **Institut National de la Recherche Scientifique, Institut Armand-Frappier, Université du Québec**

"POMx, a highly potent pomegranate extract prepared from skin and arils minus seeds and standardized to ellagitannin content (37% punicalagins by HPLC), resulted in inhibition of cell proliferation and induction of apoptosis" **… Division of Pediatric Endocrinology, Mattel Children's Hospital, David Geffen School of Medicine, UCLA**

"Here we show that, in addition to causing cell death of hormone-refractory prostate cancer cells, PJ also increases cell adhesion and decreases cell migration of the cells that do not die." … **Department of Cell Biology and Neuroscience, University of California Riverside**

"These results demonstrate that an ellagitannin-rich pomegranate extract can inhibit tumor-associated angiogenesis as one of several potential mechanisms for slowing the growth of prostate cancer in chemopreventive applications." … **Center for Human Nutrition, Los Angeles**

"Here, we provide evidence of remarkable tumor growth inhibitory effects of PFE using the TRAMP model" … **Department of Dermatology, School of Medicine and Public Health, University of Wisconsin**

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VITAMIN D3

"This study supports the hypothesis that higher serum 25(OH)D levels reduce the risk of breast cancer"… **Department of Family and Preventive Medicine, University of California San Diego**

"Colorectal cancer mortality was inversely related to serum 25(OH)D level, with levels 80 nmol/L or higher associated with a 72% risk reduction"… **Division of Cancer Epidemiology and Genetics, National Cancer Institute**

"…we conclude that higher plasma levels of 25(OH)D are associated with a lower risk of colorectal cancer in older women, particularly for cancers at the distal colon and rectum" … **Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School**

"Improving calcium and vitamin D nutritional status substantially reduces all-cancer risk in postmenopausal women"… **Osteoporosis Research Center, Creighton University, Omaha, NE**

"Intake of 2000 IU/day of Vitamin D3, and, when possible, very moderate exposure to sunlight, could raise serum 25(OH)D to 52 ng/ml, a level associated with reduction by 50% in incidence of breast cancer, according to observational studies"… **University of California, San Diego, Department of Family and Preventive Medicine… Harvard School of Public Health**

“The evidence to date suggests that daily intake of 1000-2000 IU/day of vitamin D(3) could reduce the incidence of colorectal with minimal risk”… **University of California San Diego, Department of Family and Preventive Medicine, School of Medicine**

“In two U.S. cohorts, higher intakes of vitamin D were associated with lower risks for pancreatic cancer. Our results point to a potential role for vitamin D in the pathogenesis and prevention of pancreatic cancer”… **Department of Preventive Medicine, Feinberg School of Medicine, Northwestern University … Harvard School of Public Health, Harvard Medical School, Dana-Farber Cancer Institute**

“We conclude that low levels of 25-VD associated with an increased risk for subsequent earlier exposure and more aggressive development of prostate cancer, especially before the andropause”… **University of Tampere, Medical School, Finland**

“Studies over the past several decades have tended to support that higher levels of vitamin D may decrease risk of colorectal cancer”… **Channing Laboratory, Department of Medicine, Harvard Medical School and Brigham and Women's Hospital**

“It is projected that raising the minimum year-around serum 25(OH)D level to 40 to 60 ng/mL (100-150 nmol/L) would prevent approximately 58,000 new cases of breast cancer and 49,000 new cases of colorectal cancer each year, and three fourths of deaths from these diseases in the United States and Canada, based on observational studies combined with a randomized trial. Such intakes also are expected to reduce case-fatality rates of patients who have breast, colorectal, or prostate cancer by half”… **Department of Family and Preventive Medicine, University of California San Diego**

“From multivariable models, an increment of 25 nmol/L in predicted 25(OH)D level was associated with a 17% reduction in total cancer incidence (multivariable relative risk [RR] = 0.83, 95% confidence interval [CI] = 0.74 to 0.92), a 29% reduction in total cancer mortality (RR = 0.71, 95% CI = 0.60 to 0.83), and a 45% reduction in digestive-system cancer mortality (RR = 0.55, 95% CI = 0.41 to 0.74)”… **Channing Laboratory, Department of Medicine, Harvard Medical School and Brigham and Women's Hospital**

“In this prospective study, plasma 25(OH)D levels and common variation among several vitamin D–related genes were associated with lethal prostate cancer risk, suggesting that vitamin D is relevant for lethal prostate cancer”…. **Department of and Department of Nutrition, Harvard School of Public Health … Harvard Medical School …Medical University of South Carolina**

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THE SCIENCE BEHIND RECNAC

INGREDIENTS

CURCUMIN

GINGER EXTRACT

GREEN TEA EXTRACT

POMEGRANATE EXTRACT (men's formula only)

VITAMIN D3

INSERT TABLE WITH FORMULAS HERE

CURCUMIN

According to the National Cancer Institute: "A phytopolylphenol pigment isolated from the plant Curcuma longa, commonly known as turmeric, with a variety of pharmacologic properties. Curcumin blocks the formation of reactive-oxygen species, possesses anti-inflammatory properties as a result of inhibition of cyclooxygenases (COX) and other enzymes involved in inflammation; and disrupts cell signal transduction by various mechanisms including inhibition of protein kinase C. These effects may play a role in the agent's observed antineoplastic properties, which include inhibition of tumor cell proliferation and suppression of chemically induced carcinogenesis and tumor growth in animal models of cancer."** Over 240 published studies have appeared in the global scientific literature in the past year. Many researchers believe that curcumin's multimodal effects act to simultaneously counter ten discrete causative factors in cancer development. It intervenes at each stage in the complex sequence of events that must occur in order for a cancer to develop, progress, invade, and ultimately metastasize to healthy tissue. The multi-targeted mechanisms of curcumin have yielded compelling results in combating a broad array of cancers, including those of the breast, uterus, cervix, prostate and gastrointestinal tract. According to the American Cancer Society, while "Human studies of curcumin in cancer prevention and treatment are in the very early stages," nonetheless "A number of studies of curcumin have shown promising results. Curcumin can kill cancer cells in laboratory dishes and also reduces growth of surviving cells. Curcumin also has been found to reduce development of several forms of cancer in laboratory animals and to shrink animal tumors." The National Cancer Institute at the National Institutes of Health currently lists 12 active and 10 closed clinical trials involving the use of curcumin in fighting cancer.** The Meriva® version of the extract chosen for the RECNAC formula has a proprietary delivery form of curcumin, is clinically supported in terms of efficacy and safety and has been validated for improved oral absorption by a human PK study.*

For a list of scientific references, click here.

For the full library of abstracts, click here.

GINGER

According to the National Cancer Institute: “An extract of the rhizome of the perennial plant Zingiber officinale with potential antineoplastic activity. Ginger extract contains a number of different phenolic compounds, some of which have displayed antineoplastic, anti-inflammatory, and antioxidant activities. This agent also exhibits antiemetic properties.”** Some research has shown that ginger appears to offer a two-pronged attack on cancer cells: it makes them commit suicide, known as apoptosis, and self-digest, known as autophagy. The anti-carcinogenic properties come from the pungent constituents such as valinoids, gingeroids, and paradols, as well as some of the other components like shogaois and zingerone found in the aromatic rhizome of the herb.*

For a list of scientific references, click here.

For the full library of abstracts, click here.

GREEN TEA

According to the National Cancer Institute at the NIH: "Some research suggests that green tea may have a protective effect against cardiovascular disease and against various forms of cancer …. Catechins are polyphenol compounds in tea that are associated with many of tea's proposed health benefits… Epigallocatechin gallate (EGCG), the most abundant catechin in tea, acts as an androgen antagonist and can suppress prostate cancer cell proliferation, suppress production of prostate-specific antigen (PSA) by prostate cancer cells, and increase prostate cancer cell death in vitro …. Results from one in vitro study showed that prostate cancer cells were less susceptible to radiation-induced apoptosis when exposed to EGCG 30 minutes before radiation exposure …. Oral intake of either a green tea catechin solution or EGCG alone was associated with reduced development of prostate cancer in studies with transgenic adenocarcinoma of the mouse prostate (TRAMP) mice …. Results from a small placebo-controlled study of green tea catechins in men with high-grade prostatic intraepithelial neoplasia (HGPIN) showed a statistically significant decrease in the development of prostate cancer among men who were randomly assigned to receive the catechin supplement. A larger, multicenter, randomized trial is now under way…. Studies of orally administered mixtures of tea catechins in men with prostate cancer have begun to provide information about biologic effects in this setting but are too preliminary to draw conclusions about clinical effectiveness …. Green tea has been well tolerated in clinical studies of prostate cancer patients, with the most common side effects being mild gastrointestinal symptoms."*** The National Cancer Institute lists 9 active clinical trials underway currently as well as 3 closed trials.*

For a list of scientific references, click here.

For the full library of abstracts, click here.

For the full library of abstracts, click here.

GREEN TEA SCIENCE REVIEW

1.

J Nutr. 2003 Oct;133(10):3262S-3267S.

Mechanisms of cancer prevention by tea constituents.

Lambert JD, Yang CS.

Source

Department of Chemical Biology, Ernest Mario School of Pharmacy, Rutgers, The State University of New Jersey, Piscataway, NJ 08854, USA.

Abstract

Consumption of tea (Camellia sinensis) has been suggested to prevent cancer, heart disease and other diseases. Animal studies have shown that tea and tea constituents inhibit carcinogenesis of the skin, lung, oral cavity, esophagus, stomach, liver, prostate and other organs. In some studies, the inhibition correlated with an increase in tumor cell apoptosis and a decrease in cell proliferation. Studies with human cancer cell lines have demonstrated that epigallocatechin-3-gallate (EGCG), a major tea polyphenol, inhibits mitogen-activated protein kinases, cyclin-dependent kinases, growth factor-related cell signaling, activation of activator protein 1 (AP-1) and nuclear factor kappaB (NFkappaB), topoisomerase I and matrix metalloproteinases as well as other potential targets. Although some studies report effects of EGCG at submicromolar levels, most experiments require concentrations of >10 or 20 micromol/L to demonstrate the effect. In humans, tea polyphenols undergo glucuronidation, sulfation, methylation, and ring fission. The peak plasma concentration of EGCG is approximately 1 micromol/L. The possible relevance of each of the proposed mechanisms to human cancer prevention is discussed in light of current bioavailability data for tea polyphenols and the potential limitations of animal models of carcinogenesis. Such discussion, it is hoped, will clarify some misunderstandings of cancer prevention by tea and stimulate new research efforts.

2.

Carcinogenesis. 2000 Jan;21(1):63-7.

Comparative chemopreventive mechanisms of green tea, black tea and selected polyphenol extracts measured by in vitro bioassays.

Steele VE, Kelloff GJ, Balentine D, Boone CW, Mehta R, Bagheri D, Sigman CC, Zhu S, Sharma S.

Source

Chemoprevention Branch, Division of Cancer Prevention, National Cancer Institute, NIH, Bethesda, MD 20892, USA. vsly@nih.gov

Abstract

Black tea extracts (hot aqueous, polyphenols and theaflavins) and green tea extracts (hot aqueous, polyphenols, epicatechin, epicatechin gallate, epigallocatechin and epigallocatechin gallate) were tested in nine standardized cell culture assays for comparative cancer chemopreventive properties. Most black and green tea extracts strongly inhibited neoplastic transformation in mouse mammary organ cultures, rat tracheal epithelial cells and human lung tumor epithelial cells. Nearly all tea fractions strongly inhibited benzo[a]pyrene adduct formation with human DNA. Induction of phase II enzymes, glutathione-S-transferase and quinone reductase, were enhanced by nearly all tea fractions, while glutathione was induced by only a few fractions. Ornithine decarboxylase activity was inhibited by nearly all the green tea fractions, but none of the black tea fractions. 12-O-tetradecanoylphorbol-13-acetate-induced free radicals were inhibited by most tea fractions. These results provide strong evidence of both anti-mutagenic, anti-proliferative and anti-neoplastic activities for both black and green tea extracts. Such anticancer mechanisms may well be responsible for the cancer preventive efficacies seen in both experimental and human studies.

3.

Am J Clin Nutr. 2004 Dec;80(6):1558-64.

Bioavailability and antioxidant activity of tea flavanols after consumption of green tea, black tea, or a green tea extract supplement.

Henning SM, Niu Y, Lee NH, Thames GD, Minutti RR, Wang H, Go VL, Heber D.

Source

Center for Human Nutrition, David Geffen School of Medicine and the Department of Biostatistics, School of Public Health, University of California, Los Angeles, 90095, USA. shenning@mednet.ucla.edu

Abstract

BACKGROUND:

Green and black tea polyphenols have been extensively studied as cancer chemopreventive agents. Many in vitro experiments have supported their strong antioxidant activity. Additional in vivo studies are needed to examine the pharmacokinetic relation of absorption and antioxidant activity of tea polyphenols administered in the form of green or black tea or tea extract supplements.

OBJECTIVE:

The purpose of this study was to compare the pharmacokinetic disposition of tea polyphenols and their effect on the antioxidant capacity in plasma 8 h after a bolus consumption of either green tea, black tea, or a green tea extract supplement.

DESIGN:

Thirty healthy subjects were randomly assigned to 3 different sequences of green tea, black tea, or a green tea extract supplement in a 3 x 3 crossover design with a 1-wk washout period in between treatments.

RESULTS:

Flavanol absorption was enhanced when tea polyphenols were administered as a green tea supplement in capsule form and led to a small but significant increase in plasma antioxidant activity compared with when tea polyphenols were consumed as black tea or green tea. All 3 interventions provided similar amounts of (-)-epigallocatechin-3-gallate.

CONCLUSIONS:

Our observations suggest that green tea extract supplements retain the beneficial effects of green and black tea and may be used in future chemoprevention studies to provide a large dose of tea polyphenols without the side effects of caffeine associated with green and black tea beverages.

4.

Annu Rev Pharmacol Toxicol. 2002;42:25-54.

Inhibition of carcinogenesis by tea.

Yang CS, Maliakal P, Meng X.

Source

Laboratory for Cancer Research, Department of Chemical Biology, College of Pharmacy, Rutgers, The State University of New Jersey, Piscataway, New Jersey 08854-8020, USA. csyang@rci.rutgers.edu

Abstract

Tea has received a great deal of attention because tea polyphenols are strong antioxidants, and tea preparations have inhibitory activity against tumorigenesis. The bioavailability and biotransformation of tea polyphenols, however, are key factors limiting these activities in vivo. The inhibition of tumorigenesis by green or black tea preparations has been demonstrated in animal models on different organ sites such as skin, lung, oral cavity, esophagus, forestomach, stomach, small intestine, colon, pancreas, and mammary gland. Epidemiological studies, however, have not yielded clear conclusions concerning the protective effects of tea consumption against cancer formation in humans. The discrepancy between the results from humans and animal models could be due to 1) the much higher doses of tea used in animals in comparison to human consumption, 2) the differences in causative factors between the cancers in humans and animals, and 3) confounding factors limiting the power of epidemiological studies to detect an effect. It is possible that tea may be only effective against specific types of cancer caused by certain etiological factors. Many mechanisms have been proposed for the inhibition of carcinogenesis by tea, including the modulation of signal transduction pathways that leads to the inhibition of cell proliferation and transformation, induction of apoptosis of preneoplastic and neoplastic cells, as well as inhibition of tumor invasion and angiogenesis. These mechanisms need to be evaluated and verified in animal models or humans in order to gain more understanding on the effect of tea consumption on human cancer.

5.

J Agric Food Chem. 2006 Mar 8;54(5):1599-603.

Catechin and caffeine content of green tea dietary supplements and correlation with antioxidant capacity.

Seeram NP, Henning SM, Niu Y, Lee R, Scheuller HS, Heber D.

Source

Center for Human Nutrition, David Geffen School of Medicine, University of California, Los Angeles, California 90095, USA. nseeram@mednet.ucla.edu

Abstract

The health benefits associated with tea consumption have resulted in the wide inclusion of green tea extracts in botanical dietary supplements, which are widely consumed as adjuvants for complementary and alternative medicines. Tea contains polyphenols such as catechins or flavan-3-ols including epicatechin, epigallocatechin, epicatechin gallate, and epigallocatechin gallate (EGCG), as well as the alkaloid, caffeine. Polyphenols are antioxidants, and EGCG, due to its high levels, is widely accepted as the major antioxidant in green tea. Therefore, commercial green tea dietary supplements (GTDS) may be chemically standardized to EGCG levels and/or biologically standardized to antioxidant capacity. However, label claims on GTDS may not correlate with actual phytochemical content or antioxidant capacity nor provide information about the presence and levels of caffeine. In the current study, 19 commonly available GTDS were evaluated for catechin and caffeine content (using high-performance liquid chromatography) and for antioxidative activity [using trolox equivalent antioxidant capacity (TEAC) and oxygen radical antioxidant capacity (ORAC) assays]. Product labels varied in the information provided and were inconsistent with actual phytochemical contents. Only seven of the GTDS studied made label claims of caffeine content, 11 made claims of EGCG content, and five specified total polyphenol content. Caffeine, EGCG, and total polyphenol

contents in the GTDS varied from 28 to 183, 12-143, and 14-36% tablet or capsule weight, respectively. TEAC and ORAC values for GTDS ranged from 187 to 15340 and from 166 to 13690 mumol Trolox/g for tablet or capsule, respectively. The antioxidant activities for GTDS determined by TEAC and ORAC were well-correlated with each other and with the total polyphenol content. Reliable labeling information and standardized manufacturing practices, based on both chemical standardization and biological assays, are recommended for the quality control of botanical dietary supplements.

6.

Carcinogenesis. 2007 May;28(5):1074-8. Epub 2006 Dec 20.

Green tea and the prevention of breast cancer: a case-control study in Southeast China.

Zhang M, Holman CD, Huang JP, Xie X.

Source

The School of Population Health, The University of Western Australia, 35 Stirling Highway, Crawley, Perth, WA 6009, Australia. min.zhang@uwa.edu.au

Abstract

Breast cancer is the most common malignancy in women worldwide. Tea has anticarcinogenic effects against breast cancer in experimental studies. However, epidemiologic evidence that tea protects against breast cancer has been inconsistent. A case-control study was conducted in Southeast China between 2004 and 2005. The incidence cases were 1009 female patients aged 20-87 years with histologically confirmed breast cancer. The 1009 age-matched controls were healthy women randomly recruited from breast disease clinics. Information on duration, frequency, quantity, preparation, type of tea consumption, diet and lifestyle were collected by face-to-face interview using a validated and reliable questionnaire. Conditional logistic regression analyses were used to estimate odds ratios (ORs) and associated 95% confidence intervals. Compared with non-tea drinkers, green tea drinkers tended to reside in urban, have better education and have higher consumption of coffee, alcohol, soy, vegetables and fruits. After adjusting established and potential confounders, green tea consumption was associated with a reduced risk of breast cancer. The ORs were 0.87 (0.73-1.04) in women consuming 1-249 g of dried green tea leaves per annum, 0.68 (0.54-0.86) for 250-499 g per annum, 0.59 (0.45-0.77) for 500-749 g per annum and 0.61 (0.48-0.78) for >or=750 g per annum, with a statistically significant test for trend ($P < 0.001$). Similar dose-response relationships were observed for duration of drinking green tea, number of cups consumed and new batches prepared per day. We conclude that regular consumption of green tea can protect against breast cancer. More research to closely examine the relationship between tea consumption and breast cancer risk is warranted.

7.

Cancer Epidemiol Biomarkers Prev. 2007 Jun;16(6):1219-23.

Prospective cohort study of green tea consumption and colorectal cancer risk in women.

Yang G, Shu XO, Li H, Chow WH, Ji BT, Zhang X, Gao YT, Zheng W.

Source

Department of Medicine, Vanderbilt Epidemiology Center and Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville TN 37232-2587, USA.
Gong.Yang@vanderbilt.edu

Abstract

Tea and its constituents have shown anticarcinogenic activities in in vitro and animal studies. Epidemiologic studies, however, have been inconsistent. We prospectively evaluated the association between green tea consumption and colorectal cancer (CRC) risk in a cohort of 69,710 Chinese women aged 40 to 70 years. Information on tea consumption was assessed through in-person interviews at baseline and reassessed 2 to 3 years later in a follow-up survey. During 6 years of follow-up, 256 incident cases of CRC were identified. The multivariate relative risk of CRC was 0.63 (95% confidence interval, 0.45-0.88) for women who reported drinking green tea regularly at baseline compared with nonregular tea drinkers. A significant dose-response relationship was found for both the amount of tea consumed (Ptrend = 0.01) and duration in years of lifetime tea consumption (Ptrend = 0.006). The reduction in risk was most evident among those who consistently reported to drink tea regularly at both the baseline and follow-up surveys (relative risk, 0.43; 95% confidence interval, 0.24-0.77). The inverse association with regular tea drinking was observed for both colon and rectal cancers. This study suggests that regular consumption of green tea may reduce CRC risk in women.

8.

Am J Epidemiol. 2008 Jan 1;167(1):71-7. Epub 2007 Sep 29.

Green tea consumption and prostate cancer risk in Japanese men: a prospective study.

Kurahashi N, Sasazuki S, Iwasaki M, Inoue M, Tsugane S; JPHC Study Group.

Source

Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, Japan. nkurahas@gan2.res.ncc.go.jp

Abstract

The incidence of prostate cancer is much lower in Asian than Western populations. Given that environmental factors such as dietary habits may play a major role in the causation of prostate cancer and the high consumption of green tea in Asian populations, this low incidence may be partly due to the effects of green tea. The JPHC Study (Japan Public Health Center-based Prospective Study) was established in 1990 for cohort I and in 1993 for cohort II. The subjects were 49,920 men aged 40-69 years who completed a questionnaire that included their green tea consumption habit at baseline and were followed until the end of 2004. During this time, 404 men were newly diagnosed with prostate cancer, of whom 114 had advanced cases, 271 were localized, and 19 were of an undetermined stage. Green tea was not associated with localized prostate cancer. However, consumption was associated with a dose-dependent decrease in the risk of advanced prostate cancer. The multivariate relative risk was 0.52 (95% confidence interval: 0.28, 0.96) for men drinking 5 or more cups/day compared with less than 1 cup/day (p(trend) = 0.01). Green tea may be associated with a decreased risk of advanced prostate cancer.

9.

J Nutr. 2009 Feb;139(2):310-6. Epub 2008 Dec 11.

Drinking green tea modestly reduces breast cancer risk.

Shrubsole MJ, Lu W, Chen Z, Shu XO, Zheng Y, Dai Q, Cai Q, Gu K, Ruan ZX, Gao YT, Zheng W.

Source

Department of Medicine, Vanderbilt Epidemiology Center, Vanderbilt School of Medicine, Nashville, TN 37232, USA.

Abstract

Green tea is a commonly consumed beverage in China. Epidemiological and animal data suggest tea and tea polyphenols may be preventive against various cancers, including breast cancer. Catechol-O-methyltransferase (COMT) catalyzes catechol estrogens and tea polyphenols. The COMT rs4680 AA genotype leads to lower COMT activity, which may affect the relationship between green tea consumption and breast cancer risk. We evaluated whether regular green tea consumption was associated with breast cancer risk among 3454 incident cases and 3474 controls aged 20-74 y in a population-based case-control study conducted in Shanghai, China during 1996-2005. All participants were interviewed in person about green tea consumption habits, including age of initiation, duration of use, brew strength, and quantity of tea. Odds ratios (OR) and 95% CI were calculated for green tea consumption measures and adjusted for age and other confounding factors. Compared with nondrinkers, regular drinking of green tea was associated with a slightly decreased risk for breast cancer (OR, 0.88; 95% CI, 0.79-0.98). Among premenopausal women, reduced risk was observed for years of green tea drinking (P-trend = 0.02) and a dose-response relationship with the amount of tea consumed per month was also observed (P-trend = 0.046). COMT rs4680 genotypes did not have a modifying effect on the association of green tea intake with breast cancer risk. Drinking green tea may be weakly associated with a decreased risk of breast cancer.

10.

Gen Dent. 2002 Mar-Apr;50(2):140-6.

Chemoprevention of oral cancer by green tea.

Hsu SD, Singh BB, Lewis JB, Borke JL, Dickinson DP, Drake L, Caughman GB, Schuster GS.

Source

Department of Oral Biology and Maxillofacial Pathology, School of Dentistry, Medical College of Georgia, Augusta, USA.

Abstract

Green tea has been a popular beverage for many centuries. Only recently, however, has the anti-cancer power of green tea constituents been unveiled. Green tea polyphenols are found to induce apoptosis (programmed cell death) in many types of tumor cells, including oral cancer cells. However, mechanisms that enable normal cells to evade the apoptotic effect still are not understood. In this study, cell growth and invasion assays combined with apoptosis assays were used to examine the effects of green tea extracts, green tea polyphenols, and the most potent green tea polyphenol, (-)-epigallocatechin-3-gallate (EGCG), on normal human keratinocytes and oral carcinoma cells. The results showed that green tea and its constituents selectively induce apoptosis

only in oral carcinoma cells, while EGCG was able to inhibit the growth and invasion of oral carcinoma cells. These differential responses to green tea and its constituents between normal and malignant cells were correlated with the induction of p57, a cell cycle regulator. These data suggest that the chemopreventive effects of green tea polyphenols may involve a p57 mediated survival pathway in normal epithelial cells, while oral carcinoma cells undergo an apoptotic pathway. Therefore, regular consumption of green tea could be beneficial in the prevention of oral cancer.

11.

Mutation research [1999, 428(1-2):339-344]

Green tea and cancer chemoprevention.

Suganuma M, Okabe S, Sueoka N, Sueoka E, Matsuyama S, Imai K, Nakachi K, Fujiki H

Affiliation: Saitama Cancer Center Research Institute, Ina, Kitaadachi-gun, Saitama 362-0806, Japan.

Abstract:
Worldwide interest in green tea as a cancer preventive agent for humans has increased, because it is non-toxic and it is effective in a wide range of organs. (-)-Epigallocatechin gallate (EGCG) is the main constituent of green tea; the others are (-)-epicatechin gallate, (-)-epigallocatechin and (-)-epicatechin (EC). This paper reports the results of our latest pharmacological and biochemical studies with 3H-EGCG, along with studies on human subjects. The study on bioavailability of 3H-EGCG in mice revealed the wide distribution of radioactivity in multiple organs. Specifically, radioactivity was found in all reported target organs of EGCG and green tea extract (digestive tract, liver, lung, pancreas, mammary gland and skin) as well as other organs (brain, kidney, uterus and ovary or testes) in mice. Recently, we demonstrated that EC enhanced incorporation of 3H-EGCG into human lung cancer cell line PC-9 cells. EC along with another cancer preventive agent sulindac also synergistically enhanced apoptosis in PC-9 cells induced by EGCG. Moreover, a case-control study on breast cancer patients revealed that high daily consumption of green tea was associated with a lower recurrence rate among Stages I and II patients. All the results suggest that consumption of green tea is a practical and effective cancer preventive both before cancer onset and after cancer treatment.

12.

J Nutr. 2002 Aug;132(8):2307-11.

Green tea inhibits vascular endothelial growth factor (VEGF) induction in human breast cancer cells.

Sartippour MR, Shao ZM, Heber D, Beatty P, Zhang L, Liu C, Ellis L, Liu W, Go VL, Brooks MN.

