





PROSTATE CANCER (CHEMOTHERAPY)

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Major advantages of "early" administration of endocrine combination therapy in advanced prostate cancer.

Labrie F, Dupont A, Cusan L, Gomez JL, Diamond P
Endocrine Research Clinic, CHUL Research Center, Quebec City, Quebec, Canada.
Clin Invest Med 1993 Dec;16(6):493-8

Combination therapy with the antiandrogen flutamide and the luteinizing hormone-releasing hormone (LHRH) agonist [D-Trp6, des-Gly-NH2(10)] LHRH ethylamide or orchiectomy was administered to 268 patients with previously untreated metastatic stage D2 prostate cancer for an average of 1,191 d (3.26 y). Only 17 of the 268 evaluable patients (6.5%) showed no objective positive response to the combination therapy assessed according to the National Prostatic Cancer Project objective criteria of response. The median duration of the disease-free response was 2.23 y and median overall survival was 3.58 y. The median survival for patients with only 1-5 bone metastases was not yet reached at 8 y, but for patients with 6-10 bone lesions, 11-40 bone lesions, and multiple bone metastases (superscan), median survival was markedly reduced to 3.56, 2.36, and 1.76 y, respectively. Analysis of patients according to general symptomatology, pain, and performance status showed median survivals of 5.47, 2.71, and 2.1 y for minimal, moderate, and severe symptoms, respectively. The present data demonstrate that administration of combination therapy to stage D2 prostate cancer patients having 1-5 bone metastases adds a minimum of 4.4 y of good quality life compared with patients whose disease is slightly more advanced. Our findings clearly demonstrate the major importance of starting combination therapy as soon as possible after diagnosis of metastatic prostatic cancer.

Maximal androgen blockade: final analysis of EORTC phase III trial 30853. EORTC Genito-Urinary Tract Cancer Cooperative Group and the EORTC Data Center.

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Department of Urology, A.Z. Middelheim, Antwerp, Belgium.
Eur Urol 1998;33(2):144-51

OBJECTIVES: This prospective, randomized phase III study was initiated to compare the efficacy and side effects of bilateral orchiectomy versus a combination of a luteinizing hormone-releasing hormone agonist depot formulation, goserelin acetate (3.6 mg s.c. once every 4 weeks) and flutamide (250 mg 3 x daily) in patients with metastatic prostate cancer.

METHODS: Relative treatment efficacy was assessed by comparing the two treatment groups with respect to response, time to first progression, progression-free survival, duration of survival and time to death due to malignant disease.

RESULTS: There was a difference in response only with respect to a more frequent decrease to normal of the serum prostate acid phosphatase in patients assigned to maximal androgen blockade treatment. Additionally, maximal androgen blockade treatment showed significantly better results for duration of survival ($p = 0.04$), time to death due to malignant disease ($p = 0.008$), time to first progression ($p = 0.009$) and progression-free survival ($p = 0.02$). The most frequent side effects for both treatments included hot flushes and gynaecomastia.

CONCLUSIONS: Increased time to progression and duration of survival is achieved by the combination of flutamide and goserelin when compared to bilateral orchiectomy.

Treatment with finasteride following radical prostatectomy for prostate cancer.

Andriole G, Lieber M, Smith J, Soloway M, Schroeder F, Kadmon D, DeKernion J, Rajfer J, Boake R, Crawford D, et al
Merck Research Laboratories, Rahway, New Jersey.
Urology 1995 Mar;45(3):491-7

OBJECTIVES. The objective of this study was to evaluate the effect of finasteride (10 mg/d) or placebo on serum prostate-specific antigen (PSA) and recurrence rates in men with detectable PSA levels after radical prostatectomy.

METHODS. A total of 120 men, 48 to 89 years old, previously treated with radical prostatectomy for prostate cancer within the past 10 years, with serum PSA levels between 0.6 and 10.0 ng/mL, with no evidence of skeletal metastasis on bone scan, and with no previous androgen deprivation therapy, were treated with 10 mg finasteride or placebo in a double-blind fashion for 12 months. After the first year, all patients were treated with finasteride for an additional 12 months. Primary endpoints were serum PSA levels and recurrence rates defined as positive bone scan or positive biopsy.

RESULTS. Patients treated with finasteride had a delayed increase in serum PSA compared with placebo of approximately 9 months in the first year and 14 months by the end of the second year. Patients with baseline PSA levels less than 1.0 ng/mL had no significant increase in serum PSA during the 2 years of treatment. Fewer recurrences were observed in the finasteride group, but these differences were not statistically significant. Finasteride was well tolerated, and side effects were balanced between treatment groups.

CONCLUSIONS. The results of this study indicate that treatment with finasteride delays but does not prevent the rise in serum PSA observed in untreated patients with detectable PSA levels after radical prostatectomy. The reduction in local and distant recurrences in the finasteride group suggests that the effect on PSA reflects a direct effect on tumor growth without affecting the initial response to subsequent hormonal therapy. These data require confirmation by studies that are longer and larger, focused on demonstrating significant differences in progression rates and survival before the use of finasteride can be considered as an option for men with detectable PSA levels after radical prostatectomy.

Finasteride and flutamide as potency-sparing androgen-ablative therapy for advanced adenocarcinoma of the prostate.

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Division of Medical Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts, USA.
Urology 1997 Jun;49(6):913-20

OBJECTIVES: Androgen ablation with luteinizing hormone-releasing hormone (LHRH) agonists, orchiectomy, or oral estrogens has significant untoward sexual side effects. We evaluated a combination of finasteride and flutamide as potency-sparing androgen ablative therapy (AAT) for advanced adenocarcinoma of the prostate. In addition, we evaluated whether finasteride provided additional intraprostatic androgen blockade to flutamide.

METHODS: Twenty men with advanced prostate cancer were given flutamide, 250 mg orally three times daily. Serum prostate-specific antigen (PSA) values were measured weekly. At a nadir PSA value, finasteride, 5 mg orally every day, was added. PSA values were then measured weekly until a second nadir PSA value was achieved. Sexual function was evaluated at baseline, at the second nadir PSA value, and every 3 months thereafter. Testosterone, dihydrotestosterone (DHT), and dehydroepiandrosterone (DHEA) levels were measured at baseline and at the first and second nadir PSA values.

RESULTS: The median follow-up period was 16.9 months. Therapy failed in 1 patient with Stage D2 disease at 12 months, but an additional response to subsequent LHRH agonist therapy was observed. One patient developed National Cancer Institute grade 3 diarrhea and was withdrawn from the study. Seven of 20 men developed mild gynecomastia, and 3 of 20 developed mild transient liver function test elevations. Mean PSA levels were 94.6 +/- 38.2 ng/mL at baseline and 7.8 +/- 2.7 and 4.7 +/- 2.2 ng/mL at the first and second PSA nadir values, respectively (P = 0.034). Mean percent decline in PSA value from baseline was 87.0 +/- 3.1% with flutamide alone and 94.0 +/- 1.9% with both flutamide and finasteride (P = 0.001). Eleven of 20 men were potent at baseline. At the second nadir PSA value, 9 (82%) of 11 were potent, whereas 2 (18%) of 11 were impotent. With longer follow-up (median 16.4 months), 6 (55%) of 11 men were potent, 2 (18%) of 11 were partially potent, and 3 (27%) of 11 were impotent. With flutamide

alone, testosterone rose a mean of 77 +/- 14.7% of baseline (P = 0.0001), DHEA fell a mean of 32.4 +/- 4.6% (P = 0.0001), and DHT was unchanged. With the addition of finasteride, testosterone rose another 14 +/- 6% (P = 0.06, not significant), DHEA was unchanged, and DHT fell a mean of 34.8 +/- 4.7% (P = 0.0009).

CONCLUSIONS: Finasteride and flutamide were safe and well tolerated as AAT for advanced prostate cancer. Finasteride provided additional intraprostatic androgen blockade to flutamide, as measured by additional PSA suppression. Sexual potency was preserved initially in most patients, although there was a reduction in potency and libido in some patients on longer follow-up. Further evaluation of this therapy is needed.

A case for synchronous reduction of testicular androgen, adrenal androgen and prolactin for the treatment of advanced carcinoma of the prostate.

