

PROSTATE CANCER ADJUVANT THERAPY

Printing? Use This!

Table of [Contents](#) 

- > Prevention of radioinduced cystitis by orgotein: a randomized study.
- > Pathological features of hereditary prostate cancer.
- > Familial risk factors for prostate cancer.
- > Mendelian inheritance of familial prostate cancer.
- > Family history and the risk of prostate cancer.
- > Familial patterns of prostate cancer: a case-control analysis.
- > Inhibition of arachidonate 5-lipoxygenase triggers massive apoptosis in human prostate cancer cells.
- > Induction of cyclo-oxygenase-2 mRNA by prostaglandin E2 in human prostatic carcinoma cells.
- > Prostate cancer and supplementation with alpha-tocopherol and beta-carotene: incidence and mortality in a controlled trial.
- > Vitamin E inhibits the high-fat diet promoted growth of established human prostate LNCaP tumors in nude mice.
- > Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized controlled trial. Nutritional Prevention of Cancer Study Group.
- > Inhibitory effects of selenium on the growth of DU-145 human prostate carcinoma cells in vitro.
- > Genistein inhibits proliferation and in vitro invasive potential of human prostatic cancer cell lines.
- > Genistein and biochanin A inhibit the growth of human prostate cancer cells but not epidermal growth factor receptor tyrosine autophosphorylation.
- > Antiproliferative effect of *Pygeum africanum* extract on rat prostatic fibroblasts.

- > 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.
 - > Protective and therapeutic effect of silymarin on the development of latent liver damage.
 - > Protective effects of silymarin against photocarcinogenesis in a mouse skin model.
 - > Protective effects of silymarin against photocarcinogenesis in a mouse skin model.
 - > Proceedings of the American Association for Cancer Research Annual Meeting 36 (0): p 593 1995
 - > Hereditary prostate cancer: epidemiologic and clinical features.
 - > Genetic epidemiology of prostate cancer in the Utah Mormon Genealogy.
 - > Dietary phytoestrogens and prostate cancer.
 - > Inhibition of epidermal growth factor receptor (EGFr) tyrosine kinase activity by silymarin, a polyphenolic antioxidant and potent cancer chemopreventive agent.
 - > Familial clustering of cancers of the breast and prostate in a population-based sample of postmenopausal women.
 - > The anti-oxidant revolution.
 - > Enter the zone.
 - > The Anti-aging zone.
 - > Natural vitamin E (gamma-tocopherol) demonstrates greater inhibition of growth on a human prostate cancer cell line than synthetic vitamin E.
-

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 rectitis 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.

Bastacky SI, Wojno KJ, Walsh PC, Carmichael MJ, Epstein JI

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.

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

Department of Epidemiology, School of Hygiene and Public Health, Johns Hopkins Medical Institutions, Baltimore, Maryland 21205.

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.

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

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.

Ghosh J, Myers CE
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.

Tjandrawinata RR, Dahiya R, Hughes-Fulford M
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.

JAMA 1996 Dec 25;276(24):1957-63

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.

Santibanez JF, Navarro A, Martinez J
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 (IC₅₀ 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
Laboratoires Debat, groupe Fournier, Garches, France.
J Urol 1997 Jun;157(6):2381-7
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.

Zi X, Grasso AW, Kung HJ, Agarwal R
Department of Dermatology, Case Western Reserve University, Cleveland, Ohio 44106, USA.
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.

Kropacova K, Misurova E, Hakova H

Department of Cellular and Molecular Biology Faculty of Sciences, University of P. J. Safarik, Kosice, Slovakia.

kbmb@kosice.upjs.sk

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 aberration 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.

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

Katiyar SK, Korman NJ, Mukhtar H, Agarwal R

Department of Dermatology, Case Western Reserve University, Cleveland, OH 44106, USA.

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.

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

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.

Proceedings of the American Association for Cancer Research Annual Meeting

Eighty-sixth Annual Meeting of the American Association for Cancer Research
Toronto, Ontario, Canada March 18-22, 1995
36 (0): p 593 1995

No abstract.

Hereditary prostate cancer: epidemiologic and clinical features.

Carter BS, Bova GS, Beaty TH, Steinberg GD, Childs B, Isaacs WB, Walsh PC
Department of Urology, Johns Hopkins Medical Institutions, Baltimore, Maryland 21287-2101.
J Urol 1993 Sep;150(3):797-802

No abstract.

Genetic epidemiology of prostate cancer in the Utah Mormon Genealogy.

Cancer Surv 1:47-69, 1982.

No abstract.

Dietary phytoestrogens and prostate cancer.

Proc Annu Meet Am Assoc Cancer Res 36:687, 1995.

No abstract.

Inhibition of epidermal growth factor receptor (EGFr) tyrosine kinase activity by silymarin, a polyphenolic antioxidant and potent cancer chemopreventive agent.

Proc Annu Meet Am Assoc Cancer Res 38:A1766, 1997.

No abstract.

Familial clustering of cancers of the breast and prostate in a population-based sample of postmenopausal women.

Proc Annu Meet Am Assoc Cancer Res 35:A1724, 1994.

No abstract.

The anti-oxidant revolution.

Thomas Nelson Publisher. 1994.

No abstract.

Enter the zone.

Regan Books, 1995.

No abstract.

The Anti-aging zone.

Regan Books, 1999.

No abstract.

Natural vitamin E (gamma-tocopherol) demonstrates greater inhibition of growth on a human prostate cancer cell line than synthetic vitamin E. (in press)

No abstract.

All Contents Copyright © 1995-2009 Life Extension Foundation All rights reserved.

LifeExtension®

These statements have not been evaluated by the FDA. These products are not intended to diagnose, treat, cure or prevent any disease. The information provided on this site is for informational purposes only and is not intended as a substitute for advice from your physician or other health care professional or any information contained on or in any product label or packaging. You should not use the information on this site for diagnosis or treatment of any health problem or for prescription of any medication or other treatment. You should consult with a healthcare professional before starting any diet, exercise or supplementation program, before taking any medication, or if you have or suspect you might have a health problem. You should not stop taking any medication without first consulting your physician.