Chemoprevention of prostate cancer: lessons learned

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INTRODUCTION

Prostate cancer, which affects one man in six in the USA, is an ideal tumour to target with preventive efforts, for several reasons:

• It develops and causes morbidity and mortality late in life, and therefore any reduction in risk or delay in diagnosis could have a significant effect on mortality.
• There are many potential causes.
• There are many possible preventive agents and interventions.

With the continued increase in the lifetime risk of a diagnosis of prostate cancer, as well as the focus on the cost of care and risk of complications, interest in preventing this disease will almost certainly increase over time.

Since the inception of the Prostate Cancer Prevention Trial (PCPT) in 1993 and the first report of its outcome in 2003, several other phase III studies have been initiated in addition to many small studies. Here I examine eight lessons that have been learned from those studies.

MEN ARE INTERESTED IN CHEMOPREVENTION

It is clear that ageing men in the USA and in other countries are interested in reducing their risk of prostate cancer. The first evidence of this interest came from the high initial accrual rates of the PCPT [1]. Although we anticipated that the accrual of 18 000 men would take 3 years, 18 882 were accrued in this period. The initial interest was overwhelming, in 2003, several other phase III studies have been initiated in addition to many small studies. Here I examine eight lessons that have been learned from those studies.

PREVENTION STUDIES CAN BE DONE

A challenge to the prevention of prostate cancer is its fundamental basis; a man who is disease-free must take an agent that might have side-effects to reduce his risk of disease. Although the lifetime risk of prostate cancer in the USA is 18% [3], the converse is that the use of preventive agents in the USA is unnecessary in at least 82% of men. With this in mind, before the PCPT it was not certain whether chemoprevention studies could be completed, given that a healthy, asymptomatic population was required to be enrolled. Other challenges include the need for regular dosing, regular follow-up, and even prostate biopsy in some designs. Despite these challenges, three phase III studies and one relatively large phase IIb study were successfully completed, i.e. the PCPT (finasteride) [4], the REDUCE trial (dutasteride) [5], the SELECT trial (selenium, α-tocopherol) [6] and the GTX-006-211 (toremifene) [7].

PREVENTION IS POSSIBLE

Although extensive epidemiological evidence suggests that lifestyle and exposure might be associated with 43–58% of the risk of prostate cancer [42–57% of the risk might be genetic] [8,9], until 2003 it was unknown whether a preventive strategy could significantly reduce a man’s risk of prostate cancer. Fifteen months before the final scheduled biopsy of the PCPT, which investigated the 5α-reductase inhibitor finasteride, the independent Data and Safety Monitoring Committee recommended the study be closed because of overwhelming evidence that the study’s results were positive; there was a 24.8% reduction in the risk of prostate cancer in men receiving finasteride [10]. Recently, we described an intriguing observation related to detecting cancer in men receiving finasteride; the drug improves the sensitivity of the PSA test to detect all cancers and to detect high-grade disease [11]. These data suggest that the magnitude of the reduction in risk might be >24.8%, and they might help to explain the increase in high-grade cancers observed, and that most of the high-grade disease was found in biopsies taken because of elevated PSA levels and abnormality on the DRE.

Recent decision analyses showed that, even if an increase in high-grade disease occurred, as was noted in the study, the substantial reduction in incidence of disease of Gleason score ≤6 would be expected to reduce the risk of prostate cancer death in the population [12].

IT IS NOT REALLY PREVENTION, IT IS RISK REDUCTION

When a person takes an 81 mg aspirin tablet to prevent heart disease, he or she is doing so not to eliminate the risk of disease but to reduce the risk of disease. Similarly, ‘chemoprevention’ of prostate cancer might not be the best term for this strategy, and it should be called ‘risk reduction’. This terminology helps patients to consider the value of prevention against the background of other options to control the disease. Currently, with PSA screening, a Caucasian man in the USA has an 18% lifetime risk of a diagnosis of prostate cancer and a 3% risk of death from prostate cancer. Because it is unknown whether current risk-reduction strategies will affect mortality rates [and such data will probably not be forthcoming because of the sizes of study that would be required, i.e. almost 100 000 men to receive one treatment vs placebo], a man considering a risk-reduction strategy might frame the decision in the manner outlined below, using the PCPT results as an example.

• Without finasteride: 18% lifetime risk; 3% mortality [3];
• With finasteride: relative risk reduced by 24.8% [4], which would result in a 13.5% lifetime risk if this risk reduction did not change over time; unknown change in mortality.

These estimates are crude, at best; the current lifetime risk of 18% reflects the fact that only about half of man in the USA have regular PSA screening. Also, the PCPT risk-reduction results might only be achieved with regular PSA screening and with the 7-year biopsy, as was done in the study. Among a population of
men undergoing more regular screening tests, the lifetime risk would be expected to be greater and therefore, with a reduction in risk of a quarter, the absolute reduction would similarly be greater.

**CHANGING PRACTICE FOR PREVENTION REQUIRES THAT A HIGHER HURDLE IS OVERCOME**

After publishing the results of the PCPT, initial interest in the use of finasteride to prevent prostate cancer was limited, primarily because of the increased risk of high-grade disease. Interest might have increased recently as a result of new information related to the performance of PSA in men receiving finasteride and after other analyses of the outcomes of the study.