Rana A, Habib FK, Halliday P, Ross M, Wild R, Elton RA, Chisholm GD
University Department of Surgery/Urology, Western General Hospital, Edinburgh, U.K.
Eur J Cancer 1995 Jun;31A(6):871-5

The present study was undertaken mainly to investigate whether prolactin manipulation combined with maximal androgen blockage improves the effectiveness of treatment in advanced prostatic cancer. The efficacy of oral hydrocortisone as an alternative to commercial anti-androgens in reducing the adrenal androgens, and of bromocriptine in reducing the prolactin level were also examined. A consecutive series of 30 patients with untreated and advanced prostatic cancer were entered into a three-arm prospective randomised trial. 10 patients received subcapsular orchiectomy alone (arm 1), another 10 had subcapsular orchiectomy plus flutamide (arm 2), and the remaining 10 had subcapsular orchiectomy plus oral hydrocortisone and bromocriptine (arm 3). Clinical and biochemical parameters, including trans-rectal ultrasound-determined prostatic volumes, hormonal profiles and radionuclide bone scan were evaluated at regular intervals. At 12 months, serum testosterone was reduced by more than 90% in all arms, however, maximum suppression of androstenedione, prolactin, and reduction of prostatic volumes were only observed in arm 3; this was reflected by the significant improvement in clinical response in arm 3 compared with other arms. This study suggests that a combined maximal suppression of androgens and prolactin offers a significant improvement in response over conventional treatments without prolactin suppression in the treatment of advanced prostatic cancer. Importantly, a better clinical outcome in arm 3 was still apparent at the end of 36 months.

Prevention of radioinduced cystitis by orgotein: a randomized study.

Sanchiz F, Milla A, Artola N, Julia JC, Moya LM, Pedro A, Vila A
Center of Radiotherapy and Oncology of Catalonia, Clinica Platon, Barcelona, Spain.
Anticancer Res 1996 Jul-Aug;16(4A):2025-8

On the basis of previous experiences indicating that the anti-oxidant agent Cu/Zn superoxide dismutase (SOD) is an effective drug in reducing acute and late radiation-induced tissue injury, in the Center of Radiotherapy and Oncology of Catalonia, Barcelona, Spain in 1990 we implemented a randomized prospective study to analyze the incidence and grade of side effects in a group of bladder cancer patients. After surgery patients were randomly allocated to receive either: Option A: Radiotherapy or Option B: Radiotherapy + SOD 8 mgr/IM/day, after each radiotherapeutic application. Between January 1990 and January 1995 a total of 448 patients were included (226 A/ 222 B). Apart from cutaneous side effects, a highly significant incidence of radioinduced acute cystitis and proctitis was detected in patients not treated by SOD. Which was similar to the delayed side effects. From our data we can conclude that SOD is effective in decreasing acute radioinduced damage, and also in preventing the appearance of more delayed disorders.

Pathological features of hereditary prostate cancer.

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Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, Maryland 21287-2101.
J Urol 1995 Mar;153(3 Pt 2):987-92

The aim of this study was to characterize the pathological features of hereditary prostate cancer, a recently recognized variant of prostate cancer with an autosomal dominant inheritance of a rare highly penetrant gene associated with early onset of disease. We compared the histology at radical prostatectomy of clinical stage T2 prostate cancer, including its relationship to prostatic

intraepithelial neoplasia, in men with a family history of prostate cancer to those without a family history of prostate cancer. Three cohorts (hereditary, familial and sporadic) were identified based on pedigree analysis. A hereditary subgroup (28 patients) met 1 of the following 3 criteria: 1) cluster of greater than 3 affected relatives within the nuclear family, 2) occurrence of prostate cancer in each of 3 generations in either the proband paternal or maternal lineage, or 3) a cluster of 2 relatives affected at an early age of less than 55 years. This subgroup was compared to an age-matched subgroup with family history of prostate cancer (26 patients) yet the aforementioned conditions for inclusion within the hereditary subgroup were not met and to a sporadic subgroup without a family history of prostate cancer (27 patients). All parameters were statistically similar among the groups except that hereditary and familial group multifocal tumors were of lower grade ($p = 0.0001$), sporadic cases had a greater proportion of small multifocal cancers associated with prostatic intraepithelial neoplasia ($p = 0.02$) and the familial group had a weaker correlation between total tumor volume and grade. In conclusion, our analysis failed to demonstrate substantial pathological differences among hereditary, familial and sporadic forms of prostate cancer. Rather, our data are remarkable for the wide range of all parameters studied in each group. Even the sporadic cases had features, such as increased numbers of precursor lesions and tumor multifocality, which in other organs are commonly associated with either hereditary cancer or cancer arising in a field effect due to diffuse exposure to a carcinogen.

Familial risk factors for prostate cancer.

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Cancer Surv 1991;11:5-13

This chapter describes the application of the genetic epidemiological approach to the study of human prostate cancer. We review the evidence for the familial clustering of prostate cancer and the Mendelian nature of this aggregation. The nature of this clustering is such that the closer genetically a man is to an affected relative and the greater number of relatives affected in a man's family, the greater his risk of prostate cancer. A complex segregation analysis of the 691 prostate cancer families showed that prostate cancer clustering can be explained by Mendelian inheritance of a rare autosomal gene producing prostate cancer at an early age. A model of inherited prostate cancer in the setting of multistep carcinogenesis is presented. The implications of these data for clinicians who diagnose and treat prostate cancer are also discussed.

Mendelian inheritance of familial prostate cancer.

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Department of Epidemiology, Johns Hopkins School of Hygiene and Public Health, Baltimore, MD.

Proc Natl Acad Sci U S A 1992 Apr 15;89(8):3367-71

Previous studies have demonstrated familial clustering of prostate cancer. To define the nature of this familial aggregation and to assess whether Mendelian inheritance can explain prostate cancer clustering, proportional hazards and segregation analyses were performed on 691 families ascertained through a single prostate cancer proband. The proportional hazards analyses revealed that two factors, early age at onset of disease in the proband and multiple affected family members, were important determinants of risk of prostate cancer in these families. Furthermore, segregation analyses revealed that this clustering can be best explained by autosomal dominant inheritance of a rare ($q = 0.0030$) high-risk allele leading to an early onset of prostate cancer. The estimated cumulative risk of prostate cancer for carriers revealed that the allele was highly penetrant: by age 85, 88% of carriers compared to only 5% of noncarriers are projected to be affected with prostate cancer. The best fitting autosomal dominant model further suggested that this inherited form of prostate cancer accounts for a significant proportion of early onset disease but overall is responsible for a small proportion of prostate cancer occurrence (9% by age 85). These data provide evidence that prostate cancer is inherited in Mendelian fashion in a subset of families and provide a foundation for gene mapping studies of heritable prostate cancer. Characterization of genes involved in inherited prostate cancer could provide important insight into the development of this disease in general.

Family history and the risk of prostate cancer.

Steinberg GD, Carter BS, Beaty TH, Childs B, Walsh PC

Brady Urological Institute, Johns Hopkins Hospital, Baltimore, MD 21205.

Prostate 1990;17(4):337-47

A case-control study was performed to estimate the relative risk of developing prostate cancer for men with a positive family history. Extensive cancer pedigrees were obtained on 691 men with prostate cancer and 640 spouse controls. Fifteen percent of the cases but only 8% of the controls had a father or brother affected with prostate cancer (P less than .001). Men with a father or brother affected were twice as likely to develop prostate cancer as men with no relatives affected. In addition, there was a trend of increasing risk with increasing number of affected family members such that men with two or three first degree relatives affected had a five and 11-fold increased risk of developing prostate cancer. Recognizing that 9-10% of U.S. men will develop prostate cancer in their lifetime, men with a family history of prostate cancer should be advised of their significantly increased prostate cancer risk and should undergo appropriate screening measures for this disease.

Familial patterns of prostate cancer: a case-control analysis.

Spitz MR, Currier RD, Fueger JJ, Babaian RJ, Newell GR

Department of Cancer Prevention and Control, University of Texas M.D. Anderson Cancer Center, Houston.

