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A review of phase III clinical trials of prostate cancer chemoprevention

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ABSTRACT

INTRODUCTION Prostate cancer is an excellent target for chemoprevention strategies; given its late age of onset, any delay in carcinogenesis would lead to a reduction in its incidence. This article reviews all the completed and on-going phase III trials in prostate cancer chemoprevention.

PATIENTS AND METHODS All phase III trials of prostate cancer chemoprevention were identified within a Medline search using the keywords 'clinical trial, prostate cancer, chemoprevention'.

RESULTS In 2003, the Prostate Cancer Prevention Trial (PCPT) became the first phase III clinical trial of prostate cancer prevention. This landmark study was terminated early due to the 24.8% reduction of prostate cancer prevalence over a 7-year period in those men taking the 5α-reductase inhibitor, finasteride. This article reviews the PCPT and the interpretation of the excess high-grade prostate cancer (HGPC) cases in the finasteride group. The lack of relationship between cumulative dose and the HGPC cases, and the possible sampling error of biopsies due to gland volume reduction in the finasteride group refutes the suggestion that this is a genuine increase in HGPC cases. The other on-going phase III clinical trials of prostate cancer chemoprevention – the REDUCE study using dutasteride, and the SELECT study using vitamin E and selenium – are also reviewed.

CONCLUSIONS At present, finasteride remains the only intervention shown in long-term prospective phase III clinical trials to reduce the incidence of prostate cancer. Until we have the results of trials using alternative agents including the on-going REDUCE and SELECT trials, the advice given to men interested in prostate cancer prevention must include discussion of the results of the PCPT. The increased rate of HGPC in the finasteride group continues to generate debate; however, finasteride may still be suitable for prostate cancer prevention, particularly in men with lower urinary tract symptoms.

KEYWORDS

Prostate cancer – Chemoprevention – Phase III clinical trials – Finasteride – Prostate Cancer Prevention Trial – REDUCE trial – SELECT trial

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Prostate cancer is now the most common non-dermatological male malignancy and is the second most common cause of male cancer related death in the UK; approximately 1 in 14 men in the UK will be diagnosed with prostate cancer in their life-time.[1] Prostate cancer is strongly associated with increasing age, with the mean age of onset being 72–74 years[2] and 96% cases occurring in men over 60 years.[3] Cancer chemoprevention can be thought to include reversal and delay of carcinogenesis, in addition to prevention. The high incidence and late age of onset make prostate cancer an ideal target for chemoprevention strategies. Even a modest delay in carcinogenesis would significantly reduce the incidence of the disease. This article reviews completed and on-going phase III clinical trials, of various compounds proposed as prostate cancer preventive agents. It will also discuss the future of research in this area.

Patients and Methods

A Medline search using the keywords 'clinical trial, prostate cancer, chemoprevention' identified all the

completed and on-going prostate cancer prevention phase III trials. Selected papers from the reference lists of these articles were also included. A Medline search using the keywords 'PCPT finasteride' identified papers and reference lists therein concerning analysis of the Prostate Cancer Prevention Trial (PCPT).

Results and Discussion

5α-Reductase inhibitors

FINASTERIDE

5α-Reductase is the enzyme responsible for conversion of circulating testosterone to the more potent dihydrotestosterone (DHT), responsible for prostate epithelial proliferation.[4] The PCPT, using the 5α-reductase inhibitor finasteride, was the first randomised controlled phase III trial of prostate cancer prevention.[5] Between October 1993 and March 2003, the PCPT recruited 18,882 men aged 55 years or older who had normal digital rectal examinations (DRE) and a prostate specific antigen (PSA) concentration of 3.0 ng/ml or less. The men were randomised to finasteride 5 mg/day or placebo for 7 years. Prostate biopsies were performed if PSA exceeded 4.0 ng/ml or the DRE became abnormal. The PSA of men on finasteride was multiplied by 2–2.3x to ensure equal rates of biopsy in the two arms. Men not diagnosed with prostate cancer during the trial were invited to have an end-of-study biopsy. Prostate cancer was detected in 18.4% of those taking finasteride compared with 24.4% of controls and this led to the trial being ended early. The finasteride group experienced more sexual side-effects and the placebo group experienced more urinary side-effects. Tumours of Gleason grade 7–10, however, were more frequent amongst the finasteride group (6.4%) compared with the placebo group (5.1%).

The reasons for the increased rate of high-grade prostate cancer (HGPC) in the finasteride group have been fiercely debated. Concern over this issue has prevented wide-spread translation of prostate cancer prevention by finasteride into clinical practice. There are a number of reasons, however, why this result should not prevent the introduction of this intervention.

