Literaturservice I-GAP
Lycopene and Prostata CA

1: Carcinogenesis 2009 Jan;

Nitric oxide synthase gene polymorphisms and prostate cancer risk.

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Nitric oxide (NO) induces cytotoxicity and angiogenesis, and may play a role in prostate carcinogenesis, potentially modulated by environmental exposures. We evaluated the association of prostate cancer with genetic polymorphisms in two genes related to intracellular NO: NOS2A [i-NOS; -2892T>C, Ex16+14C>T (S608L), IVS16+88T>G, and IVS20+524G>A] and NOS3 [e-NOS; IVS1-762C>T, Ex7-43C>T (D258D), IVS7-26A>G, Ex8-63G>T (E298D), and IVS15-62G>T]. Prostate cancer cases (n=1,320) from the screening arm of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial were frequency-matched to controls (n=1,842), by age, race, time since initial screening, and year of blood draw. An antioxidant score (range 3-12; low [3-7] vs. high [8-12]) was created by summing the quartile levels of vitamin E, beta-carotene, and lycopene, which were coded from 1 to 4, respectively. The global tests for all 8 SNPs (excluding NOS2 -2892T>C, with low minor allele frequency) were statistically significant for prostate cancer (P=0.005), especially for aggressive cancer (Stage III-IV or Gleason score>/=7) (P=0.01). The NOS2A IVS16+88 GT/TT was associated with increased prostate caner risk (OR=1.24, 95% CI=1.00-1.54), whereas the IVS20+524 AG/GG was associated with decreased risk (0.77, 0.66-0.90). The NOS3 IVS7-26 GG was associated with increased prostate caner risk (1.33, 1.07-1.64). All these SNPs showed significant associations with aggressive cancer and not for non-aggressive cancer. In the evaluation of effect modification, the effect of the NOS2A IVS16+88 GT/TT on aggressive cancer was stronger among subjects with higher antioxidant intake (1.61, 1.18-2.19; P(interaction)=0.01). Our results suggest that NOS gene polymorphisms are genetic susceptibility factors for aggressive prostate cancer.

2: Urologe A 2009 Jan;

[A critical assessment of phytotherapy for prostate cancer.]

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Prostate cancer patients increasingly use complementary and alternative medicines to support the body's immune system in addition to conventional treatment to minimize morbidity associated with conventional treatment, to enhance the quality of life, and ultimately in the hope to cure cancer when conventional treatment fails. As there is a large variety of phytomedicines promoted as potential treatment for prostate cancer, the aim of this review was to differentiate between preventive and therapeutic approaches and evaluate which phytochemicals might be suited for therapy of prostate cancer. Therefore, preclinical in vitro and in vivo data as well as

clinical trials with phytosubstances such as genistein, lycopene, epigallocatechin gallate, resveratrol, and mistletoe were assessed. The presented data show that at present there is no clinical evidence that phytochemicals might have a therapeutic use in prostate cancer in relation to reduction of tumor progression or improved survival. The question about an improved immune function or quality of life remains open. Potentially the use of phytochemicals could play a role in a preventive setting.

3: J Urol 2009 Jan;

Lycopene for Advanced Hormone Refractory Prostate Cancer: A Prospective, Open Phase II Pilot Study.

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PURPOSE: We investigated the influence of lycopene on the clinical and laboratory course in men with hormone refractory prostate cancer. To our knowledge this study represents the first time that subjective assessments of the course of therapy have been recorded. MATERIAL AND METHODS: We performed a prospective, open phase II pilot study, in which patients with progressive hormone refractory prostate cancer were included. Lycopene supplementation (15 mg) was given daily for 6 months. Followup laboratory tests and clinical examinations were done monthly. Changes to analgesic use and quality of life (European Organisation for Research and Treatment of Cancer QLQ-C30) were measured. The study end point was a significant change in serum prostate specific antigen, clinical progression or the end of the 6-month observation period. RESULTS: A total of 18 patients 64 to 85 years old (median age 73) were enrolled in the study during a 20-month period, of whom 17 could be analyzed. Five of the 17 patients (29%) withdrew from the study prematurely, including 4 of 5 because of prostate specific antigen progression and/or tumor associated complications, and 1 due to an allergic reaction to lycopene. Median prostate specific antigen doubled in 6 months from 42.7 ng/ml (range 13.8 to 521.6) in 17 patients to 96.4 ng/ml (range 13.5 to 1,240) in 12. Stable prostate specific antigen was observed in 5 of 17 patients (29%). None of the patients had a greater than 50% decrease in prostate specific antigen. Patients experienced a slight deterioration in mean health status at the end of the study compared to the outset. However, two-thirds of the patients experienced an improved or unchanged situation regardless of the clinical and biochemical course. CONCLUSIONS: No clinically relevant benefits were shown for patients with advanced stages of the disease.

PMID: 19150092 [found with GoPubMed]

4: Biomed Sci Instrum 2008;44:465-70

A comparison of the morphological changes associated with conventional and sustained treatment with pigallocatechin3gallate, thymoquinone, and tannic acid on lncap cells.

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A number of epidemiological studies have suggested that certain antioxidants, such as vitamin E, lycopene, selenium, and their derivatives may be effective in combating prostate cancer and decreasing the risk of prostate cancer in men as well as other cancers in the body. Ongoing research has been targeted towards examining these agents in specific populations and in prostate epithelial cell lines to determine whether risk is reduced and the magnitude of risk reduction (Ni et al., 2007 and Morrissey et al., 2007). In this study, three antioxidants, epigallocatehin -3-gallate (EGCG), thymoquinone (TQ), and tannic acid (TA) were analyzed to observe their morphological responses to both conventional and sustained treatment with both low and high doses of EGCG, TQ, and TA at 24, 48, and 72 hours. Cells treated with high doses of EGCG and TQ were fewer in number and irregular in appearance in comparison to the control cells after 48 and 72 hours of incubation. Sustained treatment with EGCG, TQ, TA, and TCP demonstrated the greatest reduction in cell number in comparison to the control and other groups in the study. Overall findings of this study demonstrated that conventional and sustained treatment with the antioxidants EGCG, TQ, TA, and TCP suppressed cell number as well as cell growth by causing disruptions in certain cell-cycle checkpoints. The results of this study also demonstrated that antioxidants may be excellent candidates with chemopreventive and chemotherapeutic properties against various cancers. Since understanding is limited regarding the processes involved in cancer initiation and growth, more research is needed in this era so that physicians caring for men and women with various types of cancer can be aware of these remedies and provide further avenues for treatment and managing the disease.

5: Mol Nutr Food Res 2008 Dec;

Prostate cancer and vegetable consumption.

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Epidemiological studies have shown marked variations in prostate cancer incidence and mortality across different geographic regions, leading to the rising interest in the role of nutrition in prostate cancer risk. There is also a large body of evidence that a diverse diet, rich in vegetables, can reduce the risk of prostate cancer. In this review, the role of various kinds of vegetables and their bioactive compounds associated with prostate cancer risk, and the underlying mechanisms of these associations are summarized. There is accumulating evidence to support the consumption of lycopene, in particular tomato and tomato-based products, as protective factors against prostate cancer. Evidence on the protective role of beta-carotene was inconsistent from cohort and case-control studies. Evidence on the effect of pulses or soy consumption on prostate cancer risk was limited but suggestive of decreased risk with increased pulses or soy consumption. However, the role of vitamin C, vitamin E, allium vegetables, and cruciferous vegetables on prostate cancer risk remains to be determined due to limited evidence. Although the impact on prostate cancer risk differs among various vegetables and their constituent nutrients, the overall benefits of plant based diet on cancer prevention and other diet-related diseases should be promoted.

6: Mol Nutr Food Res 2008 Dec;

Can the Mediterranean diet prevent prostate cancer?