J Urol 1991 Nov;146(5):1305-7

Epidemiological data have not yet enabled physicians to look beyond age and race to identify men at increased risk for prostate cancer. We conducted a hospital-based case-control study of familial patterns of prostate cancer with self-reported data from a risk-factor questionnaire. There were 385 patients with histologically confirmed prostate cancer, and 385 race and age-matched (+/- 5 years) controls with other cancers. Family history, available for 378 patients and 383 controls, was positive for prostate cancer in 13.0% versus 5.7%, respectively. The difference was significant at $p = 0.01$. The over-all age-adjusted risk estimate for men with a first-degree relative with prostate cancer was significantly elevated (odds ratio of 2.41), as were the individual risk estimates for having a father or brother with prostate cancer (odds ratio of 2.24 and 2.66). Having a second-degree relative (grandfather or uncle) with prostate cancer also conferred elevated but not statistically significant risk. These data accord well with the few previously published case-control studies of familiarity of prostate cancer. On the basis of these findings, one should consider recommending participation in early detection programs for prostate cancer in a man whose father or brother has had the disease.

Inhibition of arachidonate 5-lipoxygenase triggers massive apoptosis in human prostate cancer cells.

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University of Virginia Cancer Center, Charlottesville, VA 22908, USA.

Proc Natl Acad Sci U S A 1998 Oct 27;95(22):13182-7

Diets high in fat are associated with an increased risk of prostate cancer, although the molecular mechanism is still unknown. We have previously reported that arachidonic acid, an omega-6 fatty acid common in the Western diet, stimulates proliferation of prostate cancer cells through production of the 5-lipoxygenase metabolite, 5-HETE (5-hydroxyeicosatetraenoic acid). We now show that 5-HETE is also a potent survival factor for human prostate cancer cells. These cells constitutively produce 5-HETE in serum-free medium with no added stimulus. Exogenous arachidonate markedly increases the production of 5-HETE. Inhibition of 5-lipoxygenase by MK886 completely blocks 5-HETE production and induces massive apoptosis in both hormone-responsive (LNCaP) and -nonresponsive (PC3) human prostate cancer cells. This cell death is very rapid: cells treated with MK886 showed mitochondrial permeability transition between 30 and 60 min, externalization of phosphatidylserine within 2 hr, and degradation of DNA to nucleosomal subunits beginning within 2-4 hr posttreatment. Cell death was effectively blocked by the thiol antioxidant, N-acetyl-L-cysteine, but not by androgen, a powerful survival factor for prostate cancer cells. Apoptosis was specific for 5-lipoxygenase-programmed cell death, was not observed with inhibitors of 12-lipoxygenase, cyclooxygenase, or cytochrome P450 pathways of arachidonic acid metabolism. Exogenous 5-HETE protects these cells from apoptosis induced by 5-lipoxygenase inhibitors, confirming a critical role of 5-lipoxygenase activity in the survival of these cells. These findings provide a possible molecular mechanism by which dietary fat may influence the progression of prostate cancer.

Induction of cyclo-oxygenase-2 mRNA by prostaglandin E2 in human prostatic carcinoma cells.

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Department of Medicine, University of California, San Francisco, USA.

Br J Cancer 1997;75(8):1111-8

Prostaglandins are synthesized from arachidonic acid by the enzyme cyclo-oxygenase. There are two isoforms of cyclooxygenases: COX-1 (a constitutive form) and COX-2 (an inducible form). COX-2 has recently been categorized as an immediate-early gene and is associated with cellular growth and differentiation. The purpose of this study was to investigate the effects of exogenous dimethylprostaglandin E2 (dmPGE2) on prostate cancer cell growth. Results of these experiments demonstrate that administration of dmPGE2 to growing PC-3 cells significantly increased cellular proliferation (as measured by the cell number), total DNA content and endogenous PGE2 concentration. DmPGE2 also increased the steady-state mRNA levels of its own inducible synthesizing enzyme, COX-2, as well as cellular growth to levels similar to those seen with fetal calf serum and phorbol ester. The same results were observed in other human cancer cell types, such as the androgen-dependent LNCaP cells, breast cancer MDA-MB-134 cells and human colorectal carcinoma DiFi cells. In PC-3 cells, the dmPGE2 regulation of the COX-2 mRNA levels was both time dependent, with maximum stimulation seen 2 h after addition, and dose dependent on dmPGE2 concentration, with maximum stimulation seen at 5 microg ml⁻¹. The non-steroidal anti-inflammatory drug flurbiprofen (5 microM), in the presence of exogenous dmPGE2, inhibited the up-regulation of COX-2 mRNA and PC-3 cell growth. Taken together, these data suggest that PGE2 has a specific role in the maintenance of human cancer cell growth and that the activation of COX-2 expression depends primarily upon newly synthesized PGE2, perhaps resulting from changes in local cellular PGE2 concentrations.

Prostate cancer and supplementation with alpha-tocopherol and beta-carotene: incidence and mortality in a controlled trial.

Heinonen OP, Albanes D, Virtamo J, Taylor PR, Huttunen JK, Hartman AM, Haapakoski J, Malila N, Rautalahti M, Ripatti S, Maenpaa H, Teerenhovi L, Koss L, Virolainen M, Edwards BK
Department of Public Health, University of Helsinki, Finland.
J Natl Cancer Inst 1998 Mar 18;90(6):440-6

BACKGROUND: Epidemiologic studies have suggested that vitamin E and beta-carotene may each influence the development of prostate cancer. In the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, a controlled trial, we studied the effect of alpha-tocopherol (a form of vitamin E) and beta-carotene supplementation, separately or together, on prostate cancer in male smokers.

METHODS: A total of 29133 male smokers aged 50-69 years from southwestern Finland were randomly assigned to receive alpha-tocopherol (50 mg), beta-carotene (20 mg), both agents, or placebo daily for 5-8 years (median, 6.1 years). The supplementation effects were estimated by a proportional hazards model, and two-sided P values were calculated.

RESULTS: We found 246 new cases of and 62 deaths from prostate cancer during the follow-up period. A 32% decrease (95% confidence interval [CI] = -47% to -12%) in the incidence of prostate cancer was observed among the subjects receiving alpha-tocopherol (n = 14564) compared with those not receiving it (n = 14569). The reduction was evident in clinical prostate cancer but not in latent cancer. Mortality from prostate cancer was 41% lower (95% CI = -65% to -1%) among men receiving alpha-tocopherol. Among subjects receiving beta-carotene (n = 14560), prostate cancer incidence was 23% higher (95% CI = -4%-59%) and mortality was 15% higher (95% CI = -30%-89%) compared with those not receiving it (n = 14573). Neither agent had any effect on the time interval between diagnosis and death.

CONCLUSIONS: Long-term supplementation with alpha-tocopherol substantially reduced prostate cancer incidence and mortality in male smokers. Other controlled trials are required to confirm the findings.

Vitamin E inhibits the high-fat diet promoted growth of established human prostate LNCaP tumors in nude mice.

Fleshner N, Fair WR, Huryk R, Heston WD
Urologic Oncology Research Laboratory, Sloan Kettering Institute For Cancer Research, New York, New York, USA.
J Urol 1999 May;161(5):1651-4

PURPOSE: Prostate cancer has become an important public health problem in the Western world. It is currently the most common diagnosed cancer and the second leading cause of cancer deaths among North American men. Prostate cancer possesses a unique descriptive epidemiology which suggests that environmental factors (such as dietary fat consumption) play a pivotal role in tumor progression. Data from our institution have demonstrated that diets high in fat content can accelerate the growth of human LNCaP prostate cancer cells. One of the hypothesized mechanisms of dietary fat induced growth is oxidative stress. Our purpose was to determine the effect of supplemental Vitamin E, a potent intracellular antioxidant, on the high-fat

promoted growth of transplanted LNCaP cells in the athymic mouse.

MATERIALS AND METHODS: Tumors were induced by subcutaneous injection of 10(6) LNCaP cells. Mice were fed a control diet consisting of 40.5% of total calories from dietary fat. Once tumors were formed, PSA values were obtained and animals were randomized into 4 groups of 12. The animals were then assigned to one of 4 dietary plans. Group 1 received the control diet of 40.5%-kcal fat. Group 2 received the 40.5%-kcal fat diet plus supplemental Vitamin E. Group 3 received a diet of 21.2%-kcal fat. Group 4 received the 21.2%-kcal fat diet plus supplemental Vitamin E. Food intake, animal weights, and tumor volumes were recorded weekly. Survival analyses with time to a target volume of 0.523 cm³ (defined as failure) were used to compare tumor growth among the 4 groups. Two-sided tests (log rank test) with alpha set at 0.05 were used to determine significance.

