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A systematic review of dietary, nutritional, and physical activity interventions for the prevention of prostate cancer progression and mortality.

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Abstract

PURPOSE:

Given the long-term, although potentially fatal, nature of prostate cancer, there is increasing observational evidence for the reduction in disease progression and mortality through changes in lifestyle factors.

METHODS:

We systematically reviewed dietary, nutritional, and physical activity randomized interventions aimed at modifying prostate cancer progression and disease-specific mortality, including a detailed assessment of risk of bias and methodological quality.

RESULTS:

Forty-four randomized controlled trials of lifestyle interventions, with prostate cancer progression or mortality outcomes, were identified. Substantial heterogeneity of the data prevented a meta-analysis. The included trials involved 3,418 prostate cancer patients, median 64 men per trial, from 13 countries. A trial of a nutritional supplement of pomegranate seed, green tea, broccoli, and turmeric; a trial comparing flaxseed, low-fat diet, flaxseed, and low-fat diet versus usual diet; and a trial supplementing soy, lycopene, selenium, and coenzyme Q10, all demonstrated beneficial effects. These trials were also assessed as having low risk of bias and high methodological quality (as were seven other trials with no evidence of benefit). The remaining trials were either underpowered, at high or unclear risk of bias, inadequately reported, of short duration or measured surrogate outcomes of unproven relationship to mortality or disease progression, which precluded any benefits reported being reliable.

CONCLUSION:

Large, well-designed randomized trials with clinical endpoints are recommended for lifestyle modification interventions.

KEYWORDS:

Diet; Nutrition; Physical activity; Prostate cancer; Randomized controlled trials; Systematic review

Chemoprevention of prostatic carcinoma

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Chemoprevention of prostate cancer is the administration of agents to prevent, inhibit, or delay progression of prostate cancer. Asian men have a much lower incidence of prostate cancer than men in Europe or the USA. Asian food includes low-fat, high-fiber diets, which provide a rich supply of weak dietary estrogens. These estrogens have been proposed as chemopreventive agents. In addition to their estrogenic activity, many of these plant compounds can interfere with steroid metabolism and bioavailability and can also inhibit enzymes, such as tyrosine kinase or topoisomerase, which are important for cellular proliferation. In addition, nutritional factors such as reduced fat intake, vitamin E, vitamin D, and selenium may have a protective effect against prostate cancer. The fact was proven in large epidemiological studies as well as experimental observations. In the animal model, the progression of established tumors can be inhibited by these agents. A number of studies to investigate the effect of possible chemopreventive agents for men at high risk of prostate cancer are established. End points for evaluation are mainly based on changes in PSA, changes of histological precursors, or time of onset of clinical disease. The concept of chemoprevention in prostate cancer might have a significant impact on the incidence and mortality of this disease.

Curr Cancer Drug Targets. 2008 Mar;8(2):146-55. BenthamDirect www.bentham-direct.org Links

Natural and synthetic agents targeting inflammation and angiogenesis for chemoprevention of prostate cancer.

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Prostate cancer is the most common cancer in men and one of the leading causes of cancer-related deaths in Western countries. The extraordinary biological heterogeneity, the increasing incidence of this disease, and the presence of putative premalignant conditions make prostate cancer a crucial pathology to study and test pharmacological or nutritional chemopreventive strategies. It has been demonstrated that the incidence of prostate cancer is lower in Asian people, and that it increases in Asian men living in Western countries; these data point to a pivotal role of diet in the onset of prostate cancer. A large amount of work has been done in investigating chemopreventive properties of dietary compounds widely used in Asian countries (i.e. soy, soybeans, green tea, fish) in respect of the oxidants- and meat-rich diet typical of Western people, particularly of central and northern Europe. Some dietary products appear promising as chemo-preventive agents for prostate cancer, because they display both anti-oxidant and anti-inflammatory activity - and inflammation is crucial for the aetiology of adeno-carcinoma of the prostate. There is increasing evidence for close correlation between inflammation, the microenvironment and tumour-associated neo-angiogenesis causing the adverse outcomes of prostate cancer. It may thus be useful to develop new strategies to couple the treatment of inflammation-related prostate cancer and the generation of angiopreventive or antiinflammatory molecules to prevent this disease. The search for compounds with few or no adverse effects - particularly cardiovascular - as compared with the agents currently in use is therefore of greatest relevance.

Urology. 2001 Apr;57(4 Suppl 1):224-9. ELSEVIER FULL-TEXT ARTICLE Links

Prostate cancer chemoprevention: Strategies for designing efficient clinical trials.

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A chemoprevention (CP) strategy has evolved for conducting efficient clinical trials for prostate cancer (PCa) prevention. It integrates five key components, including agents, biomarkers, cohorts, designs, and endpoints. The rationale for the CP strategy relates to the natural history of prostate cancer. There is a wide array of natural and synthetic agents that hold promise for inhibiting, reversing, or modulating the transition from normal to precancer and from precancer to cancer. These agent classes include antiandrogens, antiestrogens, phytoestrogens, antioxidants, anti-inflammatory (proapoptotic) agents, antiproliferation/antidifferentiation agents, signal transduction modulators of receptor tyrosine kinase and ras farnesylation, antiangiogenesis agents, insulinlike growth factor (IGF)-1, peroxisome proliferator-activator receptor modulators (-gamma and -delta), and gene-based interventions. Biomarkers and endpoints are guided by the level of evidence required (eg, phase 1, 2, 3). Two candidate surrogate endpoints (SE) based on histology are high-grade prostatic intraepithelial neoplasia (HGPIN) and computer-assisted image analysis of dysplastic lesions. Phase 1 trials use standard endpoints of safety, pharmacokinetics and limited pharmacodynamics. Phase 2 trials use endpoints of modulation of biomarkers and correlation with histology. Phase 3 trials use endpoints of clinical benefit, such as cancer incidence reduction and quality of life. Validation of a biomarker as a SE involves correlation of the biomarker with clinical benefit. Cohorts (target populations) for phase 2/3 trials include the general population of men over age 50 with a normal prostate-specific antigen (PSA), subjects with a strong family history of PCa, subjects with elevated PSA/negative biopsy, and subjects with HGPIN/negative biopsy. These at-risk populations reflect key individual risk factors (age, race, serum PSA [free/total]; serum IGF-1/IGF binding protein (IGFBP)-3; 1, 25(OH)(2) D3; family history of PCa; carriers of

PCa susceptibility genes [ELAC2, CYP3A4, SRD5A2, etc.]; and histology such as atypia and HGPIN) that could be combined into a multivariate risk model for PCa. The probability of cancer risk (recurrence) is a key factor that impacts on the clinical trial design (power, sample size, and primary endpoint). Multivariate predictive mathematical models for biochemical recurrence after radical prostatectomy by decreasing sample size and time to clinical outcomes maximize trial efficiency and identify the patients most likely to benefit from secondary prevention. The two large primary prevention trials, Prostate Cancer Prevention Trial/Seleninium and Vitamin E Chemoprevention Trial (PCPT/ SELECT), in low- and average-risk subjects have sample sizes of 18,000 to 32,000, with a treatment duration of 7 years to detect a 25% reduction in biopsy-proven PCa. Subjects with HGPIN have the highest known cancer risk (approximately 50% at 3 years), and thus require a small sample size (n = 450) to detect a 33% reduction in cancer incidence. A schema involving three sequential trials for agent registration is described. In summary, a CP strategy that incorporates well-defined agents, clinical and validated SE, and high-risk cohorts defined by genetic and acquired risk factors in a series of well-designed randomized controlled trials provides an efficient pathway for evaluating and approving new agents for PCa prevention.

Isoflavone

Br J Nutr. 2008 May;99 E Suppl 1:ES78-108.

Isoflavones and the prevention of breast and prostate cancer: new perspectives opened by nutrigenomics.

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Epidemiological evidence together with preclinical data from animal and in vitro studies strongly support a correlation between soy isoflavone

consumption and protection towards breast and prostate cancers. The biological processes modulated by isoflavones, and especially by genistein, have been extensively studied, yet without leading to a clear understanding of the cellular and molecular mechanisms of action involved. This review discusses the existing gaps in our knowledge and evaluates the potential of the new nutrigenomic approaches to improve the study of the molecular effects of isoflavones. Several issues need to be taken into account for the proper interpretation of the results already published for isoflavones. Too often knowledge on isoflavone bioavailability is not taken into account; supra-physiological doses are frequently used. Characterization of the individual variability as defined by the gut microflora composition and gene polymorphisms may also help to explain the discrepancies observed so far in the clinical studies. Finally, the complex inter-relations existing between tissues and cell types as well as cross-talks between metabolic and signalling pathways have been insufficiently considered. By appraising critically the abundant literature with these considerations in mind, the mechanisms of action that are the more likely to play a role in the preventive effects of isoflavones towards breast and prostate cancers are reviewed. Furthermore, the new perspectives opened by the use of genetic, transcriptomic, proteomic and metabolomic approaches are highlighted.