As the authors of the PCPT suggest, if finasteride had genuinely induced HGPC, the ratio between HGPC in the finasteride and placebo groups would have gradually increased with cumulative dose. In fact, the ratio was highest at 3.6 during year 2, lowest at 1 during year 4 and finished the trial at 1.6 in year 7.[6] The apparent increase in HGPC may have been due to the fact that grading of prostate tumours was more accurate in the finasteride group. If a patient had a HGPC at radical prostatectomy, the likelihood that this was found at biopsy was 70.3% in the finasteride group and 50% in the placebo group.[5] The prostate volume reduction due to finasteride therapy leading to detection-bias may explain this difference. Adjusting for age, race, family history and PSA, the odds ratio for HGPC (finasteride group versus placebo group) was 1.28, suggesting that finasteride genuinely increased the risk of HGPC. This excess risk, however, disappeared when adjusted for the number of biopsy cores and gland volume, the odds ratio dropped to 1.03.[7] Finally, even if finasteride genuinely increases the rate of HGPC, there is evidence that this would be outweighed by the overall reduction in prostate cancer incidence. Assuming a 24.8% reduction in the incidence of prostate cancer for 5 years in the US, it has been estimated that 316,760 person-years could be saved. This benefit would only be reduced to 262,567 person-years assuming an increase of 6.9% in the proportion of men with HGPC.[8] Another recent analysis of mortality benefit potentially attributable to finasteride estimates an increase of 1.7 months in 15-year, cause-specific survival in a population in which patients are treated with radical prostatectomy, even assuming finasteride increases HGPC.[9] The size of this benefit, however, is highly dependent on the particular population study used for population estimates of prostate cancer incidence and mortality.[10] At present for the man worried about the risk of prostate cancer, particularly in the presence of lower urinary tract symptoms, finasteride is worthy of frank discussion.

DUTASTERIDE

Dutasteride is an alternative 5α-reductase inhibitor that is currently under investigation in the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial. DHT synthesis from testosterone is catalysed by 5α-reductase types I and II. Finasteride selectively inhibits the type II isoenzyme whereas dutasteride is a dual inhibitor.[11] There is evidence that type I 5α-reductase is over-expressed in some prostate malignancies.[12] Dutasteride results in an overall 90–94% suppression of DHT compared with 67–76% by finasteride.[13] Retrospective analysis of data from three trials designed to study dutasteride's efficacy and safety in patients with benign prostatic hyperplasia suggest that prostate cancer incidence was reduced by dutasteride.[14] The REDUCE trial is a 4-year, prospective, multicentre, randomised, placebo-controlled phase III trial that is currently investigating dutasteride in men with an increased risk of prostate cancer. A total of 8000 men, 50–75 years old have been enrolled and allocated to receive 0.5 mg dutasteride or placebo. Their PSA must be 2.5–10 ng/ml (50–60 years) or 3.0–10 ng/ml (60–75 years). Free PSA must be 25% or less. A 6–12 core

prostate biopsy showing no evidence of malignancy or high-grade prostatic intra-epithelial neoplasia must have been performed within 6 months prior to recruitment.[15] Men with international prostate symptom scores > 25 or prostate volumes > 80 ml are excluded in order to reduce the number of men requiring surgery for benign prostatic hyperplasia. The primary end-points will be the histology of prostate biopsies performed at 24 and 48 months.

Selenium and vitamin E

The Selenium and Vitamin E Cancer Prevention Trial (SELECT) is a phase III, randomised, placebo-controlled trial of prostate cancer prevention that is expected to report in 2013.[16] Selenium is an anti-oxidant micronutrient. Data arising from The Netherlands Cohort Study suggest an inverse relationship between selenium and prostate cancer.[17] Selenium content was measured in toenail clippings as a marker of dietary intake. A total of 58,279 men were followed up for a mean of 6.3 years; 540 incident prostate carcinoma cases were identified. Prostate cancer incidence was reduced by 31% in the highest quintile for selenium content, although this effect was most apparent in ex-smokers and smokers rather than men who had never smoked. In a similar case-control study within the Health Professionals Follow-up Study, selenium content of toenails was negatively associated with the risk of advanced prostate cancer; comparing the highest and lowest quintiles of selenium content, the odds ratio was 0.49.[18] The Nutritional Prevention of Cancer Study was an interventional trial that used 200 μg/day selenium supplements administered over an average of 7.5 years to 927 men; the relative risk of prostate cancer diagnosis was 0.51.[19] However, there are a number of weaknesses in this trial: many more men in the control group underwent prostate biopsy, this could not be explained by differences in PSA levels; prostate cancer reduction was confined to those men who were selenium deficient prior to supplementation and only those men with a baseline PSA = 4 ng/ml; and finally, the proportion of subjects reporting previous cancers was 35% lower in the selenium group than in the placebo group.[19,20]