RESULTS: Tumor growth rates were highest in the animals fed a 40.5%-kcal fat diet ($p < 0.05$ group 1). Tumors in animals fed 40.5%-kcal fat plus Vitamin E, 21.2%-kcal fat, and 21.2%-kcal fat plus Vitamin E, experienced statistically indistinguishable growth rates. No significant differences were noted in total ingested calories, animal weight gain or initial PSA levels.

CONCLUSIONS: These data suggest that the mechanism of dietary fat induced growth of human prostate cancer cells is mediated by oxidative stress. It also raises the possibility of a therapeutic benefit of vitamin E in preventing prostate cancer.

Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized controlled trial. Nutritional Prevention of Cancer Study Group.

Clark LC, Combs GF Jr, Turnbull BW, Slate EH, Chalker DK, Chow J, Davis LS, Glover RA, Graham GF, Gross EG, Krongrad A, Leshner JL Jr, Park HK, Sanders BB Jr, Smith CL, Taylor JR
Arizona Cancer Center, College of Medicine, University of Arizona, Tucson, USA.
Published erratum appears in JAMA 1997 May 21;277(19):1520

OBJECTIVE: To determine whether a nutritional supplement of selenium will decrease the incidence of cancer.

DESIGN: A multicenter, double-blind, randomized, placebo-controlled cancer prevention trial.

SETTING: Seven dermatology clinics in the eastern United States.

PATIENTS: A total of 1312 patients (mean age, 63 years; range, 18-80 years) with a history of basal cell or squamous cell carcinomas of the skin were randomized from 1983 through 1991. Patients were treated for a mean (SD) of 4.5 (2.8) years and had a total follow-up of 6.4 (2.0) years.

INTERVENTIONS: Oral administration of 200 microg of selenium per day or placebo.

MAIN OUTCOME MEASURES: The primary end points for the trial were the incidences of basal and squamous cell carcinomas of the skin. The secondary end points, established in 1990, were all-cause mortality and total cancer mortality, total cancer incidence, and the incidences of lung, prostate, and colorectal cancers.

RESULTS: After a total follow-up of 8271 person-years, selenium treatment did not significantly affect the incidence of basal cell or squamous cell skin cancer. There were 377 new cases of basal cell skin cancer among patients in the selenium group and 350 cases among the control group (relative risk [RR], 1.10; 95% confidence interval [CI], 0.95-1.28), and 218 new squamous cell skin cancers in the selenium group and 190 cases among the controls (RR, 1.14; 95% CI, 0.93-1.39). Analysis of secondary end points revealed that, compared with controls, patients treated with selenium had a nonsignificant reduction in all-cause mortality (108 deaths in the selenium group and 129 deaths in the control group [RR; 0.83; 95% CI, 0.63-1.08]) and significant reductions in total cancer mortality (29 deaths in the selenium treatment group and 57 deaths in controls [RR, 0.50; 95% CI, 0.31-0.80]), total cancer incidence (77 cancers in the selenium group and 119 in controls [RR, 0.63; 95% CI, 0.47-0.85]), and incidences of lung, colorectal, and prostate cancers. Primarily because of the apparent reductions in total cancer mortality and total cancer incidence in the selenium group, the blinded phase of the trial was stopped early. No cases of selenium toxicity occurred.

CONCLUSIONS: Selenium treatment did not protect against development of basal or squamous cell carcinomas of the skin. However, results from secondary end-point analyses support the hypothesis that supplemental selenium may reduce the incidence of, and mortality from, carcinomas of several sites. These effects of selenium require confirmation in an independent trial of appropriate design before new public health recommendations regarding selenium supplementation can be made

Inhibitory effects of selenium on the growth of DU-145 human prostate carcinoma cells in vitro.

Webber MM, Perez-Ripoll EA, James GT
Biochem Biophys Res Commun 1985 Jul 31;130(2):603-9

The growth of DU-145 human prostate carcinoma cells is reduced to 50% of control by 1×10^{-6} M to 2×10^{-6} M selenium and to 2% of control at 10^{-4} M selenium. These cells show greater sensitivity to inhibition of growth or DNA synthesis by selenium than human W1-38 and HeLa cells and mouse mammary tumor cells. It has been shown that selenium inhibits carcinogenesis and reduces the incidence of chemical carcinogen and virus-induced tumors of a variety of organs in animals. Selenium may also inhibit the growth of certain tumor cells of non-human origin. To our knowledge, this is the first study on the effects of selenium on the growth of human tumor cells. From extrapolation, it is deduced that selenium serum levels in humans living in high selenium areas may be as high as 10^{-6} M and could be effective in inhibiting the growth of tumor cells in vivo. These findings have implications in the prevention and intervention of prostate cancer in man.

Genistein inhibits proliferation and in vitro invasive potential of human prostatic cancer cell lines.

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Unidad de Biología Celular, INTA, Universidad de Chile, Santiago, Chile.
Anticancer Res 1997 Mar-Apr;17(2A):1199-204

Genistein -a natural flavone compound with antitumor activity- has been proposed as an effective agent to prevent the expression of metastatic capacity in hormone-dependent cancers. The present study represents an effort to assess the efficacy of Genistein in inhibiting the proliferation and expression of the in vitro invasive capacity of tumoral prostatic cells with different invasive potential. In a cell culture system, genistein appeared to be cytotoxic and inhibitory of migration through a Matrigel barrier to PC-3 cells, the more aggressive invasive cell-line studied. DU-145 and LNCaP cells, which are less invasive than PC-3, are less affected by Genistein both with respect to proliferation rate and inhibition of u-PA and 72 kDa Gelatinase secretion. Measurement of the level of tyrosine-phosphoproteins in the three cell lines studied also showed that PC-3 cells are the most sensitive cells, with a possible molecular target in a membrane-bound protein of 130 kDa.

Genistein and biochanin A inhibit the growth of human prostate cancer cells but not epidermal growth factor receptor tyrosine autophosphorylation.

Peterson G, Barnes S
Department of Biochemistry, University of Alabama, Birmingham 35294-0019.
Prostate 1993;22(4):335-45

The effect of the isoflavones, genistein, daidzein, and biochanin A on the growth of the LNCaP and DU-145 human prostate cancer cell lines has been examined. Genistein and biochanin A, but not daidzein, inhibit both serum and EGF-stimulated growth of LNCaP and DU-145 cells (IC_{50} values from 8.0 to 27 micrograms/ml for serum and 4.3 to 15 micrograms/ml for EGF), but have no significant effect on the EGF receptor tyrosine autophosphorylation. In contrast, tyrphostin 25, a specific EGF receptor tyrosine kinase inhibitor, inhibits EGF-stimulated growth and EGF receptor tyrosine autophosphorylation in these whole cells, but does not inhibit serum-stimulated growth. These data suggest that the mechanism of action of genistein and biochanin A does not depend on inhibition of EGF receptor tyrosine autophosphorylation, but on a more distal event in the EGF receptor-mediated signal transduction cascade.

Antiproliferative effect of Pygeum africanum extract on rat prostatic fibroblasts.

Yablonsky F, Nicolas V, Riffaud JP, Bellamy F
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Published erratum appears in J Urol 1997 Sep;158(3 Pt 1):889

The effect of a *Pygeum africanum* extract (Tadenan) (Pa), used in the treatment of micturition disorders associated with BPH, has been examined on the proliferation of rat prostatic stromal cells stimulated by different growth factors. EGF, bFGF, and IGF-I but

not KGF are mitogenic for prostatic fibroblasts in culture. Pygeum africanum inhibits both basal and stimulated growth with IC50 values of 4.5, 7.7 and 12.6 micrograms./ml. for EGF, IGF-I and bFGF, respectively, compared to 14.4 micrograms./ml. for untreated cells, the inhibition being stronger towards EGF. Pygeum africanum inhibited the proliferation induced by TPA or PDBu in a concentration-dependent manner with IC50 values of 12.4 and 8.1 micrograms./ml. respectively. The antiproliferative effects of Pa were not ascribed to cytotoxicity. These results show that Pygeum africanum is a potent inhibitor of rat prostatic fibroblast proliferation in response to direct activators of protein kinase C, the defined growth factors bFGF, EGF and IGF-I, and the complex mixture of mitogens in serum depending on the concentration used. PKC activation appears to be an important growth factor-mediated signal transduction for this agent. These data suggest that therapeutic effect of Pygeum africanum may be due at least in part to the inhibition of growth factors responsible for the prostatic overgrowth in man.