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Prostate cancer is the second most common cancer in men worldwide. Despite the global importance of this cancer, until recently little was known about risk factors apart from the well-established factors: age, family history and country of birth. The large worldwide variation in prostate cancer risk and increased risk in migrants moving from low to high risk countries provides strong support for modifiable environmental factors. We have based our review on the findings of a systematic review undertaken by an expert panel on behalf of the World Cancer Research Fund and the American Institute for Cancer Research, and new data since then, linking identified foods and nutrients with prostate cancer. Evidence indicates that foods containing lycopene, as well as selenium and foods containing it, probably protect against prostate cancer, and excess consumption of foods or supplements containing calcium are a probable cause of this cancer. The expert panel also concluded that it is unlikely that beta-carotene (whether from foods or supplements) has a substantial effect on the risk of this cancer. A recent review on environmental factors in human prostate cancer also found that there were protective effects of vitamin E, pulses, soy foods and high plasma 1,25-dihydroxyvitamin D levels. The Mediterranean diet is abundant in foods that may protect against prostate cancer and is associated with longevity and reduced cardiovascular and cancer mortality. Compared with many Western countries Greece has lower prostate cancer mortality and Greek migrant men in Australia have retained their low risk for prostate cancer. Consumption of a traditional Mediterranean diet, rich in bioactive nutrients, may confer protection to Greek migrant men, and this dietary pattern offers a palatable alternative for prevention of this disease.

7: Nutr Res 2007 Dec;27(12):794-801

Phytoene, Phytofluene, and Lycopene from Tomato Powder Differentially Accumulate in Tissues of Male Fisher 344 Rats.

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Tomato product consumption is inversely related to prostate cancer incidence, and lycopene (LYC) has been implicated in reduced prostate cancer risk. The contribution of other tomato carotenoids, phytoene (PE) and phytofluene (PF), towards prostate cancer risk has not been adequately studied. The relative uptake and tissue distribution of tomato carotenoids are not known. We hypothesize that PE and PF are bioavailable from a tomato powder diet or from a purified source and accumulate in androgen-sensitive tissues. In this study, 4 wk old male Fisher 344 rats were pre-fed an AIN-93G powder diet composed of 10% tomato powder containing PE, PF, and LYC (0.015, 0.012, and 0.011 g/kg diet, respectively). After 30 d tomato powder feeding, hepatic PF concentrations (168 +/- 20 nmol/g) were higher than PE or LYC (104 +/- 13 and 104 +/- 13 nmol/g, respectively). In contrast, LYC, followed by PF, had the highest accumulation of the measured carotenoids in the prostate lobes and seminal vesicles. When tomato powder-fed rats received a single oral dose of either approximately 2.7 mg PE or PF, an increase in the dosed carotenoid concentration was observed in all measured

tissues, except the adrenal. Percent increases of PF were greater than that of PE in liver, serum, and adipose (37, 287 and 49% versus 16, 179 and 23%, respectively). Results indicate that the relative tomato carotenoid biodistribution differs in liver and androgen-sensitive tissues, suggesting that minor changes in the number of sequential double bonds in carotenoid structures alter absorption and/or metabolism of tomato carotenoids.

8: J Nutr 2008 Dec;138(12):2367-71

Lycopene biodistribution is altered in 15,15'-carotenoid monooxygenase knockout mice.

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15,15'-carotenoid monooxygenase (CMO I) is generally recognized as the central carotenoid cleavage enzyme responsible for converting provitamin A carotenoids to vitamin A, while having little affinity for nonprovitamin A carotenoids, such as lycopene. To investigate the role of CMO I in carotenoid metabolism, approximately 90-d-old C57BL/6 x 129/SvJ [CMO I wild-type (WT)] and B6;129S6-Bcmo1tm1Dnp [CMO I knockout (KO)] mice were fed a high-fat, moderate vitamin A, cholesterol-containing diet supplemented with 150 mg/kg diet of beta-carotene, lycopene, or placebo beadlets for 60 d (n = 12-14). CMO I KO mice fed lycopene (Lyc-KO) exhibited significant decreases in hepatic, spleen, and thymus lycopene concentrations and significant increases in prostate, seminal vesicles, testes, and brain lycopene concentrations compared with WT mice fed lycopene (Lyc-WT). Furthermore, in the serum and all tissues analyzed, excluding the testes, there was a significant increase in the percent lycopene cis isomers in Lyc-KO mice compared with Lyc-WT mice. CMO I KO mice fed beta-carotene (betaC-KO) had significantly lower hepatic vitamin A concentrations (17% of WT mice fed beta-carotene [betaC-WT]). Concordantly, betaC-KO mice had higher serum and tissue beta-carotene concentrations than betaC-WT mice. In addition, phenotypically CMO I KO mice had significantly higher final body weights and CMO I KO female mice had significantly lower uterus weights than CMO I WT mice. In conclusion, CMO I KO mice fed low levels of vitamin A have altered lycopene biodistribution and isomer patterns and do not cleave beta-carotene to vitamin A at appreciable levels.

9: Arch Biochem Biophys 2008 Nov;

Are the health attributes of lycopene related to its antioxidant function?

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A variety of epidemiological trials have suggested that higher intake of lycopene-containing foods (primarily tomato products) or blood lycopene concentrations are associated with decreased cardiovascular disease and prostate cancer risk. Of the carotenoids tested, lycopene has been demonstrated to be the most potent in vitro antioxidant leading many

researchers to conclude that the antioxidant properties of lycopene are responsible for disease prevention. In our review of human and animal trials with lycopene, or lycopene-containing extracts, there is limited support for the in vivo antioxidant function for lycopene. Moreover, tissue levels of lycopene appear to be too low to play a meaningful antioxidant role. We conclude that there is an overall shortage of supportive evidence for the "antioxidant hypothesis" as lycopene's major in vivo mechanism of action. Our laboratory has postulated that metabolic products of lycopene, the lycopenoids, may be responsible for some of lycopene's reported bioactivity.

10: J Urol 2008 Dec;180(6):2314-21; discussion 2721-2

Diet and dietary supplement intervention trials for the prevention of prostate cancer recurrence: a review of the randomized controlled trial evidence.

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PURPOSE: We review the effect of diet and dietary supplement interventions on prostate cancer progression, recurrence and survival. MATERIALS AND METHODS: A literature search was conducted in MEDLINE, EMBASE and CINAHL to identify diet and dietary supplement intervention studies in men with prostate cancer using prostate specific antigen or prostate specific antigen doubling time as a surrogate serum biomarker of prostate cancer recurrence and/or survival. RESULTS: Of the 32 studies identified 9 (28%) were randomized controlled trials and the focus of this review. In these studies men had confirmed prostate cancer and elevated or increasing prostate specific antigen. Only 1 trial included men with metastatic disease. When body mass index was reported, men were overweight or obese. A significant decrease in prostate specific antigen was observed in some studies using a low fat vegan diet, soy beverage or lycopene supplement. While not often reported as an end point, a significant increase in prostate specific antigen doubling time was observed in a study on lycopene supplementation. In only 1 randomized controlled trial in men undergoing orchiectomy was a survival end point of fewer deaths with lycopene supplementation reported. CONCLUSIONS: A limited number of randomized controlled trials were identified in which diet and dietary supplement interventions appeared to slow disease progression in men with prostate cancer, although results vary. Studies were limited by reliance on the surrogate biomarker prostate specific antigen, sample size and study duration. Well designed trials are warranted to expand knowledge, replicate findings and further assess the impact of diet and dietary supplement interventions on recurrence and treatment associated morbidities.

11: Carcinogenesis 2008 Dec;29(12):2335-40

Manganese superoxide dismutase (MnSOD) gene polymorphism, interactions with carotenoid levels and prostate cancer risk.

