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Prostate cancer prevention trials in the USA

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Abstract

There is dramatic international variation in prostate cancer mortality rates. The variation suggests that the disease has an environmental cause and encourages the search for a way to prevent it. Androgenic stimulation over a period of time, perhaps due to a high fat diet, has been suggested as a cause of prostate cancer. The corollary to this hypothesis is that lowering androgenic stimulation over time will prevent prostate cancer. 5-Alpha-reductase inhibition through drugs like finasteride have been shown to decrease androgenic stimulation of the prostate. A clinical trial is underway using finasteride to assess this hypothesis. Epidemiological and laboratory studies also suggest that those with high selenium and vitamin E intake have a lower risk of prostate cancer. Recent serendipitous findings of two randomised clinical trials support this. A study to assess these compounds is currently being designed. Other promising but less developed interventions in the chemoprevention of prostate cancer include vitamin D supplementation and diet modification.

Keywords: Prostate; Prostate cancer; Chemoprevention; Clinical trials; 5-Alpha-reductase inhibitor; Selenium; Alpha tocopherol

1. Introduction

There is dramatic international variation in prostate cancer mortality rates. This combined with evidence that risk can be increased through migration from areas of low risk to areas of high risk suggests that environmental elements are important in its aetiology and provides some hope that interventions may decrease prostate cancer risk. Biomarkers, including testosterone and insulin-like growth factor, and nutritional factors, especially meat, fat and dairy intake, have been linked to a greater risk of disease. Higher consumption of selenium and vitamin E, fructose/fruits and tomatoes have all been associated with a reduced occurrence of prostate cancer, but as yet their efficacy for prevention remains unproven [1–3].

A relatively new direction for cancer prevention and control is chemoprevention [4]. Chemoprevention is defined as the use of specific natural and synthetic chemical agents to reverse or suppress carcinogenesis and prevent the development of invasive cancer. Chemoprevention depends on the ability of certain chemical agents to block mutagenesis and control cellular differentiation and proliferation in epithelial tissues. Important to the chemoprevention is the fact that carcinogenesis is a process over time, involving cellular growth and division. Inhibition of or slowing the process can prevent cancers. Already, retinoids and tamoxifen have been shown efficacious in reversing premalignancy and preventing second primary tumours. Especially because the nature of chemoprevention is the treatment of healthy subjects, chemopreventive agents must have low toxicity in order to be clinically useful [5–7].

Several interventions are sufficiently mature that they can be tested in largescale prostate cancer chemoprevention trials. Among them: selenium, alpha-tocopherol and 5-alpha-reductase inhibitors. Data supporting the testing of vitamin D, and of dietary modification are developing [8,9]. Diet modification has little or no morbidity and may have additional benefits by decreasing mortality from other malignancies and cardiac disease.

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2. 5-Alpha-reductase inhibition

The 5-alpha-reductase inhibitor, finasteride, is being tested in the US National Cancer Institute clinical cooperative groups in the Prostate Cancer Prevention Trial (PCPT) which began in 1993 [10]. Key to the hypothesis that 5-alpha-reductase will prevent prostate cancer is the fact that studies of prostate biology support the concept that long-term androgenic stimulation is important to prostate carcinogenesis. Studies further suggest that dihydrotestosterone is the principal androgen responsible for normal and hyperplastic growth of the prostate gland.

Dihydrotestosterone is 10 times more potent an androgen than testosterone. Given that cancer is a process of malignant transformation evolving over time. Therefore, an altered endocrine state, such as suppression of dihydrotestosterone synthesis activity, may have an impact on prostate cells inhibiting carcinogenic transformation. *In vitro* and *in vivo* preclinical observations support this hypothesis [11,12].

In vitro studies have demonstrated that finasteride has a negative influence on the growth of previously established prostate cancer cell lines [13,14]. In studies of prostate cancer tumour grafting into animals, the 5-alpha-reductase inhibitor, turosteride was an effective inhibitor of tumour growth [15–17].