Cancer Invest. 2003;21(5):744-57. Links
Comment in:
Cancer Invest. 2003;21(5):817-8.

Soy isoflavones and cancer prevention.

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Epidemiological studies have shown a significant difference in cancer incidence among different ethnic groups, which is believed to be partly attributed to dietary habits. The incidences of breast and prostate cancers are much higher in the United States and European countries compared with Asian countries such as Japan and China. One of the major differences in diet

between these populations is that the Japanese and the Chinese consume a traditional diet high in soy products. Soy isoflavones have been identified as dietary components having an important role in reducing the incidence of breast and prostate cancers. Genistein, the predominant isoflavones found in soy, has been shown to inhibit the carcinogenesis in animal models. There are growing body of experimental evidence that show the inhibition of human cancer cells by genistein through the modulation of genes that are related to the control of cell cycle and apoptosis. Moreover, it has been shown that genistein inhibits the activation of NF-kappa B and Akt signaling pathways, both of which are known to maintain a homeostatic balance between cell survival and apoptosis. Genistein is commonly known as phytoestrogen, which targets estrogen- and androgen-mediated signaling pathways in the processes of carcinogenesis. Furthermore, genistein has been found to have antioxidant property, and shown to be a potent inhibitor of angiogenesis and metastasis. Taken together, both in vivo and in vitro studies have clearly shown that genistein, one of the major soy isoflavones, is a promising reagent for cancer chemoprevention and/or treatment. In this article, we attempt to provide evidence for these effects of genistein in a succinct manner to provide comprehensive state-of-the-art knowledge of the biological and molecular effects of the isoflavone genistein in cancer cells.

Front Biosci. 2004 Sep 1;9:2714-24. Links

The role of isoflavones in cancer chemoprevention.

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Cancer is one of the major health problems around the world. However, it has been estimated that more than two-thirds of human cancers could be prevented by modification of lifestyle including dietary modification.The incidences of hormone-related cancers are much higher in Western countries

compared to Asian countries. One of the major differences in diet between these populations is that the Asians consume a traditional diet high in isoflavones. Epidemiologic evidence together with data from animal and in vitro studies strongly supports relationship between isoflavones and the lower risk of cancers.Isoflavones have been shown to inhibit carcinogenesis in vivo in animal experiments. It has been known that genistein, one of the major isoflavones, inhibits the growth of various cancer cells through the modulation of genes that are related to the control of cell cycle, apoptosis, and cell signaling pathways. Moreover, genistein has been found to be a potent inhibitor of oxidative stress, angiogenesis, and metastasis.Therefore, isoflavones exert beneficial effects on human health and may be promising agents for cancer prevention and/or treatment. However, further in depth experimental investigations along with clinical trials are needed to fully evaluate the value of isoflavones in human cancer prevention and/or treatment.

Clin Cancer Res. 2004 Aug 1;10(15):5282-92. Links

A concentrated aglycone isoflavone preparation (GCP) that demonstrates potent anti-prostate cancer activity in vitro and in vivo.

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PURPOSE: Isoflavones have anticancer activities, but naturally occurring isoflavones are predominantly glycosylated and poorly absorbed. Genistein combined polysaccharide (GCP; Amino Up Chemical Co., Sapporo, Japan), is a fermentation product of soy extract and basidiomycetes mycillae that is enriched in biologically active aglycone isoflavones. This study analyzes GCP in vitro and in vivo for potential utility as a prostate cancer chemopreventative agent. EXPERIMENTAL DESIGN: Androgen-sensitive LNCaP and androgen-

independent PC-3 cells were grown with various concentrations of GCP. In vitro cell growth was analyzed by the WST-1 assay, and apoptosis was assessed by fluorescence-activated cell sorting and detection of poly(ADP-ribose) polymerase cleavage using Western blot techniques. Effects of GCP on expression of cell cycle-regulatory proteins p53 (LNCaP only), p21, and p27 and the protein kinase Akt were considered using Western blot techniques. An in vivo LNCaP xenograft model was used to study the effects of a 2% GCP-supplemented diet on tumor growth in comparison with a control diet. RESULTS: GCP significantly suppressed LNCaP and PC-3 cell growth over 72 h (89% and 78% in LNCaP and PC-3, respectively, at 10 microg/ml; $P < 0.0001$). This reduction was associated with apoptosis in LNCaP cells, but not in PC-3 cells. GCP induced p27 and p53 (LNCaP only) protein expression within 6 h and suppressed phosphorylated Akt in both cell lines. The 2% GCP-supplemented diet significantly slowed LNCaP tumor growth, increasing apoptosis ($P < 0.001$), and decreasing proliferation ($P < 0.001$) over 4 weeks. CONCLUSIONS: GCP has potent growth-inhibitory effects against prostate cancer cell lines in vitro and in vivo. These data suggest GCP has potential as an effective chemopreventive agent against prostate cancer cell growth.

Clin Cancer Res. 2007 Oct 15;13(20):6204-16. 

Links

Combination treatment of prostate cancer cell lines with bioactive soy isoflavones and perifosine causes increased growth arrest and/or apoptosis.

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PURPOSE: To determine whether targeting the androgen receptor (AR) and Akt pathways using a combination of genistein combined polysaccharide (GCP) and perifosine is more effective at inducing growth arrest/apoptosis in prostate cancer cells compared with treatment with GCP or perifosine as single agents. EXPERIMENTAL DESIGN: The effect of GCP and perifosine treatment was assessed in five prostate cancer cell lines: LNCaP (androgen

sensitive), LNCaP-R273H, C4-2, Cds1, and PC3 (androgen insensitive). A clonogenic assay assessed the long-term effects on cell growth and survival. Flow cytometry and Western blot analysis of poly(ADP)ribose polymerase cleavage were used to assess short-term effects. Preliminary studies to investigate mechanism of action included Western blot for P-Akt, Akt, P-p70S6K, p70S6K, p53, and p21; prostate-specific antigen analysis; and the use of myristoylated Akt and AR-specific small interfering RNA. RESULTS: Combination treatment with GCP and perifosine caused a decrease in clonogenic potential in all cell lines. In short-term assays, growth arrest was observed in the majority of cell lines, as well as increased inhibition of Akt activity and induction of p21 expression. Increased apoptosis was only observed in LNCaP. Knockdown of AR caused a further increase in apoptosis. CONCLUSION: Combination treatment with GCP and perifosine targets the Akt pathway in the majority of the prostate cancer cell lines and causes increased inhibition of cell growth and clonogenicity. In LNCaP, combination treatment targets both the Akt and AR pathways and causes increased apoptosis. These data warrant clinical validation in prostate cancer patients.

Cancer Lett. 2008 May 18. [Epub ahead of print]ELSEVIER FULL-TEXT ARTICLE Links

Multi-targeted therapy of cancer by genistein.

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Soy isoflavones have been identified as dietary components having an important role in reducing the incidence of breast and prostate cancers in Asian countries. Genistein, the predominant isoflavone found in soy products, has been shown to inhibit the carcinogenesis in animal models. There is a growing body of experimental evidence showing that the inhibition of human cancer cell growth by genistein is mediated via the modulation of genes that are related to the control of cell cycle and apoptosis. It has been shown that genistein inhibits the activation of NF-kappaB and Akt signaling pathways,

both of which are known to maintain a homeostatic balance between cell survival and apoptosis. Moreover, genistein antagonizes estrogen- and androgen-mediated signaling pathways in the processes of carcinogenesis. Furthermore, genistein has been found to have antioxidant properties, and shown to be a potent inhibitor of angiogenesis and metastasis. Taken together, both in vivo and in vitro studies have clearly shown that genistein, one of the major soy isoflavones is a promising agent for cancer chemoprevention and further suggest that it could be an adjunct to cancer therapy by virtue of its effects on reversing radioresistance and chemoresistance. In this review, we attempt to provide evidence for these preventive and therapeutic effects of genistein in a succinct manner highlighting comprehensive state-of-the-art knowledge regarding its multi-targeted biological and molecular effects in cancer cells.