A flavonoid antioxidant, silymarin, inhibits activation of erbB1 signaling and induces cyclin-dependent kinase inhibitors, G1 arrest, and anticarcinogenic effects in human prostate carcinoma DU145 cells.

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Cancer Res 1998 May 1;58(9):1920-9

Prostate cancer (PCA) is the most common nonskin malignancy and the second leading cause of cancer deaths in United States males. One practical and translational approach to control PCA is to define a mechanism-based anticarcinogenic agent(s). Recently, we showed that silymarin, a flavonoid antioxidant isolated from milk thistle, possesses exceptionally high to complete protective effects against experimentally induced tumorigenesis. Because the epidermal growth factor receptor (erbB1) and other members of the erbB family have been shown to play important roles in human PCA, efforts should be directed to identify inhibitors of this pathway for PCA intervention. In this study, we assessed whether silymarin inhibits erbB1 activation and associated downstream events and modulates cell cycle regulatory proteins and progression, leading to growth inhibition of human prostate carcinoma DU145 cells. Treatment of serum-starved cells with silymarin resulted in a significant inhibition of transforming growth factor alpha-mediated activation of erbB1 but no change in its protein levels. Silymarin treatment of cells also resulted in a significant decrease in tyrosine phosphorylation of an immediate downstream target of erbB1, the adapter protein SHC, together with a decrease in its binding to erbB1. In the studies analyzing cell cycle regulatory molecules, silymarin treatment of cells also resulted in a significant induction of cyclin-dependent kinase inhibitors (CDKIs) Cip1/p21 and Kip1/p27, concomitant with a significant decrease in CDK4 expression, but no change in the levels of CDK2 and CDK6 and their associated cyclins E and D1, respectively. Cells treated with silymarin also showed an increased binding of CDKIs with CDKs, together with a marked decrease in the kinase activity of CDKs and associated cyclins. In additional studies, treatment of cells grown in 10% serum with anti-epidermal growth factor receptor monoclonal antibody clone 225 or different doses of silymarin also resulted in significant inhibition of constitutive tyrosine phosphorylation of both erbB1 and SHC but no change in their protein levels. Furthermore, whereas silymarin treatment resulted in a significant increase in the protein levels of both Cip1/p21 and Kip1/p27, monoclonal antibody 225 showed an increase only in Kip1/p27. These findings suggest that silymarin also inhibits constitutive activation of erbB1 and that the observed effect of silymarin on an increase in CDKI protein levels is mediated via inhibition of erbB1 activation only in the case of Kip1/p27; however, additional pathways independent of inhibition of erbB1 activation are possibly responsible for the silymarin-caused increase in Cip1/p21 in DU145 cells. In other studies, silymarin treatment also induced a G1 arrest in the cell cycle progression of DU145 cells and resulted in a highly significant to complete inhibition of both anchorage-dependent and anchorage-independent growth of DU145 cells in a dose- and time-dependent manner. Taken together, these results suggest that silymarin may exert a strong anticarcinogenic effect against PCA and that this effect is likely to involve impairment of erbB1-SHC-mediated signaling pathway, induction of CDKIs, and a resultant G1 arrest.

Protective and therapeutic effect of silymarin on the development of latent liver damage.

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Radiats Biol Radioecol 1998 May-Jun;38(3):411-5

Radioprotective and therapeutical effect of silymarin (Flavobion) on development and repair of latent injury in rat liver was examined by its application during the continual gamma irradiation (dose rates 0.2 and 0.6 Gy/day) or after acute gamma irradiation (dose 6 Gy). Silymarin influence was evaluated on the basis of mitotic index and chromosomal aberration frequency in the liver regenerating after partial hepatectomy. We have found that silymarin application stimulates the process of liver regeneration in non-irradiated rats as well as in irradiated ones. Positive effect of silymarin (100 mg per kg p.o. ones per day) was manifested at both dose rates of continual irradiation with increase in mitotic activity and mitigation of chromosomal erration frequency in the

regenerating liver in comparison with non-protected irradiated animals. Curative effect of silymarin (70 mg/kg p.o., twice per day) was shown especially after 14 days of its postradiation application.

Protection against tumor promotion in mouse skin by silymarin .

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Eighty-sixth Annual Meeting of the American Association for Cancer Research

Toronto, Ontario, Canada March 18-22, 1995

Proceedings of the American Association for Cancer Research Annual Meeting 36 (0): p 593 1995

No abstract.

Protective effects of silymarin against photocarcinogenesis in a mouse skin model.

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J Natl Cancer Inst 1997 Apr 16;89(8):556-66

BACKGROUND: Nonmelanoma skin cancer is the most common cancer among humans; solar UV is its major cause. Therefore, it is important to identify agents that can offer protection against this cancer.

PURPOSE: We evaluated the protective effects of silymarin, a flavonoid compound isolated from the milk thistle plant, against UVB radiation-induced nonmelanoma skin cancer in mice and delineated the mechanism(s) of its action.

METHODS: For long-term studies, three different protocols of treatment were employed, each evaluating protection by silymarin at a different stage of carcinogenesis. Female SKH-1 hairless mice were subjected to 1) UVB-induced tumor initiation followed by phorbol ester-mediated tumor promotion, 2) 7,12-dimethylbenz[a]anthracene-induced tumor initiation followed by UVB-mediated tumor promotion, and 3) UVB-induced complete carcinogenesis. Forty mice were used in each protocol and were divided into control and treatment groups. Silymarin was applied topically at a dose of 9 mg per application before UVB exposure, and its effects on tumor incidence (% of mice with tumors), tumor multiplicity (number of tumors per mouse), and average tumor volume per mouse were evaluated. In short-term studies, the following parameters were measured: formation of sunburn and apoptotic cells, skin edema, epidermal catalase and cyclooxygenase (COX) activities, and enzymatic activity and messenger RNA (mRNA) expression for ornithine decarboxylase (ODC), a frequently observed marker at tumor promotion stage. Fisher's exact test was used to evaluate differences in tumor incidence, two-sample Wilcoxon rank sum test was used for tumor multiplicity and tumor volume, and Student's t test was used for all other measurements. All statistical tests were two-sided.

RESULTS: In the protocol with UVB-induced tumor initiation, silymarin treatment reduced tumor incidence from 40% to 20% ($P = .30$), tumor multiplicity by 67% ($P = .10$), and tumor volume per mouse by 66% ($P = .14$). In the protocol with UVB-induced tumor promotion, silymarin treatment reduced tumor incidence from 100% to 60% ($P < .003$), tumor multiplicity by 78% ($P < .0001$), and tumor volume per mouse by 90% ($P < .003$). The effect of silymarin was much more profound in the protocol with UVB-induced complete carcinogenesis, where tumor incidence was reduced from 100% to 25% ($P < .0001$), tumor multiplicity by 92% ($P < .0001$), and tumor volume per mouse by 97% ($P < .0001$). In short-term experiments, silymarin application resulted in statistically significant inhibition in UVB-caused sunburn and apoptotic cell formation, skin edema, depletion of catalase activity, and induction of COX and ODC activities and ODC mRNA expression.

CONCLUSIONS AND IMPLICATION: Silymarin can provide substantial protection against different stages of UVB-induced carcinogenesis, possibly via its strong antioxidant properties. Clinical testing of its usefulness is warranted.

Genistein inhibits the growth of human-patient BPH and prostate cancer in histoculture.

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Prostate 1998 Feb 1;34(2):75-9

BACKGROUND: There is strong epidemiological evidence that prostate disease is significantly less prevalent in the Orient, where the intake of soy products is very high, than in the United States. We therefore undertook a study of the effects of genistein, a major component of soy, on growth of human-patient benign prostatic hypertrophy (BPH) and prostate cancer tissue in three-dimensional collagen gel-supported histoculture.