Source

Department of Surgery, Division of Oncology and Center for Human Nutrition, University of California, Los Angeles 90095, USA.

Abstract

Investigators have shown that green tea and its main catechin epigallocatechin-3 gallate (EGCG) may decrease the risk of cancer. Our previous study showed that green tea extract (GTE) as well as its

individual catechin components inhibited MDA-MB231 breast cancer cell and human umbilical vein endothelial cell (HUVEC) proliferation. Further, GTE suppressed breast cancer xenograft size and decreased the tumor vessel density in vivo. In the current study, we investigated the effect of GTE on the major angiogenic factor vascular endothelial growth factor (VEGF) in an in vitro experiment. GTE or EGCG (40 mg/L) significantly decreased the levels of the VEGF peptide secreted into conditioned media. This occurred in both HUVEC and human breast cancer cells and the effect was dose dependent. Furthermore, GTE and EGCG decreased the RNA levels of VEGF in MDA-MB231 cells. This inhibition occurred at the transcriptional regulation level and was accompanied by a significant decrease in VEGF promoter activity. We also showed that GTE decreased c-fos and c-jun RNA transcripts, suggesting that activator protein (AP)-1-responsive regions present in the human VEGF promoter may be involved in the inhibitory effect of GTE. Furthermore, GTE suppressed the expression of protein kinase C, another VEGF transcription modulator, in breast cancer cells. Inhibition of VEGF transcription appeared to be one of the molecular mechanism(s) involved in the antiangiogenic effects of green tea, which may contribute to its potential use for breast cancer treatment and/or prevention.

13.

Cancer Prev Res (Phila). 2009 Nov;2(11):931-41.

Phase II randomized, placebo-controlled trial of green tea extract in patients with high-risk oral premalignant lesions.

Tsao AS, Liu D, Martin J, Tang XM, Lee JJ, El-Naggar AK, Wistuba I, Culotta KS, Mao L, Gillenwater A, Sagesaka YM, Hong WK, Papadimitrakopoulou V.

Source

Department of Thoracic/Head and Neck Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas 77030, USA.

Comment in: Oral cancer prevention advances with a translational trial of green tea.*Shin DM. Cancer Prev Res (Phila). 2009 Nov; 2(11):919-21.*

Abstract

Epidemiologic and preclinical data support the oral cancer prevention potential of green tea extract (GTE). We randomly assigned patients with high-risk oral premalignant lesions (OPL) to receive GTE at 500, 750, or 1,000 mg/m(2) or placebo thrice daily for 12 weeks, evaluating biomarkers in baseline and 12-week biopsies. The OPL clinical response rate was higher in all GTE arms (n = 28; 50%) versus placebo (n = 11; 18.2%; P = 0.09) but did not reach statistical significance. However, the two higher-dose GTE arms [58.8% (750 and 1,000 mg/m(2)), 36.4% (500 mg/m(2)), and 18.2% (placebo); P = 0.03] had higher responses, suggesting a dose-response effect. GTE treatment also improved histology (21.4% versus 9.1%; P = 0.65), although not statistically significant. GTE was well tolerated, although higher doses increased insomnia/nervousness but produced no grade 4 toxicity. Higher mean baseline stromal vascular endothelial growth factor (VEGF) correlated with a clinical (P = 0.04) but not histologic response. Baseline scores of other biomarkers (epithelial VEGF, p53, Ki-67, cyclin D1, and p16 promoter methylation) were not associated with a response or survival. Baseline p16 promoter methylation (n = 5) was associated with a shorter cancer-free survival. Stromal VEGF and cyclin D1 expression were downregulated in clinically responsive GTE patients and upregulated in nonresponsive patients at 12 weeks (versus at baseline). An extended (median, 27.5 months) follow-up showed a median time to oral cancer of 46.4 months. GTE may suppress OPLs, in part through reducing angiogenic stimulus (stromal VEGF). Higher doses of GTE may improve short-term (12-

week) OPL outcome. The present results support longer-term clinical testing of GTE for oral cancer prevention.

14.

Carcinogenesis. 2002 Sep;23(9):1497-503.

Urinary tea polyphenols in relation to gastric and esophageal cancers: a prospective study of men in Shanghai, China.

Sun CL, Yuan JM, Lee MJ, Yang CS, Gao YT, Ross RK, Yu MC.

Source

USC/Norris Comprehensive Cancer Center, University of Southern California Keck School of Medicine, 1441 Eastlake Avenue, Los Angeles, CA 90089-9176, USA. canlan@hsc.usc.edu

Abstract

Experimental studies have shown that tea and tea polyphenols have anticarcinogenic properties. There have been no prospective investigations examining the relationship between tea polyphenols and cancer risk using validated biomarkers. In the present study, a nested case-control study design was used to investigate the association between prediagnostic urinary tea polyphenol markers and subsequent risk of gastric and esophageal cancers. One hundred and ninety incident cases of gastric cancer and 42 cases of esophageal cancer occurring in members of the Shanghai Cohort (18 244 men aged 45-64 years at recruitment with up to 12 years of follow-up) were compared with 772 cohort control subjects. The control subjects were individually matched to the index cases by age, month and year of sample collection, and neighborhood of residence (case-control ratio = 1:3 for gastric cancer, 1:5 for esophageal cancer). Urinary tea polyphenols, including epigallocatechin (EGC) and epicatechin (EC), and their respective metabolites 5-(3',4',5'-trihydroxyphenyl)-gamma-valerolactone (M4) and 5-(3',4'-dihydroxyphenyl)-gamma-valerolactone (M6), were measured in all study subjects by means of a validated assay. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated from logistic regression models. After exclusion of cases diagnosed under 4 years follow-up, urinary EGC positivity showed a statistically significant inverse association with gastric cancer (OR = 0.52, 95% CI = 0.28-0.97) after adjustment for Helicobacter pylori seropositivity, smoking, alcohol drinking, and level of serum carotenes. The protective effect was primarily seen among subjects with low (below population median) serum carotenes. The odds ratio for EGC positivity was 0.49 (95% CI = 0.26-0.94) among subjects with low serum carotenes while the corresponding odds ratio among subjects with higher levels of serum carotenes was 1.02 (95% CI = 0.46-2.28). Similar tea polyphenol-cancer risk associations were observed when the gastric cancer and esophageal cancer sites were combined. The present study provides direct evidence that tea polyphenols may act as chemopreventive agents against gastric and esophageal cancer development.

15.

BioFactors; Volume 13, Issue 1-4, pages 49–54, 2000

Preventive effects of drinking green tea on cancer and cardiovascular disease: Epidemiological evidence for multiple targeting prevention

1. Kei Nakachi*,
2. Satoru Matsuyama,
3. Satoshi Miyake,
4. Masami Suganuma,
5. Kazue Imai

Article first published online: 16 DEC 2008
DOI: 10.1002/biof.5520130109

Issue

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Abstract

The significance of drinking green tea in prevention of two of the main lifestyle-related diseases, cancer and cardiovascular disease, was demonstrated in terms of a prospective cohort study on a total of 8,552 general residents in Saitama Prefecture, Japan. On the basis of the follow-up study, we revealed decreased relative risk of cancer incidence for those consuming over 10 cups a day, compared with those consuming below 3 cups: 0.54 (95% men, 0.57 (0.34–0.98) for women, and 0.59 (0.35–0.98) for both sexes. Furthermore, a significant delay in cancer onset was associated with increased consumption of green tea. Next, decreased relative risk of death from cardiovascular disease was 0.58 (0.34–0.99) for men, 0.82 (0.49–1.38) for women, and 0.72 (0.60–1.04) for members of both sexes consuming over 10 cups a day. Finally, we evaluated the life-prolonging effects of drinking green tea on cumulative survival, using the life table.

POMEGRANATE EXTRACT (men's formula only)

According to the National Cancer Institute: "The pomegranate (Punica granatum L.) is native to Asia and cultivated widely throughout world. Various components of the pomegranate fruit contain bioactive compounds, including phenolics, flavonoids, and anthocyanins, some of which have antioxidant activity…. Pomegranate juice and extract, as well as some of their bioactive components, inhibit the proliferation of various prostate cancer cell lines in vitro and induce apoptotic cell death in a dose-dependent manner…. Cytochrome P450 enzyme inhibition and effects on insulin-like growth factor binding protein -3 (IGFBP-3) have been identified as being involved in the in vitro anticancer activity…. Studies in rodent models of prostate cancer have shown that ingestion of pomegranate juice can decrease the rate of development, growth, and spread of prostate cancer…. The only fully reported clinical trial of the use of pomegranate juice in men with prostate cancer showed that, on average, study participants who drank the juice had an increase in their prostate-specific antigen (PSA) doubling time…. No serious adverse effects have been reported in clinical trials of pomegranate juice administration (8oz per day for up to 33 months)…."*** The NCI shows 3 active clinical trials underway involving pomegranate juice and pomegranate extract in pill form.*

For a list of scientific references, click here.

For the full library of abstracts, click here.

VITAMIN D3

A vitamin D receptor (VDR), a protein encoded by the VDR gene plays a role in the vitamin D pathway such that higher levels are associated with higher risks of dying from cancer. These receptors are associated with low vitamin D levels. Vitamin D3 has been shown to decrease cell proliferation and boost apoptosis. Dozens of studies suggest an association between low vitamin D3 levels and increased many types of prevalent cancers. Some research suggests that sufficient levels of Vitamin D3 could help to prevent breast cancer, colorectal cancer and possibly prostate cancer. Vitamin D3 has been the most studied and documented of the natural cancer preventatives. It is being used and researched in many clinical settings as a preventative and treatment. The National Cancer Institute of the NIH currently shows 19 active and 33 closed clinical trials involving Vitamin D3.*

For a list of scientific references, click here.

For the full library of abstracts, click here.

(Earl, wherever you see click here or there is a link, it needs to go through to the correct page. The info is on the flash drive so I can't link it though from here)

*These statements have not been approved by the FDA

** http://www.cancer.gov/drugdictionary

*** http://www.cancer.gov/cancertopics/pdq/cam/prostatesupplements/healthprofessional/page5

NEGDA Mens Formula		
Supplemental Facts Serving Size: 1 Vegetable Capsule Servings per Container: 30 Directions: Take one capsule with breafast or as directed by a health care practitioner.		
	per capsule	**% DV**
BCM-95 Bio-Curcumin®	250mg	*
Vitamin D3	1800iu	450
Ginger Extract	50mg	*
Green Tea Extract	113mg	*
Pomegranate Extract	200mg	*
* % Daily Values (DV) not established		

NEGDA Womens Formula		
Supplemental Facts Serving Size: 1 Vegetable Capsule Servings per Container: 30 Directions: Take one capsule with breafast or as directed by a health care practitioner.		
	per capsule	**% DV**
BCM-95 Bio-Curcumin®	250mg	*
Vitamin D3	1800iu	450
Ginger Extract	50mg	*
Green Tea Extract	90mg	*
** % Daily Values (DV) not established		

RESEARCH REFERENCES AND ABSTRACTS

IN THIS SECTION WE PRESENT A LIST OF RESEARCH REFERENCES & ASSOCIATED ABSTRACTS BY INGREDIENT

BIOCURCUMIN

GINGER ROOT EXTRACT

GREEN TEA LEAF EXTRACT

POMEGRANATE EXTRACT (men's formula only)

VITAMIN D3

BIOCURCUMIN

REFERENCES

a) Kakarala, M. et al., "Targeting breast stem cells with cancer prevention compounds curcumin and piperine," Breast Cancer Research & Treatment, 2009; b) Oyagbemi AA, Saba AB, Ibraheem, AO, Curcumin: "From food spice to cancer prevention," Asian Pacific Journal of Cancer Prevention 2009:10(6);963-7; c) Goel A and Aggarwal BB (2010). Curcumin, the golden spice from Indian saffron, is a chemosensitizer and radiosensitizer for tumors; and chemoprotector and radioprotector for normal organs. Nutrition and Cancer 62(7): 919-930; d) Bachmeier BE, Killian P, Pfeffer U, Nerlich AG, "Novel aspects for the application of curcumin in chemoprevention of various cancers," Front Biosci (Schol Ed) 2010 Jan1,2:697-717; e) Banerjee M, Singh P, Panda D, "Curcumin suppresses the dynamic instability of microtubules, activates the mitotic checkpoint and induces apoptosis in MCF-7 cells," FEBS J 2010 Aug: 277 (16); 3437-48; f) Goel A, Jhurani S, and Aggarwal BB (2008). Multi-targeted therapy with curcumin: How spicy is it? Molecular Nutrition and Food Research 52(9): 1010-1030; g) Duvoix A et al; Laboratoire de Biologie Moléculaire et Cellulaire du Cancer, Hôpital Kirchberg, 9, rue Edward Steichen, L-2540 Luxembourg, Luxembourg; "Chemopreventive and therapeutic effects of curcumin"; Cancer Lett. 2005 Jun 8;223(2):181-90. Epub 2004 Nov 11; h) Bisht S et al; Department of Pathology, The Sol Goldman Pancreatic Cancer Research Center, Johns Hopkins University School of Medicine; Systemic delivery of curcumin: 21st century solutions for an ancient conundrum.; Curr Drug Discov Technol. 2009 Sep;6(3):192-9. Epub 2009 Sep 1; i) Aggarwal S et al; Cytokine Research Laboratory, Department of Experimental Therapeutics, The University of Texas MD Anderson Cancer Center; "Curcumin (diferuloylmethane) down-regulates expression of cell proliferation and antiapoptotic and metastatic gene products through suppression of IkappaBalpha kinase and Akt activation"; Mol Pharmacol. 2006 Jan;69(1):195-206. Epub 2005 Oct 11 j) Lin YG et al; Department of Gynecologic Oncology, The University of Texas M. D. Anderson Cancer Center; "Curcumin inhibits tumor growth and angiogenesis in ovarian carcinoma by targeting the nuclear factor-kappaB pathway"; Clin Cancer Res. 2007 Jun 1;13(11):3423-30; k) Devasena T et al; Department of Biochemistry, Annamalai University, Tamil Nadu, India; "Anticarcinogenic effect of bis-1,7-(2-hydroxyphenyl)-hepta-1,6-diene-3,5-dione a curcumin analog on DMH-induced colon

cancer model"; Pharmacol Res. 2003 Feb;47(2):133-40 l) Killian PH et al; Institute of Laboratory Medicine, Ludwig-Maximilians-University, Munich, Germany; "Curcumin inhibits prostate cancer metastasis in vivo by targeting the inflammatory cytokines CXCL1 and -2"; Carcinogenesis. 2012 Oct 26. [Epub ahead of print]; m) Giuseppe Garcea et al; 1Cancer Biomarkers and Prevention Group, Departments of Oncology and Biochemistry, University of Leicester and 2Department of Hepatobiliary Surgery, University Hospitals of Leicester, Leicester General Hospital, Leicester, United Kingdom; "Consumption of the Putative Chemopreventive Agent Curcumin by Cancer Patients: Assessment of Curcumin Levels in the Colorectum and their Pharmacodynamic Consequences"; Cancer Epidemiol Biomarkers Prev January 2005 14; 120;n) Carroll Robert E et al; Department of Medicine, University of Illinois at Chicago, and Chicago Veterans Administration Medical Center (West Side Division), Chicago, Illinois; Departments of 2Internal Medicine and 3Pharmacology, University of Michigan, Ann Arbor, Michigan; 4Division of Cancer Prevention, National Cancer Institute, Bethesda, Maryland; 5Veterans Administration Medical Center, Ann Arbor, Michigan; 6Chao Family Comprehensive Cancer Center (Orange) and 7Department of Epidemiology, University of California, Irvine, Irvine, California; "Phase IIa Clinical Trial of Curcumin for the Prevention of Colorectal Neoplasia"; Cancer Prev Res March 2011 4; 354.

RESEARCH ABSTRACTS

1.

Breast Cancer Res Treat. 2010 August; 122(3): 777–785.

Targeting Breast Stem Cells with the Cancer Preventive Compounds Curcumin and Piperine

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Corresponding Author: Madhuri Kakarala MD, PhD, 2150 Cancer Center, 1500 E. Medical Center Dr., University of Michigan, Ann Arbor, MI 48109-5290

Abstract

Background

The cancer stem cell hypothesis asserts that malignancies arise in tissue stem and/or progenitor cells through the dysregulation or acquisition of self-renewal. In order to determine whether the dietary polyphenols, curcumin and piperine, are able to modulate the self-renewal of normal and malignant

breast stem cells, we examined the effects of these compounds on mammosphere formation, on expression of the breast stem cell marker aldehyde dehydrogenase (ALDH), and on Wnt signaling.

Design

Mammosphere formation assays were performed after curcumin, piperine and control treatment in unsorted normal breast epithelial cells and normal stem and early progenitor cells, selected by ALDH positivity. Wnt signaling was examined using a Topflash assay.

Results

Both curcumin and piperine inhibited mammosphere formation, serial passaging and percent of ALDH+ cells, by 50% at 5 μM and completely at 10 μM concentration in normal and malignant breast cells. There was no effect on cellular differentiation. Wnt signaling was inhibited by both curcumin and piperine by 50% at 5 μM and completely at 10μM.

Conclusion

Curcumin and piperine separately, and in combination, inhibit breast stem cell self renewal but do not cause toxicity to differentiated cells. These compounds could be potential cancer preventive agents. Mammosphere formation assays may be a quantifiable biomarker to assess cancer preventive agent efficacy and Wnt signaling assessment a mechanistic biomarker for use in human clinical trials.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3039120/

2.

FEBS J. 2010 Aug;277(16):3437-48. Epub 2010 Jul 14.

Curcumin suppresses the dynamic instability of microtubules, activates the mitotic checkpoint and induces apoptosis in MCF-7 cells.

Banerjee M, Singh P, Panda D.

Source

Department of Biosciences & Bioengineering, Indian Institute of Technology Bombay, Mumbai, India.

Abstract

In this study, curcumin, a potential anticancer agent, was found to dampen the dynamic instability of individual microtubules in living MCF-7 cells. It strongly reduced the rate and extent of shortening states, and modestly reduced the rate and extent of growing states. In addition, curcumin decreased the fraction of time microtubules spent in the growing state and strongly increased the time microtubules spent in the pause state. Brief treatment with curcumin depolymerized mitotic microtubules, perturbed microtubule-kinetochore attachment and disturbed the mitotic spindle structure. Curcumin also perturbed the localization of the kinesin protein Eg5 and induced monopolar spindle formation. Further, curcumin increased the accumulation of Mad2 and BubR1 at the kinetochores, indicating that it activated the mitotic checkpoint. In addition, curcumin treatment increased the metaphase/anaphase ratio, indicating that it can delay mitotic progression from the metaphase to anaphase. We provide evidence suggesting that the affected cells underwent apoptosis via the p53-dependent apoptotic pathway. The results support the idea that kinetic

stabilization of microtubule dynamics assists in the nuclear translocation of p53. Curcumin exerted additive effects when combined with vinblastine, a microtubule depolymerizing drug, whereas the combination of curcumin with paclitaxel, a microtubule-stabilizing drug, produced an antagonistic effect on the inhibition of MCF-7 cell proliferation. The results together suggested that curcumin inhibited MCF-7 cell proliferation by inhibiting the assembly dynamics of microtubules.

3.

National Cancer Institute at the National Institutes of Health

NCI Drug Dictionary

Biocurcumin

A phytopolylphenol pigment isolated from the plant Curcuma longa, commonly known as turmeric, with a variety of pharmacologic properties. Curcumin blocks the formation of reactive-oxygen species, possesses anti-inflammatory properties as a result of inhibition of cyclooxygenases (COX) and other enzymes involved in inflammation; and disrupts cell signal transduction by various mechanisms including inhibition of protein kinase C. These effects may play a role in the agent's observed antineoplastic properties, which include inhibition of tumor cell proliferation and suppression of chemically induced carcinogenesis and tumor growth in animal models of cancer. Check for active clinical trials or closed clinical trials using this agent. (NCI Thesaurus)

http://www.cancer.gov/drugdictionary?cdrid=440023

4.

Mol Nutr Food Res. 2008 Sep;52(9):1010-30.

Multi-targeted therapy by curcumin: how spicy is it?

Goel A, Jhurani S, Aggarwal BB.

Source

Gastrointestinal Cancer Research Laboratory, Department of Internal Medicine, Charles A Sammons Cancer Center and Baylor Research Institute, Baylor University Medical Center, Dallas, TX, USA.

Abstract

Although traditional medicines have been used for thousands of years, for most such medicines neither the active component nor their molecular targets have been very well identified. Curcumin, a yellow component of turmeric or curry powder, however, is an exception. Although inhibitors of cyclooxygenase-2, HER2, tumor necrosis factor, EGFR, Bcr-abl, proteosome, and vascular endothelial cell growth factor have been approved for human use by the United States Food and Drug Administration (FDA), curcumin as a single agent can down-regulate all these targets. Curcumin can also activate apoptosis, down-regulate cell survival gene products, and up-regulate p53, p21, and p27. Although curcumin is poorly absorbed after ingestion, multiple studies have suggested that even low levels of physiologically achievable concentrations of curcumin may be sufficient for its chemopreventive and chemotherapeutic activity. Thus, curcumin regulates multiple targets (multitargeted therapy), which is needed for treatment of most diseases, and it is inexpensive and has been found to be safe in human clinical trials. The present article reviews the key molecular

mechanisms of curcumin action and compares this to some of the single-targeted therapies currently available for human cancer.

5.

Asian Pac J Cancer Prev. 2009;10(6):963-7.

Biocurcumin: from food spice to cancer prevention.

Oyagbemi AA, Saba AB, Ibraheem AO.

Source

Department of Veterinary Physiology, Biochemistry and Pharmacology, Faculty of Veterinary Medicine, University of Ibadan, Oyo State, Nigeria. ademolaoyagbemi@yahoo.com

Abstract

Curcumin [1, 7-bis (4-hydroxy-3-methoxyphenyl)-1, 6 heptadiene-3, 5-dione] is an orange-yellow component of turmeric (Curcuma longa), a spice often found in curry powder. It is known to have a variety of biologic and pharmacologic activities, including anti-inflammatory, anti-oxidant, and anticarcinogenic potential. It is a potent inhibitor of cytochrome P450 with capacity to simultaneously induce detoxifying enzymes such as glutathione S-transferase and as such may find application as a chemopreventive agent. Curcumin is a potent inhibitor of cyclooxygenase-2, lipooxygenase, ornithine decarboxylase (ODC), nuclear factor-kappaB, c-Jun N-terminal kinase and protein kinase C and has also been demonstrated to play a vital role against pathological conditions such as cancer, atherosclerosis, and neurodegenerative diseases.

6.

Front Biosci (Schol Ed). 2010 Jan 1;2:697-717.

Novel aspects for the application of Curcumin in chemoprevention of various cancers.

Bachmeier BE, Killian P, Pfeffer U, Nerlich AG.

Source

Department of Clinical Chemistry and Clinical Biochemistry, Ludwig-Maximilians University Munich, München, Germany. bachmeier@med.uni-muenchen.de

Abstract

Chemoprevention of malignant tumor growth is a novel and potentially powerful approach for tumor therapy. Recent in vitro and in vivo investigations provide increasing evidence that naturally occurring substances may exhibit significant chemopreventive activities. To this regard, the spice Curcumin, widely used in Indian cuisine, has been identified to show considerable anti-tumor effects. Most interestingly, numerous studies have not shown toxic side effects of this substance. Curcumin induces tumor cell apoptosis along with a reduction of tumor cell invasion and metastasis. Recent molecular studies provide evidence that Curcumin acts via a control of the NFkappaB pathway exerting most of the various modulating and moderating effects on malignant cells. Along with these in vitro studies, ex vivo and first clinical investigations confirm the anti-tumor effects of Curcumin, either as an isolated chemoprevention substance or in combination with chemotherapeutic agents as supportive measure reducing pharmaceutical resistance of tumor cells

to certain chemotherapeutics. Despite our increasing knowledge on this interesting substance there still remain many unknown effects that deserve intense investigation.

7.

Nutr Cancer. 2010;62(7):919-30.

Curcumin, the golden spice from Indian saffron, is a chemosensitizer and radiosensitizer for tumors and chemoprotector and radioprotector for normal organs.

Goel A, Aggarwal BB.

Source

Department of Internal Medicine, Baylor University Medical Center, Dallas, Texas, USA.

Abstract

Curcumin (diferuloylmethane), the yellow pigment in Indian saffron (Curcuma longa; also called turmeric, haldi, or haridara in the East and curry powder in the West), has been consumed by people for centuries as a dietary component and for a variety of proinflammatory ailments. Extensive research within the last decade in cell culture and in rodents has revealed that curcumin can sensitize tumors to different chemotherapeutic agents including doxorubicin, 5-FU, paclitaxel, vincristine, melphalan, butyrate, cisplatin, celecoxib, vinorelbine, gemcitabine, oxaliplatin, etoposide, sulfinosine, thalidomide, and bortezomib. Chemosensitization has been observed in cancers of the breast, colon, pancreas, gastric, liver, blood, lung, prostate, bladder, cervix, ovary, head and neck, and brain and in multiple myeloma, leukemia, and lymphoma. Similar studies have also revealed that this agent can sensitize a variety of tumors to gamma radiation including glioma, neuroblastoma, cervical carcinoma, epidermal carcinoma, prostate cancer, and colon cancer. How curcumin acts as a chemosensitizer and radiosensitizer has also been studied extensively. For example, it downregulates various growth regulatory pathways and specific genetic targets including genes for NF-κB, STAT3, COX2, Akt, antiapoptotic proteins, growth factor receptors, and multidrug-resistance proteins. Although it acts as a chemosensitizer and radiosensitizer for tumors in some cases, curcumin has also been shown to protect normal organs such as liver, kidney, oral mucosa, and heart from chemotherapy and radiotherapy-induced toxicity. The protective effects of curcumin appear to be mediated through its ability to induce the activation of NRF2 and induce the expression of antioxidant enzymes (e.g., hemeoxygenase-1, glutathione peroxidase, modulatory subunit of gamma-glutamyl-cysteine ligase, and NAD(P)H:quinone oxidoreductase 1, increase glutathione (a product of the modulatory subunit of gamma-glutamyl-cysteine ligase), directly quench free radicals, and inhibit p300 HAT activity. These preclinical studies are expected to lead to clinical trials to prove the potential of this age-old golden spice for treating cancer patients.

8.

Cancer Lett. 2005 Jun 8;223(2):181-90. Epub 2004 Nov 11.

Chemopreventive and therapeutic effects of curcumin.

Duvoix A, Blasius R, Delhalle S, Schnekenburger M, Morceau F, Henry E, Dicato M, Diederich M.

Source

Laboratoire de Biologie Moléculaire et Cellulaire du Cancer, Hôpital Kirchberg, 9, rue Edward Steichen, L-2540 Luxembourg, Luxembourg.

Abstract

Chemoprevention is a promising anti-cancer approach with reduced secondary effects in comparison to classical chemotherapy. Curcumin, one of the most studied chemopreventive agents, is a natural compound extracted from Curcuma longa L. that allows suppression, retardation or inversion of carcinogenesis. Curcumin is also described as an anti-tumoral, anti-oxidant and anti-inflammatory agent capable of inducing apoptosis in numerous cellular systems. In this review, we describe both properties and mode of action of curcumin on carcinogenesis, gene expression mechanisms and drug metabolism.