Med Hypotheses. 2006;66(6):1093-114. Epub 2006 Mar 2.  Links

Isoflavones made simple - genistein's agonist activity for the beta-type estrogen receptor mediates their health benefits.

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Soy isoflavones, the focus of much research and controversy, are often referred to as "weak estrogens". In fact, genistein is a relatively potent agonist for the recently characterized beta isoform of the estrogen receptor (ERbeta). The low nanomolar serum concentrations of unconjugated free genistein achieved with high-nutritional intakes of soy isoflavones are near the binding affinity of genistein for this receptor, but are about an order of magnitude lower than genistein's affinity for the "classical" alpha isoform of the estrogen receptor (ERalpha). Moreover, these concentrations are far too low to inhibit tyrosine kinases or topoisomerase II, in vitro activities of genistein often cited as potential mediators of its physiological effects. The thesis that these physiological effects are in fact mediated by ERbeta activation provides a

satisfying rationale for genistein's clinical activities. Hepatocytes do not express ERbeta; this explains why soy isoflavones, unlike oral estrogen, neither modify serum lipids nor provoke the prothrombotic effects associated with increased risk for thromboembolic disorders. The lack of uterotrophic activity of soy isoflavones reflects the fact that ERalpha is the exclusive mediator of estrogen's impact in this regard. Vascular endothelium expresses both ERalpha and ERbeta, each of which has the potential to induce and activate nitric oxide synthase; this may account for the favorable influence of soy isoflavones on endothelial function in postmenopausal women and ovariectomized rats. The ERbeta expressed in osteoblasts may mediate the reported beneficial impact of soy isoflavones on bone metabolism. Suggestive evidence that soy-rich diets decrease prostate cancer risk, accords well with the observation that ERbeta appears to play an antiproliferative role in healthy prostate. In the breast, ERalpha promotes epithelial proliferation, whereas ERbeta has a restraining influence in this regard - consistent with the emerging view that soy isoflavones do not increase breast cancer risk, and possibly may diminish it. Premenopausal women enjoy a relative protection from kidney failure; since ERbeta is an antagonist of TGF-beta signaling in mesangial cells, soy isoflavones may have nephroprotective potential. Estrogen also appears to protect women from left ventricular hypertrophy, and recent evidence suggests that this effect is mediated by ERbeta. In conjunction with reports that isoflavones may have a modestly beneficial impact on menopausal symptoms - perhaps reflecting the presence of ERbeta in the hypothalamus - these considerations suggest that soy isoflavone regimens of sufficient potency may represent a safe and moderately effective alternative to HRT in postmenopausal women. Further clinical research is required to characterize the impact of optimal genistein intakes on endothelial and bone function in men. Studies with ERbeta-knockout mice could be helpful for clarifying whether ERbeta does indeed mediate the chief physiological effects of low nanomolar genistein. S-equol, a bacterial metabolite of daidzein, has an affinity for ERbeta nearly as high as that of genistein; whether this compound contributes meaningfully to the physiological efficacy of soy isoflavones in some individuals is still unclear.

Nutr Cancer. 2007;59(1):1-7. Links

Lycopene and soy isoflavones in the treatment of prostate cancer.

Vaishampayan U, **Hussain M**, **Banerjee M**, **Seren S**, **Sarkar FH**, **Fontana J**, **Forman JD**, **Cher ML**, **Powell I**, **Pontes JE**, **Kucuk O**.

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Dietary intake of lycopene and soy has been associated with a lower risk of prostate cancer. In vitro studies with lycopene and genistein, a soy isoflavone, have shown induction of apoptosis and inhibition of cell growth in androgen-sensitive (LNCaP) and androgen-independent (PC3 and VeCaP) prostate cancer cell lines. In a previous Phase II clinical trial in prostate cancer patients, we observed prostate-specific antigen (PSA) stabilization with soy isoflavone intake. In this Phase II clinical trial, we investigated the efficacy of lycopene alone or in combination with soy isoflavones on serum PSA levels in men with prostate cancer. To be eligible for the study, men with prostate cancer had to have rising serum PSA following local therapy or while on hormone therapy. Study population included 71 eligible patients who had 3 successive rising PSA levels or a minimum PSA of 10 ng/ml at 2 successive evaluations prior to starting therapy. Subjects were randomly assigned to receive a tomato extract capsule containing 15 mg of lycopene alone (n = 38) or together with a capsule containing 40 mg of a soy isoflavone mixture (n = 33) twice daily orally for a maximum of 6 mo. One patient on the lycopene arm did not receive therapy due to his inability to ingest the study pill. There was no decline in serum PSA in either group qualifying for a partial or complete response. However, 35 of 37 (95%) evaluable patients in the lycopene group and 22 of 33 (67%) evaluable patients in the lycopene plus soy isoflavone group achieved stable disease described as stabilization in serum PSA level. The data suggest that lycopene and soy isoflavones have activity in prostate cancer patients with PSA relapse disease and may delay progression of both hormone-refractory and hormone-sensitive prostate cancer. However, there may not be an additive effect between the 2 compounds when taken together. Future studies are warranted to further investigate the efficacy of lycopene and

soy isoflavones in prostate cancer as well as the mechanism of potential negative interaction between them.

BMC Cancer. 2008 May 11;8:132.  
Links

Phase II trial of isoflavone in prostate-specific antigen recurrent prostate cancer after previous local therapy.

Pendleton JM, **Tan WW**, **Anai S**, **Chang M**, **Hou W**, **Shiverick KT**, **Rosser CJ**.
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BACKGROUND: Data exist that demonstrate isoflavones' potent antiproliferative effects on prostate cancer cells. We evaluated the efficacy of isoflavone in patients with PSA recurrent prostate cancer after prior therapy. We postulated that isoflavone therapy would slow the rate of rise of serum PSA. METHODS: Twenty patients with rising PSA after prior local therapy were enrolled in this open-labeled, Phase II, nonrandomized trial (Trial registration # NCT00596895). Patients were treated with soy milk containing 47 mg of isoflavonoid per 8 oz serving three times per day for 12 months. Serum PSA, testosterone, lipids, isoflavone levels (genistein, daidzein, and equol), and quality of life (QOL) were measured at various time points from 0 to 12 months. PSA outcome was evaluated. RESULTS: Within the mixed regression model, it was estimated that PSA had increased 56% per year before study entry and only increased 20% per year for the 12-month study period ($p = 0.05$). Specifically, the slope of PSA after study entry was significantly lower than that before study entry in 6 patients and the slope of

PSA after study entry was significantly higher than before study entry in 2 patients. For the remaining 12 patients, the change in slope was statistically insignificant. Nearly two thirds of the patients were noted to have significant levels of free equol in their serum while on therapy. CONCLUSION: Dietary intervention with isoflavone supplementation may have biologic activity in men with biochemical recurrent prostate cancer as shown by a decline in the slope of PSA. This study may lend support to the literature that nutritional supplements have biologic activity in prostate cancer and therefore, further studies with these agents in randomized clinical trials should be encouraged.

LYKOPENE

Exp Biol Med (Maywood). 2002 Nov;227(10):881-5. 

Links

Effects of lycopene supplementation in patients with localized prostate cancer.

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Epidemiological studies have shown an inverse association between dietary intake of lycopene and prostate cancer risk. We conducted a clinical trial to investigate the biological and clinical effects of lycopene supplementation in patients with localized prostate cancer. Twenty-six men with newly diagnosed prostate cancer were randomly assigned to receive a tomato oleoresin extract containing 30 mg of lycopene (n = 15) or no supplementation (n = 11) for 3 weeks before radical prostatectomy. Biomarkers of cell proliferation and

apoptosis were assessed by Western blot analysis in benign and cancerous prostate tissues. Oxidative stress was assessed by measuring the peripheral blood lymphocyte DNA oxidation product 5-hydroxymethyl-deoxyuridine (5-OH-mdU). Usual dietary intake of nutrients was assessed by a food frequency questionnaire at baseline. Prostatectomy specimens were evaluated for pathologic stage, Gleason score, volume of cancer, and extent of high-grade prostatic intraepithelial neoplasia. Plasma levels of lycopene, insulin-like growth factor-1, insulin-like growth factor binding protein-3, and prostate-specific antigen were measured at baseline and after 3 weeks of supplementation or observation. After intervention, subjects in the intervention group had smaller tumors (80% vs 45%, less than 4 ml), less involvement of surgical margins and/or extra-prostatic tissues with cancer (73% vs 18%, organ-confined disease), and less diffuse involvement of the prostate by high-grade prostatic intraepithelial neoplasia (33% vs 0%, focal involvement) compared with subjects in the control group. Mean plasma prostate-specific antigen levels were lower in the intervention group compared with the control group. This pilot study suggests that lycopene may have beneficial effects in prostate cancer. Larger clinical trials are warranted to investigate the potential preventive and/or therapeutic role of lycopene in prostate cancer.