METHODS: Surgical specimens of human BPH and cancer were histocultured for 5 days to study the effects of genistein on growth, as measured by inhibition of ³H-thymidine incorporation per microgram protein on day 5.

RESULTS: Genistein in doses of 1.25-10 micrograms/ml decreased the growth of BPH tissue in histoculture in a dose-dependent manner, with little additional effect at higher doses. Prostate cancer tissue in histoculture was similarly inhibited by these doses of genistein.

CONCLUSIONS: Genistein decreases the growth of both BPH and prostate cancer tissue in histoculture. The data suggest that genistein has potential as a therapeutic agent for BPH and prostate cancer.

Treatment of early recurrent prostate cancer with 1,25-dihydroxyvitamin D3.

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J Urol 1998 Jun;159(6):2035-9; discussion 2039-40

Published erratum appears in J Urol 1998 Sep;160(3 Pt 1):840

PURPOSE: Substantial experimental and epidemiological data indicate that 1,25-dihydroxyvitamin D3 (calcitriol) has potent antiproliferative effects on human prostate cancer cells. We performed an open label, nonrandomized pilot trial to determine whether calcitriol therapy is safe and efficacious for early recurrent prostate cancer. Our hypothesis was that calcitriol therapy slows the rate of rise of prostate specific antigen (PSA) compared with the pretreatment rate.

MATERIALS AND METHODS: After primary treatment with radiation or surgery recurrence was indicated by rising serum PSA levels documented on at least 3 occasions. Seven subjects completed 6 to 15 months of calcitriol therapy, starting with 0.5 microg. calcitriol daily and slowly increasing to a maximum dose of 2.5 microg. daily depending on individual calciuric and calcemic responses. Each subject served as his own control, comparing the rate of PSA rise before and after calcitriol treatment.

RESULTS: As determined by multiple regression analysis, the rate of PSA rise during versus before calcitriol therapy significantly decreased in 6 of 7 patients, while in the remaining man a deceleration in the rate of PSA rise did not reach statistical significance. Overall the decreased rate of PSA rise was statistically significant ($p = 0.02$ Wilcoxon signed rank test). Dose dependent hypercalciuria limited the maximal calcitriol therapy given (range 1.5 to 2.5 microg. daily).

CONCLUSIONS: This pilot study provides preliminary evidence that calcitriol effectively slows the rate of PSA rise in select cases, although dose dependent calciuric side effects limit its clinical usefulness. The development of calcitriol analogues with decreased calcemic side effects is promising, since such analogues may be even more effective for treating prostate cancer.

19-nor-hexafluoride analogue of vitamin D3: a novel class of potent inhibitors of proliferation of human breast cell lines.

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Cancer Res 1997 Oct 15;57(20):4545-50

Breast cancer cells express vitamin D3 receptors and 1,25-dihydroxyvitamin D3 suppressed growth of these cells. We have synthesized six novel vitamin D3 analogues to identify those with expanded capacity to inhibit the proliferative ability of breast cancer cells. These analogues incorporated many of the structural motifs shown previously to have antiproliferative activity in several cell types. Six breast cancer cell lines were used as targets. Dose-response studies showed that each of the analogues had antiproliferative activities, and LH [1,25-(OH)₂-16-ene-23-yne-26,27-F₆-19-nor D3] was the most potent analogue, suppressing at 10⁻¹¹ M greater than 50% clonal proliferation (ED₅₀) of the MCF-7 and SK-BR-3 breast cancer cells, increasing the proportion of MCF-7 cells in the G₀-G₁ phase, and decreasing those in the S phase of the cell cycle. Pulse-exposure studies showed that a

3-day exposure to LH (10⁻⁷ M) in liquid culture was adequate to achieve a 50% inhibition of MCF-7 clonal growth in soft agar in the absence of the analogue, suggesting that the growth inhibition mediated by LH is irreversible. The cyclin-dependent kinase inhibitor known as p27Kip1 helps regulate the cell cycle and can mediate growth arrest in response to extracellular growth inhibitors. The analogue LH (10⁻⁷ M) induced elevated expression of p27Kip1 in MCF-7 and SK-BR-3 cells. Taken together, these results indicate that LH is an extremely potent vitamin D3 analogue markedly inhibiting clonal growth of MCF-7 and SK-BR-3 cells with concomitant cell cycle arrest at G0-G1 and increased expression of p27Kip1. Compound LH is worthy of in vivo analysis for possible future clinical trials.

The effect of calcium supplementation on the circadian rhythm of bone resorption.

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Department of Human Metabolism and Clinical Biochemistry, University of Sheffield, England.
J Clin Endocrinol Metab 1994 Sep;79(3):730-5

Bone resorption shows a circadian rhythm in human subjects, but the physiological mechanisms underlying this rhythm are unknown. We compared the circadian rhythm of bone collagen degradation in 18 premenopausal women before and after oral calcium supplementation (1000 mg calcium for 14 days). Subjects were randomized to receive calcium at either 0800 h or 2300 h. Continuous 48-h urine collections and 1 day of 4-h urine collections were obtained before and after the 14-day supplementation period. We measured urinary deoxypyridinoline (Dpd) and the cross-linked N-telopeptide of type I collagen (NTx) as biochemical markers of bone resorption. There was a significant effect of time of day on excretion of Dpd and NTx (analysis of variance, $P < 0.001$) with peak excretion between 0300-0700 h and a nadir between 1500-1900 h. The mean amplitude (peak to trough) was similar for Dpd and NTx (70.3% and 63.3%, respectively). Evening calcium supplementation resulted in marked suppression of the nocturnal increase in Dpd and NTx and reversed the usual nocturnal increase in the level of parathyroid hormone. In contrast, morning calcium supplementation had no significant effect on the circadian rhythm of Dpd or NTx. Evening calcium supplementation suppressed overall daily excretion of Dpd by 20.1% ($P = 0.03$) and NTx by 18.1% ($P = 0.03$). Morning calcium supplementation had no significant effect on overall daily excretion of either Dpd or NTx. We conclude that evening calcium supplementation suppresses the circadian rhythm of bone resorption. The daily rhythm of PTH secretion or calcium intake is likely to be an important determinant of this rhythm. Experimental protocols designed to investigate the effect of calcium supplementation on bone mineral density should take the timing of supplementation into account.

Why drinking green tea could prevent cancer.

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Nature 1997 Jun 5;387(6633):561

No abstract.

Selective inhibition of steroid 5 alpha-reductase isozymes by tea epicatechin-3-gallate and epigallocatechin-3-gallate.

Liao S, Hiipakka RA
Ben May Institute, University of Chicago, IL 60637, USA.
Biochem Biophys Res Commun 1995 Sep 25;214(3):833-8

Inhibitors of 5 alpha-reductase may be effective in the treatment of 5 alpha-dihydrotestosterone-dependent abnormalities, such as benign prostate hyperplasia, prostate cancer and certain skin diseases. The green tea catechins, (-)epigallocatechin-3-gallate and (-)epicatechin-3-gallate, but not (-)epicatechin and (-)epigallocatechin, are potent inhibitors of type 1 but not type 2 5 alpha-reductase. (-)Epigallocatechin-3-gallate also inhibits accessory sex gland growth in the rat. These results suggest that certain tea gallates can regulate androgen action in target organs.

Growth inhibition and regression of human prostate and breast tumors in athymic mice by tea epigallocatechin gallate.

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Cancer Lett 1995 Sep 25;96(2):239-43

The human prostate cancer cell lines, PC-3 (androgen-insensitive) and LNCaP 104-R (androgen-repressed) were inoculated subcutaneously into nude mice to produce prostate tumors. Intraperitoneal injection of green tea (-)epigallocatechin-3-gallate but not structurally related catechins, such as (-)epicatechin-3-gallate, inhibited the growth and rapidly reduced the size of human prostate tumors in nude mice. (-)Epigallocatechin-3-gallate also rapidly inhibited the growth of tumor growth formed by the human mammary cancer cell line MCF-7 in nude mice. It is possible that there is a relationship between the high consumption of green tea and the low incidence of prostate and breast cancers in some Asian countries.