Several animal studies involving rats have demonstrated that 5-alpha-reductase inhibition can prevent or slow the growth of prostate cancer [15,18]. In these studies rats are administered an initiator and testosterone to promote prostate carcinogenesis. Half the rats are treated with a 5-alpha-reductase inhibitor and their rates of development of prostate cancer compared with that of the half that was not treated with the possible preventive agent. Tsukamoto and colleagues had an especially interesting finding in which finasteride appeared more effective at preventing abnormal prostate pathology than the androgen receptor blocker, bicalutamide [15,19].

5-Alpha-reductase inhibitors inhibit the enzyme that converts testosterone to dihydrotestosterone. Finasteride (Proscar) is the first 5-alpha-reductase inhibitor to enter human trials and it has been approved by multiple regulatory bodies for the treatment of benign prostatic hyperplasia (BPH). It lowers dihydrotesterone levels and slightly increases intra-prostatic testosterone levels [4,20,21]. In clinical trials and in common usage, finasteride has a very good safety profile. In a randomised double-blind study, a very small but statistically significant proportion of men reported impotence and/or loss of libido on therapy when compared with men treated with placebo [21]. Finasteride is a well-tolerated and effective alternative to watchful waiting in the treatment of moderate BPH [16,18,22] and has been approved by the US Food and Drug Administration for the treatment of male pattern baldness [16,22–25].

The primary endpoint of PCPT is the reduction of biopsy-proven prostate cancer incidence over a defined period (also known as the period prevalence of the disease). A total of 18 882 healthy men, aged 55 years and older, have been randomised. Half are receiving finasteride (5 mg/day) and half are receiving placebo (one matching tablet per day) for 7 years. All men are screened annually for prostate cancer with digital rectal examination (DRE) and prostate specific antigen (PSA) is performed in a central laboratory. The trial is designed to have a 92% power to detect a 25% reduction in the period prevalence of biopsy-proven disease using a two-sided test with $\alpha = 0.05$. The blinding of the trial is complicated by the known impact of finasteride on the major screening test for prostate cancer, prostate specific antigen (PSA) [26]. PSA levels in finasteride-treated patients do allow for appropriate interpretation of PSA values and does not mask the detection of PCa [25,27]. At 7 years all survivors will undergo a sextant biopsy to determine the period prevalence of prostate cancer. This 10-year study began in 1993 and will achieve its primary endpoint in October 2004 [28].

While the primary objective of this study is to determine whether finasteride can reduce the period prevalence of prostate cancer over a 7-year period, the biological and data resources of this study will provide multiple opportunities to better understand this most common cancer in the US [19,29].

3. Selenium

Selenium is found in a number of food products and there is tremendous geographic variance in terms of its availability. In a laboratory study selenomethionine administration to cancer cell lines resulted in apoptotic cell death and aberrant mitoses [5],

There was enough support for the hypothesis that selenium prevented squamous and basal cell skin cancers such that a randomised placebo controlled trial was conducted. A total of 974 men were randomised [30]. This trial did not find a protective effect in terms of skin cancer but there was a serendipitous finding of a lower rate of prostate cancer. 16 cases in the placebo group versus 4 cases in the treatment group among the 843 men who began the study with a serum PSA less than 4 ng/ml. ($RR = 0.26$ $P = 0.009$). There were significant health benefits also for the other secondary endpoints of total cancer mortality and the incidence of total, lung and colorectal cancer [30].

4. Vitamin E (alpha-tocopherol)

Experimental and epidemiological investigations have suggested that alpha-tocopherol (the most prevalent

chemical form of vitamin E found in vegetable oils, seeds, grains, nuts and other foods might reduce the risk of cancer, particularly lung cancer. This was tested by the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC Study). In the ATBC study a total of 29 133 men aged 50–69 years who smoked five or more cigarettes daily were randomly assigned to receive alpha-tocopherol (50 mg), beta-carotene (20 mg), alpha-tocopherol and beta-carotene, or a placebo daily for 5–8 years (median: 6.1 years). The study is most cited for finding an increase in lung cancer risk among men administered beta-carotene supplements and it also did not find lung cancer benefit for vitamin E administration but did find a substantial 33% reduction in prostate cancer risk in this group; 99 cases among men randomised to vitamin E and 151 among men randomised to receive the vitamin E placebo [31,32].