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BACKGROUND: The manganese superoxide dismutase (MnSOD) gene encodes an antioxidant enzyme (SOD2) that may protect cells from oxidative damage. The MnSOD allele with Val as amino acid 16 encodes a protein that has 30-40% lower activity compared with the MnSOD Ala variant, hence possibly increasing susceptibility to oxidative stress. On the other hand, some epidemiologic studies suggest that the Ala allele is associated with a higher risk of cancer, including prostate cancer. METHODS: We conducted a nested case-control study in the Health Professionals Follow-up Study with 612 incident prostate cancer cases and 612 matched controls to investigate the role of the MnSOD gene Ala16Val polymorphism and its joint association with plasma carotenoid concentrations in relation to risk of total prostate cancer and aggressive prostate cancer (advanced stage or Gleason sum > or =7). RESULTS: The allele frequencies in the controls were 49.8% for Ala and 50.2% for Val. No association was found between the MnSOD genotype and risk of total and aggressive prostate cancer. Furthermore, no statistically significant interaction was observed between the MnSOD genotype and any of the plasma carotenoids in relation to risk of total and aggressive prostate cancer. In analyses in which we combined data from plasma and dietary carotenoids and created a quintile score to reflect long-term carotenoid status, a 3-fold [95% confidence interval: 1.37-7.02] increased risk of aggressive prostate cancer was observed among men with the Ala/Ala genotype in the presence of low long-term lycopene status (P-value, test for interaction = 0.02) as compared with men with the Ala/Val+Val/Val genotypes with low long-term lycopene status. CONCLUSION: In this cohort of mainly white men, the MnSOD gene Ala16Val polymorphism was not associated with total or aggressive prostate cancer risk. However, men with the MnSOD Ala/Ala genotype who had low long-term lycopene status had a higher risk of aggressive prostate cancer compared with individuals with the other genotypes. These results are consistent with findings from earlier studies that reported when antioxidant status is low, the MnSOD Ala/Ala genotype may be associated with an increased risk of aggressive prostate cancer.

12: Br J Nutr 2008 Aug;:1-8

Reduced growth and integrin expression of prostate cells cultured with lycopene, vitamin E and fish oil in vitro.

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Integrins are transmembrane proteins that facilitate the interaction of cells with the extracellular environment. They have also been implicated in cancer progression. The effects of nutrients thought to be involved in the prevention of prostate cancer on integrin expression have not been determined. Prostate cancer cell lines representing a range of malignancy from normal (RWPE-1) to highly invasive phenotypes (22Rv1 < LNCaP < PC-3) were cultured with or without lycopene (10 nm), vitamin E (5 mum) or fish oil (100 mum) for 48 h. Growth and integrin (alpha2beta1, alphavbeta3 and alphavbeta5) expression were assessed using Trypan Blue exclusion and monoclonal antibodies combined with flow cytometry. Vitamin E enhanced (P < 0.001) whereas fish oil reduced the growth of all the cell lines tested (P < 0.001). Lycopene had no effect on growth. All the malignant cell lines exhibited lower expression of alpha2beta1 with the addition of lycopene to culture media. Supplemental fish oil reduced alpha2beta1 in most invasive cell lines (LNCaP and PC-3). Each nutrient at physiological levels reduced

integrins alphavbeta3 and alphavbeta5 in most invasive cell lines (PC-3). The results suggest that integrins may represent an additional target of bioactive nutrients and that the effects of nutrients may be dependent on the type of cell line used.

13: Arch Ital Urol Androl 2008 Jun;80(2):65-78

Activity of Serenoa repens, lycopene and selenium on prostatic disease: evidences and hypotheses.

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An increasing number of preclinical data, epidemiological evidences and clinical trials point to a potential role of natural compounds like herbal extracts, carotenoids and specific metals in the prevention and/or treatment of different prostate conditions, like hyperplasia, inflammation, cancer. The present article reviews some of the major and most recent findings on the therapeutic properties of three of the most widely used compounds, i.e. Serenoa repens, lycopene and selenium. Although the mechanism of action of these compounds ought to be further characterized by focused investigation, it appears that a common feature of these agents may be a dual activity on proliferative disorders as well as on inflammatory conditions at the level of the prostate gland.

14: Eur J Cancer Care (Engl) 2008 Sep;17(5):492-9

The use of complementary therapy by men with prostate cancer in the UK.

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The study aims were to determine the use of complementary therapies (CT) by men with prostate cancer, and to explore factors influencing CT use and attitudes toward CT use. A cross-sectional survey design was used in which a postal questionnaire was mailed to an eligible sample of 405 patients with prostate cancer receiving outpatient treatment in a London teaching hospital. The primary outcomes were the prevalence of CT use and the relationship between CT use and mental health status. Two hundred and ninety-four patients (73%) responded, of whom 25% were using CT. The most frequently used CTs were vitamins, low-fat diets, lycopene and green tea. Multivariate analyses revealed no differences in mental health scores between CT users and non-users. CT users were younger (OR 0.93, 95% CI 0.89-0.97) and were more likely to be receiving conservative management in the form of 'active surveillance' (OR 5.23, 95% CI 1.78-15.41) compared with non-users. Over half of the participants (55%) wanted to learn more about CT. Forty-three per cent of CT users had not informed any doctor about their CT use. Clinicians need to be aware of the prevalence of CT use amongst patients with prostate cancer, considering the potential harm that could be caused by interactions with conventional treatments.

15: Int J Food Sci Nutr 2008 Apr;:1-16

Tangerine tomatoes increase total and tetra-cis-lycopene isomer concentrations more than red tomatoes in healthy adult humans.

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Lycopene, or the foods that contain it, may prevent prostate cancer. Studies suggest that some cis-lycopene isomers are more bioavailable than the trans-lycopene isomer. We hypothesized that tangerine tomatoes, which predominantly contain the tetra-cis isomer, should be a good source of bioavailable lycopene. We fed lunches containing 300 g tangerine or red tomato sauce per day to 21 healthy adults in a double-blind crossover design. We collected blood at baseline and after each treatment and washout period. We measured tetra-cis, other cis, and trans lycopene, as well as other carotenoids, by reversed-phase high-performance liquid chromatography. Both tomato sauces increased lycopene concentrations in blood, but the tangerine tomato sauce caused a greater increase of total and tetra-cis-lycopene. The cis isomer(s) may also have facilitated absorption of the trans-lycopene isomer. Indices of oxidative damage decreased as serum lycopene concentrations increased. Our results suggest that total lycopene concentrations can be increased by substituting tetra-cis-lycopene-rich tangerine tomatoes for common red tomatoes in the diet.

16: Cancer Lett 2008 Oct;269(2):339-51

Multitargeted therapy of cancer by lycopene.

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Lycopene (psi,psi-carotene) is the most abundant carotenoid in tomatoes and is the red pigment of not only tomatoes but also rosehips, watermelon, papaya, pink grapefruit, and guava. Unlike beta-carotene, lycopene lacks a beta-ionone ring and therefore has no pro-vitamin A activity. However, the 11 conjugated and two non-conjugated double bonds in lycopene make it highly reactive towards oxygen and free radicals, and this anti-oxidant activity probably contributes to its efficacy as a chemoprevention agent. The reactivity of lycopene also explains why it isomerizes rapidly in blood and tissues from the biosynthetic all-trans form to a mixture of cis-isomers. Prospective and retrospective epidemiological studies indicating an inverse relationship between lycopene intake and prostate cancer risk have been supported by in vitro and in vivo experiments showing that oral lycopene is bioavailable, accumulates in prostate tissue and is localized to the nucleus of prostate epithelial cells. In addition to antioxidant activity, in vitro experiments indicate other mechanisms of chemoprevention by lycopene including induction of apoptosis and antiproliferation in cancer cells, anti-metastatic activity, and the upregulation of the antioxidant response element leading to the synthesis of cytoprotective enzymes. Lycopene is a substrate for carotene-9',10'-monooxygenase (CMO2) and can be converted to apo-10'-carotenal. Although Phase I and II studies

have been published that establish the safety of lycopene supplementation, carefully designed and adequately powered clinical studies of lycopene are still needed to confirm its efficacy as a chemoprevention agent.

17: Cancer Res 2008 Jun;68(11):4384-91

Interaction of tomato lycopene and ketosamine against rat prostate tumorigenesis.