Biochim Biophys Acta. 2005 May 30;1740(2):202-5. Epub 2005 Mar 13.  Links

Role of lycopene and tomato products in prostate health.

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Epidemiological evidence associating the decreased risk of prostate cancer with frequent consumption of tomato products inspired us to conduct a small intervention trial among patients diagnosed with prostate adenocarcinoma. Tomato sauce pasta was consumed daily for 3 weeks before their scheduled prostatectomy, and biomarkers of tomato intake, prostate cancer progression and oxidative DNA damage were followed in blood and the available prostate

tissue. The whole food intervention was so well accepted by the subjects that the blood lycopene (the primary carotenoid in tomatoes responsible for their red color) doubled and the prostate lycopene concentration tripled during this short period. Oxidative DNA damage in leukocytes and prostate tissues was significantly diminished, the latter mainly in the tumor cell nuclei, possibly due to the antioxidant properties of lycopene. Quite surprising was the decrease in blood prostate-specific antigen, which was explained by the increase in apoptotic death of prostate cells, especially in carcinoma regions. Prostate cancer cell cultures (LNCaP) were also sensitive to lycopene in growth medium, which caused an increased apoptosis and arrested the cell cycle. A possible explanation of these promising results may reside in lycopene effects on the genes governing the androgen stimulation of prostate growth, cytokines and on the enzymes producing reactive oxygen species, all of which were recently discovered by nutrigenomic techniques. Other phytochemicals in tomato may act in synergy with lycopene to potentiate protective effects and to help in the maintenance of prostate health.

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Lycopene inhibits disease progression in patients with benign prostate hyperplasia.

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Lycopene is a promising nutritional component for chemoprevention of prostate cancer (PCa). A possibly beneficial role of lycopene in patients diagnosed with benign prostate hyperplasia (BPH), who are at increased risk of developing PCa, has been suggested, although clinical data are lacking. Therefore, this pilot study aimed to investigate the effects of lycopene supplementation in elderly men diagnosed with BPH. A total of 40 patients with histologically proven BPH free of PCa were randomized to receive either lycopene at a dose of 15 mg/d or placebo for 6 mo. The effects of the

intervention on carotenoid status, clinical diagnostic markers of prostate proliferation, and symptoms of the disease were assessed. The primary endpoint of the study was the inhibition or reduction of increased serum prostate-specific antigen (PSA) levels. The 6-mo lycopene supplementation decreased PSA levels in men ($P < 0.05$), whereas there was no change in the placebo group. The plasma lycopene concentration increased in the group taking lycopene ($P < 0.0001$) but other plasma carotenoids were not affected. Whereas progression of prostate enlargement occurred in the placebo group as assessed by trans-rectal ultrasonography ($P < 0.05$) and digital rectal examination ($P < 0.01$), the prostate did not enlarge in the lycopene group. Symptoms of the disease, as assessed via the International Prostate Symptom Score questionnaire, were improved in both groups with a significantly greater effect in men taking lycopene supplements. In conclusion, lycopene inhibited progression of BPH.

VITAMIN E

Prostate. 2008 Jun 1;68(8):849-60.

In vivo and in vitro studies of anticancer actions of alpha-TEA for human prostate cancer cells.

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BACKGROUND: Vitamin E analog, 2,5,7,8-tetramethyl-2R-(4R,8R, 12-trimethyltridecyl) chroman-6-yloxyacetic acid, referred to as alpha-TEA induces apoptosis in a variety of human cancer cells in cell culture and reduces tumor burden and metastases in preclinical animal models of breast and ovarian cancer. The goal of this study was to determine in vivo anticancer efficacy of alpha-TEA against human prostate cancer cells and identify mechanisms of action. METHODS: A PC-3-GFP xenograft model was used to assess the effects of alpha-TEA formulated in liposomes and administered orally on tumor burden and metastases. Tumor tissue was examined by immunohistochemical staining for percentage of cells undergoing apoptosis by TUNEL or cell proliferation by Ki-67. In vitro analyses of mechanisms employed western immunoblotting to examine effects of alpha-TEA-treatments in LNCaP and PC-3-GFP cells on levels of pro-survival and pro-death factors. Functional

significance was determined using ectopically expressed constitutively active forms, inhibitors, or siRNA. RESULTS: alpha-TEA significantly reduced tumor burden and metastases, increased apoptosis and decreased proliferation of tumor cells ($P < 0.05$). alpha-TEA treatment of both LNCaP and PC-3-GFP cells in vitro reduced levels of pAkt1, pAkt2; FOXO1, c-FLIP(L) and survivin. Constitutively active Akt1, Akt2, c-FLIP or survivin reduced alpha-TEA-induced apoptosis. PI3K inhibitor enhanced apoptosis. Constitutively active FOXO1 enhanced alpha-TEA induced Fas ligand expression; whereas, FOXO1 siRNA reduced alpha-TEA induced Fas ligand expression. CONCLUSIONS: alpha-TEA is an effective anticancer agent for human prostate cancer cells. Downregulation of pro-survival and upregulation of pro-death factors play roles in alpha-TEA-induced apoptosis. (c) 2008 Wiley-Liss, Inc. Prostate. 2008 Mar 1;68(4):427-41. 

Links

Critical roles for JNK, c-Jun, and Fas/FasL-Signaling in vitamin E analog-induced apoptosis in human prostate cancer cells.

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BACKGROUND: Alpha-tocopherol ether-linked acetic acid (alpha-TEA), an analog of vitamin E (RRR-alpha-tocopherol), is a potent pro-apoptotic agent for human cancer cells in vivo and in vitro. METHODS: alpha-TEA-induced apoptosis was investigated in LNCaP and PC-3 human prostate cancer cells. Apoptosis was measured by DAPI-staining and FACS analyses of the sub-G1 fraction. Signaling molecules involved in apoptosis were measured by Western immunoblot analyses with or without prior immunoprecipitation, FACS analyses of cell surface membrane expression, RT-PCR analyses of mRNA levels, and chromatin immunoprecipitation. Functional significance was determined using siRNAs, dominant negative mutant, chemical inhibitor, or neutralizing antibody. RESULTS: Alpha-TEA treatment increased Fas and Fas ligand mRNA and protein levels; as well as, levels of cell surface membrane Fas in both cell lines. Blockage of Fas signaling attenuated alpha-TEA-induced apoptosis. alpha-TEA treatment also produced prolonged, elevated levels of activated (phosphorylated) c-Jun N-terminal kinase (JNK) and its substrate c-Jun, both of which were demonstrated to be necessary for alpha-TEA-induced apoptosis. Chromatin immunoprecipitation results showed

binding of c-Jun to the promoters of both Fas and FasL in alpha-TEA treated cells. Investigations of alpha-TEA-triggered apoptosis showed dual signaling from Fas with essential roles for both FADD and Daxx with FADD initiating the classical pathway mediated by caspase-8 activation and Daxx initiating an alternate pathway involving activation of JNK, c-Jun, and increased levels of Fas and FasL. CONCLUSIONS: Collectively, data support critical roles for JNK, c-Jun, and dual signaling from Fas/FasL via FADD and Daxx in alpha-TEA-induced apoptosis of human prostate cancer cells. Copyright 2008 Wiley-Liss, Inc.

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Links

Serum and dietary vitamin E in relation to prostate cancer risk.