9.

Curr Drug Discov Technol. 2009 Sep;6(3):192-9. Epub 2009 Sep 1.

Systemic delivery of curcumin: 21st century solutions for an ancient conundrum.

Bisht S, Maitra A.

Source

Department of Pathology, The Sol Goldman Pancreatic Cancer Research Center, Johns Hopkins University School of Medicine, Baltimore, MD 21231, USA.

Abstract

Curcumin, a polyphenolic compound derived from the dietary spice turmeric, possesses diverse pharmacologic effects including anti-inflammatory, anti-oxidant, anti-proliferative and anti-angiogenic activities. Accumulating experimental evidence suggests that curcumin interferes with a variety of molecular targets and processes involved in cancer. Further, data obtained in multiple preclinical models, as well as in preliminary clinical trials, have documented minimal toxicity of curcumin, even at relatively high doses. However, the clinical advancement of this promising molecule has been hindered by its poor water solubility, short biological half-life, and low bioavailability after oral administration. A variety of approaches are being pursued to overcome these limitations, which include synthesis of curcumin analogues, the use of adjuvants (e.g. piperine), and the development of improved delivery platforms for the parental compound, including liposomal, nanoparticulated and phospholipid complex formulations of curcumin. This review is intended to provide the reader an update on the bioavailability and pharmacokinetic pitfalls of free curcumin, and a comprehensive cataloging of ongoing approaches that have been undertaken to resolve these issues, with the goal of harnessing the true potential of this anti-cancer agent in the clinical arena.

10.

Mol Pharmacol. 2006 Jan;69(1):195-206. Epub 2005 Oct 11.

Curcumin (diferuloylmethane) down-regulates expression of cell proliferation and antiapoptotic and metastatic gene products through suppression of IkappaBalpha kinase and Akt activation.

Aggarwal S, Ichikawa H, Takada Y, Sandur SK, Shishodia S, Aggarwal BB.

Source

Cytokine Research Laboratory, Department of Experimental Therapeutics, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030-4009, USA.

Abstract

Curcumin (diferuloylmethane), an anti-inflammatory agent used in traditional medicine, has been shown to suppress cellular transformation, proliferation, invasion, angiogenesis, and metastasis through a mechanism not fully understood. Because several genes that mediate these processes are regulated by nuclear factor-kappaB (NF-kappaB), we have postulated that curcumin mediates its activity by modulating NF-kappaB activation. Indeed, our laboratory has shown previously that curcumin can suppress NF-kappaB activation induced by a variety of agents (J Biol Chem 270:24995-50000, 1995). In the present study, we investigated the mechanism by which curcumin manifests its effect on NF-kappaB and NF-kappaB-regulated gene expression. Screening of 20 different analogs of curcumin showed that curcumin was the most potent analog in suppressing the tumor necrosis factor (TNF)-induced NF-kappaB activation. Curcumin inhibited TNF-induced NF-kappaB-dependent reporter gene expression in a dose-dependent manner. Curcumin also suppressed NF-kappaB reporter activity induced by tumor necrosis factor receptor (TNFR)1, TNFR2, NF-kappaB-inducing kinase, IkappaB kinase complex (IKK), and the p65 subunit of NF-kappaB. Such TNF-induced NF-kappaB-regulated gene products involved in cellular proliferation [cyclooxygenase-2 (COX-2), cyclin D1, and c-myc], antiapoptosis [inhibitor of apoptosis protein (IAP)1, IAP2, X-chromosome-linked IAP, Bcl-2, Bcl-x(L), Bfl-1/A1, TNF receptor-associated factor 1, and cellular Fas-associated death domain protein-like interleukin-1beta-converting enzyme inhibitory protein-like inhibitory protein], and metastasis (vascular endothelial growth factor, matrix metalloproteinase-9, and intercellular adhesion molecule-1) were also down-regulated by curcumin. COX-2 promoter activity induced by TNF was abrogated by curcumin. We found that curcumin suppressed TNF-induced nuclear translocation of p65, which corresponded with the sequential suppression of IkappaBalpha kinase activity, IkappaBalpha phosphorylation, IkappaBalpha degradation, p65 phosphorylation, p65 nuclear translocation, and p65 acetylation. Curcumin also inhibited TNF-induced Akt activation and its association with IKK. Glutathione and dithiothreitol reversed the effect of curcumin on TNF-induced NF-kappaB activation. Overall, our results indicated that curcumin inhibits NF-kappaB activation and NF-kappaB-regulated gene expression through inhibition of IKK and Akt activation.

11.

Clin Cancer Res. 2007 Jun 1;13(11):3423-30.

Curcumin inhibits tumor growth and angiogenesis in ovarian carcinoma by targeting the nuclear factor-kappaB pathway.

Lin YG, Kunnumakkara AB, Nair A, Merritt WM, Han LY, Armaiz-Pena GN, Kamat AA, Spannuth WA, Gershenson DM, Lutgendorf SK, Aggarwal BB, Sood AK.

Source

Department of Gynecologic Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX 77030, USA.

Abstract

PURPOSE:

Curcumin, a component of turmeric, has been shown to suppress inflammation and angiogenesis largely by inhibiting the transcription factor nuclear factor-kappaB (NF-kappaB). This study evaluates the effects of curcumin on ovarian cancer growth using an orthotopic murine model of ovarian cancer.

EXPERIMENTAL DESIGN:

In vitro and in vivo experiments of curcumin with and without docetaxel were done using human ovarian cancer cell lines SKOV3ip1, HeyA8, and HeyA8-MDR in athymic mice. NF-kappaB modulation was ascertained using electrophoretic mobility shift assay. Evaluation of angiogenic cytokines, cellular proliferation (proliferating cell nuclear antigen), angiogenesis (CD31), and apoptosis (terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling) was done using immunohistochemical analyses.

RESULTS:

Curcumin inhibited inducible NF-kappaB activation and suppressed proliferation in vitro. In vivo dose-finding experiments revealed that 500 mg/kg orally was the optimal dose needed to suppress NF-kappaB and signal transducers and activators of transcription 3 activation and decrease angiogenic cytokine expression. In the SKOV3ip1 and HeyA8 in vivo models, curcumin alone resulted in 49% ($P = 0.08$) and 55% ($P = 0.01$) reductions in mean tumor growth compared with controls, whereas when combined with docetaxel elicited 96% ($P < 0.001$) and 77% reductions in mean tumor growth compared with controls. In mice with multidrug-resistant HeyA8-MDR tumors, treatment with curcumin alone and combined with docetaxel resulted in significant 47% and 58% reductions in tumor growth, respectively ($P = 0.05$). In SKOV3ip1 and HeyA8 tumors, curcumin alone and with docetaxel decreased both proliferation ($P < 0.001$) and microvessel density ($P < 0.001$) and increased tumor cell apoptosis ($P < 0.05$).

CONCLUSIONS:

Based on significant efficacy in preclinical models, curcumin-based therapies may be attractive in patients with ovarian carcinoma.

12.

Pharmacol Res. 2003 Feb;47(2):133-40.

Anticarcinogenic effect of bis-1,7-(2-hydroxyphenyl)-hepta-1,6-diene-3,5-dione a curcumin analog on DMH-induced colon cancer model.

Devasena T, Rajasekaran KN, Gunasekaran G, Viswanathan P, Menon VP.

Source

Department of Biochemistry, Faculty of Science, Annamalai University, Annamalai Nagar 608 002, Tamil Nadu, India.

Abstract

1,2-Dimethylhydrazine (DMH) is a toxic environmental pollutant which was reported also to be a colon-specific carcinogen. This study was performed to study the effect of bis-1,7-(2-hydroxyphenyl)-

hepta-1,6-diene-3,5-dione, a bisdemethoxycurcumin analog (BDMC-A) on DMH-induced colon carcinogenesis in male Wistar rats and effects were compared with that of the reference drug, curcumin. Rats were given a weekly subcutaneous injection of DMH (20mg/kg body weight) in the groin, for 15 weeks. After a total experimental period of 32 weeks (including 2 weeks of acclimatization) tumor incidence was 100% in DMH-treated rats. Tumor was identified histologically as adenocarcinoma. Dysplasia, papillary pattern, cellular pleomorphism and carcinomatous glands were also noticed in DMH-treated rats. However, there was no colonic tumor in DMH+BDMC-A- and DMH+curcumin-treated rats but, lymphocyte infiltrations were observed. The levels of total bile acids and cholesterol in 24h fecal samples were significantly lower in DMH administered rats when compared to control rats, while, the excretion of bile acids and cholesterol were significantly increased and was near normal levels in DMH+BDMC-A- and DMH+curcumin-treated rats. In DMH-induced tumor bearing rats the levels of colonic and intestinal cholesterol was significantly increased whereas, the levels of phospholipid was decreased with a concomitant increase in the activities of phospholipase A (PLA) and phospholipase C (PLC), compared to untreated control rats. Intragastric administration of BDMC-A and curcumin to DMH administered rats significantly lowered the cholesterol content and raised the phospholipid content and lowered the activities of PLA and PLC towards near normal values. Our study shows that the protective effect of BDMC-A during DMH-induced colon carcinogenesis may be due to its modulatory effects on (i). histological changes, (ii). bile acids, (iii). cholesterol, and (iv). phospholipid metabolism in the target organ. Absence of histological changes in the colon of rats treated with BDMC-A, shows that long term administration of BDMC-A is nontoxic to experimental animals. Our study suggest that BDMC-A may emerge as a potent anticarcinogenic agent against colon cancer. As both BDMC-A and curcumin are equipotent in inhibiting the DMH-induced colon tumor incidence and normalizing histological changes, it could be concluded that the terminal phenolic group and the conjugated double bonds in the central seven carbon change may be responsible for the beneficial effects.

13.

Carcinogenesis. 2012 Oct 26. [Epub ahead of print]

Curcumin inhibits prostate cancer metastasis in vivo by targeting the inflammatory cytokines CXCL1 and -2.

Killian PH, Kronski E, Michalik KM, Barbieri O, Astigiano S, Sommerhoff CP, Pfeffer U, Nerlich AG, Bachmeier BE.

Source

Institute of Laboratory Medicine, Ludwig-Maximilians-University, Munich, Germany.

Abstract

In America and Western Europe, prostate cancer is the second leading cause of death in men. Emerging evidence suggests that chronic inflammation is a major risk factor for the development and metastatic progression of prostate cancer. We previously reported that the chemopreventive polyphenol curcumin inhibits the expression of the proinflammatory cytokines CXCL1 and -2 leading to diminished formation of breast cancer metastases. In this study, we analyze the effects of curcumin on prostate carcinoma growth, apoptosis and metastasis. We show that curcumin inhibits translocation of NFκB to the nucleus through the inhibition of the IκB-kinase (IKKβ, leading to stabilization of the inhibitor of NFκB, IκBα, in PC-3 prostate carcinoma cells. Inhibition of NFκB activity reduces expression of CXCL1 and -2 and abolishes the autocrine/paracrine loop that links the

two chemokines to NFκB. The combination of curcumin with the synthetic IKKβ inhibitor, SC-541, shows no additive or synergistic effects indicating that the two compounds share the target. Treatment of the cells with curcumin and siRNA-based knockdown of CXCL1 and -2 induce apoptosis, inhibit proliferation and downregulate several important metastasis-promoting factors like COX2, SPARC and EFEMP. In an orthotopic mouse model of hematogenous metastasis, treatment with curcumin inhibits statistically significantly formation of lung metastases. In conclusion, chronic inflammation can induce a metastasis prone phenotype in prostate cancer cells by maintaining a positive proinflammatory and prometastatic feedback loop between NFκB and CXCL1/-2. Curcumin disrupts this feedback loop by the inhibition of NFκB signaling leading to reduced metastasis formation in vivo.

14.

Cancer Epidemiol Biomarkers Prev January 2005 14; 120

Consumption of the Putative Chemopreventive Agent Curcumin by Cancer Patients: Assessment of Curcumin Levels in the Colorectum and their Pharmacodynamic Consequences

10. Giuseppe Garcea1,
11. David P. Berry2,
12. Donald J.L. Jones1,
13. Raj Singh1,
14. Ashley R. Dennison2,
15. Peter B. Farmer1,
16. Ricky A. Sharma1,
17. William P. Steward1 and
18. Andreas J. Gescher1

- Author Affiliations

2. [1]*Cancer Biomarkers and Prevention Group, Departments of Oncology and Biochemistry, University of Leicester and* [2]*Department of Hepatobiliary Surgery, University Hospitals of Leicester, Leicester General Hospital, Leicester, United Kingdom*

Abstract

Curcumin, a constituent of the spice turmeric, has been shown to reduce the adenoma burden in rodent models of colorectal cancer accompanied by a reduction of levels of the oxidative DNA adduct 3-(2-deoxy-**β**-di-erythro-pentafuranosyl)-pyr[1,2-α]-purin-10(3*H*)one (M_1G) and of expression of the enzyme cyclooxygenase-2 (COX-2). We tested the hypothesis that pharmacologically active levels of curcumin can be achieved in the colorectum of humans as measured by effects on levels of M_1G and COX-2 protein. Patients with colorectal cancer ingested curcumin capsules (3,600, 1,800, or 450 mg daily) for 7 days. Biopsy samples of normal and malignant colorectal tissue, respectively, were obtained at diagnosis and at 6 to 7 hours after the last dose of curcumin. Blood was taken 1 hour after the last dose of curcumin. Curcumin and its metabolites were detected and quantitated by high-performance liquid chromatography with detection by UV spectrophotometry or mass spectrometry. M_1G levels and COX-2 protein expression were measured by immunoslot blot and Western blotting, respectively. The concentrations of curcumin in normal and malignant colorectal tissue of patients receiving 3,600 mg of curcumin were 12.7 ± 5.7 and 7.7 ± 1.8 nmol/g, respectively. Curcumin sulfate and curcumin glucuronide were identified in the tissue of these patients. Trace levels of curcumin were found in the peripheral circulation. M_1G levels were 2.5-fold higher in malignant tissue as compared with normal tissue ($P < 0.05$ by ANOVA). Administration of curcumin (3,600 mg) decreased M_1G levels from 4.8 ± 2.9 adducts per 107 nucleotides in malignant colorectal

tissue to 2.0 ± 1.8 adducts per 107 nucleotides ($P < 0.05$ by ANOVA). COX-2 protein levels in malignant colorectal tissue were not affected by curcumin. The results suggest that a daily dose of 3.6 g curcumin achieves pharmacologically efficacious levels in the colorectum with negligible distribution of curcumin outside the gut.

15

Cancer Prev Res March 2011 4; 354

Phase IIa Clinical Trial of Curcumin for the Prevention of Colorectal Neoplasia

12. Robert E. Carroll1,
13. Richard V. Benya1,
14. Danielle Kim Turgeon2,
15. Shaiju Vareed2,
16. Malloree Neuman3,
17. Luz Rodriguez4,
18. Madhuri Kakarala5,5,
19. Philip M. Carpenter2,
20. Christine McLaren6,7,
21. Frank L. Meyskens, Jr6, and
22. Dean E. Brenner2,3,5

- Author Affiliations

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Abstract

Curcumin is derived from the spice tumeric and has antiinflammatory and antineoplastic effects *in vitro* and in animal models, including preventing aberrant crypt foci (ACF) and adenomas in murine models of colorectal carcinogenesis. Inhibiting the production of the procarcinogenic eicosanoids prostaglandin E_2 (PGE_2) and 5-hydroxyeicosatetraenoic acid (5-HETE) can suppress carcinogenesis in rodents. Curcumin reduces mucosal concentrations of PGE_2 (via inhibition of cyclooxygenases 1 and 2) and 5-HETE (via inhibition of 5-lipoxygenase) in rats. Although preclinical data support curcumin activity in many sites, the poor bioavailability reported for this agent supports its use in the colorectum. We assessed the effects of oral curcumin (2 g or 4 g per day for 30 days) on PGE_2 within ACF (primary endpoint), 5-HETE, ACF number, and proliferation in a nonrandomized, open-label clinical trial in 44 eligible smokers with eight or more ACF on screening colonoscopy. We assessed pre- and posttreatment concentrations of PGE_2 and 5-HETE by liquid chromatography tandem mass spectroscopy in ACF and normal-tissue biopsies; ACF number via rectal endoscopy; proliferation by Ki-67 immunohistochemistry; and curcumin concentrations by high-performance liquid chromatography in serum and rectal mucosal samples. Forty-one subjects completed the study. Neither dose of curcumin reduced PGE_2 or 5-HETE within ACF or normal mucosa or reduced Ki-67 in normal mucosa. A significant 40% reduction in ACF number occurred with the 4-g dose ($P < 0.005$),

whereas ACF were not reduced in the 2-g group. The ACF reduction in the 4-g group was associated with a significant, five-fold increase in posttreatment plasma curcumin/conjugate levels (versus pretreatment; *P* = 0.009). Curcumin was well tolerated at both 2 g and 4 g. Our data suggest that curcumin can decrease ACF number, and this is potentially mediated by curcumin conjugates delivered systemically.

(click here to return to top of page)

GINGER

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RESEARCH ABSTRACTS

1.

BMC Complement Altern Med. 2007 Dec 20;7:44.

Ginger inhibits cell growth and modulates angiogenic factors in ovarian cancer cells.

Rhode J, Fogoros S, Zick S, Wahl H, Griffith KA, Huang J, Liu JR.

Source

Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, University of Michigan, Ann Arbor, MI, USA. JnMRhode@aol.com

Abstract

BACKGROUND:

Ginger (Zingiber officinale Rosc) is a natural dietary component with antioxidant and anticarcinogenic properties. The ginger component [6]-gingerol has been shown to exert anti-inflammatory effects through mediation of NF-kappaB. NF-kappaB can be constitutively activated in

epithelial ovarian cancer cells and may contribute towards increased transcription and translation of angiogenic factors. In the present study, we investigated the effect of ginger on tumor cell growth and modulation of angiogenic factors in ovarian cancer cells in vitro.

METHODS:

The effect of ginger and the major ginger components on cell growth was determined in a panel of epithelial ovarian cancer cell lines. Activation of NF-kappaB and and production of VEGF and IL-8 was determined in the presence or absence of ginger.

RESULTS:

Ginger treatment of cultured ovarian cancer cells induced profound growth inhibition in all cell lines tested. We found that in vitro, 6-shogaol is the most active of the individual ginger components tested. Ginger treatment resulted in inhibition of NF-kB activation as well as diminished secretion of VEGF and IL-8.

CONCLUSION:

Ginger inhibits growth and modulates secretion of angiogenic factors in ovarian cancer cells. The use of dietary agents such as ginger may have potential in the treatment and prevention of ovarian cancer.

2.

Cancer Prev Res (Phila). 2011 Nov;4(11):1929-37. Epub 2011 Oct 11.

Phase II Study of the Effects of Ginger Root Extract on Eicosanoids in Colon Mucosa in People at Normal Risk for Colorectal Cancer.

Zick SM, Turgeon DK, Vareed SK, Ruffin MT, Litzinger AJ, Wright BD, Alrawi S, Normolle DP, Djuric Z, Brenner DE.

Source

24 Frank Lloyd Wright Drive, Lobby M, P.O. Box 385, University of Michigan Medical Center, Ann Arbor, MI 48105. szick@med.umich.edu.

Abstract

Inhibitors of COX indicate that upregulation of inflammatory eicosanoids produced by COX, and in particular prostaglandin E(2) (PGE(2)), are early events in the development of colorectal cancer (CRC). Ginger has shown downregulation of COX in vitro and decreased incidence/multiplicity of adenomas in rats. This study was conducted to determine if 2.0 g/d of ginger could decrease the levels of PGE(2), 13-hydroxy-octadecadienoic acids, and 5-, 12-, and 15-hydroxyeicosatetraenoic acid (5-, 12-, and 15-HETE), in the colon mucosa of healthy volunteers. To investigate this aim, we randomized 30 subjects to 2.0 g/d ginger or placebo for 28 days. Flexible sigmoidoscopy at baseline and day 28 was used to obtain colon biopsies. A liquid chromatography mass spectrometry method was used to determine eicosanoid levels in the biopsies, and levels were expressed per protein or per free arachidonic acid. There were no significant differences in mean percent change between baseline and day 28 for any of the eicosanoids, when normalized to protein. There was a significant decrease in mean percent change in PGE(2) (P = 0.05) and 5-HETE (P = 0.04), and a trend toward significant decreases in 12-HETE (P = 0.09) and 15-HETE (P = 0.06) normalized to free arachidonic acid. There was no difference between the groups in terms of total adverse events P = 0.55). On the

basis of these results, it seems that ginger has the potential to decrease eicosanoid levels, perhaps by inhibiting their synthesis from arachidonic acid. Ginger also seemed to be tolerable and safe. Further investigation in people at high risk for CRC seems warranted. Cancer Prev Res; 4(11); 1929-37. ©2011 AACR.

http://cancerpreventionresearch.aacrjournals.org/content/early/2011/10/07/1940-6207.CAPR-11-0224.abstract

3.

Food Chem Toxicol. 2007 May;45(5):683-90. Epub 2006 Nov 12.

Cancer preventive properties of ginger: a brief review.

Shukla Y, Singh M.

Source

Environmental Carcinogenesis Division, Industrial Toxicology Research Centre, P.O. Box 80, M.G. Marg, Lucknow 226 001, Uttar Pradesh, India. yogeshwer_shukla@hotmail.com <yogeshwer_shukla@hotmail.com>

Abstract

Ginger, the rhizome of Zingiber officinalis, one of the most widely used species of the ginger family, is a common condiment for various foods and beverages. Ginger has a long history of medicinal use dating back 2500 years. Ginger has been traditionally used from time immemorial for varied human ailments in different parts of the globe, to aid digestion and treat stomach upset, diarrhoea, and nausea. Some pungent constituents present in ginger and other zingiberaceous plants have potent antioxidant and anti-inflammatory activities, and some of them exhibit cancer preventive activity in experimental carcinogenesis. The anticancer properties of ginger are attributed to the presence of certain pungent vallinoids, viz. [6]-gingerol and [6]-paradol, as well as some other constituents like shogaols, zingerone etc. A number of mechanisms that may be involved in the chemopreventive effects of ginger and its components have been reported from the laboratory studies in a wide range of experimental models. 4.

Crit Rev Food Sci Nutr. 2011 Jul;51(6):499-523.

Update on the chemopreventive effects of ginger and its phytochemicals.

Baliga MS, Haniadka R, Pereira MM, D'Souza JJ, Pallaty PL, Bhat HP, Popuri S.

Source

Research and Development, Father Muller Medical College, Father Muller Hospital Road, Kankanady, Mangalore, 575002, Karnataka, India. msbaliga@gmail.com

Abstract

The rhizomes of Zingiber officinale Roscoe (Zingiberaceae), commonly known as ginger, is one of the most widely used spice and condiment. It is also an integral part of many traditional medicines and has been extensively used in Chinese, Ayurvedic, Tibb-Unani, Srilankan, Arabic, and African traditional medicines, since antiquity, for many unrelated human ailments including common colds,

fever, sore throats, vomiting, motion sickness, gastrointestinal complications, indigestion, constipation, arthritis, rheumatism, sprains, muscular aches, pains, cramps, hypertension, dementia, fever, infectious diseases, and helminthiasis. The putative active compounds are nonvolatile pungent principles, namely gingerols, shogaols, paradols, and zingerone. These compounds are some of the extensively studied phytochemicals and account for the antioxidant, anti-inflammatory, antiemetic, and gastroprotective activities. A number of preclinical investigations with a wide variety of assay systems and carcinogens have shown that ginger and its compounds possess chemopreventive and antineoplastic effects. A number of mechanisms have been observed to be involved in the chemopreventive effects of ginger. The cancer preventive activities of ginger are supposed to be mainly due to free radical scavenging, antioxidant pathways, alteration of gene expressions, and induction of apoptosis, all of which contribute towards decrease in tumor initiation, promotion, and progression. This review provides concise information from preclinical studies with both cell culture models and relevant animal studies by focusing on the mechanisms responsible for the chemopreventive action. The conclusion describes directions for future research to establish its activity and utility as a human cancer preventive and therapeutic drug. The above-mentioned mechanisms of ginger seem to be promising for cancer prevention; however, further clinical studies are warranted to assess the efficacy and safety of ginger.

http://www.ncbi.nlm.nih.gov/pubmed/21929329

5.

British Journal of Nutrition 2011 Aug 18:1-12. [Epub ahead of print]

Benefits of whole ginger extract in prostate cancer.

Karna P, Chagani S, Gundala SR, Rida PC, Asif G, Sharma V, Gupta MV, Aneja R.

Source
Department of Biology, Georgia State University, Atlanta, GA 30303, USA.

Abstract

It is appreciated far and wide that increased and regular consumption of fruits and vegetables is linked with noteworthy anticancer benefits. Extensively consumed as a spice in foods and beverages worldwide, ginger (Zingiber officinale Roscoe) is an excellent source of several bioactive phenolics, including non-volatile pungent compounds such as gingerols, paradols, shogaols and gingerones. Ginger has been known to display anti-inflammatory, antioxidant and antiproliferative activities, indicating its promising role as a chemopreventive agent. Here, we show that whole ginger extract (GE) exerts significant growth-inhibitory and death-inductory effects in a spectrum of prostate cancer cells. Comprehensive studies have confirmed that GE perturbed cell-cycle progression, impaired reproductive capacity, modulated cell-cycle and apoptosis regulatory molecules and induced a caspase-driven, mitochondrially mediated apoptosis in human prostate cancer cells. Remarkably, daily oral feeding of 100 mg/kg body weight of GE inhibited growth and progression of PC-3 xenografts by approximately 56 % in nude mice, as shown by measurements of tumour volume. Tumour tissue from GE-treated mice showed reduced proliferation index and widespread apoptosis compared with controls, as determined by immunoblotting and immunohistochemical methods. Most importantly, GE did not exert any detectable toxicity in normal, rapidly dividing tissues such as gut and bone marrow. To the best of our knowledge, this is the first report to demonstrate the in vitro and in vivo anticancer activity of whole GE for the management of prostate cancer.

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6.

Int J Cancer. 2011 Jul 25. doi: 10.1002/ijc.26316. [Epub ahead of print]

Administration of 6-gingerol greatly enhances the number of tumor-infiltrating lymphocytes in murine tumors.

Ju SA, Park SM, Lee YS, Bae JH, Yu R, An WG, Suh JH, Kim BS.

Source

Biomedical Research Center, Ulsan University Hospital, College of Medicine, University of Ulsan, Ulsan, Republic of Korea.