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Prior investigations on the beneficial effect of dietary processed tomato products and lycopene on prostate cancer risk suggested that lycopene may require the presence of other constituents to exert its chemopreventive potential. We investigated whether ketosamines, a group of carbohydrate derivatives present in dehydrated tomato products, may interact with lycopene against prostate tumorigenesis. One ketosamine, FruHis, strongly synergized with lycopene against proliferation of the highly metastatic rat prostate adenocarcinoma MAT-LyLu cell line in vitro. The FruHis/lycopene combination significantly inhibited in vivo tumor formation by MAT-LyLu cells in syngeneic Copenhagen rats. Energy-balanced diets, supplemented with tomato paste, tomato powder, or tomato paste plus FruHis, were fed to Wistar-Unilever rats (n = 20 per group) treated with N-nitroso-N-methylurea and testosterone to induce prostate carcinogenesis. Survival from carcinogenesis was lowest in the control group (median survival time, 40 weeks) and highest in the group fed the tomato paste/FruHis diet (51 weeks; P = 0.004, versus control). The proportions of dying rats with macroscopic prostate tumors in the control, tomato paste, tomato powder, and tomato paste/FruHis groups were 63% (12 of 19), 39% (5 of 13), 43% (6 of 14), and 18% (2 of 11), respectively. FruHis completely blocked DNA oxidative degradation at >250 micromol/L in vitro, whereas neither ascorbate nor phenolic antioxidants from tomato were effective protectors in this assay. FruHis, therefore, may exert tumor-preventive effect through its antioxidant activity and interaction with lycopene.

18: Prostate 2008 Sep;68(12):1307-18

Agents used for chemoprevention of prostate cancer may influence PSA secretion independently of cell growth in the LNCaP model of human prostate cancer progression.

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BACKGROUND: The aim of this study was to evaluate the inhibitory growth effects of different potential chemopreventive agents in vitro and to determine their influence on PSA mRNA and protein expression with an established screening platform. METHODS: LNCaP and C4-2 cells were incubated with genistein, seleno-L-methionine, lycopene, DL-alpha-tocopherol, and trans-beta-carotene at three different concentrations and cell growth was determined by the MTT assay. PSA mRNA expression was assessed by quantitative real-time RT-PCR and secreted PSA protein levels

were quantified by the microparticle enzyme immunoassay. RESULTS: Genistein, seleno-l-methionine and lycopene inhibited LNCaP cell growth, and the proliferation of C4-2 cells was suppressed by seleno-L-methionine and lycopene. PSA mRNA expression was downregulated by genistein in LNCaP but not C4-2 cells. No other compound tested altered PSA mRNA expression. PSA protein expression was downregulated by genistein, seleno-L-methionine, DL-alpha-tocopherol in LNCaP cells. In C4-2 cells only genistein significantly reduced the secretion of PSA protein. CONCLUSIONS: In the LNCaP progression model PSA expression depends on the compound, its concentration and on the hormonal dependence of the cell line used and does not necessarily reflect cell growth or death. Before potential substances are evaluated in clinical trials using PSA as a surrogate end point marker, their effect on PSA mRNA and protein expression has to be considered to correctly assess treatment response by PSA.

19: Nutr Cancer 2008;60(2):145-54

A combination of tomato and soy products for men with recurring prostate cancer and rising prostate specific antigen.

Grainger, Elizabeth M, Schwartz, Steven J, Wang, Shihua, Unlu, Nuray Z, Boileau, Thomas W-M, Ferketich, Amy K, Monk, J Paul, Gong, Michael C, Bahnson, Robert R, DeGroff, Valerie L, Clinton, Steven K

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Tomato and soy products are hypothesized to reduce the risk of prostate cancer or enhance efficacy of therapy. A study was completed to determine if men with active prostate cancer will adhere to a dietary intervention rich in tomato products and a soy protein supplement men (n = 41) with recurrent, asymptomatic prostate cancer were randomized among 2 groups: Group A (n = 20) consumed tomato products (no soy) for Weeks 0 through 4, targeting a minimum of 25 mg of lycopene/day. Group B (n = 21) consumed soy (no tomatoes) for Weeks 0 through 4, providing 40 g of soy protein/day. For Weeks 4 through 8, all men consumed a combined tomato-rich diet and soy supplements. No grade II through IV toxicities were observed. During Weeks 0 through 4, mean daily lycopene intake for Group A was 43 mg (+/- 15 mg) and mean soy intake for Group B was 39 g (+/- 1 g), remaining similar during Weeks 4 through 8. Serum lycopene increased from 0.72 +/- 0.09 micromol/l to 1.21 +/- 0.10 micromol/l ($P < 0.0001$) and urinary isoflavone excretion increased from not detectable to 54.1 +/- 5.7 micromol/l ($P < 0.05$) with 8 wk of diet intervention. Serum prostate-specific antigen decreased between Weeks 0 and 8 for 14 / 41 men (34%). Mean serum vascular endothelial growth factor for the entire group was reduced from 87 to 51 ng/ml ($P < 0.05$) over 8 wk. In conclusion, prostate cancer patients will consume diets rich in tomato products and soy with excellent compliance and bioavailability of phytochemicals. Further studies combining tomato and soy foods to determine efficacy for prostate cancer prevention or management are encouraged.

20: Toxicol In Vitro 2008 Aug;22(5):1297-300

Lycopene has limited effect on cell proliferation in only two of seven human cell lines (both cancerous and noncancerous) in an in vitro system with doses across the physiological range.

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Epidemiological studies have shown a relationship between diets rich in tomato and/or lycopene and a reduction in cancer rates. Several studies reported reductions in proliferation of certain cell lines when treated with lycopene. This study used seven human cell lines to measure the effect of lycopene on cell proliferation across normal human plasma concentrations of lycopene. Seven cell types, cancerous and noncancerous, were treated with lycopene from 0.0001 to 10 microM for 24, 48, and 72 h and counted electronically. Controls and experimental samples were compared using the Mann-Whitney U-test at a 95% confidence level. All cells grew normally and there was no significant difference between any of the controls. The Hep-G2, liver adenocarcinoma cell line, showed a reduction at the high doses after 24 h and the IMR-90, noncancerous lung cell line, showed a reduction at the highest dose after 72 h when compared to the solvent control. The A431, skin carcinoma, DU-145, prostate carcinoma, HS-68, noncancerous skin, A549, lung carcinoma, and HS-578T, breast carcinoma, all showed no reduction in proliferation. This indicated that lycopene at the physiological range does not significantly affect cell proliferation in an in vitro model and requires more careful investigations.

21: J Toxicol Environ Health B Crit Rev 2008 Mar;11(3-4):242-59

Role of hormonal and other factors in human prostate cancer.

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American men have a lifetime risk of about 18% for prostate cancer diagnosis. Large international variations in prostate cancer risks and increased risks among migrants from low- to high-risk countries indicate important roles for environmental factors. Major known risk factors include age, family history, and country/ethnicity. Type 2 diabetes appears to reduce risk, while high birth weight and adult height are linked to increased risk of aggressive prostate cancer. Limited evidence supports an association with a history of sexually transmitted infections. A previous meta-analysis of eight cohort studies indicated no associations with plasma androgen, estrogen, or sex hormone binding globulin (SHBG) levels. However, there were dose-response relationships with baseline plasma testosterone levels in two studies that adjusted for other serum hormones and obesity. Finasteride (a drug that blocks testosterone activation) reduced prostate cancer risk by 25%. Low-frequency genes linked to familial prostate cancer only explain a small fraction of all cases. Sporadic cases were linked to relatively common polymorphisms of genes involved in (1) androgen synthesis, activation, inactivation and excretion, (2) hormone and vitamin D receptors, (3) carcinogen metabolism, and (4) DNA repair. Epidemiologic evidence supports protective roles for dietary selenium, vitamin E, pulses, tomatoes/lycopene, and soy foods, and high plasma 1,25-dihydroxyvitamin D levels. There is inadequate evidence that vegetables, fruit, carotenoids, and vitamins A and C reduce risk and that animal fat, alpha-linoleic acid, meat, coffee, and tea increase risk. Two major cohort studies found dose-response relationships with dietary calcium intake. Total dietary energy intake may enhance risk. Limited evidence supports a protective role for physical activity and elevated risk for farmers and other men with occupational pesticide exposure, particularly to organochlorine compounds

and phenoxy herbicides. There is inadequate evidence for a relationship with alcohol or smoking. Most known or suspected external risk factors may act through hormonal mechanisms, but our review found little supporting evidence, and substantial further research is needed.

22: J Soc Integr Oncol 2008;6(1):29-36

Lycopene in the prevention of prostate cancer.