Weinstein SJ, **Wright ME**, **Lawson KA**, **Snyder K**, **Männistö S**, **Taylor PR**, **Virtamo J**, **Albanes D**.
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Alpha-tocopherol supplementation (50 mg daily for 5-8 years) reduced prostate cancer incidence by 32% in the alpha-Tocopherol, beta-Carotene Cancer Prevention Study. We investigated whether serum alpha-tocopherol or intake of vitamin E (eight tocopherols and tocotrienols) was associated with prostate cancer risk with up to 19 years of follow-up in the alpha-Tocopherol, beta-Carotene Cancer Prevention Study cohort. Of the 29,133 Finnish male smokers, ages 50 to 69 years recruited into the study, 1,732 were diagnosed with incident prostate cancer between 1985 and 2004. Baseline serum alpha-tocopherol was measured by high-performance liquid chromatography and the components of vitamin E intake were estimated based on a 276-item food frequency questionnaire and food chemistry analyses. Proportional hazard models were used to determine multivariate-adjusted relative risks (RR) and 95% confidence intervals (95% CI). Higher serum alpha-tocopherol was associated with reduced risk of prostate cancer (RR, 0.80; 95% CI, 0.66-0.96

for highest versus lowest quintile; Ptrend = 0.03) and was strongly and inversely related to the risk of developing advanced disease (RR, 0.56; 95% CI, 0.36-0.85; Ptrend = 0.002). The inverse serum alpha-tocopherol-prostate cancer association was greater among those who were supplemented with either alpha-tocopherol or beta-carotene during the trial. There were no associations between prostate cancer and the individual dietary tocopherols and tocotrienols. In summary, higher prediagnostic serum concentrations of alpha-tocopherol, but not dietary vitamin E, was associated with lower risk of developing prostate cancer, particularly advanced prostate cancer.

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

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BACKGROUND: Vitamin E, beta-carotene, and vitamin C are micronutrient antioxidants that protect cells from oxidative damage involved in prostate carcinogenesis. In separate trials, supplemental vitamin E was associated with a decreased risk of prostate cancer among smokers and supplemental beta-carotene was associated with a decreased risk of prostate cancer among men with low baseline plasma beta-carotene levels. METHODS: We evaluated the association between intake of these micronutrient antioxidants from foods and supplements and the risk of prostate cancer among men in the screening arm of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. At baseline, trial participants completed a 137-item food frequency questionnaire that included detailed questions on 12 individual supplements. Cox proportional hazards models were used to estimate relative risks (RRs) and 95% confidence intervals (CIs). All statistical tests were two-sided. RESULTS: We identified 1338 cases of prostate cancer among 29 361 men during up to 8

years of follow-up. Overall, there was no association between prostate cancer risk and dietary or supplemental intake of vitamin E, beta-carotene, or vitamin C. However, among current and recent (i.e., within the previous 10 years) smokers, decreasing risks of advanced prostate cancer (i.e., Gleason score > or = 7 or stage III or IV) were associated with increasing dose (RR for > 400 IU/day versus none = 0.29, 95% CI = 0.12 to 0.68; Ptrend = .01) and duration (RR for > or = 10 years of use versus none = 0.30, 95% CI = 0.09 to 0.96; Ptrend = .01) of supplemental vitamin E use. Supplemental beta-carotene intake at a dose level of at least 2000 microg/day was associated with decreased prostate cancer risk in men with low (below the median of 4129 microg/day) dietary beta-carotene intake (RR = 0.52, 95% CI = 0.33 to 0.81). Among smokers, the age-adjusted rate of advanced prostate cancer was 492 per 100,000 person-years in those who did not take supplemental vitamin E, 153 per 100,000 person-years in those who took more than 400 IU/day of supplemental vitamin E, and 157 per 100,000 person-years in those who took supplemental vitamin E for 10 or more years. Among men with low dietary beta-carotene intake, the age-adjusted rate of prostate cancer was 1122 per 100,000 person-years in those who did not take supplemental beta-carotene, and 623 per 100,000 person-years in those who took at least 2000 microg/day of supplemental beta-carotene. CONCLUSIONS: Our results do not provide strong support for population-wide implementation of high-dose antioxidant supplementation for the prevention of prostate cancer. However, vitamin E supplementation in male smokers and beta-carotene supplementation in men with low dietary beta-carotene intakes were associated with reduced risk of this disease.

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Links

Serum and dietary vitamin E in relation to prostate cancer risk.

Weinstein SJ, **Wright ME**, **Lawson KA**, **Snyder K**, **Männistö S**, **Taylor PR**, **Virtamo J**, **Albanes D**.

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Alpha-tocopherol supplementation (50 mg daily for 5-8 years) reduced prostate cancer incidence by 32% in the alpha-Tocopherol, beta-Carotene Cancer Prevention Study. We investigated whether serum alpha-tocopherol or intake of vitamin E (eight tocopherols and tocotrienols) was associated with prostate cancer risk with up to 19 years of follow-up in the alpha-Tocopherol, beta-Carotene Cancer Prevention Study cohort. Of the 29,133 Finnish male smokers, ages 50 to 69 years recruited into the study, 1,732 were diagnosed with incident prostate cancer between 1985 and 2004. Baseline serum alpha-tocopherol was measured by high-performance liquid chromatography and the components of vitamin E intake were estimated based on a 276-item food frequency questionnaire and food chemistry analyses. Proportional hazard models were used to determine multivariate-adjusted relative risks (RR) and 95% confidence intervals (95% CI). Higher serum alpha-tocopherol was associated with reduced risk of prostate cancer (RR, 0.80; 95% CI, 0.66-0.96 for highest versus lowest quintile; Ptrend = 0.03) and was strongly and inversely related to the risk of developing advanced disease (RR, 0.56; 95% CI, 0.36-0.85; Ptrend = 0.002). The inverse serum alpha-tocopherol-prostate cancer association was greater among those who were supplemented with either alpha-tocopherol or beta-carotene during the trial. There were no associations between prostate cancer and the individual dietary tocopherols and tocotrienols. In summary, higher prediagnostic serum concentrations of alpha-tocopherol, but not dietary vitamin E, was associated with lower risk of developing prostate cancer, particularly advanced prostate cancer.

Vitamin D

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Vitamin D receptor polymorphisms, circulating vitamin D metabolites, and risk of prostate cancer in United States physicians.

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Prostatic cells express vitamin D receptor (VDR), which mediates the functions of 1,25-dihydroxyvitamin D. Two recent case-control studies suggested strong inverse associations between two VDR polymorphisms, TaqI and poly(A), and risk of prostate cancer. These two and a third polymorphism, BsmI, are closely linked. In a case-control study nested in the Physicians' Health Study, a randomized double-blind trial of aspirin and beta-carotene among 22,071 United States male physicians, we examined the associations between BsmI and TaqI and prostate cancer risk and whether the associations varied according to age and vitamin D metabolite levels among 372 incident cases and 591 controls. Among controls, the BB genotype was significantly associated with higher 1,25-dihydroxyvitamin D (median = 36.2 pg/ml for the BB versus 33.9 pg/ml for the bb genotype; P = 0.02), suggesting an association of the VDR polymorphisms with VDR function. Overall, we observed no significant associations of these VDR polymorphisms with prostate cancer risk: relative risk (RR) = 0.86 [95% confidence interval (CI) = 0.57-1.29] for the BB genotype and RR = 0.92 (95% CI = 0.69-1.22) for the Bb genotype, compared with the bb genotype (results were similar for the TaqI polymorphism). Stratification by age (< or = 61 and > 61 years) and tumor aggressiveness showed no significant associations. However, in an analysis restricted to men with plasma 25-hydroxyvitamin D below the median, we observed a 57% reduction (RR = 0.43, 95% CI = 0.19-0.98) in risk for those with the BB versus the bb genotype; the risk reduction was particularly marked among older men (RR = 0.18, 95% CI = 0.05-0.68). We did not observe this inverse association among men with 25-hydroxyvitamin D levels above the median, nor did we observe it among younger men.

PLoS Med. 2007 Mar;4(3):e103. Links

A prospective study of plasma vitamin D metabolites, vitamin D receptor polymorphisms, and prostate cancer.