Abstract

Tumor-infiltrating lymphocytes (TILs) play critical roles in host anti-tumor immune responses. It is known that cancer patients with tumor-reactive lymphocyte infiltration in their tumors have better prognoses, while patients with tumors infiltrated by immunosuppressive cells have worse prognoses. We found that administration of 6-gingerol, which is a component of ginger, inhibited tumor growth in several types of murine tumors, such as B16F1 melanomas, Renca renal cell carcinomas and CT26 colon carcinomas, which were established by inoculating tumor cells on the flanks of mice. However, administration of 6-gingerol did not lead to complete eradication of the tumors. 6-Gingerol treatment of tumor-bearing mice caused massive infiltration of CD4 and CD8 T-cells and B220(+) B-cells, but reduced the number of CD4(+) Foxp3(+) regulatory T-cells. The CD8 tumor-infiltrating T lymphocytes in 6-gingerol-treated mice strongly expressed IFN-γ, a marker of activation of CTL CD107a, and chemokine receptors that are expressed on T(H) 1 cells, such as CXCR3 and CCR5. To test whether 6-gingerol could promote infiltration of tumor antigen-specific CD8 T-cells into tumors, we adoptively transferred CFSE-labeled OT-I CD8 T-cells into EG7 tumor-bearing mice. We found that CD8 T cells isolated from 6-gingerol pre-treated OT-I mice, but not from control OT-I mice, massively infiltrated tumors and tumor draining lymph nodes and divided several times. Our results strongly suggest that 6-gingerol can be used in tumor immunotherapy to increase the number of TILs.

7.

Carcinogenesis. 2011 Jun;32(6):904-12. Epub 2011 Mar 22.

1'-Acetoxychavicol acetate suppresses angiogenesis-mediated human prostate tumor growth by targeting VEGF-mediated Src-FAK-Rho GTPase-signaling pathway.

Pang X, Zhang L, Lai L, Chen J, Wu Y, Yi Z, Zhang J, Qu W, Aggarwal BB, Liu M.

Source

Institute of Biomedical Sciences and School of Life Sciences, East China Normal University, 500 Dongchuan Road, Shanghai 200241, China. xfpang@bio.ecnu.edu.cn

Abstract

Cancer therapeutic agents that are safe, effective and affordable are urgently needed. We describe that 1'-acetoxychavicol acetate (ACA), a component of Siamese ginger (Languas galanga), can suppress prostate tumor growth by largely abrogating angiogenesis. ACA suppressed vascular endothelial growth factor (VEGF)-induced proliferation, migration, adhesion and tubulogenesis of primary cultured human umbilical vascular endothelial cells (HUVECs) in a dose-dependent manner. ACA also inhibited VEGF-induced microvessel sprouting from aortic rings ex vivo and suppressed new vasculature formation in Matrigel plugs in vivo. We further demonstrated that the mechanisms of this chavicol were to block the activation of VEGF-mediated Src kinase, focal adhesion kinase (FAK) and Rho family of small guanosine triphosphatases (GTPases) (Rac1 and Cdc42 but not RhoA) in HUVECs. Furthermore, treatment of human prostate cancer cells (PC-3) with ACA resulted in decreased cell viability and suppression of angiogenic factor production by interference with dual Src/FAK kinases. After subcutaneous administration to mice bearing human prostate cancer PC-3 xenografts, ACA (6 mg/kg/day) remarkably inhibited tumor volume and tumor weight and decreased levels of Src, CD31, VEGF and Ki-67. As indicated by immunohistochemistry and TUNEL analysis, microvessel density and cell proliferation were also dramatically suppressed in tumors from ACA-treated mice. Taken together, our findings suggest that ACA targets the Src-FAK-Rho GTPase pathway, leading to the suppression of prostate tumor angiogenesis and growth.

8.

Curr Med Chem. 2011;18(21):3190-210.

Pharmacokinetic profiles of anticancer herbal medicines in humans and the clinical implications.

Chen XW, Sneed KB, Zhou SF.

Source

Department of General Surgery, Shunde First People's Hospital Affiliated to Southern Medical University, Foshan, Guangdong, China.

Abstract

A number of herbal medicines are increasingly used by cancer patients worldwide, despite the fact that the clinical evidence that supports their use to fight cancer is weak or lacking. Pharmacokinetic studies have been integrated into modern drug development, but they are generally not needed for herbal remedies. To update our knowledge in this field, this paper highlights the pharmacokinetic properties of anticancer herbal medicines and the clinical relevance. To retrieve relevant data, the authors have searched through computer-based literatures by full text search in Medline (via Pubmed), ScienceDirect, Current Contents Connect (ISI), Cochrance Library, CINAHL (EBSCO), CrossRef Search and Embase ((all from inception to May 2011). An extensive literature search indicatesthat there are limited data on the pharmacokinetic properties of anticancer herbal medicines in humans. There are increasing pharmacokinetic studies of anticancer herbal remedies, but these studies are mainly focused on a small number of herbal medicines including curcumin, ginseng, ginkgo, ginger and milk thistle. For an anticancer herbal medicine, the pharmacological activity is gained when the active agents or the active metabolites reach and sustain proper levels at their sites of action. Both the dose levels and pharmacokinetic processes of active herbal components in the body determine their target-site concentrations and thus the anticancer effect. In this regard, a safe and optimal use of anticancer herbal medicines requires a full understanding of their pharmacokinetic profiles. To optimize the use of anticancer herbal remedies, further studies to

explore their pharmacokinetic properties and the relevance to pharmacodynamics and toxicity in humans are certainly warranted.

(click here to return to top of page)

GREEN TEA

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a) Lambert JD et al; Department of Chemical Biology, Ernest Mario School of Pharmacy, Rutgers; "Mechanisms of cancer prevention by tea constituents"; J Nutr. 2003 Oct;133(10):3262S-3267S; b) Steele VE et al; Chemoprevention Branch, Division of Cancer Prevention, National Cancer Institute, NIH; "Comparative chemopreventive mechanisms of green tea, black tea and selected polyphenol extracts measured by in vitro bioassays"; Carcinogenesis. 2000 Jan;21(1):63-7; c) Henning SM et al; Center for Human Nutrition, David Geffen School of Medicine and the Department of Biostatistics, School of Public Health, University of California, Los Angeles; "Bioavailability and antioxidant activity of tea flavanols after consumption of green tea, black tea, or a green tea extract supplement"; Am J Clin Nutr. 2004 Dec;80(6):1558-64; d) Yang CS et al; Laboratory for Cancer Research, Department of Chemical Biology, College of Pharmacy, Rutgers; "Inhibition of carcinogenesis by tea"; Annu Rev Pharmacol Toxicol. 2002;42:25-54; e) Seeram NP et al; Center for Human Nutrition, David Geffen School of Medicine, University of California, Los Angeles; "Catechin and caffeine content of green tea dietary supplements and correlation with antioxidant capacity"; J Agric Food Chem. 2006 Mar 8;54(5):1599-603; f) Zhang M et al; The School of Population Health, The University of Western Australia; "Green tea and the prevention of breast cancer: a case-control study in Southeast China"; Carcinogenesis. 2007 May;28(5):1074-8. Epub 2006 Dec 20; g) Yang G et al; Department of Medicine, Vanderbilt Epidemiology Center and Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine; "Prospective cohort study of green tea consumption and colorectal cancer risk in women"; Cancer Epidemiol Biomarkers Prev. 2007 Jun;16(6):1219-23; h) Kurahashi N et al; Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, Japan; "Green tea consumption and prostate cancer risk in Japanese men: a prospective study"; Am J Epidemiol. 2008 Jan 1;167(1):71-7. Epub 2007 Sep 29; i) Shrubsole MJ et al; Department of Medicine, Vanderbilt Epidemiology Center, Vanderbilt School of Medicine; "Drinking green tea modestly reduces breast cancer risk"; J Nutr. 2009 Feb;139(2):310-6. Epub 2008 Dec 11; j) Hsu SD et al; Department of Oral Biology and Maxillofacial Pathology, School of Dentistry, Medical College of Georgia; "Chemoprevention of oral cancer by green tea"; Gen Dent. 2002 Mar-Apr;50(2):140-6; k) Suganuma M et al; Saitama Cancer Center Research Institute, Ina, Kitaadachi-gun, Saitama 362-0806, Japan; "Green tea and cancer chemoprevention"; Mutation research [1999, 428(1-2):339-344]; l) Sartippour MR et al; Department of Surgery, Division of Oncology and Center for Human Nutrition, University of California, Los Angeles; "Green tea inhibits vascular endothelial growth factor (VEGF) induction in human breast cancer cells"; J Nutr. 2002 Aug;132(8):2307-11; m) Tsao AS et al; Department of Thoracic/Head and Neck Medical Oncology, The University of Texas M. D. Anderson Cancer Center; "Phase II randomized, placebo-controlled trial of green tea extract in patients with high-risk oral premalignant lesions"; Cancer Prev Res (Phila). 2009 Nov;2(11):931-41; n) Sun CL et al; USC/Norris Comprehensive Cancer Center, University of Southern California Keck School of Medicine; "Urinary tea polyphenols in relation to gastric and esophageal cancers: a prospective study of men in Shanghai, China"; Carcinogenesis. 2002 Sep;23(9):1497-503; o) Nakachi Kei et al; Saitama Cancer Center Research Institute, 818 Komuro, Ina, Saitama 362-0806, Japan; "Preventive effects of drinking green tea on cancer and cardiovascular disease: Epidemiological evidence for multiple targeting prevention"; BioFactors; Volume 13, Issue 1-4, pages 49–54, 2000; p) Bettuzzi S et al; Department of Medicina Sperimentale, Sezione di Biochimica, University of Parma; "Chemoprevention of human prostate cancer by oral administration of green tea catechins in volunteers with high-grade prostate intraepithelial neoplasia: a preliminary report from a one-year

proof-of-principle study"; Department of Medicina Sperimentale, Sezione di Biochimica, University of Parma; Cancer Res. 2006 Jan 15;66(2):1234-40.; q) Brausi M, Rizzi F, Bettuzzi S: Chemoprevention of human prostate cancer by green tea catechins: two years later. A follow-up update. Eur Urol 54 (2): 472-3, 2008.

RESEARCH ABSTRACTS

1.

J Nutr. 2003 Oct;133(10):3262S-3267S.

Mechanisms of cancer prevention by tea constituents.

Lambert JD, Yang CS.

Source

Department of Chemical Biology, Ernest Mario School of Pharmacy, Rutgers, The State University of New Jersey, Piscataway, NJ 08854, USA.

Abstract

Consumption of tea (Camellia sinensis) has been suggested to prevent cancer, heart disease and other diseases. Animal studies have shown that tea and tea constituents inhibit carcinogenesis of the skin, lung, oral cavity, esophagus, stomach, liver, prostate and other organs. In some studies, the inhibition correlated with an increase in tumor cell apoptosis and a decrease in cell proliferation. Studies with human cancer cell lines have demonstrated that epigallocatechin-3-gallate (EGCG), a major tea polyphenol, inhibits mitogen-activated protein kinases, cyclin-dependent kinases, growth factor-related cell signaling, activation of activator protein 1 (AP-1) and nuclear factor kappaB (NFkappaB), topoisomerase I and matrix metalloproteinases as well as other potential targets. Although some studies report effects of EGCG at submicromolar levels, most experiments require concentrations of >10 or 20 micromol/L to demonstrate the effect. In humans, tea polyphenols undergo glucuronidation, sulfation, methylation, and ring fission. The peak plasma concentration of EGCG is approximately 1 micromol/L. The possible relevance of each of the proposed mechanisms to human cancer prevention is discussed in light of current bioavailability data for tea polyphenols and the potential limitations of animal models of carcinogenesis. Such discussion, it is hoped, will clarify some misunderstandings of cancer prevention by tea and stimulate new research efforts.

2.

Carcinogenesis. 2000 Jan;21(1):63-7.

Comparative chemopreventive mechanisms of green tea, black tea and selected polyphenol extracts measured by in vitro bioassays.

Steele VE, Kelloff GJ, Balentine D, Boone CW, Mehta R, Bagheri D, Sigman CC, Zhu S, Sharma S.

Source

Chemoprevention Branch, Division of Cancer Prevention, National Cancer Institute, NIH, Bethesda, MD 20892, USA. vsly@nih.gov

Abstract

Black tea extracts (hot aqueous, polyphenols and theaflavins) and green tea extracts (hot aqueous, polyphenols, epicatechin, epicatechin gallate, epigallocatechin and epigallocatechin gallate) were tested in nine standardized cell culture assays for comparative cancer chemopreventive properties. Most black and green tea extracts strongly inhibited neoplastic transformation in mouse mammary organ cultures, rat tracheal epithelial cells and human lung tumor epithelial cells. Nearly all tea fractions strongly inhibited benzo[a]pyrene adduct formation with human DNA. Induction of phase II enzymes, glutathione-S-transferase and quinone reductase, were enhanced by nearly all tea fractions, while glutathione was induced by only a few fractions. Ornithine decarboxylase activity was inhibited by nearly all the green tea fractions, but none of the black tea fractions. 12-O-tetradecanoylphorbol-13-acetate-induced free radicals were inhibited by most tea fractions. These results provide strong evidence of both anti-mutagenic, anti-proliferative and anti-neoplastic activities for both black and green tea extracts. Such anticancer mechanisms may well be responsible for the cancer preventive efficacies seen in both experimental and human studies.

3.

Am J Clin Nutr. 2004 Dec;80(6):1558-64.

Bioavailability and antioxidant activity of tea flavanols after consumption of green tea, black tea, or a green tea extract supplement.

Henning SM, Niu Y, Lee NH, Thames GD, Minutti RR, Wang H, Go VL, Heber D.

Source

Center for Human Nutrition, David Geffen School of Medicine and the Department of Biostatistics, School of Public Health, University of California, Los Angeles, 90095, USA.
shenning@mednet.ucla.edu

Abstract

BACKGROUND:

Green and black tea polyphenols have been extensively studied as cancer chemopreventive agents. Many in vitro experiments have supported their strong antioxidant activity. Additional in vivo studies are needed to examine the pharmacokinetic relation of absorption and antioxidant activity of tea polyphenols administered in the form of green or black tea or tea extract supplements.

OBJECTIVE:

The purpose of this study was to compare the pharmacokinetic disposition of tea polyphenols and their effect on the antioxidant capacity in plasma 8 h after a bolus consumption of either green tea, black tea, or a green tea extract supplement.

DESIGN:

Thirty healthy subjects were randomly assigned to 3 different sequences of green tea, black tea, or a green tea extract supplement in a 3 x 3 crossover design with a 1-wk washout period in between treatments.

RESULTS:

Flavanol absorption was enhanced when tea polyphenols were administered as a green tea supplement in capsule form and led to a small but significant increase in plasma antioxidant activity compared with when tea polyphenols were consumed as black tea or green tea. All 3 interventions provided similar amounts of (-)-epigallocatechin-3-gallate.

CONCLUSIONS:

Our observations suggest that green tea extract supplements retain the beneficial effects of green and black tea and may be used in future chemoprevention studies to provide a large dose of tea polyphenols without the side effects of caffeine associated with green and black tea beverages.

4.

Annu Rev Pharmacol Toxicol. 2002;42:25-54.

Inhibition of carcinogenesis by tea.

Yang CS, Maliakal P, Meng X.

Source

Laboratory for Cancer Research, Department of Chemical Biology, College of Pharmacy, Rutgers, The State University of New Jersey, Piscataway, New Jersey 08854-8020, USA. csyang@rci.rutgers.edu

Abstract

Tea has received a great deal of attention because tea polyphenols are strong antioxidants, and tea preparations have inhibitory activity against tumorigenesis. The bioavailability and biotransformation of tea polyphenols, however, are key factors limiting these activities in vivo. The inhibition of tumorigenesis by green or black tea preparations has been demonstrated in animal models on different organ sites such as skin, lung, oral cavity, esophagus, forestomach, stomach, small intestine, colon, pancreas, and mammary gland. Epidemiological studies, however, have not yielded clear conclusions concerning the protective effects of tea consumption against cancer formation in humans. The discrepancy between the results from humans and animal models could be due to 1) the much higher doses of tea used in animals in comparison to human consumption, 2) the differences in causative factors between the cancers in humans and animals, and 3) confounding factors limiting the power of epidemiological studies to detect an effect. It is possible that tea may be only effective against specific types of cancer caused by certain etiological factors. Many mechanisms have been proposed for the inhibition of carcinogenesis by tea, including the modulation of signal transduction pathways that leads to the inhibition of cell proliferation and transformation, induction of apoptosis of preneoplastic and neoplastic cells, as well as inhibition of tumor invasion and angiogenesis. These mechanisms need to be evaluated and verified in animal models or humans in order to gain more understanding on the effect of tea consumption on human cancer.

5.

J Agric Food Chem. 2006 Mar 8;54(5):1599-603.

Catechin and caffeine content of green tea dietary supplements and correlation with antioxidant capacity.

Seeram NP, Henning SM, Niu Y, Lee R, Scheuller HS, Heber D.

Source

Center for Human Nutrition, David Geffen School of Medicine, University of California, Los Angeles, California 90095, USA. nseeram@mednet.ucla.edu

Abstract

The health benefits associated with tea consumption have resulted in the wide inclusion of green tea extracts in botanical dietary supplements, which are widely consumed as adjuvants for complementary and alternative medicines. Tea contains polyphenols such as catechins or flavan-3-ols including epicatechin, epigallocatechin, epicatechin gallate, and epigallocatechin gallate (EGCG), as well as the alkaloid, caffeine. Polyphenols are antioxidants, and EGCG, due to its high levels, is widely accepted as the major antioxidant in green tea. Therefore, commercial green tea dietary supplements (GTDS) may be chemically standardized to EGCG levels and/or biologically standardized to antioxidant capacity. However, label claims on GTDS may not correlate with actual phytochemical content or antioxidant capacity nor provide information about the presence and levels of caffeine. In the current study, 19 commonly available GTDS were evaluated for catechin and caffeine content (using high-performance liquid chromatography) and for antioxidative activity [using trolox equivalent antioxidant capacity (TEAC) and oxygen radical antioxidant capacity (ORAC) assays]. Product labels varied in the information provided and were inconsistent with actual phytochemical contents. Only seven of the GTDS studied made label claims of caffeine content, 11 made claims of EGCG content, and five specified total polyphenol content. Caffeine, EGCG, and total polyphenol contents in the GTDS varied from 28 to 183, 12-143, and 14-36% tablet or capsule weight, respectively. TEAC and ORAC values for GTDS ranged from 187 to 15340 and from 166 to 13690 mumol Trolox/g for tablet or capsule, respectively. The antioxidant activities for GTDS determined by TEAC and ORAC were well-correlated with each other and with the total polyphenol content. Reliable labeling information and standardized manufacturing practices, based on both chemical standardization and biological assays, are recommended for the quality control of botanical dietary supplements.

6.

Carcinogenesis. 2007 May;28(5):1074-8. Epub 2006 Dec 20.

Green tea and the prevention of breast cancer: a case-control study in Southeast China.

Zhang M, Holman CD, Huang JP, Xie X.

Source

The School of Population Health, The University of Western Australia, 35 Stirling Highway, Crawley, Perth, WA 6009, Australia. min.zhang@uwa.edu.au

Abstract

Breast cancer is the most common malignancy in women worldwide. Tea has anticarcinogenic effects against breast cancer in experimental studies. However, epidemiologic evidence that tea protects against breast cancer has been inconsistent. A case-control study was conducted in

Southeast China between 2004 and 2005. The incidence cases were 1009 female patients aged 20-87 years with histologically confirmed breast cancer. The 1009 age-matched controls were healthy women randomly recruited from breast disease clinics. Information on duration, frequency, quantity, preparation, type of tea consumption, diet and lifestyle were collected by face-to-face interview using a validated and reliable questionnaire. Conditional logistic regression analyses were used to estimate odds ratios (ORs) and associated 95% confidence intervals. Compared with non-tea drinkers, green tea drinkers tended to reside in urban, have better education and have higher consumption of coffee, alcohol, soy, vegetables and fruits. After adjusting established and potential confounders, green tea consumption was associated with a reduced risk of breast cancer. The ORs were 0.87 (0.73-1.04) in women consuming 1-249 g of dried green tea leaves per annum, 0.68 (0.54-0.86) for 250-499 g per annum, 0.59 (0.45-0.77) for 500-749 g per annum and 0.61 (0.48-0.78) for >or=750 g per annum, with a statistically significant test for trend (P < 0.001). Similar dose-response relationships were observed for duration of drinking green tea, number of cups consumed and new batches prepared per day. We conclude that regular consumption of green tea can protect against breast cancer. More research to closely examine the relationship between tea consumption and breast cancer risk is warranted.

7.

Cancer Epidemiol Biomarkers Prev. 2007 Jun;16(6):1219-23.

Prospective cohort study of green tea consumption and colorectal cancer risk in women.

Yang G, Shu XO, Li H, Chow WH, Ji BT, Zhang X, Gao YT, Zheng W.

Source

Department of Medicine, Vanderbilt Epidemiology Center and Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville TN 37232-2587, USA.
Gong.Yang@vanderbilt.edu

Abstract

Tea and its constituents have shown anticarcinogenic activities in in vitro and animal studies. Epidemiologic studies, however, have been inconsistent. We prospectively evaluated the association between green tea consumption and colorectal cancer (CRC) risk in a cohort of 69,710 Chinese women aged 40 to 70 years. Information on tea consumption was assessed through in-person interviews at baseline and reassessed 2 to 3 years later in a follow-up survey. During 6 years of follow-up, 256 incident cases of CRC were identified. The multivariate relative risk of CRC was 0.63 (95% confidence interval, 0.45-0.88) for women who reported drinking green tea regularly at baseline compared with nonregular tea drinkers. A significant dose-response relationship was found for both the amount of tea consumed (Ptrend = 0.01) and duration in years of lifetime tea consumption (Ptrend = 0.006). The reduction in risk was most evident among those who consistently reported to drink tea regularly at both the baseline and follow-up surveys (relative risk, 0.43; 95% confidence interval, 0.24-0.77). The inverse association with regular tea drinking was observed for both colon and rectal cancers. This study suggests that regular consumption of green tea may reduce CRC risk in women.

8.

Am J Epidemiol. 2008 Jan 1;167(1):71-7. Epub 2007 Sep 29.

Green tea consumption and prostate cancer risk in Japanese men: a prospective study.

Kurahashi N, Sasazuki S, Iwasaki M, Inoue M, Tsugane S; JPHC Study Group.

Source

Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, Japan. nkurahas@gan2.res.ncc.go.jp

Abstract

The incidence of prostate cancer is much lower in Asian than Western populations. Given that environmental factors such as dietary habits may play a major role in the causation of prostate cancer and the high consumption of green tea in Asian populations, this low incidence may be partly due to the effects of green tea. The JPHC Study (Japan Public Health Center-based Prospective Study) was established in 1990 for cohort I and in 1993 for cohort II. The subjects were 49,920 men aged 40-69 years who completed a questionnaire that included their green tea consumption habit at baseline and were followed until the end of 2004. During this time, 404 men were newly diagnosed with prostate cancer, of whom 114 had advanced cases, 271 were localized, and 19 were of an undetermined stage. Green tea was not associated with localized prostate cancer. However, consumption was associated with a dose-dependent decrease in the risk of advanced prostate cancer. The multivariate relative risk was 0.52 (95% confidence interval: 0.28, 0.96) for men drinking 5 or more cups/day compared with less than 1 cup/day (p(trend) = 0.01). Green tea may be associated with a decreased risk of advanced prostate cancer.

9.

J Nutr. 2009 Feb;139(2):310-6. Epub 2008 Dec 11.

Drinking green tea modestly reduces breast cancer risk.

Shrubsole MJ, Lu W, Chen Z, Shu XO, Zheng Y, Dai Q, Cai Q, Gu K, Ruan ZX, Gao YT, Zheng W.

Source

Department of Medicine, Vanderbilt Epidemiology Center, Vanderbilt School of Medicine, Nashville, TN 37232, USA.

Abstract

Green tea is a commonly consumed beverage in China. Epidemiological and animal data suggest tea and tea polyphenols may be preventive against various cancers, including breast cancer. Catechol-O-methyltransferase (COMT) catalyzes catechol estrogens and tea polyphenols. The COMT rs4680 AA genotype leads to lower COMT activity, which may affect the relationship between green tea consumption and breast cancer risk. We evaluated whether regular green tea consumption was associated with breast cancer risk among 3454 incident cases and 3474 controls aged 20-74 y in a population-based case-control study conducted in Shanghai, China during 1996-2005. All participants were interviewed in person about green tea consumption habits, including age of initiation, duration of use, brew strength, and quantity of tea. Odds ratios (OR) and 95% CI were calculated for green tea consumption measures and adjusted for age and other confounding factors. Compared with nondrinkers, regular drinking of green tea was associated with a slightly decreased risk for breast cancer (OR, 0.88; 95% CI, 0.79-0.98). Among premenopausal women, reduced risk was observed for years of green tea drinking (P-trend = 0.02) and a dose-response relationship with the amount of tea consumed per month was also observed (P-trend = 0.046). COMT rs4680 genotypes did not have a modifying effect on the association of green tea intake with breast cancer risk. Drinking green tea may be weakly associated with a decreased risk of breast cancer.

10.

Gen Dent. 2002 Mar-Apr;50(2):140-6.

Chemoprevention of oral cancer by green tea.

Hsu SD, Singh BB, Lewis JB, Borke JL, Dickinson DP, Drake L, Caughman GB, Schuster GS.

Source

Department of Oral Biology and Maxillofacial Pathology, School of Dentistry, Medical College of Georgia, Augusta, USA.

Abstract

Green tea has been a popular beverage for many centuries. Only recently, however, has the anti-cancer power of green tea constituents been unveiled. Green tea polyphenols are found to induce apoptosis (programmed cell death) in many types of tumor cells, including oral cancer cells. However, mechanisms that enable normal cells to evade the apoptotic effect still are not understood. In this study, cell growth and invasion assays combined with apoptosis assays were used to examine the effects of green tea extracts, green tea polyphenols, and the most potent green tea polyphenol, (-)-epigallocatechin-3-gallate (EGCG), on normal human keratinocytes and oral carcinoma cells. The results showed that green tea and its constituents selectively induce apoptosis only in oral carcinoma cells, while EGCG was able to inhibit the growth and invasion of oral carcinoma cells. These differential responses to green tea and its constituents between normal and malignant cells were correlated with the induction of p57, a cell cycle regulator. These data suggest that the chemopreventive effects of green tea polyphenols may involve a p57 mediated survival pathway in normal epithelial cells, while oral carcinoma cells undergo an apoptotic pathway. Therefore, regular consumption of green tea could be beneficial in the prevention of oral cancer.

11.

Mutation research [1999, 428(1-2):339-344]

Green tea and cancer chemoprevention.

Suganuma M, Okabe S, Sueoka N, Sueoka E, Matsuyama S, Imai K, Nakachi K, Fujiki H

Affiliation: Saitama Cancer Center Research Institute, Ina, Kitaadachi-gun, Saitama 362-0806, Japan.

Abstract:

Worldwide interest in green tea as a cancer preventive agent for humans has increased, because it is non-toxic and it is effective in a wide range of organs. (-)-Epigallocatechin gallate (EGCG) is the main constituent of green tea; the others are (-)-epicatechin gallate, (-)-epigallocatechin and (-)-epicatechin (EC). This paper reports the results of our latest pharmacological and biochemical studies with 3H-EGCG, along with studies on human subjects. The study on bioavailability of 3H-EGCG in mice revealed the wide distribution of radioactivity in multiple organs. Specifically, radioactivity was found in all reported target organs of EGCG and green tea extract (digestive tract, liver, lung, pancreas, mammary gland and skin) as well as other organs (brain, kidney, uterus and ovary or testes) in mice. Recently, we demonstrated that EC enhanced incorporation of 3H-EGCG into human lung cancer cell line PC-9 cells. EC along with another cancer preventive agent sulindac also synergistically enhanced apoptosis in PC-9 cells induced by EGCG. Moreover, a case-control

study on breast cancer patients revealed that high daily consumption of green tea was associated with a lower recurrence rate among Stages I and II patients. All the results suggest that consumption of green tea is a practical and effective cancer preventive both before cancer onset and after cancer treatment.