Intake of carotenoids and retinol in relation to risk of prostate cancer.

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Natl Cancer Inst 1995 Dec 6;87(23):1767-76

BACKGROUND: Several human studies have observed a direct association between retinol (vitamin A) intake and risk of prostate cancer; other studies have found either an inverse association or no association of intake of beta-carotene (the major provitamin A) with risk of prostate cancer. Data regarding carotenoids other than beta-carotene in relation to prostate cancer risk are sparse.

PURPOSE: We conducted a prospective cohort study to examine the relationship between the intake of various carotenoids, retinol, fruits, and vegetables and the risk of prostate cancer.

METHODS: Using responses to a validated, semiquantitative food-frequency questionnaire mailed to participants in the Health Professionals Follow-up Study in 1986, we assessed dietary intake for a 1-year period for a cohort of 47,894 eligible subjects initially free of diagnosed cancer. Follow-up questionnaires were sent to the entire cohort in 1988, 1990, and 1992. We calculated the relative risk (RR) for each of the upper categories of intake of a specific food or nutrient by dividing the incidence rate of prostate cancer among men in each of these categories by the rate among men in the lowest intake level. All P values resulted from two-sided tests.

RESULTS: Between 1986 and 1992, 812 new cases of prostate cancer, including 773 non-stage A1 cases, were documented. Intakes of the carotenoids beta-carotene, alpha-carotene, lutein, and beta-cryptoxanthin were not associated with risk of non-stage A1 prostate cancer; only lycopene intake was related to lower risk (age- and energy-adjusted RR = 0.79; 95% confidence interval [CI] = 0.64-0.99 for high versus low quintile of intake; P for trend = .04). Of 46 vegetables and fruits or related products, four were significantly associated with lower prostate cancer risk; of the four--tomato sauce (P for trend = .001), tomatoes (P for trend = .03), and pizza (P for trend = .05), but not strawberries--were primary sources of lycopene. Combined intake of tomatoes, tomato sauce, tomato juice, and pizza (which accounted for 82% of lycopene intake) was inversely associated with risk of prostate cancer (multivariate RR = 0.65; 95% CI = 0.44-0.95, for consumption frequency greater than 10 versus less than 1.5 servings per week; P for trend = .01) and advanced (stages C and D) prostate cancers (multivariate RR = 0.47; 95% CI = 0.22-1.00; P for trend = .03). No consistent association was observed for dietary retinol and risk of prostate cancer.

CONCLUSIONS: These findings suggest that intake of lycopene or other compounds in tomatoes may reduce prostate cancer risk, but other measured carotenoids are unrelated to risk.

IMPLICATIONS: Our findings support recommendations to increase vegetable and fruit consumption to reduce cancer incidence but suggest that tomato-based foods may be especially beneficial regarding prostate cancer risk.

Effects of lycopene on spontaneous mammary tumour development in SHN virgin mice.

Nagasawa H, Mitamura T, Sakamoto S, Yamamoto K

Experimental Animal Research Laboratory, Meiji University, Kanagawa, Japan.

Anticancer Res 1995 Jul-Aug;15(4):1173-8

Effects of the chronic ingestion of lycopene, a carotenoid from tomato, on the development of spontaneous mammary tumours were examined in a high mammary tumour strain of SHN virgin mice. Beginning at 40 days of age, the control and the experimental groups were allowed free access to an AIN-76TM diet and a diet supplemented further with lycopene at the concentration of $5.0 \times 10^{-5}\%$, respectively. The treatment significantly suppressed the mammary tumour development, which suppression was associated with the decrease in the mammary gland activity of thymidylate synthetase, and serum levels of free fatty acid and prolactin. Body weight was little affected and no deleterious side-effects of lycopene were detected. All results show that lycopene could be promising as a chemopreventive agent for mammary and other types of tumours.

Identification of tricyclic analogs related to ellagic acid as potent/selective tyrosine protein kinase inhibitors.

Dow RL, Chou TT, Bechle BM, Goddard C, Larson ER
Central Research Division, Pfizer Inc., Groton, Connecticut 06340.
J Med Chem 1994 Jul 8;37(14):2224-31

The plant-derived natural product ellagic acid (1) has recently been identified as a potent, though nonselective, inhibitor of the tyrosine-specific protein kinase pp60src. This report details efforts directed toward the identification of tricyclic structures related to ellagic acid, with enhanced specificity for inhibition of pp60src over other protein kinases. Phenanthridinone and carbazole core structures were selected for investigation, since N-functionalization allows for the synthesis of numerous analogs which can be utilized to probe enzyme-inhibitor interactions. These ring systems were prepared via a general sequence of biaryl bond formation followed by cyclization to form the desired tricyclic ring systems. N-Alkylation, -acylation, or -sulfonylation and deprotection with boron tribromide afford the target tetraphenolic phenanthridinones 5 and carbazoles 9. Several analogs from both of these series have potencies comparable to that of 1 and exhibit substantially enhanced selectivities for inhibition of pp60src relative to protein kinase A (PKA), a serine/threonine protein kinase. Carbazole-based analogs 9j,m,p are submicromolar inhibitors of pp60src, with potency for the target tyrosine kinase comparable to that of ellagic acid (1), however with 2 orders of magnitude greater selectivity versus that for PKA. As seen for ellagic acid, members of the phenanthridinone-based series (e.g., 5a) exhibited inhibition of pp60src in a manner which is partial mixed noncompetitive with respect to ATP, while analogs in the carbazole series (e.g., 9a) inhibit pp60src in an ATP competitive manner.

Ellagic acid induces transcription of the rat glutathione S-transferase-Ya gene.

Barch DH, Rundhaugen LM, Pillay NS
Department of Medicine, Lakeside Veterans Affairs Medical Center, Chicago, IL.
Carcinogenesis 1995 Mar;16(3):665-8

Induction of glutathione S-transferase (GST) enzymes can increase detoxification of carcinogens and reduce carcinogen-induced mutagenesis and tumorigenesis. To determine if the anticarcinogen ellagic acid induces cellular enzymes which detoxify carcinogens, we examined the effect of ellagic acid on the expression of glutathione S-transferase-Ya. Rats fed ellagic acid demonstrated significant increases in total hepatic GST activity, hepatic GST-Ya activity and hepatic GST-Ya mRNA. To determine if the observed increase in GST-Ya mRNA was due to ellagic acid inducing transcription of the GST-Ya gene, transfection studies were performed with plasmid constructs containing various portions of the 5' regulatory region of the rat GST-Ya gene. The transfection studies demonstrated that ellagic acid increased GST-Ya mRNA by inducing transcription of the GST-Ya gene and demonstrated that this induction is mediated through the antioxidant responsive element of the GST-Ya gene.

Combination of screening and preoperative endocrine therapy: the potential for an important decrease in prostate cancer mortality.

Labrie F, Cusan L, Gomez JL, Diamond P, Candas B
Prostate Cancer Research Unit, CHUL Research Center, Le Centre Hospitalier de l'Universite Laval, Quebec, Canada.
J Clin Endocrinol Metab 1995 Jul;80(7):2002-13

Prostate cancer is the second cause of cancer death in men in the Western world; its medical and social impact is comparable to that of breast cancer in women. Although it is well recognized that early treatment is the only possibility for reducing the high rate of death from prostate cancer, screening and even early treatment are controversial issues due mainly to arguments based upon

old literature and lack of awareness of the significant advances recently made in this field. As it is well known that surgical removal of organ-confined prostate cancer cures the disease, and it has been demonstrated that annual screening with prostate-specific antigen coupled with digital rectal examination followed, when indicated, by transrectal ultrasonography of the prostate more than doubles the proportion of organ-confined disease, screening alone offers the possibility of at least doubling the number of patients curable from prostate cancer or the potential for a cure to an estimated 45% of prostate cancer patients compared to a maximum of 20% in the absence of screening. It is important to mention that screening does not detect small and insignificant cancers, especially when random biopsies are not performed routinely. The critical volume of prostate cancer is estimated at 0.3 cm or a tumor 7.5 mm in diameter, if spherical. Such a tumor should increase serum prostate-specific antigen by 0.5 ng/mL. Contrary to the belief that screening detects cancers that are too small, the fact is that screening detects prostate cancer too late or nonorgan- or nonspecimen-confined cancer in 35-50% of cases. There is, thus, a narrow window when prostate cancer can be detected at a curable stage, and even the best available screening techniques cannot succeed in all cases. It should be mentioned that the recent improvements of the technique of radical prostatectomy have markedly improved the acceptability of surgery. Concerning the recent publicity related to watchful waiting, it is essential to indicate that all such reports support the notion that prostate cancer grows slowly, but steadily and irremediably, with increasing malignancy and risk of distant metastases and death if sufficient time is allowed. Another serious limitation of watchful waiting is that the available prognostic factors have a large margin of error and cannot predict with certainty the rate of progression of the tumor.