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BACKGROUND: Vitamin D insufficiency is a common public health problem nationwide. Circulating 25-hydroxyvitamin D3 (25[OH]D), the most commonly used index of vitamin D status, is converted to the active hormone 1,25 dihydroxyvitamin D3 (1,25[OH]2D), which, operating through the vitamin D receptor (VDR), inhibits in vitro cell proliferation, induces differentiation and apoptosis, and may protect against prostate cancer. Despite intriguing results from laboratory studies, previous epidemiological studies showed inconsistent associations of circulating levels of 25(OH)D, 1,25(OH)2D, and several VDR polymorphisms with prostate cancer risk. Few studies have explored the joint association of circulating vitamin D levels with VDR polymorphisms. METHODS AND FINDINGS: During 18 y of follow-up of 14,916 men initially free of diagnosed cancer, we identified 1,066 men with incident prostate cancer (including 496 with aggressive disease, defined as stage C or D, Gleason 7-10, metastatic, and fatal prostate cancer) and 1,618 cancer-free, age- and smoking-matched control participants in the Physicians' Health Study. We examined the associations of prediagnostic plasma levels of 25(OH)D and 1,25(OH)2D, individually and jointly, with total and aggressive disease, and explored whether relations between vitamin D metabolites and prostate cancer were modified by the functional VDR FokI polymorphism, using conditional logistic regression. Among these US physicians, the median plasma 25(OH)D levels were 25 ng/ml in the blood samples collected during the winter or spring and 32 ng/ml in samples collected during the summer or

fall. Nearly 13% (summer/fall) to 36% (winter/spring) of the control participants were deficient in 25(OH)D (<20 ng/ml) and 51% (summer/fall) and 77% (winter/spring) had insufficient plasma 25(OH)D levels (<32 ng/ml). Plasma levels of 1,25(OH)2D did not vary by season. Men whose levels for both 25(OH)D and 1,25(OH)2D were below (versus above) the median had a significantly increased risk of aggressive prostate cancer (odds ratio [OR] = 2.1, 95% confidence interval [CI] 1.2-3.4), although the interaction between the two vitamin D metabolites was not statistically significant (pinteraction = 0.23). We observed a significant interaction between circulating 25(OH)D levels and the VDR FokI genotype (pinteraction < 0.05). Compared with those with plasma 25(OH)D levels above the median and with the FokI FF or Ff genotype, men who had low 25(OH)D levels and the less functional FokI ff genotype had increased risks of total (OR = 1.9, 95% CI 1.1-3.3) and aggressive prostate cancer (OR = 2.5, 95% CI 1.1-5.8). Among men with plasma 25(OH)D levels above the median, the ff genotype was no longer associated with risk. Conversely, among men with the ff genotype, high plasma 25(OH)D level (above versus below the median) was related to significant 60% approximately 70% lower risks of total and aggressive prostate cancer. CONCLUSIONS: Our data suggest that a large proportion of the US men had suboptimal vitamin D status (especially during the winter/spring season), and both 25(OH)D and 1,25(OH)2D may play an important role in preventing prostate cancer progression. Moreover, vitamin D status, measured by 25(OH)D in plasma, interacts with the VDR FokI polymorphism and modifies prostate cancer risk. Men with the less functional FokI ff genotype (14% in the European-descent population of this cohort) are more susceptible to this cancer in the presence of low 25(OH)D status.

J Natl Cancer Inst. 2008 Jun 4;100(11):796-804. Epub 2008 May 27.  Links

Comment in:
J Natl Cancer Inst. 2008 Jun 4;100(11):759-61.

Serum vitamin D concentration and prostate cancer risk: a nested case-control study.

Ahn J, Peters U, Albanes D, Purdue MP, Abnet CC, Chatterjee N, Horst RL, Hollis BW, Huang WY, Shikany JM, Hayes RB; Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial Project Team.

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BACKGROUND: Epidemiological studies have yielded inconsistent associations between vitamin D status and prostate cancer risk, and few studies have evaluated whether the associations vary by disease aggressiveness. We investigated the association between vitamin D status, as determined by serum 25-hydroxyvitamin D [25(OH)D] level, and risk of prostate cancer in a case-control study nested within the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. METHODS: The study included 749 case patients with incident prostate cancer who were diagnosed 1-8 years after blood draw and 781 control subjects who were frequency matched by age at cohort entry, time since initial screening, and calendar year of cohort entry. All study participants were selected from the trial screening arm (which includes annual standardized prostate cancer screening). Conditional logistic regression was used to estimate adjusted odds ratios (ORs) with 95% confidence intervals (CIs) by quintile of season-standardized serum 25(OH)D concentration. Statistical tests were two-sided. RESULTS: No statistically significant trend in overall prostate cancer risk was observed with increasing season-standardized serum 25(OH)D level. However, serum 25(OH)D concentrations greater than the lowest quintile (Q1) were associated with increased risk of aggressive (Gleason sum > or = 7 or clinical stage III or IV) disease (in a model adjusting for matching factors, study center, and history of diabetes, ORs for Q2 vs Q1 = 1.20, 95% CI = 0.80 to 1.81, for Q3 vs Q1 =1.96, 95% CI = 1.34 to 2.87, for Q4 vs Q1 = 1.61, 95% CI = 1.09 to 2.38, and for Q5 vs Q1 = 1.37, 95% CI = 0.92 to 2.05; P(trend) = .05). The rates of aggressive prostate cancer for increasing quintiles of serum 25(OH)D were 406, 479, 780, 633, and 544 per 100 000 person-years. In exploratory analyses, these associations with aggressive disease were consistent across subgroups defined by age, family history of prostate cancer, diabetes, body mass index, vigorous physical activity, calcium intake, study center, season of blood collection, and assay batch. CONCLUSION: The

findings of this large prospective study do not support the hypothesis that vitamin D is associated with decreased risk of prostate cancer; indeed, higher circulating 25(OH)D concentrations may be associated with increased risk of aggressive disease.

SELEN

Cancer Genomics Proteomics. 2005 Apr;2(2):97-114. Links

Microarray Data Mining for Potential Selenium Targets in Chemoprevention of Prostate Cancer.

Zhang H, **Dong Y**, **Zhao H**, **Brooks JD**, **Hawthorn L**, **Nowak N**, **Marshall JR**, **Gao AC**, **Ip C**.

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BACKGROUND: A previous clinical trial showed that selenium supplementation significantly reduced the incidence of prostate cancer. We report here a bioinformatics approach to gain new insights into selenium molecular targets that might be relevant to prostate cancer chemoprevention. MATERIALS AND METHODS: We first performed data mining analysis to identify genes which are consistently dysregulated in prostate cancer using published datasets from gene expression profiling of clinical prostate specimens. We then devised a method to systematically analyze three selenium microarray datasets from the LNCaP human prostate cancer cells, and to match the analysis to the cohort of genes implicated in prostate carcinogenesis. Moreover, we compared the selenium datasets with two datasets obtained from expression profiling of androgen-stimulated LNCaP cells. RESULTS: We found that selenium reverses the expression of genes implicated in prostate carcinogenesis. In addition, we found that selenium could counteract the effect of androgen on the expression of a subset obtained from androgen-regulated genes. CONCLUSIONS: The above information provides us with a treasure of new clues to investigate the

mechanism of selenium chemoprevention of prostate cancer. Furthermore, these selenium target genes could also serve as biomarkers in future clinical trials to gauge the efficacy of selenium intervention.

Prostate. 2006 Jul 1;66(10):1070-5. Links

Monomethylated selenium inhibits growth of LNCaP human prostate cancer xenograft accompanied by a decrease in the expression of androgen receptor and prostate-specific antigen (PSA).

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OBJECTIVES: Epidemiological studies and prevention trials suggest selenium is a promising preventive agent for prostate cancer. Selenium-containing compounds inhibited the growth of prostate cancer cell lines including androgen sensitive LNCaP and androgen insensitive DU145 and PC3 cells in vitro. Previous study revealed a novel mechanism of selenium action in which selenium (methylseleninic acid (MSA)) markedly reduced androgen receptor (AR) signaling in prostate cancer cells, suggesting that selenium might act as an antiandrogen, which could serve as a therapeutic agent for prostate cancer. In this study, we tested whether selenium (methylselenocysteine (MSC)) affects tumor growth of human prostate cancer cells by targeting AR signaling in vivo. METHODS: Prostate tumor xenografts were established in nude mice by co-inoculating LNCaP cells with Matrigel. The mice-bearing tumors were treated with or without MSC (100 microg/mouse/day) via intraperitoneal injection for 2 weeks. The effect of MSC on tumor growth, AR, and prostate-specific antigen (PSA) expression was examined. RESULTS: Methylselenocysteine (MSC) significantly inhibited LNCaP tumor growth ($P < 0.05$). AR expression in tumor tissues and serum PSA levels were considerably decreased in MSC-treated mice compared to the vehicle controls. CONCLUSIONS: Pharmacological dose of MSC inhibits the growth

of LNCaP human prostate cancer in vivo accompanied by a decrease in the expression of AR and PSA. These findings suggest that selenium (MSC) can serve as a therapeutic agent aimed at disruption of AR signaling for prostate cancer. Copyright 2005 Wiley-Liss, Inc.

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Links

Molecular chemoprevention by selenium: a genomic approach.