α-Tocopherol is the most powerful anti-oxidant of the tocopherols collectively known as vitamin E. There is evidence that vitamin E protects against death from prostate cancer. A case-control study of 145 men found that prostate cancer risk was reduced in those with the highest serum α-tocopherol concentrations. The odds ratio was 0.65 for the highest versus the lowest quintiles.[21] A 17-year follow-up study found that low levels of vitamin E were associated with higher rates of prostate cancer deaths in smokers (RR = 8.3).[22] A cohort study of 47,780 men (Health Professional Follow-up Study) showed that smokers were at increased risk of prostate cancer and that this increased risk was abolished by vitamin E supplementation.[23] The most powerful assessment, so far, of the effect of vitamin E on prostate cancer came in the Alpha-Tocopherol, Beta Carotene Cancer Prevention Trial.[24] This interventional trial was primarily designed to examine whether these agents could reduce lung cancer in smokers, prostate cancer incidence was a secondary endpoint. The study enrolled 29,133 male smokers aged 50–69 years. For those receiving 50 mg α-tocopheryl acetate supplements over a mean period of 6.1 years, the prostate cancer incidence fell to 11.7 per 100,000 compared with 17.8 per 100,000 in those not receiving α-tocopherol. However, 99% of the participants were current or past smokers and it is, therefore, unknown if these results are applicable to non-smokers.[24]

The SELECT study has a 2x2 factorial design where the study population is divided into three treatment groups (200 mg selenium, 400 mg α-tocopherol and both agents) and a placebo group to assess prostate cancer prevention.[16] A total of 32,400 men, ≥ 50 years of age for African Americans and ≥ 55 years for Caucasians, with normal DRE and PSA ≤ 4 ng/ml have already been recruited to undergo a minimum of 7 years and a maximum of 12 years intervention.[25] The primary end-point of prostate cancer diagnosis will be assessed by annual DRE, PSA measurement and appropriate biopsies. There will be no end of trial biopsy.

Other agents/future directions

The ideal chemopreventive agent should be non-toxic, cheap and with good bioavailability following oral administration. Numerous epidemiological, *in vitro* and early clinical studies have identified a range of low toxicity dietary factors with potential prostate cancer preventive effects. In the future, we can look forward to clinical trials of many nutritional agents including genistein, lycopene, tea polyphenols and omega-3 fatty acids.[26] The transgenic mouse model of prostate carcinoma (TRAMP) is a powerful tool with which to screen potential agents in order to prioritise future phase III clinical trials.[27] This model develops prostate carcinoma that mimics the heterogeneity of human disease and metastasises to lymph nodes, lung and occasionally bone or kidney.[28] To date, the TRAMP model has been used to show that: (i) celecoxib delays prostate carcinogenesis, reduces primary tumour size and prevents metastasis;[29,30] (ii) green tea polyphenols[31] and doxazocin[32] reduce primary tumour growth and inhibit metastasis completely; and (iii) genistein from soy reduces the incidence of poorly differentiated carcinoma.[33]

The development of biomarkers will be a necessary step in the effective screening of all the potential agents

in smaller phase II trials. Trials with clinical end-points such as cancer incidence and survival take many years and several thousand participants. Biomarkers such as PSA and insulin-like growth factor (IGF)-1[34,35] will act as surrogate end-points in smaller, shorter trials and identify those agents that justify the resources required to run a large phase III clinical trial. The challenge is to validate biomarkers whose laboratory measurements predict, with sufficient confidence, the clinical course of disease. A phase II clinical trial involving 100 mg of soy isoflavone taken twice daily by 41 men with known prostate cancer, for 3–6 months demonstrated a decrease in the PSA rise, with PSA stabilisation occurring in 83% of patients with hormone-sensitive disease and in 35% of hormone-refractory cases.[36] In a similar trial, 59 men with early prostate cancer were treated for 12 weeks with 60 mg of soy isoflavones; PSA was reduced or stable in 69% of treated men compared with 55% of controls.[37] A phase II trial of lycopene in men with newly diagnosed prostate cancer showed lycopene to reduce PSA, IGF-1 and connexin 43 expression; in the prostatectomy specimens, high-grade prostatic intraepithelial neoplasia and tumour growth were both reduced.[38]

Conclusions

At present, finasteride remains the only intervention shown in long-term prospective phase III clinical trials to reduce the incidence of prostate cancer. Until we have the results of trials using alternative agents including the on-going REDUCE and SELECT trials, the advice given to men interested in prostate cancer prevention must include discussion of the results of the PCPT. The increased rate of high-grade prostate cancer in the finasteride group continues to generate debate; however, finasteride may still be suitable for prostate cancer prevention, particularly in men with lower urinary tract symptoms.

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