12.

J Nutr. 2002 Aug;132(8):2307-11.

Green tea inhibits vascular endothelial growth factor (VEGF) induction in human breast cancer cells.

Sartippour MR, Shao ZM, Heber D, Beatty P, Zhang L, Liu C, Ellis L, Liu W, Go VL, Brooks MN.

Source

Department of Surgery, Division of Oncology and Center for Human Nutrition, University of California, Los Angeles 90095, USA.

Abstract

Investigators have shown that green tea and its main catechin epigallocatechin-3 gallate (EGCG) may decrease the risk of cancer. Our previous study showed that green tea extract (GTE) as well as its individual catechin components inhibited MDA-MB231 breast cancer cell and human umbilical vein endothelial cell (HUVEC) proliferation. Further, GTE suppressed breast cancer xenograft size and decreased the tumor vessel density in vivo. In the current study, we investigated the effect of GTE on the major angiogenic factor vascular endothelial growth factor (VEGF) in an in vitro experiment. GTE or EGCG (40 mg/L) significantly decreased the levels of the VEGF peptide secreted into conditioned media. This occurred in both HUVEC and human breast cancer cells and the effect was dose dependent. Furthermore, GTE and EGCG decreased the RNA levels of VEGF in MDA-MB231 cells. This inhibition occurred at the transcriptional regulation level and was accompanied by a significant decrease in VEGF promoter activity. We also showed that GTE decreased c-fos and c-jun RNA transcripts, suggesting that activator protein (AP)-1-responsive regions present in the human VEGF promoter may be involved in the inhibitory effect of GTE. Furthermore, GTE suppressed the expression of protein kinase C, another VEGF transcription modulator, in breast cancer cells. Inhibition of VEGF transcription appeared to be one of the molecular mechanism(s) involved in the antiangiogenic effects of green tea, which may contribute to its potential use for breast cancer treatment and/or prevention.

13.

Cancer Prev Res (Phila). 2009 Nov;2(11):931-41.

Phase II randomized, placebo-controlled trial of green tea extract in patients with high-risk oral premalignant lesions.

Tsao AS, Liu D, Martin J, Tang XM, Lee JJ, El-Naggar AK, Wistuba I, Culotta KS, Mao L, Gillenwater A, Sagesaka YM, Hong WK, Papadimitrakopoulou V.

Source

Department of Thoracic/Head and Neck Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas 77030, USA.

Comment in: Oral cancer prevention advances with a translational trial of green tea.*Shin DM. Cancer Prev Res (Phila). 2009 Nov; 2(11):919-21.*

Abstract

Epidemiologic and preclinical data support the oral cancer prevention potential of green tea extract (GTE). We randomly assigned patients with high-risk oral premalignant lesions (OPL) to receive GTE at 500, 750, or 1,000 mg/m(2) or placebo thrice daily for 12 weeks, evaluating biomarkers in baseline and 12-week biopsies. The OPL clinical response rate was higher in all GTE arms (n = 28; 50%) versus placebo (n = 11; 18.2%; P = 0.09) but did not reach statistical significance. However, the two higher-dose GTE arms [58.8% (750 and 1,000 mg/m(2)), 36.4% (500 mg/m(2)), and 18.2% (placebo); P = 0.03] had higher responses, suggesting a dose-response effect. GTE treatment also improved histology (21.4% versus 9.1%; P = 0.65), although not statistically significant. GTE was well tolerated, although higher doses increased insomnia/nervousness but produced no grade 4 toxicity. Higher mean baseline stromal vascular endothelial growth factor (VEGF) correlated with a clinical (P = 0.04) but not histologic response. Baseline scores of other biomarkers (epithelial VEGF, p53, Ki-67, cyclin D1, and p16 promoter methylation) were not associated with a response or survival. Baseline p16 promoter methylation (n = 5) was associated with a shorter cancer-free survival. Stromal VEGF and cyclin D1 expression were downregulated in clinically responsive GTE patients and upregulated in nonresponsive patients at 12 weeks (versus at baseline). An extended (median, 27.5 months) follow-up showed a median time to oral cancer of 46.4 months. GTE may suppress OPLs, in part through reducing angiogenic stimulus (stromal VEGF). Higher doses of GTE may improve short-term (12-week) OPL outcome. The present results support longer-term clinical testing of GTE for oral cancer prevention.

14.

Carcinogenesis. 2002 Sep;23(9):1497-503.

Urinary tea polyphenols in relation to gastric and esophageal cancers: a prospective study of men in Shanghai, China.

Sun CL, Yuan JM, Lee MJ, Yang CS, Gao YT, Ross RK, Yu MC.

Source

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Abstract

Experimental studies have shown that tea and tea polyphenols have anticarcinogenic properties. There have been no prospective investigations examining the relationship between tea polyphenols and cancer risk using validated biomarkers. In the present study, a nested case-control study design was used to investigate the association between prediagnostic urinary tea polyphenol markers and subsequent risk of gastric and esophageal cancers. One hundred and ninety incident cases of gastric cancer and 42 cases of esophageal cancer occurring in members of the Shanghai Cohort (18 244 men aged 45-64 years at recruitment with up to 12 years of follow-up) were compared with 772 cohort control subjects. The control subjects were individually matched to the index cases by age, month and year of sample collection, and neighborhood of residence (case-control ratio = 1:3 for gastric cancer, 1:5 for esophageal cancer). Urinary tea polyphenols, including epigallocatechin (EGC) and epicatechin (EC), and their respective metabolites 5-(3',4',5'-trihydroxyphenyl)-gamma-valerolactone (M4) and 5-(3',4'-dihydroxyphenyl)-gamma-valerolactone (M6), were measured in all study subjects

by means of a validated assay. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated from logistic regression models. After exclusion of cases diagnosed under 4 years follow-up, urinary EGC positivity showed a statistically significant inverse association with gastric cancer (OR = 0.52, 95% CI = 0.28-0.97) after adjustment for Helicobacter pylori seropositivity, smoking, alcohol drinking, and level of serum carotenes. The protective effect was primarily seen among subjects with low (below population median) serum carotenes. The odds ratio for EGC positivity was 0.49 (95% CI = 0.26-0.94) among subjects with low serum carotenes while the corresponding odds ratio among subjects with higher levels of serum carotenes was 1.02 (95% CI = 0.46-2.28). Similar tea polyphenol-cancer risk associations were observed when the gastric cancer and esophageal cancer sites were combined. The present study provides direct evidence that tea polyphenols may act as chemopreventive agents against gastric and esophageal cancer development.

15.

BioFactors; Volume 13, Issue 1-4, pages 49–54, 2000

Preventive effects of drinking green tea on cancer and cardiovascular disease: Epidemiological evidence for multiple targeting prevention

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Abstract

The significance of drinking green tea in prevention of two of the main lifestyle-related diseases, cancer and cardiovascular disease, was demonstrated in terms of a prospective cohort study on a total of 8,552 general residents in Saitama Prefecture, Japan. On the basis of the follow-up study, we revealed decreased relative risk of cancer incidence for those consuming over 10 cups a day, compared with those consuming below 3 cups: 0.54 (95% men, 0.57 (0.34–0.98) for women, and 0.59 (0.35–0.98) for both sexes. Furthermore, a significant delay in cancer onset was associated with increased consumption of green tea. Next, decreased relative risk of death from cardiovascular disease was 0.58 (0.34–0.99) for men, 0.82 (0.49–1.38) for women, and 0.72 (0.60–1.04) for members of both sexes consuming over 10 cups a day. Finally, we evaluated the life-prolonging effects of drinking green tea on cumulative survival, using the life table.

16.

Cancer Res. 2006 Jan 15;66(2):1234-40.

Chemoprevention of human prostate cancer by oral administration of green tea catechins in volunteers with high-grade prostate intraepithelial neoplasia: a preliminary report from a one-year proof-of-principle study.

Bettuzzi S, Brausi M, Rizzi F, Castagnetti G, Peracchia G, Corti A.

Source

Department of Medicina Sperimentale, Sezione di Biochimica, University of Parma, Via Volturno 39, 43100 Parma, Italy. saverio.bettuzzi@unipr.it

Abstract

Green tea catechins (GTCs) proved to be effective in inhibiting cancer growth in several experimental models. Recent studies showed that 30% of men with high-grade prostate intraepithelial neoplasia (HG-PIN) would develop prostate cancer (CaP) within 1 year after repeated biopsy. This prompted us to do a proof-of-principle clinical trial to assess the safety and efficacy of GTCs for the chemoprevention of CaP in HG-PIN volunteers. The purity and content of GTCs preparations were assessed by high-performance liquid chromatography [(-)-epigallocathechin, 5.5%; (-)-epicatechin, 12.24%; (-)-epigallocatechin-3-gallate, 51.88%; (-)-epicatechin-3-gallate, 6.12%; total GTCs, 75.7%; caffeine, <1%]. Sixty volunteers with HG-PIN, who were made aware of the study details, agreed to sign an informed consent form and were enrolled in this double-blind, placebo-controlled study. Daily treatment consisted of three GTCs capsules, 200 mg each (total 600 mg/d). After 1 year, only one tumor was diagnosed among the 30 GTCs-treated men (incidence, approximately 3%), whereas nine cancers were found among the 30 placebo-treated men (incidence, 30%). Total prostate-specific antigen did not change significantly between the two arms, but GTCs-treated men showed values constantly lower with respect to placebo-treated ones. International Prostate Symptom Score and quality of life scores of GTCs-treated men with coexistent benign prostate hyperplasia improved, reaching statistical significance in the case of International Prostate Symptom Scores. No significant side effects or adverse effects were documented. To our knowledge, this is the first study showing that GTCs are safe and very effective for treating premalignant lesions before CaP develops. As a secondary observation, administration of GTCs also reduced lower urinary tract symptoms, suggesting that these compounds might also be of help for treating the symptoms of benign prostate hyperplasia.

17.

Eur Urol. 2008 Aug;54(2):472-3. doi: 10.1016/j.eururo.2008.03.100. Epub 2008 Apr 4.

Chemoprevention of human prostate cancer by green tea catechins: two years later. A follow-up update.

Brausi M, Rizzi F, Bettuzzi S.

ABSTRACT WAS NOT AVAILABLE; HOWEVER, REFERENCING THE ABSTRACT, THE NATIONAL CANCER INSTITUTE AT THE NATIONAL INSTITUTES OF HEALTH REPORT THAT “In 2008, follow-up results to [THE PRECEEDING] study were published, indicating that the inhibitory effects of green tea catechins on prostate cancer progression were long-lasting.” (http://www.cancer.gov/cancertopics/pdq/cam/prostatesupplements/healthprofessional/page2)

(click here to return to top of page)

POMEGRANATE EXTRACT (men's formula only)

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a) Gasmi J, Sanderson JT; Institut National de la Recherche Scientifique, Institut Armand-Frappier, Université du Québec: Growth Inhibitory, Antiandrogenic, and Pro-apoptotic Effects of Punicic Acid in LNCaP Human Prostate Cancer Cells. J Agric Food Chem : , 2010; b) Hong MY, Seeram NP, Heber D; Center for Human Nutrition, David Geffen School of Medicine, University of California, Los Angeles: Pomegranate polyphenols down-regulate expression of androgen-synthesizing genes in human prostate cancer cells overexpressing the androgen receptor. J Nutr Biochem 19 (12): 848-55, 2008; c) Koyama S, Cobb LJ, Mehta HH, et al.; Division of Pediatric Endocrinology, Mattel Children's Hospital, David Geffen School of Medicine, University of California: Pomegranate extract induces apoptosis in human prostate cancer cells by modulation of the IGF-IGFBP axis. Growth Horm IGF Res 20 (1): 55-62, 2010; d) Malik A, Afaq F, Sarfaraz S, et al.; Department of Dermatology, University of Wisconsin, Madison: Pomegranate fruit juice for chemoprevention and chemotherapy of prostate cancer. Proc Natl Acad Sci U S A 102 (41): 14813-8, 2005; e) Kasimsetty SG, Bialonska D, Reddy MK, et al.; Department of Pharmacognosy, Research Institute for Pharmaceutical Sciences, School of Pharmacy, The University of Mississippi: Effects of pomegranate chemical constituents/intestinal microbial metabolites on CYP1B1 in 22Rv1 prostate cancer cells. J Agric Food Chem 57 (22): 10636-44, 2009; f) Wang L, Alcon A, Yuan H, et al.; Department of Cell Biology and Neuroscience, University of California Riverside: Cellular and molecular mechanisms of pomegranate juice-induced anti-metastatic effect on prostate cancer cells. Integr Biol (Camb) 3 (7): 742-54, 2011; g) Sartippour MR, Seeram NP, Rao JY, et al.; Center for Human Nutrition, Los Angeles: Ellagitannin-rich pomegranate extract inhibits angiogenesis in prostate cancer in vitro and in vivo. Int J Oncol 32 (2): 475-80, 2008; h) Adhami VM, Siddiqui IA, Syed DN, et al.; Department of Dermatology, School of Medicine and Public Health, University of Wisconsin, Madison: Oral infusion of pomegranate fruit extract inhibits prostate carcinogenesis in the TRAMP model. Carcinogenesis 33 (3): 644-51, 2012; i) Pantuck AJ, Leppert JT, Zomorodian N, et al.; Department of Urology, David Geffen School of Medicine, University of California at Los Angeles; Phase II study of pomegranate juice for men with rising prostate-specific antigen following surgery or radiation for prostate cancer. Clin Cancer Res 12 (13): 4018-26, 2006; j) Seeram NP, Aronson WJ, Zhang Y, et al.; Center for Human Nutrition, Greater Los Angeles VA Medical Center, Los Angeles: Pomegranate ellagitannin-derived metabolites inhibit prostate cancer growth and localize to the mouse prostate gland. J Agric Food Chem 55 (19): 7732-7, 2007; k) Albrecht M, Jiang W, Kumi-Diaka J, et al.; Institute of Anatomy and Cell Biology, Philipps University, Marburg, Germany: Pomegranate extracts potently suppress proliferation, xenograft growth, and invasion of human prostate cancer cells. J Med Food 7 (3): 274-83, 2004.

RESEARCH ABSTRACTS

1.

Clin Cancer Res. 2006 Jul 1;12(13):4018-26.

Phase II study of pomegranate juice for men with rising prostate-specific antigen following surgery or radiation for prostate cancer.

Pantuck AJ, Leppert JT, Zomorodian N, Aronson W, Hong J, Barnard RJ, Seeram N, Liker H, Wang H, Elashoff R, Heber D, Aviram M, Ignarro L, Belldegrun A.

Source

Department of Urology, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, California 90095-1738, USA. apantuck@mednet.ucla.edu

Abstract

PURPOSE:

Phytochemicals in plants may have cancer preventive benefits through antioxidation and via gene-nutrient interactions. We sought to determine the effects of pomegranate juice (a major source of antioxidants) consumption on prostate-specific antigen (PSA) progression in men with a rising PSA following primary therapy.

EXPERIMENTAL DESIGN:

A phase II, Simon two-stage clinical trial for men with rising PSA after surgery or radiotherapy was conducted. Eligible patients had a detectable PSA > 0.2 and < 5 ng/mL and Gleason score < or = 7. Patients were treated with 8 ounces of pomegranate juice daily (Wonderful variety, 570 mg total polyphenol gallic acid equivalents) until disease progression. Clinical end points included safety and effect on serum PSA, serum-induced proliferation and apoptosis of LNCaP cells, serum lipid peroxidation, and serum nitric oxide levels.

RESULTS:

The study was fully accrued after efficacy criteria were met. There were no serious adverse events reported and the treatment was well tolerated. Mean PSA doubling time significantly increased with treatment from a mean of 15 months at baseline to 54 months posttreatment ($P < 0.001$). In vitro assays comparing pretreatment and posttreatment patient serum on the growth of LNCaP showed a 12% decrease in cell proliferation and a 17% increase in apoptosis ($P = 0.0048$ and 0.0004, respectively), a 23% increase in serum nitric oxide ($P = 0.0085$), and significant ($P < 0.02$) reductions in oxidative state and sensitivity to oxidation of serum lipids after versus before pomegranate juice consumption.

CONCLUSIONS:

We report the first clinical trial of pomegranate juice in patients with prostate cancer. The statistically significant prolongation of PSA doubling time, coupled with corresponding laboratory effects on prostate cancer in vitro cell proliferation and apoptosis as well as oxidative stress, warrant further testing in a placebo-controlled study.

J Agric Food Chem. 2007 Sep 19;55(19):7732-7. Epub 2007 Aug 28.

2.

J Med Food. 2004 Fall;7(3):274-83.

Pomegranate extracts potently suppress proliferation, xenograft growth, and invasion of human prostate cancer cells.

Albrecht M, Jiang W, Kumi-Diaka J, Lansky EP, Gommersall LM, Patel A, Mansel RE, Neeman I, Geldof AA, Campbell MJ.

Source

Institute of Anatomy and Cell Biology, Philipps University, Marburg, Germany.

Abstract

We completed a multicenter study of the effects of pomegranate cold-pressed (Oil) or supercritical CO(2)-extracted (S) seed oil, fermented juice polyphenols (W), and pericarp polyphenols (P) on human prostate cancer cell xenograft growth in vivo, and/or proliferation, cell cycle distribution, apoptosis, gene expression, and invasion across Matrigel, in vitro. Oil, W, and P each acutely inhibited in vitro proliferation of LNCaP, PC-3, and DU 145 human cancer cell lines. The dose of P required to inhibit cell proliferation of the prostate cancer cell line LNCaP by 50% (ED(50)) was 70 microg/mL, whereas normal prostate epithelial cells (hPrEC) were significantly less affected (ED(50) = 250 g/mL). These effects were mediated by changes in both cell cycle distribution and induction of apoptosis. For example, the androgen-independent cell line DU 145 showed a significant increase from 11% to 22% in G(2)/M cells (P <.05) by treatment with Oil (35 microg/mL) with a modest induction of apoptosis. In other cell lines/treatments, the apoptotic response predominated, for example, in PC-3 cells treated with P, at least partially through a caspase 3-mediated pathway. These cellular effects coincided with rapid changes in mRNA levels of gene targets. Thus, 4-hour treatment of DU 145 cells with Oil (35 microg/mL) resulted in significant 2.3 +/- 0.001-fold (mean +/- SEM) up-regulation of the cyclin-dependent kinase inhibitor p21((waf1/cip1)) (P <.01) and 0.6 +/- 0.14-fold down-regulation of c-myc (P <.05). In parallel, all agents potently suppressed PC-3 invasion through Matrigel, and furthermore P and S demonstrated potent inhibition of PC-3 xenograft growth in athymic mice. Overall, this study demonstrates significant antitumor activity of pomegranate-derived materials against human prostate cancer.

3.

J Agric Food Chem. 2010 Nov 10. [Epub ahead of print]

Growth Inhibitory, Antiandrogenic, and Pro-apoptotic Effects of Punicic Acid in LNCaP Human Prostate Cancer Cells.

Gasmi J, Sanderson JT.

Source

Institut National de la Recherche Scientifique, Institut Armand-Frappier, Université du Québec, Laval, Québec H7 V1B7, Canada.

Abstract

Prostate cancer is a commonly diagnosed cancer in men, and dietary chemoprevention by pomegranate (Punica granatum) extracts has shown noticeable benefits. In this study, we investigated the growth inhibitory, antiandrogenic, and pro-apoptotic effects of 13 pure compounds found in the pomegranate in androgen-dependent LNCaP human prostate cancer cells. Cells deprived of steroid hormones were exposed to increasing concentrations (1-100 μM) of pomegranate compounds in the presence of 0.1 nM dihydrotestosterone (DHT), and the inhibition of cell growth was measured by WST-1 colorimetric assay after a 4 day exposure. Four compounds, epigallocatechin gallate (EGCG), delphinidin chloride, kaempferol, and punicic acid, were found to inhibit DHT-stimulated cell growth at concentrations of 10 μM and above. These four pomegranate compounds inhibited DHT-stimulated androgen receptor nuclear accumulation and the expression of the androgen receptor-dependent genes prostate specific antigen and steroid 5α-reductase type 1 at concentrations ≥10 μM. We determined the possible contribution of apoptosis to the observed decrease in cell growth and found that three compounds, EGCG, kaempferol, and, in particular, punicic acid, induced DNA fragmentation after a 24 h treatment, at concentrations in the 10-100 μM range. Punicic acid, an important fatty acid in pomegranate seeds, was further found to induce intrinsic apoptosis via a caspase-dependent pathway. In conclusion, punicic acid, the main

constituent of pomegranate seed (70-80%), exhibited potent growth inhibitory activities in androgen-dependent LNCaP cells, which appear to be mediated by both antiandrogenic and pro-apoptotic mechanisms.

4.

J Nutr Biochem. 2008 Dec;19(12):848-55. doi: 10.1016/j.jnutbio.2007.11.006. Epub 2008 May 13.

Pomegranate polyphenols down-regulate expression of androgen-synthesizing genes in human prostate cancer cells overexpressing the androgen receptor.

Hong MY, Seeram NP, Heber D.

Source

Center for Human Nutrition, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA 90095, USA.

Abstract

Prostate cancer is dependent on circulating testosterone in its early stages and is treatable with radiation and surgery. However, recurrent prostate tumors advance to an androgen-independent state in which they progress in the absence of circulating testosterone, leading to metastasis and death. During the development of androgen independence, prostate cancer cells are known to increase intracellular testosterone synthesis, which maintains cancer cell growth in the absence of significant amounts of circulating testosterone. Overexpression of the androgen receptor (AR) occurs in androgen-independent prostate cancer and has been proposed as another mechanism promoting the development of androgen independence. The LNCaP-AR cell line is engineered to overexpress AR but is otherwise similar to the widely studied LNCaP cell line. We have previously shown that pomegranate extracts inhibit both androgen-dependent and androgen-independent prostate cancer cell growth. In this study, we examined the effects of pomegranate polyphenols, ellagitannin-rich extract and whole juice extract on the expression of genes for key androgen-synthesizing enzymes and the AR. We measured expression of the HSD3B2 (3beta-hydroxysteroid dehydrogenase type 2), AKR1C3 (aldo-keto reductase family 1 member C3) and SRD5A1 (steroid 5alpha reductase type 1) genes for the respective androgen-synthesizing enzymes in LNCaP, LNCaP-AR and DU-145 human prostate cancer cells. A twofold suppression of gene expression was considered statistically significant. Pomegranate polyphenols inhibited gene expression and AR most consistently in the LNCaP-AR cell line (P=.05). Therefore, inhibition by pomegranate polyphenols of gene expression involved in androgen-synthesizing enzymes and the AR may be of particular importance in androgen-independent prostate cancer cells and the subset of human prostate cancers where AR is up-regulated.

5.

Growth Horm IGF Res. 2010 Feb;20(1):55-62. doi: 10.1016/j.ghir.2009.09.003. Epub 2009 Oct 22.

Pomegranate extract induces apoptosis in human prostate cancer cells by modulation of the IGF-IGFBP axis.

Koyama S, Cobb LJ, Mehta HH, Seeram NP, Heber D, Pantuck AJ, Cohen P.

Source

Division of Pediatric Endocrinology, Mattel Children's Hospital, David Geffen School of Medicine, University of California, Los Angeles, USA.

Abstract

The IGF axis is critical for the regulation of apoptosis in many human cancer cell lines. Recently, potent anti-tumorigenic effects of pomegranate juice and extracts have been reported. Consequently, pomegranate has potential not only as a treatment but also as a preventative measure against certain types of cancer, including prostate. In this study, we investigated the relationship between pomegranate-induced apoptosis in human prostate cancer cells and the IGF/IGFBP system. Treatment of LAPC4 prostate cancer cells with 10microg/ml POMx, a highly potent pomegranate extract prepared from skin and arils minus seeds and standardized to ellagitannin content (37% punicalagins by HPLC), resulted in inhibition of cell proliferation and induction of apoptosis. Interestingly, co-treatment with POMx and IGFBP-3 revealed synergistic stimulation of apoptosis and additive inhibition of cell growth. Western blot analysis revealed that treatment with POMx or POMx/IGFBP-3 combination resulted in increased JNK phosphorylation, and decreased Akt and mTOR activation, consistent with a growth inhibitory, pro-apoptotic function. We also investigated the relationship between IGF-1 and pomegranate-induced apoptosis in 22RV1 prostate cancer cells. Co-treatment with 100ng/ml IGF-1 completely blocked apoptosis induction by POMx. In contrast, IGF-I failed to inhibit POMx-induced apoptosis in R(-) cells, suggesting the importance of IGF-IR. POMx-treatment decreased Igf1 mRNA expression in a dose-dependent manner indicating that its actions also involve tumor-specific suppression of IGF-1. These studies revealed novel interactions between the IGF system and pomegranate-induced apoptosis.

6.

Proc Natl Acad Sci U S A. 2005 Oct 11;102(41):14813-8. Epub 2005 Sep 28.

Pomegranate fruit juice for chemoprevention and chemotherapy of prostate cancer.

Malik A, Afaq F, Sarfaraz S, Adhami VM, Syed DN, Mukhtar H.

Source

Department of Dermatology, University of Wisconsin, Madison, WI 53706, USA.

Abstract

Prostate cancer is the most common invasive malignancy and the second leading cause of cancer-related deaths among U.S. males, with a similar trend in many Western countries. One approach to control this malignancy is its prevention through the use of agents present in diet consumed by humans. Pomegranate from the tree Punica granatum possesses strong antioxidant and antiinflammatory properties. We recently showed that pomegranate fruit extract (PFE) possesses remarkable antitumor-promoting effects in mouse skin. In this study, employing human prostate cancer cells, we evaluated the antiproliferative and proapoptotic properties of PFE. PFE (10-100 microg/ml; 48 h) treatment of highly aggressive human prostate cancer PC3 cells resulted in a dose-dependent inhibition of cell growth/cell viability and induction of apoptosis. Immunoblot analysis revealed that PFE treatment of PC3 cells resulted in (i) induction of Bax and Bak (proapoptotic); (ii) down-regulation of Bcl-X(L) and Bcl-2 (antiapoptotic); (iii) induction of WAF1/p21 and KIP1/p27; (iv) a decrease in cyclins D1, D2, and E; and (v) a decrease in cyclin-dependent kinase (cdk) 2, cdk4, and cdk6 expression. These data establish the involvement of the cyclin kinase inhibitor-cyclin-cdk network during the antiproliferative effects of PFE. Oral administration of PFE (0.1% and 0.2%, wt/vol) to athymic nude mice implanted with androgen-sensitive CWR22Rnu1 cells resulted in a significant inhibition in tumor growth concomitant with a significant decrease in serum prostate-specific antigen levels. We suggest that pomegranate juice may have cancer-chemopreventive as well as cancer-chemotherapeutic effects against prostate cancer in humans.

7.