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Basic research and clinical chemoprevention trials support the protective role of selenium in cancer prevention but the mechanisms based on the molecular level remain to be fully defined. This mini-review focuses only on the elucidation of the molecular mechanisms of cancer prevention by selenium using the genomics approach; target organs discussed here are breast, prostate, colon and lung. The results described here support the utility of microarray technology in delineating the molecular mechanisms of cancer prevention by selenium. These results are based on studies employing human and rodent cell lines and tissues from animal models ranging from normal to frank cancer. The dose and the form of selenium are determining factors in cancer chemoprevention. The results of the microarray analysis reviewed here indicate that selenium, independent of its form and the target organ examined, alters several genes in a manner that can account for cancer prevention. Selenium can up regulate genes related to phase II detoxification enzymes, certain selenium-binding proteins and select apoptotic genes, while down regulating those related to phase I activating enzymes and cell proliferation. Independent of tissue type, selenium arrests cells in G1 phase of cell cycle, inhibits CYCLIN A, CYCLIN D1, CDC25A, CDK4, PCNA and E2F gene expressions while induces the expressions of P19, P21, P53, GST, SOD, NQO1, GADD153 and certain CASPASES. In addition to those described above, genes such as OPN, which is mainly involved in metastasis and

recently reported to be down regulated by selenium, should be considered as potential molecular marker in clinical chemoprevention trials. Collectively, literature data indicate that some of these genes that were altered by selenium are also involved in the development of human cancers described in this review. It appears that androgen receptor status may influence the effect of selenium on gene expression profile in prostate cancer; whether estrogen receptor may influence the effect of selenium on gene expression in breast cancer requires further studies. Knowledge from gene array data in combination with proteomics approaches, using homogenous population of cell types with the aid of laser capture microdissection, may provide an individualized dimension of information on cancer risk and potential targets for its prevention. The molecular (genetic) biomarkers presented in this review will provide the foundation for future studies of the chemopreventive properties of structurally varied selenium compounds.

GRÜNTEE EXTRAKT

Life Sci. 2006 Mar 27;78(18):2073-80. Epub 2006 Jan 30.ELSEVIER FULL-TEXT ARTICLE Links

Green tea and its polyphenolic catechins: medicinal uses in cancer and noncancer applications.

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Can drinking several cups of green tea a day keep the doctor away? This certainly seems so, given the popularity of this practice in East Asian culture and the increased interest in green tea in the Western world. Several epidemiological studies have shown beneficial effects of green tea in cancer, cardiovascular, and neurological diseases. The health benefits associated with green tea consumption have also been corroborated in animal studies of cancer chemoprevention, hypercholesterolemia, artherosclerosis, Parkinson's disease, Alzheimer's disease, and other aging-related disorders. However, the

use of green tea as a cancer chemopreventive or for other health benefits has been confounded by the low oral bioavailability of its active polyphenolic catechins, particularly epigallocatechin-3-gallate (EGCG), the most active catechin. This review summarizes the purported beneficial effects of green tea and EGCG in various animal models of human diseases. Dose-related differences in the effects of EGCG in cancer versus neurodegenerative and cardiovascular diseases, as well as discrepancies between doses used in in vitro studies and achievable plasma understanding of the in vivo effects of green tea catechins in humans, before the use of green tea is widely adopted as health-promoting measure.

Front Biosci. 2005 May 1;10:1010-23. Links

Synthetic peracetate tea polyphenols as potent proteasome inhibitors and apoptosis inducers in human cancer cells.

Kuhn D, **Lam WH**, **Kazi A**, **Daniel KG**, **Song S**, **Chow LM**, **Chan TH**, **Dou QP**.
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It has been suggested that proteasome activity is essential for tumor cell proliferation and drug resistance development. We have previously shown that natural and synthetic ester bond-containing tea polyphenols are selective inhibitors of the chymotrypsin-like activity of the proteasome. The most abundant catechin in green tea is (-)-epigallocatechin-3-gallate [(-)-EGCG], which has been found by many laboratories to exhibit the most potent anticancer activity. We have reported that (-)-EGCG is also the most effective proteasome inhibitor among all the natural green tea catechins tested. Unfortunately, (-)-EGCG is very unstable in neutral and alkaline conditions. In an attempt to increase the stability and thus the efficacy, we synthesized several (-)-EGCG analogs with acetyl protected -OH groups as prodrugs. Here

we report, for the first time, that these acetylated synthetic tea analogs are much more potent than natural (-)-EGCG in inhibiting the proteasome in cultured tumor cells. Consistently, these protected analogs showed much higher potency than (-)-EGCG to inhibit proliferation and transforming activity and to induce apoptosis in human leukemic, prostate, breast, and simian virus 40-transformed cells. Additionally, these protected analogs had greatly reduced effects on human normal and non-transformed cells. Therefore, these peracetate protected tea polyphenols are more efficacious than (-)-EGCG and possess great potential to be developed into novel anticancer drugs. Identification of the cytosolic metabolite(s) of peracetate-protected polyphenols in cultured tumor cells and examination of their in vivo tumor growth-inhibitory activity are currently underway in our laboratory.

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Links

Multitargeted therapy of cancer by green tea polyphenols.

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Tea ranks second only to water as a major component of fluid intake worldwide and has been considered a health-promoting beverage since ancient times. For the past two decades, we and others have been investigating the potential cancer preventive and therapeutic effects of green tea and its polyphenolic mixture termed GTP. It has become clear that much of these effects of GTP are mediated by its most abundant catechin, epigallocatechin gallate (EGCG). Large amount of encouraging data from in vitro and animal models has emerged making clear that green tea is a nature's gift molecule endowed with anticancer effects. Epidemiological and geographical observations suggest that these laboratory data may be applicable to human population. Clinical trials of GTP, especially in prostate cancer patients have yielded encouraging results. This article briefly reviews properties of GTP, especially EGCG with reference to multitargeted therapy of cancer.

Effect of a prodrug of the green tea polyphenol (-)-epigallocatechin-3-gallate on the growth of androgen-independent prostate cancer in vivo.

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Epigallocatechin-3-gallate (EGCG) is the major and most potent polyphenol compound of green tea that has been shown to have anticancer effects against various types of cancers. In this study, in addition to the EGCG compound, a synthetic derivative, the peracetate of EGCG (EGCG-P), was used to investigate the inhibitory effects on growth of androgen-independent prostate cancer in vivo. The advantage of EGCG-P is that it may act as a prodrug, leading to higher bioavailability than EGCG itself. The aim of our study was to compare the differences between EGCG and EGCG-P on their inhibitory effect on androgen-independent prostate cancer, CWR22R, xenograft model in nude mice. The mice were administrated daily with solvent dimethyl sulfoxide, EGCG, and EGCG-P separately through intraperitoneal injection for 20 days. Tumor volume and body weight of nude mice were recorded daily. Serum prostate-specific antigen (PSA) levels were also measured before and after the treatment. The effects of both EGCG and EGCG-P on tumor cell proliferation were assessed by immunohistochemical (IHC) method using antibodies against Ki-67 and proliferating cell nuclear antigen. The apoptotic effect was evaluated by IHC against B-cell non-Hodgkin lymphoma-2 and terminal deoxynucleotidyl transferase dUTP nick-

end labeling assay by in situ apoptosis detection kit. Moreover, the potential suppression of angiogenesis by EGCG and EGCG-P on prostate cancer was examined by IHC against CD31. Our results revealed that treatment of EGCG and EGCG-P compounds suppressed the growth of CWR22R xenografts without causing any detectable side effects in nude mice. The suppression of growth of the tumor was correlated with the decrease of serum PSA level together with the reduction in tumor angiogenesis and an increase in apoptosis on prostate cancer cells. The results showed that treatment of EGCG and EGCG-P inhibited tumor growth and angiogenesis while promoting apoptosis of the prostate cancer cells in vivo. Our results suggest that EGCG-P may be a more stable and useful compound for increasing the therapeutic anticancer effects in androgen-independent prostate cancer.

Mol Biotechnol. 2007 Sep;37(1):52-7. Links

Anti-oxidants from green tea and pomegranate for chemoprevention of prostate cancer.