5. The SELECT trial

Prostate cancer prevention was not a substantive part of the original hypothesis of the selenium study reported by Clark and colleagues nor of the ATBC study of vitamin E and beta-carotene study. Such intriguing serendipitous findings can not be ignored and must be further explored in a prospective randomised clinical trial. The US National Cancer Institute and its cooperative groups are in the process of designing such a study which has been entitled 'SELECT'. It will be a 2×2 design in which one-fourth will receive selenium, one-fourth will receive vitamin E, one-fourth will receive both drugs and one-fourth will receive placebo. The trial will likely enrol more than 32 000 men and run for more than a dozen years.

6. Conclusion

The primary prevention of prostate cancer is a relatively new concept. No agent has yet been found that clearly decreases prostate cancer risk. No promising intervention can be definitively proven without a randomised clinical trial. These trials, whilst large, expensive and long in duration, do provide an opportunity to learn and study a number of factors about the aging male.

References

1. Chan JM, Stampfer MJ, Giovannucci EL, *et al*. What causes prostate cancer A brief summary of the epidemiology? *Semin Cancer Biol* 1998, **8**, 263–273.
2. Giovannucci E, Clinton SK. Tomatoes, lycopene, and prostate cancer. *Proc Soc Exp Biol Med* 1998, **218**, 129–139.
3. Giovannucci E. Selenium and risk of prostate cancer. *Lancet* 1998, **352**, 755–756.
4. Greenwald P, Kelloff G, Burch-Whitman C, Kramer BS. Chemoprevention. *CA Cancer J Clin* 1995, **45**, 31–49.
5. Redman C, Scott JA, Baines AT, *et al*. Inhibitory effect of selenomethionine on the growth of three selected human tumor cell lines. *Cancer Lett* 1998, **125**, 103–110.
6. Hong WK, Lippman SM. Cancer chemoprevention. *J Natl Cancer Inst Monogr* 1995, 49–53.
7. Lippman SM, Benner SE, Hong WK. Cancer chemoprevention. *J Clin Oncol* 1994, **12**, 851–873.
8. Ma J, Stampfer MJ, Gann PH, *et al*. Vitamin D receptor polymorphisms, circulating vitamin D metabolites, and risk of prostate cancer in United States physicians. *Cancer Epidemiol Biomarkers Prev* 1998, **7**, 385–390.
9. Thompson IM, Coltman CAJ, Crowley J. Chemoprevention of prostate cancer: the Prostate Cancer Prevention Trial. *Prostate* 1997, **33**, 217–221.
10. Coltman CAJ, Thompson IMJ, Feigl P. Prostate Cancer Prevention Trial (PCPT) update. *Eur Urol* 1999, **35**, 544–547.
11. Brawley OW, Ford LG, Thompson I, Perlman JA, Kramer BS. 5-Alpha-reductase inhibition and prostate cancer prevention. *Cancer Epidemiol Biomarkers Prev* 1994, **3**, 177–182.
12. Trachtenberg J. Healthcare resources should be targeted to chemoprevention: the argument against. *Eur Urol* 1996, **29**(Suppl. 2), 17–18.
13. Bologna M, Muzi P, Biordi L, Festuccia C, Vicentini C. Finasteride dose-dependently reduces the proliferation rate of the LnCap human prostatic cancer cell line *in vitro*. *Urology* 1995, **45**, 282–290.
14. Delos S, Iehle C, Martin PM, Raynaud JP. Inhibition of the activity of 'basic' 5 alpha-reductase (type 1) detected in DU 145 cells and expressed in insect cells. *J Steroid Biochem Mol Biol* 1994, **48**, 347–352.
15. Tsukamoto S, Akaza H, Imada S, *et al*. Chemoprevention of rat prostate carcinogenesis by use of finasteride or casodex. *J Natl Cancer Inst* 1995, **87**, 842–843.
16. Roehrborn CG, Boyle P, Bergner D, *et al*. Serum prostate-specific antigen and prostate volume predict long-term changes in symptoms and flow rate: results of a four-year, randomized trial comparing finasteride versus placebo. PLESS Study Group. *Urology* 1999, **54**, 662–669.
17. Zaccheo T, Giudici D, di Salle E. Effect of turosteride, a 5 alpha-reductase inhibitor, on the Dunning R3327 rat prostatic carcinoma. *Prostate* 1997, **30**, 85–91.
18. Homma Y, Kaneko M, Kondo Y, Kawabe K, Kakizoe T. Inhibition of rat prostate carcinogenesis by a 5alpha-reductase inhibitor, FK143. *J Natl Cancer Inst* 1997, **89**, 803–807.
19. Zaccheo T, Giudici D, di Salle E. Effect of early treatment of prostate cancer with the 5alpha-reductase inhibitor turosteride in Dunning R3327 prostatic carcinoma in rats. *Prostate* 1998, **35**, 237–242.
20. Geller J. Clinical review: 67: approach to chemoprevention of prostate cancer. *J Clin Endocrinol Metab* 1995, **80**, 717–719.
21. Stoner E. Three-year safety and efficacy data on the use of finasteride in the treatment of benign prostatic hyperplasia. *Urology* 1994, **43**, 284–292.
22. Nickel JC, Fradet Y, Boake RC, *et al*. Efficacy and safety of finasteride therapy for benign prostatic hyperplasia: results of a 2-year randomized controlled trial (the PROSPECT study). PROscar Safety Plus Efficacy Canadian Two year Study. *CMAJ* 1996, **155**, 1251–1259.
23. Ekman P. Finasteride in the treatment of benign prostatic hypertrophy: an update. New indications for finasteride therapy. *Scand J Urol Nephrol* 1999, **203**(Suppl.), 15–20.
24. Gormley GJ. Finasteride: a clinical review. *Biomed Pharmacother* 1995, **49**, 319–324.
25. Guess HA, Gormley GJ, Stoner E, Oesterling JE. The effect of finasteride on prostate specific antigen: review of available data. *J Urol* 1996, **155**, 3–9.