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Based on the evidence from epidemiologic, animal, and in vitro data and human clinical trials, it is evident that lycopene, a non-provitamin A carotenoid, is a promising agent for prostate cancer chemoprevention. It is also clear that the form of lycopene used (purified versus food sources), dose of lycopene and concomitant use with other carotenoids and antioxidants, duration of exposure, specific target populations, and stage of disease appear to play a major role in determining agonistic or antagonistic effects. Based on our review, there is enough evidence to warrant use of lycopene in phase I and II clinical trials to examine its safety and efficacy as a potential chemopreventive agent for prostate cancer. The objective of this article is to review this evidence from epidemiologic, animal, in vitro, and clinical trials and provide the need and rationale to examine further the role of lycopene for prostate cancer prevention.

23: Carcinogenesis 2008 Apr;29(4):816-23

Lycopene inhibits IGF-I signal transduction and growth in normal prostate epithelial cells by decreasing DHT-modulated IGF-I production in co-cultured reactive stromal cells.

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Prostate stromal and epithelial cell communication is important in prostate functioning and cancer development. Primary human stromal cells from normal prostate stromal cells (PRSC) maintain a smooth muscle phenotype, whereas those from prostate cancer (6S) display reactive and fibroblastic characteristics. Dihydrotestosterone (DHT) stimulates insulin-like growth factor-I (IGF-I) production by 6S but not PSRC cells. Effects of reactive versus normal stroma on normal human prostate epithelial (NPE or PREC) cells are poorly understood. We co-cultured NPE plus 6S or PRSC cells to compare influences of different stromal cells on normal epithelium. Because NPE and PREC cells lose androgen receptor (AR) expression in culture, DHT effects must be modulated by associated stromal cells. When treated with camptothecin (CM), NPE cells, alone and in stromal co-cultures, displayed a dose-dependent increase in DNA fragmentation. NPE/6S co-cultures exhibited reduced CM-induced cell death with exposure to DHT, whereas NPE/PRSC co-cultures exhibited CM-induced cell death regardless of DHT treatment. DHT blocked CM-induced, IGF-I-mediated, NPE death in co-cultured NPE/6S cells

without, but not with, added anti-IGF-I and anti-IGF-R antibodies. Lycopene consumption is inversely related to human prostate cancer risk and inhibits IGF-I and androgen signaling in rat prostate cancer. In this study, lycopene, in dietary concentrations, reversed DHT effects of 6S cells on NPE cell death, decreased 6S cell IGF-I production by reducing AR and beta-catenin nuclear localization and inhibited IGF-I-stimulated NPE and PREC growth, perhaps by attenuating IGF-I's effects on serine phosphorylation of Akt and GSK3beta and tyrosine phosphorylation of GSK3. This study expands the understanding of the preventive mechanisms of lycopene in prostate cancer.

24: Urology 2008 Sep;72(3):633-7

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

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

25: Am J Epidemiol 2008 Apr;167(8):925-34

Dietary patterns, supplement use, and the risk of symptomatic benign prostatic hyperplasia: results from the prostate cancer prevention trial.

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This study examined dietary risk factors for incident benign prostatic hyperplasia (BPH) in 4,770 Prostate Cancer Prevention Trial (1994-2003) placebo-arm participants who were free of BPH at baseline. BPH was assessed over 7 years and was defined as medical or surgical treatment or repeated elevation (>14) on the International Prostate Symptom Score questionnaire. Diet, alcohol, and supplement use were assessed by use of a food frequency questionnaire. There were 876 incident BPH cases (33.6/1,000 person-years). The hazard ratios for the contrasts of the highest to lowest quintiles increased 31% for total fat and 27% for polyunsaturated fat and decreased 15% for protein (all p(trend) < 0.05). The risk was significantly lower in high consumers of alcoholic beverages (0 vs. > or =2/day: hazard ratio (HR) = 0.67) and vegetables (<1 vs. > or =4/day: HR = 0.68) and higher in daily (vs. <1/week) consumers of red meat (HR = 1.38). There were no associations of supplemental antioxidants with risk, and there was weak evidence for associations of lycopene, zinc, and supplemental vitamin D with reduced risk. A diet low in fat and red meat and high in protein and vegetables, as well as regular alcohol consumption, may reduce the risk of symptomatic BPH.

26: J Am Diet Assoc 2008 Feb;108(2):347-56

A very-low-fat vegan diet increases intake of protective dietary factors and decreases intake of pathogenic dietary factors.

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There is increasing evidence that dietary factors in plant-based diets are important in the prevention of chronic disease. This study examined protective (eg, antioxidant vitamins, carotenoids, and fiber) and pathogenic (eg, saturated fatty acids and cholesterol) dietary factors in a very-low-fat vegan diet. Ninety-three early-stage prostate cancer patients participated in a randomized controlled trial and were assigned to a very-low-fat (10% fat) vegan diet supplemented with soy protein and lifestyle changes or to usual care. Three-day food records were collected at baseline (n=42 intervention, n=43 control) and after 1 year (n=37 in each group). Analyses of changes in dietary intake of macronutrients, vitamins, minerals, carotenoids, and isoflavones from baseline to 1 year showed significantly increased intake of most protective dietary factors (eg, fiber increased from a mean of 31 to 59 g/day, lycopene increased from 8,693 to 34,464 mug/day) and significantly decreased intake of most pathogenic dietary factors (eg, saturated fatty acids decreased from 20 to 5 g/day, cholesterol decreased from 200 to 10 mg/day) in the intervention group compared to controls. These results suggest that a very-low-fat vegan diet can be useful in increasing intake of protective nutrients and phytochemicals and minimizing intake of dietary factors implicated in several chronic diseases.

27: BJU Int 2008 May;101(10):1227-31

Dietary modification in patients with prostate cancer on active surveillance: a randomized, multicentre feasibility study.

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OBJECTIVES: To evaluate the feasibility of implementing a diet-based intervention in men with prostate cancer on active surveillance, as changes in diet might potentially inhibit the progression of prostate cancer. PATIENTS AND METHODS: As part of the Men's Eating and Living (MEAL) Study (a multicentre pilot trial of a diet-based intervention for prostate cancer) 43 men aged 50-80 years with prostate cancer and on active surveillance were randomized to receive either telephone-based dietary counselling or standardized, written nutritional information. Telephone counselling targets included increased intakes of vegetables (particularly cruciferous vegetables and tomato products), whole grains, and beans/legumes. Dietary intakes and plasma carotenoid levels were assessed at baseline and at after 6 months. RESULTS: In the intervention arm the mean daily intakes of total vegetables, crucifers and tomato products increased by 71%, 180% and 265%, respectively ($P < 0.05$); in the control arm there were no significant changes in mean intakes of these components. Similarly, in the intervention arm, mean plasma levels of alpha-carotene, beta-carotene, lutein, lycopene and total carotenoids increased by 37%, 32%, 23%, 30% and 25%, respectively ($P < 0.05$); in the control arm there were no significant changes in plasma levels of these components. There were no significant changes in either group in whole grain, beans/legumes, or fat intake. CONCLUSIONS: Telephone-based dietary counselling increases vegetable intake and plasma concentrations of potentially anticarcinogenic carotenoids in men with prostate cancer on active surveillance. These data support the feasibility of implementing clinical trials of diet-based interventions in this population.

28: Asian Pac J Cancer Prev 2007 Jul-Sep;8(3):422-8

The risk factors of prostate cancer: a multicentric case-control study in Iran.

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Prostate cancer (PC), in Iran, is the third most frequently diagnosed visceral cancer among men and the seventh most common underlying cause of cancer mortality. We evaluated the relation between speculated factors and PC risk using data from a multicentric case-control study conducted in Iran from 2005 to 2007 on 130 cases of incident, clinicopathologically confirmed PC, and 75 controls admitted to the same network of hospitals without any malignant disease. Odds ratios (OR) and corresponding 95% confidence intervals (CIs) were estimated using conditional logistic regression models. The risk of PC was increased with aging (OR: 5.35, 95% CI: 2.17-13.19; $P<0.0001$), and with the number of sexual intercourse >or=2 times/week (OR: 3.14, 95% CI: 1.2-8.2; $P=0.02$). One unit elevation in serum estradiol and testosterone concentration was related to increase (OR: 1.04, 95% CI: 1.01-1.06; $P=0.006$) and decrease (OR: 0.79; 95% CI: 0.64-0.96; $P=0.02$) of PC risk, respectively. Cases were less likely to have a history of diabetes (OR: 0.34, 95% CI: 0.12-0.98; $P=0.04$). Increasing in dietary

consumption of lycopene and fat was associated with declined (OR: 0.45, 95% CI: 0.09-2.12) and increased (OR: 2.38, 95% CI: 0.29-19.4) PC development, respectively. Other factors including educational level, marriage status, dietary meat consumption, vasectomy and smoking have not been shown to affect PC risk in the Iranian population. Our study adds further information on the potential risk factors of PC and is the first epidemiologic report from Iran. However, justification of these results requires more well-designed studies with a larger number of participants.