J Agric Food Chem. 2009 Nov 25;57(22):10636-44. doi: 10.1021/jf902716r.

Effects of pomegranate chemical constituents/intestinal microbial metabolites on CYP1B1 in 22Rv1 prostate cancer cells.

Kasimsetty SG, Bialonska D, Reddy MK, Thornton C, Willett KL, Ferreira D.

Source

Department of Pharmacognosy, Research Institute for Pharmaceutical Sciences, School of Pharmacy, The University of Mississippi, University, MS 38677, USA.

Abstract

The cytochrome P450 enzyme, CYP1B1, is an established target in prostate cancer chemoprevention. Compounds inhibiting CYP1B1 activity are contemplated to exert beneficial effects at three stages of prostate cancer development, that is, initiation, progression, and development of drug resistance. Pomegranate ellagitannins/microbial metabolites were examined for their CYP1B1 inhibitory activity in a recombinant CYP1B1-mediated ethoxyresorufin-O-deethylase (EROD) assay. Urolithin A, a microbial metabolite, was the most potent uncompetitive inhibitor of CYP1B1-mediated EROD activity, exhibiting 2-fold selectivity over CYP1A1, while urolithin B was a noncompetitive inhibitor with 3-fold selectivity. The punicalins and punicalagins exhibited potent CYP1A1 inhibition with 5-10-fold selectivity over CYP1B1. Urolithins, punicalins, and punicalagins were tested for their 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)-induced CYP1 inhibitory activity in the 22Rv1 prostate cancer cell line. Urolithins A and B showed a decrease in their CYP1-mediated EROD inhibitory IC50 values upon increasing their treatment times from 30 min to 24 h. Urolithin C, 8-O-methylurolithin A, and 8,9-di-O-methylurolithin C caused a potent CYP1-mediated EROD inhibition in 22Rv1 cells upon 24 h of incubation. Neutral red uptake assay results indicated that urolithin C, 8-O-methylurolithin A, and 8,9-di-O-methylurolithin C induced profound cytotoxicity in the proximity of their CYP1 inhibitory IC50 values. Urolithins A and B were studied for their cellular uptake and inhibition of TCDD-induced CYP1B1 expression. Cellular uptake experiments demonstrated a 5-fold increase in urolithin uptake by 22Rv1 cells. Western blots of the CYP1B1 protein indicated that the urolithins interfered with the expression of CYP1B1 protein. Thus, urolithins were found to display a dual mode mechanism by decreasing CYP1B1 activity and expression.

8.

Integr Biol (Camb). 2011 Jul;3(7):742-54. doi: 10.1039/c0ib00122h. Epub 2011 May 19.

Cellular and molecular mechanisms of pomegranate juice-induced anti-metastatic effect on prostate cancer cells.

Wang L, Alcon A, Yuan H, Ho J, Li QJ, Martins-Green M.

Source

Department of Cell Biology and Neuroscience, University of California Riverside, 900 University Avenue, BSB room 2217, Riverside, CA 92521, USA.

Abstract

Prostate cancer is the second leading cause of cancer-related deaths among US males. Pomegranate juice (PJ), a natural product, was shown in a clinical trial to inhibit progression of this disease. However, the underlying mechanisms involved in the anti-progression effects of PJ on prostate

cancer remain unclear. Here we show that, in addition to causing cell death of hormone-refractory prostate cancer cells, PJ also increases cell adhesion and decreases cell migration of the cells that do not die. We hypothesized that PJ does so by stimulating the expression and/or activation of molecules that alter the cytoskeleton and the adhesion machinery of prostate cancer cells, resulting in enhanced cell adhesion and reduced cell migration. We took an integrative approach to these studies by using Affimetrix gene arrays to study gene expression, microRNA arrays to study the non-coding RNAs, molecules known to be disregulated in cancer cells, and Luminex Multiplex array assays to study the level of secreted pro-inflammatory cytokines/chemokines. PJ up-regulates genes involved in cell adhesion such as E-cadherin, intercellular adhesion molecule 1 (ICAM-1) and down-regulates genes involved in cell migration such as hyaluranan-mediated motility receptor (HMMR) and type I collagen. In addition, anti-invasive microRNAs such as miR-335, miR-205, miR-200, and miR-126, were up-regulated, whereas pro-invasive microRNA such as miR-21 and miR-373, were down-regulated. Moreover, PJ significantly reduced the level of secreted pro-inflammatory cytokines/chemokines such as IL-6, IL-12p40, IL-1β and RANTES, thereby having the potential to decrease inflammation and its impact on cancer progression. PJ also inhibits the ability of the chemokine SDF1α to chemoattract these cancer cells. SDF1α and its receptor CXCR4 are important in metastasis of cancer cells to the bone. Discovery of the mechanisms by which this enhanced adhesion and reduced migration are accomplished can lead to sophisticated and effective prevention of metastasis in prostate and potentially other cancers.

9.

Int J Oncol. 2008 Feb;32(2):475-80.

Ellagitannin-rich pomegranate extract inhibits angiogenesis in prostate cancer in vitro and in vivo.

Sartippour MR, Seeram NP, Rao JY, Moro A, Harris DM, Henning SM, Firouzi A, Rettig MB, Aronson WJ, Pantuck AJ, Heber D.

Source

Center for Human Nutrition, Los Angeles, CA 90095-1742, USA.

Abstract

Angiogenesis is critical to tumor growth and is stimulated by tissue hypoxia due to poor oxygen delivery. In turn, cellular hypoxia leads to angiogenesis via the induction of hypoxia-inducible factor-1alpha (HIF-1alpha) and vascular endothelial growth factor (VEGF) at a cellular level. Pomegranate juice and extracts, which are rich sources of ellagitannins, have been shown to have chemopreventive potential against prostate cancer, but there have been no studies on the effects of an ellagitannin-rich pomegranate extract on angiogenesis. Human prostate cancer cells (LNCaP) and human umbilical vein endothelial cells (HUVEC) were incubated with a pomegranate extract standardized to ellagitannin content (POMx), under normoxic and hypoxic conditions in vitro. Human prostate cancer cells (LAPC4) were injected subcutaneously into severe combined immunodeficient (SCID) mice and the effects of oral administration of POMx on tumor growth, microvessel density, and HIF-1alpha and VEGF expression were determined after 4 weeks of treatment. POMx inhibited the proliferation of LNCaP and HUVEC cells significantly under both normoxic and hypoxic conditions. HIF-1alpha and VEGF protein levels were also reduced by POMx under hypoxic conditions. POMx decreased prostate cancer xenograft size, tumor vessel density, VEGF peptide levels and HIF-1alpha expression after 4 weeks of treatment in SCID mice. These results demonstrate that an ellagitannin-rich pomegranate extract can inhibit tumor-associated angiogenesis as one of several potential mechanisms for slowing the growth of prostate cancer in chemopreventive applications. Further studies in humans are needed to confirm that angiogenesis

can be inhibited by an ellagitannin-rich pomegranate extract administered orally as a dietary supplement.

10.

Carcinogenesis. 2012 Mar;33(3):644-51. doi: 10.1093/carcin/bgr308. Epub 2011 Dec 22.

Oral infusion of pomegranate fruit extract inhibits prostate carcinogenesis in the TRAMP model.

Adhami VM, Siddiqui IA, Syed DN, Lall RK, Mukhtar H.

Source

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Abstract

We earlier provided evidence that oral consumption of pomegranate fruit extract (PFE) inhibits prostate cancer (PCa) cell growth in nude mice. To ascertain convincing evidence of chemopreventive effects of PFE against PCa, its efficacy requires to be evaluated in animal models that closely emulate human disease. Here, we provide evidence of remarkable tumor growth inhibitory effects of PFE using the TRAMP model. Mice received 0.1 and 0.2% PFE, equivalent to 250 and 500 ml of pomegranate juice, in drinking water, starting at 6 weeks and examined at 12, 20 and 34 weeks of age. In water-fed group, 100% mice developed palpable tumors by 20 weeks compared with only 30 and 20% in the 0.1 and 0.2% PFE-supplemented groups, respectively. At 34 weeks, palpable tumors were observed in 70 of 0.1% and only 50 of 0.2% PFE-supplemented mice. Compared with median survival of 43 weeks in water-fed mice, 0.1 and 0.2% PFE-supplemented mice exhibited median life expectancy of 73 and 92 weeks, respectively. Compared with respective water-fed groups, none of the mice in PFE-supplemented groups exhibited metastases to any of the distant organs at 20 weeks and only 20% mice exhibited metastasis at 34 weeks of age. Many of the PFE-supplemented animals had multiple foci of well-differentiated carcinoma but no evidence of poorly differentiated carcinoma. PFE supplementation resulted in simultaneous and significant inhibition of IGF-I/Akt/mTOR pathways in the prostate tissues and tumors. We suggest that pomegranate juice be evaluated in clinical trials in patients at high risk for developing PCa.

11.

Pomegranate ellagitannin-derived metabolites inhibit prostate cancer growth and localize to the mouse prostate gland.

Seeram NP, Aronson WJ, Zhang Y, Henning SM, Moro A, Lee RP, Sartippour M, Harris DM, Rettig M, Suchard MA, Pantuck AJ, Belldegrun A, Heber D.

Source

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Abstract

Our group has shown in a phase II clinical trial that pomegranate juice (PJ) increases prostate specific antigen (PSA) doubling time in prostate cancer (CaP) patients with a rising PSA. Ellagitannins (ETs) are the most abundant polyphenols present in PJ and contribute greatly towards its reported biological properties. On consumption, ETs hydrolyze to release ellagic acid (EA), which is then

converted by gut microflora to 3,8-dihydroxy-6H-dibenzo[b, d]pyran-6-one (urolithin A, UA) derivatives. Despite the accumulating knowledge of ET metabolism in animals and humans, there is no available data on the pharmacokinetics and tissue disposition of urolithins. Using a standardized ET-enriched pomegranate extract (PE), we sought to further define the metabolism and tissue distribution of ET metabolites. PE and UA (synthesized in our laboratory) were administered to C57BL/6 wild-type male mice, and metabolite levels in plasma and tissues were determined over 24 h. ET metabolites were concentrated at higher levels in mouse prostate, colon, and intestinal tissues as compared to other tissues after administration of PE or UA. We also evaluated the effects of PE on CaP growth in severe combined immunodeficient (SCID) mice injected subcutaneously with human CaP cells (LAPC-4). PE significantly inhibited LAPC-4 xenograft growth in SCID mice as compared to vehicle control. Finally, EA and several synthesized urolithins were shown to inhibit the growth of human CaP cells in vitro. The chemopreventive potential of pomegranate ETs and localization of their bioactive metabolites in mouse prostate tissue suggest that pomegranate may play a role in CaP treatment and chemoprevention. This warrants future human tissue bioavailability studies and further clinical studies in men with CaP.

(click here to return to top of page)

VITAMIN D3

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RESEARCH ABSTRACTS

1.

Anticancer Res. 2011 Sep;31(9):2939-48.

Serum 25-hydroxyvitamin D and prevention of breast cancer: pooled analysis.

Mohr SB, Gorham ED, Alcaraz JE, Kane CJ, Macera CA, Parsons JK, Wingard DL, Garland CF.

Source

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Abstract

BACKGROUND: *Low serum levels of 25-hydroxyvitamin D [25(OH)D] have been associated with a high risk of breast cancer. Since publication of the most current meta-analysis of 25(OH)D and breast cancer risk, two new nested case-control studies have emerged.*

MATERIALS AND METHODS*: A PubMed search for all case-control studies on risk of breast cancer by 25(OH)D concentration identified 11 eligible studies. Data from all 11 studies were combined in order to calculate the pooled odds ratio of the highest vs. lowest quantile of 25(OH)D across all studies.*

RESULTS*: The overall Peto odds ratio summarizing the estimated risk in the highest compared to the lowest quantile across all 11 studies was 0.61 (95% confidence interval 0.47, 0.80).*

CONCLUSION*: This study supports the hypothesis that higher serum 25(OH)D levels reduce the risk of breast cancer. According to the review of observational studies, a serum 25(OH)D level of 47 ng/ml was associated with a 50% lower risk of breast cancer.*

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[PubMed - indexed for MEDLINE]

http://www.ncbi.nlm.nih.gov/pubmed/21868542

2.

JNCI J Natl Cancer Inst (2007) 99 (21): 1594-1602.

Prospective Study of Serum Vitamin D and Cancer Mortality in the United States

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- Received March 7, 2007.
- Revision received July 20, 2007.
- Accepted September 26, 2007.

Abstract

Background Vitamin D has been hypothesized to reduce cancer mortality through its effects on incidence and/or survival. Epidemiologic studies of the association of 25-hydroxyvitamin D [25(OH)D] and the risk of cancer, however, have been largely limited to incident cancers at a few sites.

Methods A total of 16818 participants in the Third National Health and Nutrition Examination Survey who were 17 years or older at enrollment were followed from 1988–1994 through 2000. Levels of serum 25(OH)D were measured at baseline by radioimmunoassay. Cox proportional hazards regression models were used to examine the relationship between serum 25(OH)D levels and total cancer mortality (in the entire population or according to race/ethnicity, sex, age, and retinol status) and mortality from specific cancers. Because serum was collected in the south in cooler months and the north in warmer months, we examined associations by collection season. All statistical tests were two-sided.

Results We identified 536 cancer deaths in 146578 person-years. Total cancer mortality was unrelated to baseline vitamin D status in the entire population, men, women, non-Hispanic whites, non-Hispanic blacks, Mexican Americans, and in persons younger than 70 or 70 years or older. We found no interaction between vitamin D and season or vitamin D and serum retinol. Colorectal cancer mortality was inversely related to serum 25(OH)D level, with levels 80 nmol/L or higher

associated with a 72% risk reduction (95% confidence interval = 32% to 89%) compared with lower than 50 nmol/L, P_{trend} = .02.

Conclusions Our results do not support an association between 25(OH)D and total cancer mortality, although there was an inverse relationship between 25(OH)D levels and colorectal cancer mortality.

- Published by Oxford University Press 2007.

http://jnci.oxfordjournals.org/content/99/21/1594.abstract

3.

Cancer Epidemiol Biomarkers Prev September 2004 13; 1502

Plasma Vitamin D Metabolites and Risk of Colorectal Cancer in Women

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Abstract

Objective: Experimental evidence suggests that 1,25-dihydroxyvitamin D and its precursor, 25-hydroxyvitamin D [25(OH)D], may aid in the prevention of colorectal cancer. We therefore examined risk in relation to plasma concentrations of these vitamin D metabolites. Methods: In a nested case-control study among women in the Nurses' Health Study, we identified 193 colorectal cancer cases, ages 46 to 78 years, diagnosed up to 11 years after blood collection. Two controls were matched per case on year of birth and month of blood draw. Odds ratios (OR) for risk of colorectal cancer were calculated using conditional logistic regression adjusted for body mass index, physical activity, smoking, family history, use of hormone replacement therapy, aspirin use, and dietary intakes. Results: We found a significant inverse linear association between plasma 25(OH)D and risk of colorectal cancer (P = 0.02). Among women in the highest quintile, the OR (95% confidence interval) was 0.53 (0.27–1.04). This inverse association remained strong when limited to women ≥60 years at blood collection (P = 0.006) but was not apparent among the younger women (P = 0.70). Benefit from higher 25(OH)D concentrations was observed for cancers at the distal colon and rectum (P = 0.02) but was not evident for those at the proximal colon (P = 0.81). In contrast to 25(OH)D, we did not observe an association between 1,25-dihydroxyvitamin D and colorectal cancer, although risk

was elevated among the women in the highest quintile if they were also in the lower half of the 25(OH)D distribution (OR, 2.52; 95% confidence interval, 1.04–6.11). Conclusion: From these results and supporting evidence from previous studies, we conclude that higher plasma levels of 25(OH)D are associated with a lower risk of colorectal cancer in older women, particularly for cancers at the distal colon and rectum.

http://cebp.aacrjournals.org/content/13/9/1502.short

4.

J Steroid Biochem Mol Biol. 2004 May;89-90(1-5):575-9.

Why the optimal requirement for Vitamin D3 is probably much higher than what is officially recommended for adults.

Vieth R.

Source

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Abstract

The physiologic range for circulating 25-hydroxyvitamin D3 [25(OH)D; the measure of Vitamin D nutrient status] concentration in humans and other primates extends to beyond 200 nmol/L (>80 ng/mL). This biologic "normal" value is greater than current population norms for 25(OH)D. Concentrations of 25(OH)D that correlate with desirable effects extend to at least 70 nmol/L, with no obvious threshold. Randomized clinical trials using 20 mcg (800 IU) per day of Vitamin D show that this suppresses parathyroid hormone, preserves bone mineral density, prevents fractures, lowers blood pressure and improves balance. Calcium absorption from diet correlates with 25(OH)D in the normal range. Health effects of Vitamin D beyond osteoporosis are mostly supported by the circumstantial evidence of epidemiologic studies and laboratory research. These include prevention of cancer and the autoimmune diseases, insulin-dependent diabetes and multiple sclerosis. One mcg per day of Vitamin D(3) (cholecalciferol) increases circulating 25(OH)D by about 1 nmol/L (0.4 ng/mL). A recommended dietary allowance (RDA) is the long-term daily intake level that meets the total requirements for the nutrient by nearly all healthy individuals (it would presume no sunshine). If 70 nmol/L is regarded as a minimum desirable target 25(OH)D concentration, then current recommendations of 15 mcg per day do not meet the criterion of an RDA.

PMID:

15225842 [PubMed - indexed for MEDLINE]

www.ncbi.nlm.nih.gov/pubmed/15225842

5.

American Journal of Clinical Nutrition, Vol. 85, No. 6, 1586-1591, June 2007

***Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial*[1,2]**

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Background: Numerous observational studies have found supplemental calcium and vitamin D to be associated with reduced risk of common cancers. However, interventional studies to test this effect are lacking.

Objective: The purpose of this analysis was to determine the efficacy of calcium alone and calcium plus vitamin D in reducing incident cancer risk of all types.

Design: This was a 4-y, population-based, double-blind, randomized placebo-controlled trial. The primary outcome was fracture incidence, and the principal secondary outcome was cancer incidence. The subjects were 1179 community-dwelling women randomly selected from the population of healthy postmenopausal women aged >55 y in a 9-county rural area of Nebraska centered at latitude 41.4°N. Subjects were randomly assigned to receive 1400–1500 mg supplemental calcium/d alone (Ca-only), supplemental calcium plus 1100 IU vitamin D_3/d (Ca + D), or placebo.

Results: When analyzed by intention to treat, cancer incidence was lower in the Ca + D women than in the placebo control subjects ($P < 0.03$). With the use of logistic regression, the unadjusted relative risks (RR) of incident cancer in the Ca + D and Ca-only groups were 0.402 ($P = 0.01$) and 0.532 ($P = 0.06$), respectively. When analysis was confined to cancers diagnosed after the first 12 mo, RR for the Ca + D group fell to 0.232 (CI: 0.09, 0.60; $P < 0.005$) but did not change significantly for the Ca-only group. In multiple logistic regression models, both treatment and serum 25-hydroxyvitamin D concentrations were significant, independent predictors of cancer risk.

Conclusions: Improving calcium and vitamin D nutritional status substantially reduces all-cancer risk in postmenopausal women. This trial was registered at clinicaltrials.gov as NCT00352170.

Key Words: Serum 25-hydroxyvitamin D • cancer • women • calcium and vitamin D_3 supplementation

http://www.ajcn.org/content/85/6/1586.abstract

6.

The Journal of Steroid Biochemistry and Molecular Biology

Volume 103, Issues 3-5, March 2007, Pages 708-711

13th Workshop on Vitamin D (Victoria, British Columbia, Canada, April 2006)

Vitamin D and prevention of breast cancer: Pooled analysis

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Available online 15 March 2007.

Abstract

Background

Inadequate photosynthesis or oral intake of Vitamin D are associated with high incidence and mortality rates of breast cancer in ecological and observational studies, but the dose–response relationship in individuals has not been adequately studied.

Methods

A literature search for all studies that reported risk by of breast cancer by quantiles of 25(OH)D identified two studies with 1760 individuals. Data were pooled to assess the dose–response association between serum 25(OH)D and risk of breast cancer.

Results

The medians of the pooled quintiles of serum 25(OH)D were 6, 18, 29, 37 and 48 ng/ml. Pooled odds ratios for breast cancer from lowest to highest quintile, were 1.00, 0.90, 0.70, 0.70 and 0.50 (p trend < 0.001). According to the pooled analysis, individuals with serum 25(OH)D of approximately 52 ng/ml had 50% lower risk of breast cancer than those with serum <13 ng/ml. This serum level corresponds to intake of 4000 IU/day. This exceeds the National Academy of Sciences upper limit of 2000 IU/day. A 25(OH)D level of 52 ng/ml could be maintained by intake of 2000 IU/day and, when appropriate, about 12 min/day in the sun, equivalent to oral intake of 3000 IU of Vitamin D3.

Conclusions

Intake of 2000 IU/day of Vitamin D3, and, when possible, very moderate exposure to sunlight, could raise serum 25(OH)D to 52 ng/ml, a level associated with reduction by 50% in incidence of breast cancer, according to observational studies.

http://www.sciencedirect.com/science/article/pii/S0960076006003918

7.

Recent Results Cancer Res. 2007;174:225-34.

An estimate of cancer mortality rate reductions in Europe and the US with 1,000 IU of oral vitamin D per day.

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Source

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Abstract

Solar ultraviolet B (UVB) irradiance and/or vitamin D have been found inversely correlated with incidence, mortality, and/or survival rates for breast, colorectal, ovarian, and prostate cancer and Hodgkin's and non-Hodgkin's lymphoma. Evidence is emerging that more than 17 different types of cancer are likely to be vitamin D-sensitive. A recent meta-analysis concluded that 1,000 IU of oral vitamin D per day is associated with a 50% reduction in colorectal cancer incidence. Using this value, as well as the findings in a multifactorial ecologic study of cancer mortality rates in the US, estimates for reductions in risk of vitamin D-sensitive cancer mortality rates were made for 1,000 IU/day. These estimates, along with annual average serum 25-hydroxyvitamin D levels, were used to estimate the reduction in cancer mortality rates in several Western European and North American countries that would result from intake of 1,000 IU/day of vitamin D. It was estimated that reductions could be 7% for males and 9% for females in the US and 14% for males and 20% for females in Western European countries below 59 degrees. It is proposed that increased fortification of food and increased availability of supplements could help increase vitamin D intake and could augment small increases in production of vitamin D from solar UVB irradiance. Providing 1,000 IU of vitamin D per day for all adult Americans would cost about $1 billion; the expected benefits for cancer would be in the range of $16-25 billion in addition to other health benefits of vitamin D.

http://www.ncbi.nlm.nih.gov/pubmed/17302200

8.

Am J Prev Med. 2007 Mar;32(3):210-6.

Optimal vitamin D status for colorectal cancer prevention: a quantitative meta analysis.

Gorham ED, Garland CF, Garland FC, Grant WB, Mohr SB, Lipkin M, Newmark HL, Giovannucci E, Wei M, Holick MF.

Source

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Abstract

***BACKGROUND**: Previous studies, such as the Women's Health Initiative, have shown that a low dose of vitamin D did not protect against colorectal cancer, yet a meta-analysis indicates that a higher dose may reduce its incidence.*

***METHODS**: Five studies of serum 25(OH)D in association with colorectal cancer risk were identified using PubMed. The results of all five serum studies were combined using standard methods for pooled analysis. The pooled results were divided into quintiles with median 25(OH)D values of 6, 16, 22, 27, and 37 ng/mL. Odds ratios were calculated by quintile of the pooled data using Peto's Assumption-Free Method, with the lowest quintile of 25(OH)D as the reference group. A dose-response curve was plotted based on the odds for each quintile of the pooled data. Data were abstracted and analyzed in 2006.*

***RESULTS**: Odds ratios for the combined serum 25(OH)D studies, from lowest to highest quintile, were 1.00, 0.82, 0.66, 0.59, and 0.46 (p(trend)<0.0001) for colorectal cancer. According to the DerSimonian-Laird test for homogeneity of pooled data, the studies were homogeneous (chi(2)=1.09, df=4, p=0.90. The pooled odds ratio for the highest quintile versus the lowest was 0.49 (p<0.0001, 95% confidence interval, 0.35-0.68). A 50% lower risk of colorectal cancer was associated with a serum 25(OH)D level > or =33 ng/mL, compared to < or =12 ng/mL.*

***CONCLUSIONS**: The evidence to date suggests that daily intake of 1000-2000 IU/day of vitamin D(3) could reduce the incidence of colorectal with minimal risk.*

http://www.ncbi.nlm.nih.gov/pubmed/17296473

9.

J Epidemiol Community Health 2008;62:69-74 doi:10.1136/jech.2006.052571

Could ultraviolet B irradiance and vitamin D be associated with lower incidence rates of lung cancer?

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Accepted 31 January 2007

Abstract

Background: This study examines whether insufficient ultraviolet B (UVB) irradiance, a marker of vitamin D inadequacy, might contribute to lung cancer incidence.

Methods: The association of latitude and UVB irradiance with age-adjusted incidence rates of lung cancer in 111 countries was investigated. Independent associations with UVB irradiance, cloud cover, anthropogenic aerosols, and cigarette smoking, were assessed using multiple regression.

Results: Latitude was positively related to incidence rates in men ($R2 = 0.55$, $p<0.01$) and women ($R2 = 0.36$, $p<0.01$). In men, cigarette consumption ($p<0.001$) was positively related to risk, whereas UVB irradiance was inversely associated ($p=0.003$). There were positive associations with UVB absorbers, in particular cloud cover ($p=0.05$) and aerosol optical depth ($p=0.005$). The $R2$ for the model was 0.78 ($p<0.001$). UVB irradiance was also inversely associated with incidence rates in women ($p=0.0002$), whereas cigarette consumption ($p<0.001$), total cloud cover ($p=0.02$) and aerosol optical depth ($p=0.005$) were positively associated. The $R2$ for the model was 0.77 ($p<0.001$).

Conclusions: Lower levels of UVB irradiance were independently associated with higher incidence rates of lung cancer in 111 countries.

http://jech.bmj.com/content/62/1/69.abstract

10.

Cancer Epidemiol Biomarkers Prev September 2006 15; 1688

Vitamin D Intake and the Risk for Pancreatic Cancer in Two Cohort Studies

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4. **Walter C. Willett**2,3,4,
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Abstract

Vitamin D and its analogues exhibit potent antitumor effects in many tissues, including the pancreas. Normal and malignant pancreatic tissues were recently shown to express high levels of vitamin D 1-α-hydroxylase, which converts circulating 25-hydroxyvitamin D to active 1,25-dihydroxyvitamin D. We examined associations between dietary intake of vitamin D, calcium, and retinol and subsequent risk for pancreatic cancer. We conducted prospective studies in cohorts of 46,771 men ages 40 to 75 years as of 1986 (the Health Professionals Follow-up Study), and 75,427 women ages 38 to 65 years as of 1984 (the Nurses' Health Study), documenting incident pancreatic cancer through the year 2000. Diet was ascertained by semiquantitative food-frequency questionnaire. We identified 365 incident cases of pancreatic cancer over 16 years of follow-up. Compared with participants in the lowest category of total vitamin D intake (<150 IU/d), pooled multivariate relative risks for pancreatic cancer were 0.78 [95% confidence interval (95% CI), 0.59-1.01] for 150 to 299 IU/d, 0.57 (95% CI, 0.40-0.83) for 300 to 449 IU/d, 0.56 (95% CI, 0.36-0.87) for 450 to 599 IU/d, and 0.59 (95% CI, 0.40-0.88) for ≥600 IU/d (P_{trend} = 0.01). These associations may be stronger in men than women. After adjusting for vitamin D intake, calcium and retinol intakes were not associated with pancreatic cancer risk. In two U.S. cohorts, higher intakes of vitamin D were associated with lower risks for pancreatic cancer. Our results point to a potential role for vitamin D in the pathogenesis and prevention of pancreatic cancer. (Cancer Epidemiol Biomarkers Prev 2006;15(9):1688–95)

http://cebp.aacrjournals.org/content/15/9/1688.full

11.