Nonetheless, these results should lead us to consider how the USA healthcare system would adopt potential prevention strategies. The current focus in the USA is on frequent PSA testing, with biopsy for PSA values as low as 2.5 ng/mL. The result of this approach has been an increasing likelihood of a prostate cancer diagnosis during a man’s lifetime in the USA. Although the effect of this approach on population mortality remains unknown, there is an impact in terms of healthcare costs, as well as a reduction in the quality of life of treated patients (anxiety and changes in urinary, sexual and bowel function).

It appears that a prevention strategy, in practice, would require a much lower risk of toxicity than current screening-and-treatment approaches. That little interest has been shown in the use of finasteride for this purpose, despite its other benefits in terms of urinary function and minor impact on sexual function, is most probably due to the potentially higher risk of high-grade disease associated with finasteride use, and it illustrates that a prevention strategy for prostate cancer would currently need to have essentially no toxicity. As agents are selected for this purpose, it might be a better strategy to rank them by toxicity and side-effects rather than by efficacy.

**PREVENTION STUDIES CAN BE DONE RELATIVELY QUICKLY**

The randomized controlled trial is the method by which standards of care in clinical practice are established. Unfortunately, trials for treating prostate cancer often require many years to complete, e.g. despite enrolling a seemingly high-risk population, a recently reported study evaluating the effect of adjuvant radiotherapy for pathological T3 prostate cancer on metastasis-free survival required almost 20 years to complete [13].

By contrast, the PCPT was activated in late 1993 and enrolled its first patients in 1994, and the results were published in 2003. The rapid accrual to SELECT and the on-schedule completion of REDUCE indicate that these studies can be expected to report their results soon. These observations show that studies of prevention (risk reduction) of prostate cancer can be completed within periods in the range expected for studies of more advanced stages of the disease.

**ANCILLARY OBSERVATIONS CAN BE EXTRAORDINARY**

Large-scale prevention studies generally rely on regular surveillance of a healthy population, and the only significant difference between the study arms is the use of the medication under study. As a result of monitoring for the disease and potential toxicities in such large cohorts, other associations can easily be explored. The results of the PCPT show this effect and include the following observations.

- Prostate cancer is not uncommon at PSA levels of <4.0 ng/mL. There is no lower level of PSA below which there is no risk of prostate cancer [10].
- Previously, it was thought that high-grade cancers are occasionally found at lower levels of PSA because they ‘don’t make PSA’. An analysis of the performance of the PSA test in the PCPT among a large group of men, all of whom had a prostate biopsy, showed clearly that PSA testing performs best in the detection of high-grade cancer [14].
- Erectile dysfunction, whether prevalent or incident, is a harbinger of subsequent cardiovascular disease [15]. This association had previously been proposed but not confirmed.
- Diabetes confers a significant reduction in risk of the subsequent development of low- and high-grade prostate cancer [16]. This counterintuitive observation will lead to important investigations.
- Finasteride significantly improves the sensitivity of PSA for prostate cancer detection [11].

- It is possible, by using a group of risk factors that are independently related to prostate cancer risk, to predict an individual man’s risk of prostate cancer [17]. This relation has been posted on the Internet (at www.compass.fhcrc.org/edrnncl/bin/calculator/main.asp) as a risk calculator for physicians to use.

**BEFORE PREVENTION IS SUCCESSFUL IN GENERAL PRACTICE, EDUCATION OF PHYSICIANS AND PATIENTS WILL PROBABLY BE NECESSARY**

Discussing opportunities for reducing the risk of prostate cancer with healthy patients is challenging, for several reasons.

- Physicians have limited time for health promotion activities during routine consultations.
- The outcomes of prevention studies are complex. Imagine how difficult it is for an academic physician to understand ‘receiver operating characteristic curves’ of PSA with and without finasteride. Now imagine explaining those results to a patient considering prevention strategies during a 15-min consultation.
- There are no agents approved for the prevention of prostate cancer.

Because of these challenges, it will probably be either public health officials or primary-care practitioners who will begin to make inroads into education about risk-reduction among at-risk populations. A ‘needs assessment’ would probably identify the following high priorities.

- Extensive educational materials (DVDs, CD-ROMs and Internet sites) for patients.
- Psychometric studies to help patients weigh their priorities in making a decision.
- Web-based calculators to estimate potential risks and benefits for individual patients.
- Educational materials for physicians and other healthcare providers (these materials will be essential, because of the complexity of the risk-reduction ‘message’ that may result from clinical trials).

**CONCLUSION**

Given the tremendous body of knowledge that has emerged from chemoprevention...
trials to date, the dramatic public interest in this approach, and the growing risk of disease in developed countries, the emphasis on reducing the risk of prostate cancer can be expected to receive increasing attention. This body of knowledge can be expected to expand further with the completion of ongoing phase III studies.

CONFLICTS OF INTERESTS

The author has declared no conflicts of interests.

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Abbreviation: PCPT, Prostate Cancer Prevention Trial.