29: J Nutr 2008 Jan;138(1):49-53

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.

30: Antioxid Redox Signal 2008 Mar;10(3):475-510

Cancer chemoprevention through dietary antioxidants: progress and promise.

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It is estimated that nearly one-third of all cancer deaths in the United States could be prevented through appropriate dietary modification. Various dietary antioxidants have shown considerable promise as effective agents for cancer prevention by reducing oxidative stress which has been implicated in the development of many diseases, including cancer.

Therefore, for reducing the incidence of cancer, modifications in dietary habits, especially by increasing consumption of fruits and vegetables rich in antioxidants, are increasingly advocated. Accumulating research evidence suggests that many dietary factors may be used alone or in combination with traditional chemotherapeutic agents to prevent the occurrence of cancer, their metastatic spread, or even to treat cancer. The reduced cancer risk and lack of toxicity associated with high intake of fruits and vegetables suggest that specific concentrations of antioxidant agents from these dietary sources may produce cancer chemopreventive effects without causing significant levels of toxicity. This review presents an extensive analysis of the key findings from studies on the effects of dietary antioxidants such as tea polyphenols, curcumin, genistein, resveratrol, lycopene, pomegranate, and lupeol against cancers of the skin, prostate, breast, lung, and liver. This research is also leading to the identification of novel cancer drug targets.

31: Expert Rev Anticancer Ther 2008 Jan;8(1):43-50

Diet and prostate cancer risk reduction.

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Prostate cancer is the most commonly diagnosed malignancy in males. The current body of literature supports the role of nutritional products in the reduction of prostate cancer. This review critically addresses the natural products with the greatest potential to reduce the risk of prostate cancer, including lycopene, vitamin E, selenium, vitamin D, soy and green tea. The toxicities of the dietary products are addressed. The direction of future studies lies in clarifying the effects of these products and exploring the biological mechanisms responsible for the prevention of prostate cancer.

32: Wei Sheng Yan Jiu 2007 Sep;36(5):575-8

[Effect of lycopene on proliferation and cell cycle of hormone refractory prostate cancer PC-3 cell line]

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OBJECTIVE: To investigate the effects of lycopene on proliferation of human prostate cancer cell line PC-3 and explore its effecting mechanism. METHODS: The proliferation of PC-3 cells were analyzed by MTT and H3-TdR incorporation. The effects of cell cycle and apoptosis of synchronized cells were observed through flow cytometry. RT-PCR methods were used to explore the mRNA expression level of cyclin D1, bcl-2, bax. RESULTS: The growth and DNA synthesis of PC-3 cell were inhibited with the lycopene concentration increased, and lycopene also could change the cell cycle distribution, i. e. increasing the proportion of G0/G1 phase and descending the proportion of S and G2/M phase, and induce the apoptosis. RT-PCR analysis showed that the mRNA expression level of cyclin D1 and bcl-2 were down regulated, while the level of bax was up regulated. CONCLUSION: Lycopene can induce apoptosis of PC-3, change the cell cycle distribution

and downregulate the expression of cyclin D1 and bcl-2 and upregulate the expression of bax and then restrain cell proliferation.

33: Clin Interv Aging 2006;1(1):81-91

Vitamins in aging, health, and longevity.

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Evidence of epidemiological associations of vitamins and disease states have been found for nine vitamins. In observational studies, people with a high intake of antioxidant vitamins by regular diet or as food supplements generally have a lower risk of major chronic disease, such as myocardial infarction or stroke, than people who are low consumers of antioxidant vitamins. Prospectively, folate appears to reduce the incidence of neural tube defects. Vitamin D is associated with a decreased occurrence of fractures when taken with calcium. Zinc, betacarotene, and vitamin E appear to slow the progression of macular degeneration, but do not reduce the incidence. Vitamin E and lycopene may decrease the risk of prostate cancer. In other randomized controlled trials, the apparent beneficial results of a high intake of antioxidant vitamins seen in observational studies have not been confirmed. There is increasing concern from these trials that pharmacological supplementation of vitamins may be associated with a higher mortality risk.

35: Cancer Epidemiol Biomarkers Prev 2007 Nov;16(11):2193-203

Chemoprevention of prostate cancer through dietary agents: progress and promise.

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Prostate cancer (CaP) is second only to lung cancer as the cause of cancer-related deaths in American men and is responsible for over 29,000 deaths per year. One promising approach to reduce the incidence of CaP is through chemoprevention, which has been recognized as a plausible and cost-effective approach to reduce cancer morbidity and mortality by inhibiting precancerous events before the occurrence of clinical disease. Indeed, CaP is an ideal candidate disease for chemoprevention because it is typically diagnosed in the elderly population with a relatively slower rate of growth and progression, and therefore, even a modest delay in the development of cancer, achieved through pharmacologic or nutritional intervention, could result in substantial reduction in the incidence of clinically detectable disease. In this review, we have summarized the recent investigations and mechanistic studies on CaP chemoprevention using dietary agents, such as selenium, vitamins D and E, lycopene, phytoestrogens, flavonoids, and green tea polyphenols. Well-designed trials are required to delineate the potential clinical usefulness of these agents through issues, such as determining the optimal period and route of administration, systemic bioavailability, optimal dosing and toxicity of the agent, and single or combinatorial approach. It is hoped that, combining the knowledge based on agents with targets, effective approaches for CaP chemoprevention can be established.

36: Biochem Biophys Res Commun 2007 Dec;364(3):578-82

Serum from rats fed red or yellow tomatoes induces Connexin43 expression independently from lycopene in a prostate cancer cell line.

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Epidemiologic studies suggested a protective effect of tomatoes against prostate cancer brought by lycopene, a carotenoid conferring the red colour of tomatoes. However, intervention studies on patients have shown that the preventive effect of tomato was more potent than that of lycopene. The aim of this study was to compare the effects of red tomato, yellow tomato (devoid of lycopene) and lycopene on Connexin43 (Cx43) expression, a protein regulating cell growth, on a prostate cancer cell line expressing the androgen receptor. Cells were incubated with serum from rats fed a control diet (CS) or control diet supplemented with red tomato (RTS), yellow tomato (YTS) or lycopene beadlets (LBS). After exposure of the cells to RTS or YTS for 48h, the expression of Cx43 was significantly increased compared to cells exposed to CS. Whereas LBS effect was not significantly different. The cells incubated with RTS and LBS had similar levels of lycopene, while those incubated with YTS contained no lycopene. These data first show that serum nutritionally enriched with red and yellow tomatoes could up-regulate Cx43 turn-over in PC3AR cells independently from lycopene level. Within the physiological approach used in the present study, it can be concluded that compounds other than lycopene contribute to the preventive effect of tomatoes.

37: Nutr Cancer 2007;59(1):46-53

Plasma carotenoids and prostate cancer: a population-based case-control study in Arkansas.

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Carotenoids possess antioxidant properties and thus may protect against prostate cancer. Epidemiological studies of dietary carotenoids and this malignancy were inconsistent, partially due to dietary assessment error. In this study, we aimed to investigate the relation between plasma concentrations of carotenoids and the risk of prostate cancer in a population-based case-control study in Arkansas. Cases (n = 193) were men with prostate cancer diagnosed in 3 major hospitals, and controls (n = 197) were matched to cases by age, race, and county of residence. After adjustment for confounders, plasma levels of lycopene, lutein/zeaxanthin, and beta-cryptoxanthin were inversely associated with prostate cancer risk. Subjects in the highest quartile of plasma lycopene (513.7 microg/l) had a 55% lower risk of prostate cancer than those in the lowest quartile (140.5 microg/l; P trend = 0.042). No apparent association was observed for plasma

alpha-carotene and beta-carotene. Further adjustment for the other 4 carotenoids did not materially alter the risk estimates for plasma lycopene, lutein/zeaxanthin, and beta-cryptoxanthin but appeared to result in an elevated risk with high levels of plasma alpha-carotene and beta-carotene. The results of all analyses did not vary substantially by age, race, and smoking status. This study added to the emerging evidence that high circulating levels of lycopene, lutein/zeaxanthin, and beta-cryptoxanthin are associated with a low risk of prostate cancer.