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Among males, prostate cancer has become the second leading cause of cancer-related deaths in North America, with similar trends in many Western and developing countries. One way to control prostate cancer is through chemoprevention, which refers to the administration of synthetic or naturally occurring agents to block, reverse, or delay the process of carcinogenesis. For a variety of reasons, the most important of which is human acceptance, for chemopreventive intervention, naturally occurring diet-based agents are preferred. Prostate cancer is an ideal candidate disease for chemopreventive intervention, because it grows very slowly, likely for decades, before symptoms arise and a diagnosis is finally established, it has a long latency period, and it is typically diagnosed in men >50 years of age. Most chemopreventive agents are antioxidant in nature. We have been defining the usefulness of dietary anti-oxidants for chemoprevention of prostate and other

cancers. It is increasingly appreciated that some of these dietary anti-oxidants are nature's gift molecules endowed with cancer preventive and therapeutic properties. This review will focus on prostate cancer chemopreventive effects of polyphenolic anti-oxidants derived from green tea and pomegranate. It is a challenge to custom-tailor these gift molecules as cocktails in concentrations that can easily be consumed by humans for delaying prostate and other cancers.

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

Links

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.

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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.

Nutr Cancer. 2003;47(1):13-23. Links

Tea beverage in chemoprevention of prostate cancer: a mini-review.

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Because prostate cancer has a long latency period and is typically diagnosed in elderly men, it represents an ideal candidate disease for chemoprevention. Therefore, even a modest delay achieved through intervention could have a significant impact on the outcome of this disease. Epidemiological and laboratory studies have provided convincing evidence that diet, genetic factors, and lifestyle are major causes of prostate cancer. Although surgery,

radiotherapy, and hormone therapy are the most widely accepted curative options for a selected group of patients suffering from prostate cancer, the side effects of these treatments are many. In recent years, many dietary agents have been being described that show a wide range of chemopreventive effects in cell culture and selected animal model systems of prostate carcinogenesis. One such agent is the beverage tea, which, next to water, is the most popularly consumed beverage in the world. The epidemiological studies and recent data, amassed from various laboratories around the world, provide evidence that tea polyphenols such as epigallocatechin-3-gallate, epigallocatechin, and epicatechin-3-gallate may have the potential to lower the risk of prostate cancer in the human population. Recently, it has been shown that green tea polyphenols, when given to TRAMP, a transgenic mouse model that mimics progressive forms of human prostate cancer, exert remarkable preventive effects against prostate cancer development. Chemoprevention of prostate cancer by tea polyphenols appears to occur through the modulation of various molecular targets. This article attempts to address the issue of the possible use of tea, especially green tea, for the chemoprevention of prostate cancer.

Prostate. 2015 Feb;75(2):151-60. doi: 10.1002/pros.22900. Epub 2014 Oct 4.

Ellagic acid, a component of pomegranate fruit juice, suppresses androgen-dependent prostate carcinogenesis via induction of apoptosis.

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Abstract

BACKGROUND:

Ellagic acid (EA), a component of pomegranate fruit juice (PFJ), is a plant-derived polyphenol and has antioxidant properties. PFJ and EA have been reported to suppress various cancers, including prostate cancer. However, their chemopreventive effects on development and progression of prostate cancer using in vivo models have not been established yet.

METHODS:

The transgenic rat for adenocarcinoma of prostate (TRAP) model was used to investigate the modulating effects of PFJ and EA on prostate carcinogenesis. Three-week-old male transgenic rats were treated with EA or PFJ for 10 weeks. In vitro assays for cell growth, apoptosis, and Western blot were performed using the human prostate cancer cell lines, LNCaP (androgen-dependent), PC-3 and DU145 (androgen-independent).

RESULTS:

PFJ decreased the incidence of adenocarcinoma in lateral prostate, and both EA and PFJ suppressed the progression of prostate carcinogenesis and induced apoptosis by caspase 3 activation in the TRAP model. In addition, the level of lipid peroxidation in ventral prostate was significantly decreased by EA treatment. EA was able to inhibit cell proliferation of LNCaP, whereas this effect was not observed in PC-3 and DU145. As with the in vivo data, EA induced apoptosis in LNCaP by increasing Bax/Bcl-2 ratio and caspase 3 activation. Cell-cycle related proteins, p21(WAF) , p27(Kip) , cdk2, and cyclin E, were increased while cyclin D1 and cdk1 were decreased by EA treatment.

CONCLUSIONS:

The results indicate that PFJ and EA are potential chemopreventive agents for prostate cancer, and EA may be the active component of PFJ that exerts these anti-cancer effects.

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Pomegranate and its components as alternative treatment for prostate cancer.

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Abstract

Prostate cancer is the second leading cause of cancer deaths in men in the United States. There is a major need for less toxic but yet effective therapies to treat prostate cancer. Pomegranate fruit from the tree Punica granatum has been used for centuries for medicinal purposes and is described as "nature's power fruit". Recent research has shown that pomegranate juice (PJ) and/or pomegranate extracts (PE) significantly inhibit the growth of prostate cancer cells in culture. In preclinical murine models, PJ and/or PE inhibit growth and angiogenesis of prostate tumors. More recently, we have shown that three components of PJ, luteolin, ellagic acid and punicic acid together, have similar inhibitory effects on prostate cancer growth, angiogenesis and metastasis. Results from clinical trials are also promising. PJ and/or PE significantly prolonged the prostate specific antigen (PSA) doubling time in patients with prostate cancer. In this review we discuss data on the effects of PJ and PE on prostate cancer. We also discuss the effects of specific components of the pomegranate fruit and how they have been used to study the mechanisms involved in prostate cancer progression and their potential to be used in deterring prostate cancer metastasis.

J Steroid Biochem Mol Biol. 2014 Sep;143:19-28. doi: 10.1016/j.jsbmb.2014.02.006. Epub 2014 Feb 22.

Pomegranate extracts impact the androgen biosynthesis pathways in prostate cancer models in vitro and in vivo.

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Abstract

Castration-resistant prostate cancer (CRPC) remains largely dependent on androgen receptor (AR). Residual tissue androgens are consistently detected within CRPC tumors and play a critical role in facilitating AR-mediated signaling pathways which lead to disease progression. Testosterone and dihydrotestosterone (DHT) are the major androgens detected in tumors. They are produced through three biosynthesis pathways: Δ(4), Δ(5), and backdoor pathways. Both androgens bind to and stimulate AR activation. The current study investigates the effects of pomegranate extracts (POM) and their ability to inhibit androgen biosynthesis using PCa cell lines (22RV1 and LNCaP) in vitro as well as the PTEN knockout mouse model representing prostate cancer. Steroids were extracted using ethyl acetate or solid phase extraction, and then analyzed by UPLC/MS/MS. The results showed that POM (0-12μg/mL) reduced the production of testosterone, DHT, DHEA, androstenedione, androsterone, and pregnenolone in both cell lines. In addition our in vivo data supports this observation with a reduction in serum steroids determined after 20 weeks of POM treatment (0.17 g/L in drinking water). In accordance with these results, Western blotting of cell lysates and tPSA analysis determined that PSA was significantly decreased by the treatment of POM. Interestingly, AKR1C3 and AR levels were shown to be increased in both cell lines, perhaps as a negative feedback effect in response to steroid inhibition. Overall, these results provide mechanistic evidence to support the rationale for recent clinical reports describing efficacy of POM in CRPC patients.

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Pomegranate extract inhibits the bone metastatic growth of human prostate cancer cells and enhances the in vivo efficacy of docetaxel chemotherapy.

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Abstract

BACKGROUND:

Docetaxel treatment is the only first-line chemotherapy with a survival benefit in metastatic castration-resistant prostate cancer (PCa). Nonetheless, most patients become docetaxel resistant and inevitably progress with no cure. In this study, we investigated the potential of pomegranate extract (PE) in targeting metastatic castration-resistant PCa and improving docetaxel chemotherapy.

METHODS:

The in vitro and in vivo effect of POMx, a PE formula currently approved for clinical trials, in metastatic castration-resistant PCa cells was evaluated in experimental models.

RESULTS:

We demonstrated that POMx exhibited potent in vitro cytotoxicity in metastatic castration-resistant PCa cells. Mechanistic studies identified survivin as a novel molecular target that may mediate the anti-cancer activity of POMx, presumably through the inhibition of signal transducer and activator of transcription 3. The in vivo administration of POMx treatment effectively inhibited survivin, induced apoptosis, retarded C4-2 tumor growth in skeleton and significantly enhanced the efficacy of docetaxel in athymic nude mice.

CONCLUSION:

These results provide the first preclinical evidence that POMx may be effective in treating metastatic castration-resistant PCa and enhancing the efficacy of docetaxel chemotherapy. Prostate © 2013 Wiley Periodicals, Inc