26. Feigl P, Blumenstein B, Thompson I, *et al*. Design of the Prostate Cancer Prevention Trial (PCPT). *Control Clin Trials* 1995, **16**, 150–163.
27. Oesterling JE, Roy J, Agha A, *et al*. Biologic variability of prostate-specific antigen and its usefulness as a marker for prostate cancer: effects of finasteride. The Finasteride PSA Study Group. *Urology* 1997, **50**, 13–18.
28. Coltman CAJ, Thompson IMJ, Feigl P. Prostate Cancer Prevention Trial (PCPT) update. *Eur Urol* 1999, **35**, 544–547.
29. Thompson IM, Coltman CAJ, Crowley J. Chemoprevention of prostate cancer: the Prostate Cancer Prevention Trial. *Prostate* 1997, **33**, 217–221.
30. Clark LC, Dalkin B, Krongrad A, *et al*. Decreased incidence of prostate cancer with selenium supplementation: results of a double-blind cancer prevention trial. *Br J Urol* 1998, **81**, 730–734.
31. Albanes D, Heinonen OP, Taylor PR, *et al*. Alpha-Tocopherol and beta-carotene supplements and lung cancer incidence in the alpha-tocopherol, beta-carotene cancer prevention study: effects of base-line characteristics and study compliance. *J Natl Cancer Inst* 1996, **88**, 1560–1570.
32. Anonymous. The alpha-tocopherol, beta-carotene lung cancer prevention study: design, methods, participant characteristics, and compliance. The ATBC Cancer Prevention Study Group. *Ann Epidemiol* 1994, **4**, 1–10.