38: Nutr Cancer 2007;59(1):1-7

Lycopene and soy isoflavones in the treatment of prostate cancer.

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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.

39: Int J Antimicrob Agents 2008 Feb;31 Suppl 1:S102-7

Synergistic effect between lycopene and ciprofloxacin on a chronic bacterial prostatitis rat model.

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Traditionally, long-term antibiotic therapy has been the gold standard treatment for chronic bacterial prostatitis (CBP). However, the treatment outcome is not ideal and long-term administration of antibiotics can result in adverse effects and bacterial resistance. For these reasons, both patients and physicians are dissatisfied with the management of this disease and there is interest in phytotherapy and other alternative therapies. Lycopene, an extract of tomatoes, has been reported to have an anti-inflammatory effect via an antioxidative function. To evaluate the therapeutic effect of lycopene on CBP, we developed a CBP rat model treated with ciprofloxacin or lycopene, or both. After 2 weeks of treatment, results of microbiological cultures of the prostate and urine as well as histological findings of the prostate were analysed. The ciprofloxacin group and the lycopene/ciprofloxacin group showed a statistically significant decrease in bacterial growth and improvement in prostatic inflammation compared with the control group. The lycopene/ciprofloxacin group also showed a statistically significant decrease in bacterial growth and improvement in prostatic inflammation compared with the ciprofloxacin group. These results suggest that lycopene may have an additional (synergistic) effect with ciprofloxacin in the treatment of CBP.

40: Cancer 2007 Nov;110(9):1889-99

Prostate cancer prevention: past, present, and future.

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Prostate cancer is the most common male malignancy and the second or third leading cause of cancer death among men in the West. The descriptive epidemiology of prostate cancer suggests that it is a preventable disease. Prevention has the theoretical advantage of not only saving lives, but also reduce the morbidity of radical prostate cancer therapy. This article reviews the past, present, and future of prostate cancer prevention. In particular, the evidence and scientific data of a variety of prevention strategies are reviewed. Strategies reviewed include dietary fat reduction and supplementation with vitamins D and E, and selenium. Dietary intake of soy, green tea, and tomato-rich products (lycopene) are also reviewed. Data regarding pharmacological intervention with cyclo-oxygenease inhibitors, antiestrogens, and in particular 5-alpha reductase inhibitors are reviewed. The results of the Prostate Cancer Prevention Trial including the controversy surrounding higher-grade cancers among men randomized to finasteride are also summarized. Finally, a variety of trial designs as well as a roster of current phase 2 trials are presented. Probably no cancer is being investigated more thoroughly in the context of prevention as prostate cancer in 2007. Definitive answers to pivotal phase 3 trials will be available in the coming 2 to 7 years.

41: Am J Clin Nutr 2007 Sep;86(3):672-81

Plasma carotenoids, retinol, and tocopherols and the risk of prostate cancer in the European Prospective Investigation into Cancer and Nutrition study.

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BACKGROUND: Previous studies suggest that high plasma concentrations of carotenoids, retinol, or tocopherols may reduce the risk of prostate cancer. OBJECTIVE: We aimed to examine the associations between plasma concentrations of 7 carotenoids, retinol, alpha-tocopherol, and gamma-tocopherol and prostate cancer risk. DESIGN: A total of 137,001 men in 8 European countries participated. After a mean of 6 y, 966 incident cases of prostate cancer with plasma were available. A total of 1064 control subjects were selected and were matched for study center, age, and date of recruitment. The relative risk of prostate cancer was estimated by conditional logistic regression, which was adjusted for smoking status, alcohol intake, body mass index, marital status, physical activity, and education level. RESULTS: Overall, none of the micronutrients examined were significantly associated with prostate cancer risk. For lycopene and the sum of carotenoids, there was evidence of heterogeneity between the associations with risks of localized and advanced disease. These carotenoids were not associated with the risk of localized disease but were inversely associated with the risk of advanced disease. The risk of advanced disease for men in the highest fifth of plasma concentrations compared with men in the lowest fifth was 0.40 (95% CI: 0.19, 0.88) for lycopene and 0.35 (95% CI: 0.17, 0.78) for the sum of carotenoids. CONCLUSIONS: We observed no associations between plasma concentrations of carotenoids, retinol, or tocopherols and overall prostate cancer risk. The inverse associations of lycopene and the sum of carotenoids with the risk of advanced disease may involve a protective effect, an association of dietary choice with delayed detection of prostate cancer, reverse causality, or other factors.

42: J Urol 2007 Sep;178(3 Pt 2):S9-S13

Chemoprevention of prostate cancer: agents and study designs.

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PURPOSE: With the completion of the Prostate Cancer Prevention Trial and the ongoing performance of several additional large-scale prostate cancer prevention trials interest in this intervention has increased. We review promising agents for prostate cancer prevention, clinical trial designs and how these agents may be used clinically. MATERIALS AND METHODS: We reviewed current and completed randomized chemoprevention trials for prostate cancer

as well as the most promising agents for which evidence suggests that a decreased prostate cancer risk may result from their use. RESULTS: Evidence suggests that lycopene, decreased dietary fat, antioxidants such as alpha-tocopherol and selenium, nonsteroidal anti-inflammatory drugs and selective estrogen receptor modulators such as toremifene and 5alpha-reductase inhibitors may prove useful for decreasing the risk of prostate cancer in a man. Ongoing studies are examining these agents in the 3 general scenarios of 1) general population studies (finasteride, alpha-tocopherol and selenium), 2) increased prostate specific antigen with negative biopsy (dutasteride) and 3) prostatic intraepithelial neoplasia (toremifene and selenium). CONCLUSIONS: There are many agents that may decrease the risk of prostate cancer. It requires careful study of the agents in specific populations to determine whether risk is reduced, the magnitude of the risk reduction and the spectrum of side effects associated with the agent. Physicians caring for men entering the range of age of prostate cancer risk must be aware of these preventive opportunities.

43: Nutr Cancer 2007;58(2):171-7

Lycopene and lutein inhibit proliferation in rat prostate carcinoma cells.

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Consumption of lycopene, a carotenoid without provitamin A activity, has been associated with a lower risk of prostate and breast cancer. Lutein is another carotenoid that may be associated with a reduced risk of age-related macular degeneration, the leading cause of blindness in adults 65 years of age and older. Bioactive compounds such as lycopene and lutein, derived from natural plant sources, have been shown to act at low substrate levels through the action of intrinsic cytokines and growth factors and their receptors within tissues, particularly those of the fibroblast growth factor and transforming growth factor beta families. The effects of grapefruit-derived and commercial lycopene and lutein preparations on androgen independent cultured malignant type II tumor cells [Dunning R3327AT3 or AT3 cells (androgen-responsive, slow-growing tumor cells with well developed epithelium and stroma)] were compared to their benign parent type I tumor epithelial cells (DTE). Results demonstrated that both lycopene, in an alpha -cyclodextrin water soluble carrier, and lutein inhibited malignant AT3 cells in a concentration and time-dependent manner. No such effect was observed when benign DTE cells were examined, demonstrating selective inhibition of extremely malignant AT3 prostate cancer cells relative to their benign parent. Lutein demonstrated a similar but slightly diminished response as lycopene. When cells were treated with cocktails of lycopene and lutein, no synergistic or additive effect occurred. These studies are consistent with epidemiological studies that show inverse relationships of these carotenoids with prostate cancer.

44: J Natl Cancer Inst 2007 Jul;99(14):1074-85

The U.S. Food and Drug Administration's evidence-based review for qualified health claims: tomatoes, lycopene, and cancer.