Diagnosis of advanced or noncurable prostate cancer can be practically eliminated by prostate-specific antigen.

Labrie F, Candas B, Cusan L, Gomez JL, Diamond P, Suburu R, Lemay M
Prostate Cancer Clinical Research Unit, CHUL Research Center, Quebec, Canada.
Urology 1996 Feb;47(2):212-17

OBJECTIVES: To determine the percentage of localized and potentially curable prostate cancers diagnosed at follow-up screening visits compared with the first screening visit.

METHODS: Within the context of a prospective screening study performed in randomly chosen men aged between 45 and 80 years, up to 6-year follow-up screening visits have been performed with serum prostate-specific antigen (PSA) measurement and digital rectal examination (DRE) followed by transrectal ultrasonography of the prostate when PSA or DRE is abnormal.

RESULTS: Of the 117 prostate cancers diagnosed at 14,554 annual follow-up visits, only 1 cancer (0.9%) was metastatic compared with 8% (26/322) at 8029 first visits. Moreover, 97% of the cancers detected at follow-up visits could be identified by PSA alone compared with 86% at first visit. The incidence of 0.8% per year during 15 years of screening between the ages of 55 and 70 years would diagnose localized prostate cancer in 12% of the population, a value not too different from the 10% diagnosed with prostate cancer during life-time in the absence of screening.

CONCLUSIONS: The present data show that annual screening with PSA diagnoses clinically localized prostate cancer in more than 95% of cases, thus almost completely eliminating the diagnosis of metastatic prostate cancer. Moreover, the number of prostate cancers diagnosed is not significantly increased by screening.

Evaluation of prostASURE index in the detection of prostate cancer: a preliminary report.

Babaian RJ, Fritsche HA, Zhang Z, Zhang KH, Madyastha KR, Barnhill SD
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Urology 1998 Jan;51(1):132-6

OBJECTIVES: Although prostate-specific antigen (PSA) has revolutionized the detection of prostate cancer, it has definite limitations with respect to its clinical sensitivity and specificity. Because a substantial number (20% to 40%) of men undergoing radical prostatectomy have a PSA level of 4.0 ng/mL or less, any new test offering diagnostic improvement must perform well in patients whose PSA level is less than or equal to 4.0 ng/mL, as well as in patients whose PSA is greater than 4.0 ng/mL. The performances of two tests, the ProstASURE index and the percent free PSA test, were evaluated in detecting cancer.

METHODS: We retrospectively analyzed serum samples from 225 men who were grouped into three categories: 94 men who had a normal digital rectal examination and a serum PSA level of 4.0 ng/mL or less, 77 men who were clinically suspected of having benign prostatic hyperplasia (BPH) with a serum PSA level of 4.0 ng/mL or less, and 54 men with localized prostate cancer. The PSA assays were performed using the Hybritech and Tosoh assays and the ProstASURE index was determined by Global Health

Net, Savannah, Ga. Receiver operator characteristic (ROC) curves were constructed to evaluate the performance of these two tests, and the areas under the curve were compared for significance.

RESULTS: The sensitivity and specificity of detecting prostate cancer using ProstateScore were 93% and 81%, respectively. Using a cutoff value of 15%, the sensitivity and specificity of detecting cancer for percent free PSA were 80% and 74%, respectively (sensitivity increased to 93% and specificity to 59% for free PSA at 19%). In men with a total serum PSA level of 4.0 ng/mL or less, ProstateScore had a lower false-positive rate compared to free PSA level at 19% for men with or without clinical BPH as well as for men without clinical BPH using a 15% free PSA threshold. ProstateScore left fewer cancers undetected (7%) compared to free PSA at the 15% cutoff (20%).

CONCLUSIONS: In this study of selected men, ROC curve analysis shows a statistically significant advantage in performance ($P = 0.0023$) for the ProstateScore index compared to free PSA in detecting prostate cancer.

Prostate cancer detection in men with serum PSA concentrations of 2.6 to 4.0 ng/mL and benign prostate examination. Enhancement of specificity with free PSA measurements.

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OBJECTIVE: To determine the detection rate of prostate cancer in a screening population of men with prostate-specific antigen (PSA) concentrations of 2.6 to 4.0 ng/mL and a benign prostate examination, to assess the clinicopathological features of the cancers detected, and to assess the usefulness of measuring the ratio of free to total PSA to reduce the number of prostatic biopsies.

DESIGN: A community-based study of serial screening for prostate cancer with serum PSA measurements and prostate examinations.

SETTING: University medical center.

SUBJECTS: A total of 914 consecutive screening volunteers aged 50 years or older with serum PSA levels of 2.6 to 4.0 ng/mL who had a benign prostate examination and no prior screening tests suspicious for prostate cancer, 332 (36%) of whom underwent biopsy of the prostate.

MAIN OUTCOME MEASURES: Cancer detection rate, clinical and pathological features of cancers detected, and specificity for cancer detection using measurements of percentage of free PSA.

RESULTS: Cancer was detected in 22% (73/332) of men who underwent biopsy. All cancers detected were clinically localized, and 81% (42/52) that were surgically staged were pathologically organ confined. Ten percent of the cancers were clinically low-volume and low-grade tumors, and 17% of those surgically staged were low-volume and low-grade or moderately low-grade tumors (possibly harmless). Using a percentage of free PSA cutoff of 27% or less as a criterion for performing prostatic biopsy would have detected 90% of cancers, avoided 18% of benign biopsies, and yielded a positive predictive value of 24% in men who underwent biopsy.

CONCLUSIONS: There is an appreciable rate of detectable prostate cancer in men with serum PSA levels of 2.6 to 4.0 ng/mL. The great majority of cancers detected have the features of medically important tumors. Free serum PSA measurements may reduce the number of additional biopsies required by the lower PSA cutoff.

Prospective longitudinal evaluation of men with initial prostate specific antigen levels of 4.0 ng/ml. or less.

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PURPOSE: We evaluated the 3-year longitudinal changes in serial serum prostate specific antigen (PSA) levels in men with an

initial PSA of 4.0 ng./ml. or less and no suspicion of prostate cancer.

MATERIALS AND METHODS: A total of 760 men with an initial PSA of 4.0 ng./ml. or less plus a normal or suspicious digital rectal examination and a benign prostate biopsy was enrolled into an every 4-month PSA monitoring study.

RESULTS: Of the 559 men with an initial PSA of 2.0 ng./ml. or less only 3 (0.5%) had a persistently abnormal PSA for 3 years and 1 cancer (0.2%) was detected, and 48 men had a PSA velocity of 0.8 ng./ml. per year or more at year 1 but only 1 (2%) had a persistent rate of increase (2.4 ng./ml. Per year) at 3 years. Of the 201 men with a PSA of 2.1 to 4.0 ng./ml. 85 had an abnormal PSA but only 37 (43%) met the criteria for biopsy. Only 8 of 23 biopsies (35%) revealed cancer. Of the 201 men 24 had a PSA velocity of 0.8 ng./ml. Per year or more at year 1 but only 4 had persistence for 3 years. All 4 men had cancer but they were identified as at high risk by PSA criteria.

CONCLUSIONS: Men with a PSA of 2.0 ng./ml. or less are at low risk for an abnormal PSA or cancer within 3 years and annual monitoring may not be necessary. However, annual monitoring is clinically useful in men with an initial PSA of 2.1 to 4.0 ng./ml. Also, serial monitoring with interval testing in men whose PSA becomes greater than 4.0 ng./ml. Is beneficial in identifying a high risk group requiring biopsy. Finally, PSA velocity did not add further to cancer detection in this population.

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