Cancer Causes Control. 2000 Oct;11(9):847-52.

Prostate cancer risk and prediagnostic serum 25-hydroxyvitamin D levels (Finland).

Ahonen MH, Tenkanen L, Teppo L, Hakama M, Tuohimaa P.

Source

University of Tampere, Medical School, Finland.

Abstract

OBJECTIVES: The aim was to evaluate the association between serum vitamin D (25-hydroxyvitamin D) level and risk of prostate cancer.

METHODS: The nested case-control study was based on a 13-year follow-up of about 19,000 middle-aged men who attended the first screening visit within the Helsinki Heart Study and were free of clinically verified prostate cancer at baseline. Through record linkage with the files of the Finnish Cancer Registry, 149 prostate cancer cases were identified in the cohort. They were matched (1:4) to probability density sampled controls for age, time of sample retrieval, and residence. Serum levels of 25-hydroxyvitamin D (25-VD) at entry were measured for cases and controls. The relative risks of prostate cancer were derived using conditional logistic regression analysis.

RESULTS: Prostate cancer risk, analyzed by quartiles of the 25-VD levels, was inversely related to 25-VD. Men with 25-VD concentration below the median had an adjusted relative risk (OR) of 1.7 compared to men with 25-VD level above the median. The prostate cancer risk was highest among younger men (< 52 years) at entry and low serum 25-VD (OR 3.1 nonadjusted and 3.5 adjusted).

Among those younger men (< 52 years), low 25-VD entailed a higher risk of non-localized cancers (OR 6.3). The mean age at diagnosis of the patients with 25-VD concentration above the median was 1.8 years higher than that of patients with vitamin D below the median (63.1 vs 61.3 years).

CONCLUSIONS: We conclude that low levels of 25-VD associated with an increased risk for subsequent earlier exposure and more aggressive development of prostate cancer, especially before the andropause.

http://www.ncbi.nlm.nih.gov/pubmed/11075874

12.

Womens Health (Lond Engl). *2011 Jul;7(4):419-24.*

Vitamin D and cardiovascular disease and cancer: not too much and not too little? The need for clinical trials.

Melamed ML, Manson JE.

Source

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Abstract

Low vitamin D levels are more common in women than in men. Low vitamin D levels have been implicated in numerous disease processes including fracture risk, falls, cardiovascular disease, hypertension, diabetes mellitus and cancers. In this article we review recent evidence regarding associations between low vitamin D levels and cancers and cardiovascular disease. We also review evidence regarding associations between high vitamin D levels and vascular calcifications and pancreatic cancer. It appears that there is probably an optimal level of vitamin D that is neither too high nor too low that is required to maximize health. On going clinical trials should aid in elucidating the optimal levels of 25-hydroxyvitamin D for numerous health outcomes.

http://www.ncbi.nlm.nih.gov/pubmed/21790335

13.

J Bone Miner Res. 2007 Dec;22 Suppl 2:V81-5.

Epidemiological evidence for vitamin D and colorectal cancer.

Giovannucci E.

Source

Channing Laboratory, Department of Medicine, Harvard Medical School and Brigham and Women's Hospital, Boston, Massachusetts, USA.

Abstract

Since Garland and Garland formulated the hypothesis that vitamin D may protect against colorectal cancer in 1980, various epidemiological approaches have been undertaken to evaluate this

hypothesis. These approaches include studies based on regional solar UVB radiation, plasma- or serum-based studies, dietary studies, and those examining multiple factors that influence vitamin D status. Studies over the past several decades have tended to support that higher levels of vitamin D may decrease risk of colorectal cancer. An important implication is that current recommended dietary intakes such as 200-400 IU/d may be too low to exert appreciable benefits. To substantially reduce risk, higher levels of vitamin D associated with sunshine exposure or considerably higher intakes may be required. Recent studies also suggest a potential benefit of vitamin D on other digestive system cancers. One study suggested that a better vitamin D status at the time of diagnosis and treatment, as indicated by season of diagnosis, may improve survival from colorectal cancer. Darker-skinned individuals who tend to make less vitamin D may be at particularly high risk for digestive system cancer. The strong biological evidence for a protective role of vitamin D supports the epidemiological data. More study is needed to determine the optimal levels and intakes of this vitamin to optimally reduce colorectal cancer risk.

www.ncbi.nlm.nih.gov/pubmed/18290728

14.

Ann Epidemiol. 2009 Jul;19(7):468-83.

Vitamin D for cancer prevention: global perspective.

Garland CF, Gorham ED, Mohr SB, Garland FC.

Source

Department of Family and Preventive Medicine, University of California San Diego, La Jolla, CA, USA.

Abstract

PURPOSE: Higher serum levels of the main circulating form of vitamin D, 25-hydroxyvitamin D (25(OH)D), are associated with substantially lower incidence rates of colon, breast, ovarian, renal, pancreatic, aggressive prostate and other cancers.

***METHODS**: Epidemiological findings combined with newly discovered mechanisms suggest a new model of cancer etiology that accounts for these actions of 25(OH)D and calcium. Its seven phases are disjunction, initiation, natural selection, overgrowth, metastasis, involution, and transition (abbreviated DINOMIT). Vitamin D metabolites prevent disjunction of cells and are beneficial in other phases.*

***RESULTS/CONCLUSIONS**: It is projected that raising the minimum year-around serum 25(OH)D level to 40 to 60 ng/mL (100-150 nmol/L) would prevent approximately 58,000 new cases of breast cancer and 49,000 new cases of colorectal cancer each year, and three fourths of deaths from these diseases in the United States and Canada, based on observational studies combined with a randomized trial. Such intakes also are expected to reduce case-fatality rates of patients who have breast, colorectal, or prostate cancer by half. There are no unreasonable risks from intake of 2000 IU per day of vitamin D(3), or from a population serum 25(OH)D level of 40 to 60 ng/mL. The time has arrived for nationally coordinated action to substantially increase intake of vitamin D and calcium.*

www.ncbi.nlm.nih.gov/pubmed/19523595

15.

Cancer Epidemiol Biomarkers Prev. 2008 Apr;17(4):889-94. Epub 2008 Apr 1.

Serum levels of vitamin D metabolites and breast cancer risk in the prostate, lung, colorectal, and ovarian cancer screening trial.

Freedman DM, Chang SC, Falk RT, Purdue MP, Huang WY, McCarty CA, Hollis BW, Graubard BI, Berg CD, Ziegler RG.

Source

Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, Department of Health and Human Services, Bethesda, MD 20892-7238, USA. mf101e@nih.gov

Abstract

Experimental and epidemiologic studies suggest that vitamin D metabolites (1,25-dihydroxyvitamin D [1,25(OH)(2)D] and its precursor 25-hydroxyvitamin D [25(OH)D]) may reduce breast cancer risk. We examined subsequent breast cancer risk related to serum levels of these metabolites. In a cohort of women ages 55 to 74 years, who donated blood at baseline (1993-2001) in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, we identified 1,005 incident breast cancer cases during follow-up through 2005 (mean time between blood draw and diagnosis, 3.9 years). Noncases (n

= 1,005) were frequency matched to the cases based on age and year of entry. Sample weights that accounted for unequal probabilities of selecting cases and noncases were applied to make inferences that reflected the entire Prostate, Lung, Colorectal, and Ovarian cohort. Using Cox proportional hazards modeling, we computed breast cancer relative risks (RR) and 95% confidence intervals (95% CI) by quintile for each metabolite. The RR of breast cancer for the highest quintile of 25(OH)D concentration versus the lowest was 1.04 (95% CI, 0.75-1.45; P(trend) = 0.81). Similarly, the breast cancer RR for the highest quintile of 1,25(OH)(2)D compared with the lowest was 1.23 (95% CI, 0.91-1.68; P(trend) = 0.14). Excluding the first 2 years of follow-up did not materially alter these estimates. There was also no evidence of inverse risk in older women (> or =60 years) versus younger women (<60 years). In this prospective study of postmenopausal women, we did not observe an inverse association between circulating 25(OH)D or 1,25(OH)(2)D and breast cancer risk, although we cannot exclude an association in younger women or with long-term or earlier exposure.

www.ncbi.nlm.nih.gov/pubmed/18381472

16.

Oxford Journals; Medicine; JNCI J Natl Cancer Inst; Volume98, Issue7; Pp. 451-459.

Prospective Study of Predictors of Vitamin D Status and Cancer Incidence and Mortality in Men

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Abstract

Background: Vitamin D has potent anticancer properties, especially against digestive-system cancers. Many human studies have used geographic residence as a marker of solar ultraviolet B and hence vitamin D exposure. Here, we considered multiple determinants of vitamin D exposure (dietary and supplementary vitamin D, skin pigmentation, adiposity, geographic residence, and leisure-time physical activity—to estimate sunlight exposure) in relation to cancer risk in the Health Professionals Follow-Up Study. *Methods:* Among 1095 men of this cohort, we quantified the relation of these six determinants to plasma 25-hydroxy-vitamin D [25(OH)D] level by use of a multiple linear regression model. We used results from the model to compute a predicted 25(OH)D level for each of 47 800 men in the cohort based on these characteristics. We then prospectively examined this variable in relation to cancer risk with multivariable Cox proportional hazards models. *Results:* From 1986 through January 31, 2000, we documented 4286 incident cancers (excluding organ-confined prostate cancer and nonmelanoma skin cancer) and 2025 deaths from cancer. From multivariable models, an increment of 25 nmol/L in predicted 25(OH)D level was associated with a 17% reduction in total cancer incidence (multivariable relative risk [RR] = 0.83, 95% confidence interval [CI] = 0.74 to 0.92), a 29% reduction in total cancer mortality (RR = 0.71, 95% CI = 0.60 to 0.83), and a 45% reduction in digestive-system cancer mortality (RR = 0.55, 95% CI = 0.41 to 0.74). The absolute annual rate of total cancer was 758 per 100 000 men in the bottom decile of predicted 25(OH)D and 674 per 100 000 men for the top decile; these respective rates were 326 per 100 000 and 277 per 100 000 for total cancer mortality and 128 per 100 000 and 78 per 100 000 for digestive-system cancer mortality. Results were similar when we controlled further for body mass index or physical activity level. *Conclusions:* Low levels of vitamin D may be associated with increased cancer incidence and mortality in men, particularly for digestive-system cancers. The vitamin D supplementation necessary to achieve a 25(OH)D increment of 25 nmol/L may be at least 1500 IU/day.

In 1937, Peller and Stephenson *(1)* hypothesized that sunlight exposure lowers the risk of cancer, and in 1941, Apperly *(2)* demonstrated an association between latitude and cancer mortality. Four decades later, Garland and colleagues hypothesized that poor vitamin D status accounts for an elevated risk of risk of colon *(3),* breast *(4),* and ovarian *(5)* cancers at higher latitudes. Schwartz and colleagues *(6,7)* hypothesized a similar relationship for prostate cancer. More recently, Grant *(8)* demonstrated an inverse correlation between regional type B ultraviolet (UV-B) radiation levels and mortality rates of many cancers, particularly digestive-organ cancers, and found that in males approximately 80% of the cancers attributable to low regional solar UV-B were digestive-system cancers. Mizoue *(9)* also found an inverse correlation between averaged annual solar radiation levels and mortality from digestive system cancers (i.e., esophagus, stomach, colon, rectum, pancreas, and gallbladder and bile ducts) but not other cancer types in Japan. The vitamin D hypothesis (i.e., that

poor vitamin D status increases cancer risk) has received strong experimental support over the past two decades from the almost ubiquitous expression in cells of vitamin D receptors and 1α-hydroxylase, which converts 25-hydroxy-vitamin D [25(OH)D] into 1,25-dihydroxy-vitamin D [1,25(OH)2D], and the consistent demonstration that activation of the vitamin D receptor by 1,25(OH)2D induces differentiation and apoptosis and inhibits proliferation, invasiveness, angiogenesis, and metastatic potential *(*10*)*.

Latitude as a surrogate of solar UV-B radiation correlates inversely with vitamin D status *(*8*)*, but regional solar UV-B radiation is only one determinant of vitamin D status. Other determinants include vitamin D intake, skin pigmentation, adiposity [which lowers circulating 25(OH)D], and actual sunlight exposure *(*10*)*. No previous study, to our knowledge, has considered the combined influence of these major determinants of vitamin D status on cancer risk. To investigate this question, we analyzed a sample of men from the Health Professionals Follow-Up Study cohort who had measurements of circulating 25(OH)D levels available and used geographic region, skin pigmentation, dietary intake, supplement intake, body mass index (BMI), and leisure-time physical activity (a surrogate of exposure to solar UV-B) to develop a model to predict 25(OH)D score. We then calculated this score, which can be interpreted as an estimate of long-term 25(OH)D level, for each cohort member and investigated the relation between this score and the incidence of and mortality from total cancers, individual cancers, and digestive system cancers.

http://jnci.oxfordjournals.org/content/98/7/451.abstract

17.

Oxford Journals; Medicine; JNCI J Natl Cancer Inst; Volume99, Issue14; Pp. 1120-1129.

A Nested Case–Control Study of Plasma 25-Hydroxyvitamin D Concentrations and Risk of Colorectal Cancer

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- Received February 7, 2007.
- Revision received May 18, 2007.
- Accepted May 31, 2007.

Abstract

Background Low vitamin D status has long been implicated in colorectal carcinogenesis. We investigated this relationship in a nested case–control study within the Health Professionals Follow-up Study (HPFS), a large ongoing study of male health professionals living in the United States.

Methods Between 1993 and 2002, 179 colorectal cancer patients were diagnosed and matched to 356 control subjects by age and by month and year of blood collection. Results were also pooled with previously published results from the Nurses' Health Study (NHS) cohort, a large female cohort. Conditional logistic regression was used to analyze the association between plasma 25-hydroxyvitamin D [25(OH)D] and colorectal cancer, and pooled estimates were calculated using the method of DerSimonian and Laird. All statistical tests were two-sided.

Results In the HPFS, we observed a non–statistically significant inverse association between higher plasma 25(OH)D concentration and risk of colorectal cancer and a statistically significant inverse association for colon cancer (highest versus lowest quintile: odds ratio [OR] = 0.46, 95% confidence interval [CI] = 0.24 to 0.89; P_{trend} = .005). After pooling the results from the HPFS and NHS, higher plasma 25(OH)D concentrations were statistically significantly associated with decreased risks of both colorectal cancer (highest versus lowest quintile, OR = 0.66, 95% CI = 0.42 to 1.05; P_{trend} = .01) and colon cancer (highest versus lowest quintile, OR = 0.54, 95% CI = 0.34 to 0.86; P_{trend} = .002). Inverse associations with plasma 25(OH)D concentration did not differ by location of colon cancer (proximal versus distal), but the number of patients was small and none of the associations was statistically significant. Opposite relationships between plasma 25(OH)D levels and risk of rectal cancers were found among men (positive) and women (inverse).

Conclusion Our data provide additional support for the inverse association between vitamin D and colorectal and, in particular, colon cancer risk.

www.ncbi.nlm.nih.gov/pubmed/17623801

18.

JNCI J Natl Cancer Inst (2012) doi: 10.1093/jnci/djs189

Vitamin D–Related Genetic Variation, Plasma Vitamin D, and Risk of Lethal Prostate Cancer: A Prospective Nested Case–Control Study

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- Received September 6, 2011.
- Revision received March 7, 2012.
- Accepted March 8, 2012.

Abstract

Background The association of vitamin D status with prostate cancer is controversial; no association has been observed for overall incidence, but there is a potential link with lethal disease.

Methods We assessed prediagnostic 25-hydroxyvitamin D [25(OH)D] levels in plasma, variation in vitamin D–related genes, and risk of lethal prostate cancer using a prospective case–control study nested within the Health Professionals Follow-up Study. We included 1260 men who were diagnosed with prostate cancer after providing a blood sample in 1993–1995 and 1331 control subjects. Men with prostate cancer were followed through March 2011 for lethal outcomes (n = 114). We selected 97 single-nucleotide polymorphisms (SNPs) in genomic regions with high linkage disequilibrium (tagSNPs) to represent common genetic variation among seven vitamin D–related genes (*CYP27A1*, *CYP2R1*, *CYP27B1*, *GC*, *CYP24A1*, *RXRA*, and *VDR*). We used a logistic kernel machine test to assess whether multimarker SNP sets in seven vitamin D pathway–related genes were collectively associated with prostate cancer. Tests for statistical significance were two-sided.

Results Higher 25(OH)D levels were associated with a 57% reduction in the risk of lethal prostate cancer (highest vs lowest quartile: odds ratio = 0.43, 95% confidence interval = 0.24 to 0.76). This finding did not vary by time from blood collection to diagnosis. We found no statistically significant association of plasma 25(OH)D levels with overall prostate cancer. Pathway analyses found that the set of SNPs that included all seven genes (P = .008) as well as sets of SNPs that included *VDR* (P = .01) and *CYP27A1* (P = .02) were associated with risk of lethal prostate cancer.

Conclusion In this prospective study, plasma 25(OH)D levels and common variation among several vitamin D–related genes were associated with lethal prostate cancer risk, suggesting that vitamin D is relevant for lethal prostate cancer.

http://jnci.oxfordjournals.org/content/early/2012/04/12/jnci.djs189.abstract

19.

Tenn Med. 2010 Aug;103(7):51-2, 57.

Prevalence of 25-hydroxyvitamin D deficiency in an urban general internal medicine academic practice.

Long AN, Ray MM, Nandikanti D, Bowman B, Khan A, Lamar K, Hughes T, Adams-Graves P, Williams-Cleaves B.

Source

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Abstract

Vitamin D deficiency has received increased academic interest because of its association with many common disease processes. The goal of our study was to document the prevalence of vitamin D deficiency. A retrospective chart review of 25-hydroxyvitamin D (ng/ml) levels at the University of Tennessee Health Science Center was conducted on general internal medicine patients over an 18-month period. The 25-hydroxyvitamin D deficient patients were divided into four groups: severe (<7 ng/ml), moderate (7.0-20.9 ng/ml), mild (21-31.9 ng/ml), and sufficient (>32 ng/ml). We found that an overwhelming majority of our patients were mildly to severely deficient (87 percent) with 17 percent severely deficient, 53 percent moderately deficient, 17 percent mildly deficient, and only 13 percent sufficient. The prevalence of 25-hydroxyvitamin D deficiency among this population was higher than expected based on the prevalence of 25-hydroxyvitamin D deficiency reported in literature. Based on this data, we believe a greater percentage of the general population needs to be studied in order to discover the true prevalence of vitamin D deficiency.

http://www.ncbi.nlm.nih.gov/pubmed/20853641

VITAMIN D SCIENCE REVIEW

1.

Anticancer Res. 2011 Sep;31(9):2939-48.

Serum 25-hydroxyvitamin D and prevention of breast cancer: pooled analysis.

Mohr SB, Gorham ED, Alcaraz JE, Kane CJ, Macera CA, Parsons JK, Wingard DL, Garland CF.

Source

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Abstract

BACKGROUND: *Low serum levels of 25-hydroxyvitamin D [25(OH)D] have been associated with a high risk of breast cancer. Since publication of the most current meta-analysis of 25(OH)D and breast cancer risk, two new nested case-control studies have emerged.*

MATERIALS AND METHODS*: A PubMed search for all case-control studies on risk of breast cancer by 25(OH)D concentration identified 11 eligible studies. Data from all 11 studies were combined in order to calculate the pooled odds ratio of the highest vs. lowest quantile of 25(OH)D across all studies.*

RESULTS*: The overall Peto odds ratio summarizing the estimated risk in the highest compared to the lowest quantile across all 11 studies was 0.61 (95% confidence interval 0.47, 0.80).*

CONCLUSION*: This study supports the hypothesis that higher serum 25(OH)D levels reduce the risk of breast cancer. According to the review of observational studies, a serum 25(OH)D level of 47 ng/ml was associated with a 50% lower risk of breast cancer.*

PMID:

21868542

[PubMed - indexed for MEDLINE]

http://www.ncbi.nlm.nih.gov/pubmed/21868542

2.

JNCI J Natl Cancer Inst (2007) 99 (21): 1594-1602.

Prospective Study of Serum Vitamin D and Cancer Mortality in the United States

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- Received March 7, 2007.
- Revision received July 20, 2007.
- Accepted September 26, 2007.

Abstract

Background Vitamin D has been hypothesized to reduce cancer mortality through its effects on incidence and/or survival. Epidemiologic studies of the association of 25-hydroxyvitamin D [25(OH)D] and the risk of cancer, however, have been largely limited to incident cancers at a few sites.

Methods A total of 16818 participants in the Third National Health and Nutrition Examination Survey who were 17 years or older at enrollment were followed from 1988–1994 through 2000. Levels of serum 25(OH)D were measured at baseline by radioimmunoassay. Cox proportional hazards regression models were used to examine the relationship between serum 25(OH)D levels and total cancer mortality (in the entire population or according to race/ethnicity, sex, age, and retinol status) and mortality from specific cancers. Because serum was collected in the south in cooler months and the north in warmer months, we examined associations by collection season. All statistical tests were two-sided.

Results We identified 536 cancer deaths in 146578 person-years. Total cancer mortality was unrelated to baseline vitamin D status in the entire population, men, women, non-Hispanic whites, non-Hispanic blacks, Mexican Americans, and in persons younger than 70 or 70 years or older. We found no interaction between vitamin D and season or vitamin D and serum retinol. Colorectal cancer mortality was inversely related to serum 25(OH)D level, with levels 80 nmol/L or higher associated with a 72% risk reduction (95% confidence interval = 32% to 89%) compared with lower than 50 nmol/L, P_{trend} = .02.

Conclusions Our results do not support an association between 25(OH)D and total cancer mortality, although there was an inverse relationship between 25(OH)D levels and colorectal cancer mortality.

- Published by Oxford University Press 2007.

http://jnci.oxfordjournals.org/content/99/21/1594.abstract

3.

Cancer Epidemiol Biomarkers Prev September 2004 13; 1502

Plasma Vitamin D Metabolites and Risk of Colorectal Cancer in Women

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Abstract

Objective: Experimental evidence suggests that 1,25-dihydroxyvitamin D and its precursor, 25-hydroxyvitamin D [25(OH)D], may aid in the prevention of colorectal cancer. We therefore examined risk in relation to plasma concentrations of these vitamin D metabolites. Methods: In a nested case-control study among women in the Nurses' Health Study, we identified 193 colorectal cancer cases, ages 46 to 78 years, diagnosed up to 11 years after blood collection. Two controls were matched per case on year of birth and month of blood draw. Odds ratios (OR) for risk of colorectal cancer were calculated using conditional logistic regression adjusted for body mass index, physical activity, smoking, family history, use of hormone replacement therapy, aspirin use, and dietary intakes. Results: We found a significant inverse linear association between plasma 25(OH)D and risk of colorectal cancer (P = 0.02). Among women in the highest quintile, the OR (95% confidence interval) was 0.53 (0.27–1.04). This inverse association remained strong when limited to women ≥60 years at blood collection (P = 0.006) but was not apparent among the younger women (P = 0.70). Benefit from higher 25(OH)D concentrations was observed for cancers at the distal colon and rectum (P = 0.02) but was not evident for those at the proximal colon (P = 0.81). In contrast to 25(OH)D, we did not observe an association between 1,25-dihydroxyvitamin D and colorectal cancer, although risk was elevated among the women in the highest quintile if they were also in the lower half of the 25(OH)D distribution (OR, 2.52; 95% confidence interval, 1.04–6.11). Conclusion: From these results and supporting evidence from previous studies, we conclude that higher plasma levels of 25(OH)D are associated with a lower risk of colorectal cancer in older women, particularly for cancers at the distal colon and rectum.

http://cebp.aacrjournals.org/content/13/9/1502.short

4.

J Steroid Biochem Mol Biol. 2004 May;89-90(1-5):575-9.

Why the optimal requirement for Vitamin D3 is probably much higher than what is officially recommended for adults.

Vieth R.

Source

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Abstract

The physiologic range for circulating 25-hydroxyvitamin D3 [25(OH)D; the measure of Vitamin D nutrient status] concentration in humans and other primates extends to beyond 200 nmol/L (>80 ng/mL). This biologic "normal" value is greater than current population norms for 25(OH)D. Concentrations of 25(OH)D that correlate with desirable effects extend to at least 70 nmol/L, with no obvious threshold. Randomized clinical trials using 20 mcg (800 IU) per day of Vitamin D show that this suppresses parathyroid hormone, preserves bone mineral density, prevents fractures, lowers blood pressure and improves balance. Calcium absorption from diet correlates with 25(OH)D in the normal range. Health effects of Vitamin D beyond osteoporosis are mostly supported by the circumstantial evidence of epidemiologic studies and laboratory research. These include prevention of cancer and the autoimmune diseases, insulin-dependent diabetes and multiple sclerosis. One mcg per day of Vitamin D(3) (cholecalciferol) increases circulating 25(OH)D by about 1 nmol/L (0.4 ng/mL). A recommended dietary allowance (RDA) is the long-term daily intake level that meets the total requirements for the nutrient by nearly all healthy individuals (it would presume no sunshine). If 70 nmol/L is regarded as a minimum desirable target 25(OH)D concentration, then current recommendations of 15 mcg per day do not meet the criterion of an RDA.
PMID:

15225842 [PubMed - indexed for MEDLINE]

www.ncbi.nlm.nih.gov/pubmed/15225842

5.

American Journal of Clinical Nutrition, Vol. 85, No. 6, 1586-1591, June 2007

***Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial*[1,2]**

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Background: Numerous observational studies have found supplemental calcium and vitamin D to be associated with reduced risk of common cancers. However, interventional studies to test this effect are lacking.

Objective: The purpose of this analysis was to determine the efficacy of calcium alone and calcium plus vitamin D in reducing incident cancer risk of all types.

Design: This was a 4-y, population-based, double-blind, randomized placebo-controlled trial. The primary outcome was fracture incidence, and the principal secondary outcome was cancer incidence. The subjects were 1179 community-dwelling women randomly selected from the population of healthy postmenopausal women aged >55 y in a 9-county rural area of Nebraska centered at latitude 41.4°N. Subjects were randomly assigned to receive 1400–1500 mg supplemental calcium/d alone (Ca-only), supplemental calcium plus 1100 IU vitamin D_3/d (Ca + D), or placebo.