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Several studies have reported an inverse association between tomato and/or lycopene intake and the risk of some types of cancer. In 2004, the U.S. Food and Drug Administration (FDA) received two petitions for qualified health claims regarding tomatoes, lycopene, and the risk reduction for some forms of cancer. Health claims that characterize the relationship between a food or food component and a disease or health-related condition require premarket approval by FDA to be included on the labels of conventional foods and dietary supplements. Here we describe FDA's review of the scientific data for tomato and/or lycopene intake with respect to risk reduction for certain forms of cancer. The FDA found no credible evidence to support an association between lycopene intake and a reduced risk of prostate, lung, colorectal, gastric, breast, ovarian, endometrial, or pancreatic cancer. The FDA also found no credible evidence for an association between tomato consumption and a reduced risk of lung, colorectal, breast, cervical, or endometrial cancer. The FDA found very limited evidence to support an association between tomato consumption and reduced risks of prostate, ovarian, gastric, and pancreatic cancers.

46: Nutr Cancer 2007;57(2):130-7

A randomized trial of lycopene supplementation in Tobago men with high prostate cancer risk.

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This unblinded, randomized, Phase I clinical trial was conducted to determine whether lycopene supplementation lowered serum prostate specific antigen (PSA), surrogate endpoint for prostate cancer initiation or progression, in men with elevated prostate cancer risk. Afro-Caribbean men (n=81) with high-grade prostatic intraepithelial neoplasia, atypical foci or repeated non-cancerous biopsies, ascertained in a population-based screening program, were randomized to four months intervention with 30 mg/day lycopene (Lyc-O-Mato) plus a multivitamin, or to multivitamin, only. Serum PSA and lycopene were compared at randomization, 1, and 4 mo using two-sided chi2 and t-tests for independent samples. Treatment groups were similar at baseline. Serum lycopene levels approximately doubled in the lycopene intervention group. Serum PSA declined during the first month of treatment, but returned to randomization level by month 4. The PSA response was nearly identical in both treatment groups. No adverse effects attributed to lycopene supplementation were documented. We conclude that the PSA lowering response to antioxidant supplementation observed in previous 3-wk studies in men awaiting prostatectomy may have been a transient response, perhaps not specific to lycopene. Lowering of serum PSA may not be an appropriate endpoint for the long-term studies needed to evaluate lycopene supplementation for reducing prostate cancer initiation or progression.

47: Cancer Epidemiol Biomarkers Prev 2007 May;16(5):962-8

Serum lycopene, other carotenoids, and prostate cancer risk: a nested case-control study in the prostate, lung, colorectal, and ovarian cancer screening trial.

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BACKGROUND: Reports from several studies have suggested that carotenoids, and in particular lycopene, could be prostate cancer-preventive agents. This has stimulated extensive laboratory and clinical research, as well as much commercial and public enthusiasm. However, the epidemiologic evidence remains inconclusive. MATERIALS AND METHODS: We investigated the association between prediagnostic serum carotenoids (lycopene, alpha-carotene, beta-carotene, beta-cryptoxanthin, lutein, and zeaxanthin) and risk of prostate cancer in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, a multicenter study designed to examine methods of early detection and risk factors for cancer. The study included 692 incident prostate cancer cases, diagnosed 1 to 8 years after study entry, including 270 aggressive cases, with regional or distant stage (n = 90) or Gleason score >or=7 (n = 235), and 844 randomly selected, matched controls. As study participants were selected from those who were assigned to annual standardized screening for prostate cancer, results are unlikely to be biased by differential screening, a circumstance that is difficult to attain under non-trial conditions. RESULTS: No association was observed between serum lycopene and total prostate cancer [odds ratios (OR), 1.14; 95% confidence intervals (95% CI), 0.82-1.58 for highest versus lowest quintile; P for trend, 0.28] or aggressive prostate cancer (OR, 0.99; 95% CI, 0.62-1.57 for highest versus lowest quintile; P for trend, 0.433). beta-Carotene was associated with an increased risk of aggressive prostate cancer (OR, 1.67; 95% CI, 1.03-2.72 for highest versus lowest quintile; P for trend, 0.13); in particular, regional or distant stage disease (OR, 3.16; 95% CI, 1.37-7.31 for highest versus lowest quintile; P for trend, 0.02); other carotenoids were not associated with risk. CONCLUSION: In this large prospective study, high serum beta-carotene concentrations were associated with increased risk for aggressive, clinically relevant prostate cancer. Lycopene and other carotenoids were unrelated to prostate cancer. Consistent with other recent publications, these results suggest that lycopene or tomato-based regimens will not be effective for prostate cancer prevention.

48: Biomed Pharmacother 2007 Jul;61(6):366-9

Lycopene affects proliferation and apoptosis of four malignant cell lines.

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The beneficial effect of lycopene from tomatoes on a variety of chronic diseases and particularly its association with decreased incidence of prostate and breast cancer seems to be well established. The aim of the study was to examine its anti-proliferative and apoptotic effect on other malignant cell lines. Cells of the following lines were incubated with 1.0,

2.0, and 4.0microM of lycopene: human colon carcinoma (HuCC), B chronic lymphocytic leukemia (EHEB), human erythroleukemia (K562) and Raji, a prototype of Burkitt lymphoma cell line. The results showed that lycopene exerted a significant dose-dependent effect on the proliferation capacity of K562, Raji and HuCC lines, whereas this effect was observed in EHEB cells only with the highest dose used in the study. Increased apoptotic rate was found after incubation of HuCC cells with 2.0 and 4.0microM of lycopene and in Raji cells following incubation with 2.0microM. The findings point out that the anti-proliferative effect of lycopene on tumor cells and its effect on the apoptotic rate depends on its dosage and on the type of the malignant cells.

49: In Vivo 2007 Mar-Apr;21(2):189-204

Review. Facts and fiction of phytotherapy for prostate cancer: a critical assessment of preclinical and clinical data.

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The objective of this work was to substantially review all preclinical and clinical data on phytochemicals, such as genistein, lycopene, curcumin, epigallocatechin-gallate, and resveratrol, in terms of their effects as a potential treatment of prostate cancer. It is known, that prostate cancer patients increasingly use complementary and alternative medicines in the hope of preventing or curing cancer. The preclinical data for the phytochemicals presented in this review show a remarkable efficacy against prostate cancer cells in vitro, with molecular targets ranging from cell cycle regulation to induction of apoptosis. In addition, well-conducted animal experiments support the belief that these substances might have a clinical activity on human cancer. However, it is impossible to make definite statements or conclusions on the clinical efficacy in cancer patients because of the great variability and differences of the study designs, small patient numbers, short treatment duration and lack of a standardised drug formulation. Although some results from these clinical studies seem encouraging, reliable or long-term data on tumor recurrence, disease progression and survival are unknown. At present, there is no convincing clinical proof or evidence that the cited phythochemicals might be used in an attempt to cure cancer of the prostate.

50: Asia Pac J Clin Nutr 2007;16 Suppl 1:453-7

Tea and lycopene protect against prostate cancer.

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Prostate cancer is the most common male cancer in developed countries and is increasing in the developing world. Its long latency and geographical variation suggest the possibility of prevention or postponement of onset by dietary modification. To investigate the possible joint effect of lycopene and green tea on prostate cancer risk, a case-control study was conducted in Hangzhou, China, with 130 prostate cancer patients and 274 hospital controls. Information on tea and dietary intakes, and possible confounders

was collected using a structured questionnaire. The risk of prostate cancer for the intake of tea and lycopene and their joint effect were assessed using multivariate logistic regression models. Prostate cancer risk was reduced with increased consumption of green tea. The protective effect of green tea was significant (odds ratio 0.14, 95% CI: 0.06–0.35) for the highest quartile relative to the lowest after adjusting for total vegetables and fruits intakes and other potential confounding factors. Intakes of vegetables and fruits rich in lycopene were also inversely associated with prostate cancer risk (odds ratio 0.18, 95% CI 0.08–0.39). Interaction analysis showed that the protective effect from tea and lycopene consumption was synergistic ($p<0.01$). This study suggests that habitual drinking tea and intakes of vegetables and fruits rich in lycopene could lead to a reduced risk of prostate cancer in Chinese men. Together they have a stronger preventive effect than either component taken separately. This is the first epidemiological study to investigate the joint effect between tea drinking and lycopene intake.