Results: When analyzed by intention to treat, cancer incidence was lower in the Ca + D women than in the placebo control subjects ($P < 0.03$). With the use of logistic regression, the unadjusted relative

risks (RR) of incident cancer in the Ca + D and Ca-only groups were 0.402 ($P = 0.01$) and 0.532 ($P = 0.06$), respectively. When analysis was confined to cancers diagnosed after the first 12 mo, RR for the Ca + D group fell to 0.232 (CI: 0.09, 0.60; $P < 0.005$) but did not change significantly for the Ca-only group. In multiple logistic regression models, both treatment and serum 25-hydroxyvitamin D concentrations were significant, independent predictors of cancer risk.

Conclusions: Improving calcium and vitamin D nutritional status substantially reduces all-cancer risk in postmenopausal women. This trial was registered at clinicaltrials.gov as NCT00352170.

Key Words: Serum 25-hydroxyvitamin D • cancer • women • calcium and vitamin D_3 supplementation

http://www.ajcn.org/content/85/6/1586.abstract

6.

The Journal of Steroid Biochemistry and Molecular Biology
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Vitamin D and prevention of breast cancer: Pooled analysis

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Available online 15 March 2007.

Abstract

Background

Inadequate photosynthesis or oral intake of Vitamin D are associated with high incidence and mortality rates of breast cancer in ecological and observational studies, but the dose–response relationship in individuals has not been adequately studied.

Methods

A literature search for all studies that reported risk by of breast cancer by quantiles of 25(OH)D identified two studies with 1760 individuals. Data were pooled to assess the dose–response association between serum 25(OH)D and risk of breast cancer.

Results

The medians of the pooled quintiles of serum 25(OH)D were 6, 18, 29, 37 and 48 ng/ml. Pooled odds ratios for breast cancer from lowest to highest quintile, were 1.00, 0.90, 0.70, 0.70 and 0.50 (p trend < 0.001). According to the pooled analysis, individuals with serum 25(OH)D of approximately 52 ng/ml had 50% lower risk of breast cancer than those with serum <13 ng/ml. This serum level corresponds to intake of 4000 IU/day. This exceeds the National Academy of Sciences upper limit of 2000 IU/day. A 25(OH)D level of 52 ng/ml could be maintained by intake of 2000 IU/day and, when appropriate, about 12 min/day in the sun, equivalent to oral intake of 3000 IU of Vitamin D3.

Conclusions

Intake of 2000 IU/day of Vitamin D3, and, when possible, very moderate exposure to sunlight, could raise serum 25(OH)D to 52 ng/ml, a level associated with reduction by 50% in incidence of breast cancer, according to observational studies.

http://www.sciencedirect.com/science/article/pii/S0960076006003918

7.

Recent Results Cancer Res. 2007;174:225-34.

An estimate of cancer mortality rate reductions in Europe and the US with 1,000 IU of oral vitamin D per day.

Grant WB, Garland CF, Gorham ED.

Source

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Abstract

Solar ultraviolet B (UVB) irradiance and/or vitamin D have been found inversely correlated with incidence, mortality, and/or survival rates for breast, colorectal, ovarian, and prostate cancer and Hodgkin's and non-Hodgkin's lymphoma. Evidence is emerging that more than 17 different types of cancer are likely to be vitamin D-sensitive. A recent meta-analysis concluded that 1,000 IU of oral vitamin D per day is associated with a 50% reduction in colorectal cancer incidence. Using this value, as well as the findings in a multifactorial ecologic study of cancer mortality rates in the US, estimates for reductions in risk of vitamin D-sensitive cancer mortality rates were made for 1,000 IU/day.

These estimates, along with annual average serum 25-hydroxyvitamin D levels, were used to estimate the reduction in cancer mortality rates in several Western European and North American countries that would result from intake of 1,000 IU/day of vitamin D. It was estimated that reductions could be 7% for males and 9% for females in the US and 14% for males and 20% for females in Western European countries below 59 degrees. It is proposed that increased fortification of food and increased availability of supplements could help increase vitamin D intake and could augment small increases in production of vitamin D from solar UVB irradiance. Providing 1,000 IU of vitamin D per day for all adult Americans would cost about $1 billion; the expected benefits for cancer would be in the range of $16-25 billion in addition to other health benefits of vitamin D.

http://www.ncbi.nlm.nih.gov/pubmed/17302200

8.

Am J Prev Med. 2007 Mar;32(3):210-6.

Optimal vitamin D status for colorectal cancer prevention: a quantitative meta analysis.

Gorham ED, Garland CF, Garland FC, Grant WB, Mohr SB, Lipkin M, Newmark HL, Giovannucci E, Wei M, Holick MF.

Source

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Abstract

***BACKGROUND**: Previous studies, such as the Women's Health Initiative, have shown that a low dose of vitamin D did not protect against colorectal cancer, yet a meta-analysis indicates that a higher dose may reduce its incidence.*

***METHODS**: Five studies of serum 25(OH)D in association with colorectal cancer risk were identified using PubMed. The results of all five serum studies were combined using standard methods for pooled analysis. The pooled results were divided into quintiles with median 25(OH)D values of 6, 16, 22, 27, and 37 ng/mL. Odds ratios were calculated by quintile of the pooled data using Peto's Assumption-Free Method, with the lowest quintile of 25(OH)D as the reference group. A dose-response curve was plotted based on the odds for each quintile of the pooled data. Data were abstracted and analyzed in 2006.*

***RESULTS**: Odds ratios for the combined serum 25(OH)D studies, from lowest to highest quintile, were 1.00, 0.82, 0.66, 0.59, and 0.46 (p(trend)<0.0001) for colorectal cancer. According to the DerSimonian-Laird test for homogeneity of pooled data, the studies were homogeneous (chi(2)=1.09, df=4, p=0.90. The pooled odds ratio for the highest quintile versus the lowest was 0.49 (p<0.0001, 95% confidence interval, 0.35-0.68). A 50% lower risk of colorectal cancer was associated with a serum 25(OH)D level > or =33 ng/mL, compared to < or =12 ng/mL.*

***CONCLUSIONS**: The evidence to date suggests that daily intake of 1000-2000 IU/day of vitamin D(3) could reduce the incidence of colorectal with minimal risk.*

http://www.ncbi.nlm.nih.gov/pubmed/17296473

9.

J Epidemiol Community Health 2008;62:69-74 doi:10.1136/jech.2006.052571

Could ultraviolet B irradiance and vitamin D be associated with lower incidence rates of lung cancer?

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Accepted 31 January 2007

Abstract

Background: This study examines whether insufficient ultraviolet B (UVB) irradiance, a marker of vitamin D inadequacy, might contribute to lung cancer incidence.

Methods: The association of latitude and UVB irradiance with age-adjusted incidence rates of lung cancer in 111 countries was investigated. Independent associations with UVB irradiance, cloud cover, anthropogenic aerosols, and cigarette smoking, were assessed using multiple regression.

Results: Latitude was positively related to incidence rates in men ($R2 = 0.55$, $p<0.01$) and women ($R2 = 0.36$, $p<0.01$). In men, cigarette consumption ($p<0.001$) was positively related to risk, whereas UVB irradiance was inversely associated ($p=0.003$). There were positive associations with UVB absorbers, in particular cloud cover ($p=0.05$) and aerosol optical depth ($p=0.005$). The $R2$ for the model was 0.78 ($p<0.001$). UVB irradiance was also inversely associated with incidence rates in women ($p=0.0002$), whereas cigarette consumption ($p<0.001$), total cloud cover ($p=0.02$) and aerosol optical depth ($p=0.005$) were positively associated. The $R2$ for the model was 0.77 ($p<0.001$).

Conclusions: Lower levels of UVB irradiance were independently associated with higher incidence rates of lung cancer in 111 countries.

http://jech.bmj.com/content/62/1/69.abstract

10.

Cancer Epidemiol Biomarkers Prev September 2006 15; 1688

Vitamin D Intake and the Risk for Pancreatic Cancer in Two Cohort Studies

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Abstract

Vitamin D and its analogues exhibit potent antitumor effects in many tissues, including the pancreas. Normal and malignant pancreatic tissues were recently shown to express high levels of vitamin D 1-α-hydroxylase, which converts circulating 25-hydroxyvitamin D to active 1,25-dihydroxyvitamin D. We examined associations between dietary intake of vitamin D, calcium, and retinol and subsequent risk for pancreatic cancer. We conducted prospective studies in cohorts of 46,771 men ages 40 to 75 years as of 1986 (the Health Professionals Follow-up Study), and 75,427 women ages 38 to 65 years as of 1984 (the Nurses' Health Study), documenting incident pancreatic cancer through the year 2000. Diet was ascertained by semiquantitative food-frequency questionnaire. We identified 365 incident cases of pancreatic cancer over 16 years of follow-up. Compared with participants in the lowest category of total vitamin D intake (<150 IU/d), pooled multivariate relative risks for pancreatic cancer were 0.78 [95% confidence interval (95% CI), 0.59-1.01] for 150 to 299 IU/d, 0.57 (95% CI, 0.40-0.83) for 300 to 449 IU/d, 0.56 (95% CI, 0.36-0.87) for 450 to 599 IU/d, and 0.59 (95% CI, 0.40-0.88) for ≥600 IU/d (P_{trend} = 0.01). These associations may be stronger in men than women. After adjusting for vitamin D intake, calcium and retinol intakes were not associated with pancreatic cancer risk. In two U.S. cohorts, higher intakes of vitamin D were associated with lower risks for pancreatic cancer. Our results point to a potential role for vitamin D in the pathogenesis and prevention of pancreatic cancer. (Cancer Epidemiol Biomarkers Prev 2006;15(9):1688–95)

http://cebp.aacrjournals.org/content/15/9/1688.full

11.

Cancer Causes Control. 2000 Oct;11(9):847-52.

Prostate cancer risk and prediagnostic serum 25-hydroxyvitamin D levels (Finland).

Ahonen MH, Tenkanen L, Teppo L, Hakama M, Tuohimaa P.

Source

University of Tampere, Medical School, Finland.

Abstract

OBJECTIVES: The aim was to evaluate the association between serum vitamin D (25-hydroxyvitamin D) level and risk of prostate cancer.

METHODS: The nested case-control study was based on a 13-year follow-up of about 19,000 middle-aged men who attended the first screening visit within the Helsinki Heart Study and were free of clinically verified prostate cancer at baseline. Through record linkage with the files of the Finnish Cancer Registry, 149 prostate cancer cases were identified in the cohort. They were matched (1:4) to probability density sampled controls for age, time of sample retrieval, and residence. Serum levels of 25-hydroxyvitamin D (25-VD) at entry were measured for cases and controls. The relative risks of prostate cancer were derived using conditional logistic regression analysis.

RESULTS: Prostate cancer risk, analyzed by quartiles of the 25-VD levels, was inversely related to 25-VD. Men with 25-VD concentration below the median had an adjusted relative risk (OR) of 1.7 compared to men with 25-VD level above the median. The prostate cancer risk was highest among younger men (< 52 years) at entry and low serum 25-VD (OR 3.1 nonadjusted and 3.5 adjusted). Among those younger men (< 52 years), low 25-VD entailed a higher risk of non-localized cancers (OR 6.3). The mean age at diagnosis of the patients with 25-VD concentration above the median was 1.8 years higher than that of patients with vitamin D below the median (63.1 vs 61.3 years).

CONCLUSIONS: We conclude that low levels of 25-VD associated with an increased risk for subsequent earlier exposure and more aggressive development of prostate cancer, especially before the andropause.

http://www.ncbi.nlm.nih.gov/pubmed/11075874

12.

Womens Health (Lond Engl). *2011 Jul;7(4):419-24.*

Vitamin D and cardiovascular disease and cancer: not too much and not too little? The need for clinical trials.

Melamed ML, Manson JE.

Source

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Abstract

Low vitamin D levels are more common in women than in men. Low vitamin D levels have been implicated in numerous disease processes including fracture risk, falls, cardiovascular disease, hypertension, diabetes mellitus and cancers. In this article we review recent evidence regarding associations between low vitamin D levels and cancers and cardiovascular disease. We also review

evidence regarding associations between high vitamin D levels and vascular calcifications and pancreatic cancer. It appears that there is probably an optimal level of vitamin D that is neither too high nor too low that is required to maximize health. On going clinical trials should aid in elucidating the optimal levels of 25-hydroxyvitamin D for numerous health outcomes.

http://www.ncbi.nlm.nih.gov/pubmed/21790335

13.

J Bone Miner Res. 2007 Dec;22 Suppl 2:V81-5.

Epidemiological evidence for vitamin D and colorectal cancer.

Giovannucci E.

Source

Channing Laboratory, Department of Medicine, Harvard Medical School and Brigham and Women's Hospital, Boston, Massachusetts, USA.

Abstract

Since Garland and Garland formulated the hypothesis that vitamin D may protect against colorectal cancer in 1980, various epidemiological approaches have been undertaken to evaluate this hypothesis. These approaches include studies based on regional solar UVB radiation, plasma- or serum-based studies, dietary studies, and those examining multiple factors that influence vitamin D status. Studies over the past several decades have tended to support that higher levels of vitamin D may decrease risk of colorectal cancer. An important implication is that current recommended dietary intakes such as 200-400 IU/d may be too low to exert appreciable benefits. To substantially reduce risk, higher levels of vitamin D associated with sunshine exposure or considerably higher intakes may be required. Recent studies also suggest a potential benefit of vitamin D on other digestive system cancers. One study suggested that a better vitamin D status at the time of diagnosis and treatment, as indicated by season of diagnosis, may improve survival from colorectal cancer. Darker-skinned individuals who tend to make less vitamin D may be at particularly high risk for digestive system cancer. The strong biological evidence for a protective role of vitamin D supports the epidemiological data. More study is needed to determine the optimal levels and intakes of this vitamin to optimally reduce colorectal cancer risk.

www.ncbi.nlm.nih.gov/pubmed/18290728

14.

Ann Epidemiol. 2009 Jul;19(7):468-83.

Vitamin D for cancer prevention: global perspective.

Garland CF, Gorham ED, Mohr SB, Garland FC.

Source

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Abstract

PURPOSE: Higher serum levels of the main circulating form of vitamin D, 25-hydroxyvitamin D (25(OH)D), are associated with substantially lower incidence rates of colon, breast, ovarian, renal, pancreatic, aggressive prostate and other cancers.

***METHODS**: Epidemiological findings combined with newly discovered mechanisms suggest a new model of cancer etiology that accounts for these actions of 25(OH)D and calcium. Its seven phases are disjunction, initiation, natural selection, overgrowth, metastasis, involution, and transition (abbreviated DINOMIT). Vitamin D metabolites prevent disjunction of cells and are beneficial in other phases.*

***RESULTS/CONCLUSIONS**: It is projected that raising the minimum year-around serum 25(OH)D level to 40 to 60 ng/mL (100-150 nmol/L) would prevent approximately 58,000 new cases of breast cancer and 49,000 new cases of colorectal cancer each year, and three fourths of deaths from these diseases in the United States and Canada, based on observational studies combined with a randomized trial. Such intakes also are expected to reduce case-fatality rates of patients who have breast, colorectal, or prostate cancer by half. There are no unreasonable risks from intake of 2000 IU per day of vitamin D(3), or from a population serum 25(OH)D level of 40 to 60 ng/mL. The time has arrived for nationally coordinated action to substantially increase intake of vitamin D and calcium.*

www.ncbi.nlm.nih.gov/pubmed/19523595

15.

Cancer Epidemiol Biomarkers Prev. 2008 Apr;17(4):889-94. Epub 2008 Apr 1.

Serum levels of vitamin D metabolites and breast cancer risk in the prostate, lung, colorectal, and ovarian cancer screening trial.

Freedman DM, Chang SC, Falk RT, Purdue MP, Huang WY, McCarty CA, Hollis BW, Graubard BI, Berg CD, Ziegler RG.

Source

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Abstract

Experimental and epidemiologic studies suggest that vitamin D metabolites (1,25-dihydroxyvitamin D [1,25(OH)(2)D] and its precursor 25-hydroxyvitamin D [25(OH)D]) may reduce breast cancer risk. We examined subsequent breast cancer risk related to serum levels of these metabolites. In a cohort of women ages 55 to 74 years, who donated blood at baseline (1993-2001) in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, we identified 1,005 incident breast cancer cases during follow-up through 2005 (mean time between blood draw and diagnosis, 3.9 years). Noncases (n

= 1,005) were frequency matched to the cases based on age and year of entry. Sample weights that accounted for unequal probabilities of selecting cases and noncases were applied to make inferences that reflected the entire Prostate, Lung, Colorectal, and Ovarian cohort. Using Cox

proportional hazards modeling, we computed breast cancer relative risks (RR) and 95% confidence intervals (95% CI) by quintile for each metabolite. The RR of breast cancer for the highest quintile of 25(OH)D concentration versus the lowest was 1.04 (95% CI, 0.75-1.45; P(trend) = 0.81). Similarly, the breast cancer RR for the highest quintile of 1,25(OH)(2)D compared with the lowest was 1.23 (95% CI, 0.91-1.68; P(trend) = 0.14). Excluding the first 2 years of follow-up did not materially alter these estimates. There was also no evidence of inverse risk in older women (> or =60 years) versus younger women (<60 years). In this prospective study of postmenopausal women, we did not observe an inverse association between circulating 25(OH)D or 1,25(OH)(2)D and breast cancer risk, although we cannot exclude an association in younger women or with long-term or earlier exposure.

www.ncbi.nlm.nih.gov/pubmed/18381472

16.

Oxford Journals; Medicine; JNCI J Natl Cancer Inst; Volume98, Issue7; Pp. 451-459.

Prospective Study of Predictors of Vitamin D Status and Cancer Incidence and Mortality in Men

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Abstract

Background: Vitamin D has potent anticancer properties, especially against digestive-system cancers. Many human studies have used geographic residence as a marker of solar ultraviolet B and hence vitamin D exposure. Here, we considered multiple determinants of vitamin D exposure (dietary and supplementary vitamin D, skin pigmentation, adiposity, geographic residence, and leisure-time physical activity—to estimate sunlight exposure) in relation to cancer risk in the Health Professionals Follow-Up Study. *Methods:* Among 1095 men of this cohort, we quantified the relation of these six determinants to plasma 25-hydroxy-vitamin D [25(OH)D] level by use of a multiple linear regression model. We used results from the model to compute a predicted 25(OH)D level for each of 47 800 men in the cohort based on these characteristics. We then prospectively examined this variable in relation to cancer risk with multivariable Cox proportional hazards models. *Results:* From 1986 through January 31, 2000, we documented 4286 incident cancers (excluding organ-confined

prostate cancer and nonmelanoma skin cancer) and 2025 deaths from cancer. From multivariable models, an increment of 25 nmol/L in predicted 25(OH)D level was associated with a 17% reduction in total cancer incidence (multivariable relative risk [RR] = 0.83, 95% confidence interval [CI] = 0.74 to 0.92), a 29% reduction in total cancer mortality (RR = 0.71, 95% CI = 0.60 to 0.83), and a 45% reduction in digestive-system cancer mortality (RR = 0.55, 95% CI = 0.41 to 0.74). The absolute annual rate of total cancer was 758 per 100 000 men in the bottom decile of predicted 25(OH)D and 674 per 100 000 men for the top decile; these respective rates were 326 per 100 000 and 277 per 100 000 for total cancer mortality and 128 per 100 000 and 78 per 100 000 for digestive-system cancer mortality. Results were similar when we controlled further for body mass index or physical activity level. *Conclusions:* Low levels of vitamin D may be associated with increased cancer incidence and mortality in men, particularly for digestive-system cancers. The vitamin D supplementation necessary to achieve a 25(OH)D increment of 25 nmol/L may be at least 1500 IU/day.

In 1937, Peller and Stephenson *(1)* hypothesized that sunlight exposure lowers the risk of cancer, and in 1941, Apperly *(2)* demonstrated an association between latitude and cancer mortality. Four decades later, Garland and colleagues hypothesized that poor vitamin D status accounts for an elevated risk of risk of colon *(3),* breast *(4),* and ovarian *(5)* cancers at higher latitudes. Schwartz and colleagues *(6,7)* hypothesized a similar relationship for prostate cancer. More recently, Grant *(8)* demonstrated an inverse correlation between regional type B ultraviolet (UV-B) radiation levels and mortality rates of many cancers, particularly digestive-organ cancers, and found that in males approximately 80% of the cancers attributable to low regional solar UV-B were digestive-system cancers. Mizoue *(9)* also found an inverse correlation between averaged annual solar radiation levels and mortality from digestive system cancers (i.e., esophagus, stomach, colon, rectum, pancreas, and gallbladder and bile ducts) but not other cancer types in Japan. The vitamin D hypothesis (i.e., that poor vitamin D status increases cancer risk) has received strong experimental support over the past two decades from the almost ubiquitous expression in cells of vitamin D receptors and 1α-hydroxylase, which converts 25-hydroxy-vitamin D [25(OH)D] into 1,25-dihydroxy-vitamin D [1,25(OH)2D], and the consistent demonstration that activation of the vitamin D receptor by 1,25(OH)2D induces differentiation and apoptosis and inhibits proliferation, invasiveness, angiogenesis, and metastatic potential *(10)*.

Latitude as a surrogate of solar UV-B radiation correlates inversely with vitamin D status *(8)*, but regional solar UV-B radiation is only one determinant of vitamin D status. Other determinants include vitamin D intake, skin pigmentation, adiposity [which lowers circulating 25(OH)D], and actual sunlight exposure *(10)*. No previous study, to our knowledge, has considered the combined influence of these major determinants of vitamin D status on cancer risk. To investigate this question, we analyzed a sample of men from the Health Professionals Follow-Up Study cohort who had measurements of circulating 25(OH)D levels available and used geographic region, skin pigmentation, dietary intake, supplement intake, body mass index (BMI), and leisure-time physical activity (a surrogate of exposure to solar UV-B) to develop a model to predict 25(OH)D score. We then calculated this score, which can be interpreted as an estimate of long-term 25(OH)D level, for each cohort member and investigated the relation between this score and the incidence of and mortality from total cancers, individual cancers, and digestive system cancers.

http://jnci.oxfordjournals.org/content/98/7/451.abstract

17.

Oxford Journals; Medicine; JNCI J Natl Cancer Inst; Volume99, Issue14; Pp. 1120-1129.

A Nested Case–Control Study of Plasma 25-Hydroxyvitamin D Concentrations and Risk of Colorectal Cancer

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- Revision received May 18, 2007.
- Accepted May 31, 2007.

Abstract

Background Low vitamin D status has long been implicated in colorectal carcinogenesis. We investigated this relationship in a nested case–control study within the Health Professionals Follow-up Study (HPFS), a large ongoing study of male health professionals living in the United States.

Methods Between 1993 and 2002, 179 colorectal cancer patients were diagnosed and matched to 356 control subjects by age and by month and year of blood collection. Results were also pooled with previously published results from the Nurses' Health Study (NHS) cohort, a large female cohort. Conditional logistic regression was used to analyze the association between plasma 25-hydroxyvitamin D [25(OH)D] and colorectal cancer, and pooled estimates were calculated using the method of DerSimonian and Laird. All statistical tests were two-sided.

Results In the HPFS, we observed a non–statistically significant inverse association between higher plasma 25(OH)D concentration and risk of colorectal cancer and a statistically significant inverse association for colon cancer (highest versus lowest quintile: odds ratio [OR] = 0.46, 95% confidence interval [CI] = 0.24 to 0.89; P_{trend} = .005). After pooling the results from the HPFS and NHS, higher plasma 25(OH)D concentrations were statistically significantly associated with decreased risks of both colorectal cancer (highest versus lowest quintile, OR = 0.66, 95% CI = 0.42 to 1.05; P_{trend} = .01) and colon cancer (highest versus lowest quintile, OR = 0.54, 95% CI = 0.34 to 0.86; P_{trend} = .002). Inverse associations with plasma 25(OH)D concentration did not differ by location of colon cancer (proximal versus distal), but the number of patients was small and none of the associations was statistically significant. Opposite relationships between plasma 25(OH)D levels and risk of rectal cancers were found among men (positive) and women (inverse).

Conclusion Our data provide additional support for the inverse association between vitamin D and colorectal and, in particular, colon cancer risk.

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Vitamin D–Related Genetic Variation, Plasma Vitamin D, and Risk of Lethal Prostate Cancer: A Prospective Nested Case–Control Study

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Abstract

Background The association of vitamin D status with prostate cancer is controversial; no association has been observed for overall incidence, but there is a potential link with lethal disease.

Methods We assessed prediagnostic 25-hydroxyvitamin D [25(OH)D] levels in plasma, variation in vitamin D–related genes, and risk of lethal prostate cancer using a prospective case–control study nested within the Health Professionals Follow-up Study. We included 1260 men who were diagnosed with prostate cancer after providing a blood sample in 1993–1995 and 1331 control subjects. Men with prostate cancer were followed through March 2011 for lethal outcomes (n = 114). We selected 97 single-nucleotide polymorphisms (SNPs) in genomic regions with high linkage disequilibrium (tagSNPs) to represent common genetic variation among seven vitamin D–related genes (*CYP27A1*, *CYP2R1*, *CYP27B1*, *GC*, *CYP24A1*, *RXRA*, and *VDR*). We used a logistic kernel machine test to assess

whether multimarker SNP sets in seven vitamin D pathway–related genes were collectively associated with prostate cancer. Tests for statistical significance were two-sided.

Results Higher 25(OH)D levels were associated with a 57% reduction in the risk of lethal prostate cancer (highest vs lowest quartile: odds ratio = 0.43, 95% confidence interval = 0.24 to 0.76). This finding did not vary by time from blood collection to diagnosis. We found no statistically significant association of plasma 25(OH)D levels with overall prostate cancer. Pathway analyses found that the set of SNPs that included all seven genes (P = .008) as well as sets of SNPs that included *VDR* (P = .01) and *CYP27A1* (P = .02) were associated with risk of lethal prostate cancer.

Conclusion In this prospective study, plasma 25(OH)D levels and common variation among several vitamin D–related genes were associated with lethal prostate cancer risk, suggesting that vitamin D is relevant for lethal prostate cancer.

http://jnci.oxfordjournals.org/content/early/2012/04/12/jnci.djs189.abstract

19.

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Prevalence of 25-hydroxyvitamin D deficiency in an urban general internal medicine academic practice.

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Source

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Abstract

Vitamin D deficiency has received increased academic interest because of its association with many common disease processes. The goal of our study was to document the prevalence of vitamin D deficiency. A retrospective chart review of 25-hydroxyvitamin D (ng/ml) levels at the University of Tennessee Health Science Center was conducted on general internal medicine patients over an 18-month period. The 25-hydroxyvitamin D deficient patients were divided into four groups: severe (<7 ng/ml), moderate (7.0-20.9 ng/ml), mild (21-31.9 ng/ml), and sufficient (>32 ng/ml). We found that an overwhelming majority of our patients were mildly to severely deficient (87 percent) with 17 percent severely deficient, 53 percent moderately deficient, 17 percent mildly deficient, and only 13 percent sufficient. The prevalence of 25-hydroxyvitamin D deficiency among this population was higher than expected based on the prevalence of 25-hydroxyvitamin D deficiency reported in literature. Based on this data, we believe a greater percentage of the general population needs to be studied in order to discover the true prevalence of vitamin D deficiency.

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