Prostate cancer – chemoprevention

Fritz H. Schröder, Wytske M. van Weerden

Department of Urology, Erasmus MC, University Medical Centre, Rotterdam, The Netherlands

Introduction

Epidemiological data, specifically the large differences in the incidence and mortality of prostate cancer in different parts of the world, provide strong leads for the potential effectiveness of preventive measures applied to men at risk for prostate cancer. Candidate mechanisms and studies will be reviewed.

Definitions of prevention

Cancer prevention has been sub-classified as follows:

- **Primary prevention:** intervention to prevent the occurrence of cancer in healthy people.
- **Secondary prevention:** intervention in the subclinical phase, no cancer diagnosed, prevent disease in an 'at risk' population.
- **Tertiary prevention:** alter the course of minimal clinical disease.

All three types of prevention are subject to study. Primary prevention is population based and requires large trials ideally with the endpoint of cancer mortality. Secondary prevention entails screening for cancer with the goal of early detection in populations at risk. Tertiary prevention has the goal of slowing the progression of clinically diagnosed minimal disease. The typical situation in prostate cancer: a rising prostate specific antigen (PSA) after failed attempts of curative management.

The field of prevention of prostate cancer is developing very rapidly. A complete review is a challenge, which is difficult or impossible to meet. An attempt will be made to cover the most important aspects and to discuss them in relation to the epidemiological findings and the knowledge of endocrine dependence of the prostate and of prostate cancer specifically.

Methodology

Obviously, investigations relating to the three different definitions of cancer prevention require different methodology. Primary prevention addresses the general population at risk for a certain disease and, in the case of prostate cancer, should consider the timing and duration of the subclinical phase of the disease. To address this issue properly investigators must determine whether they wish to address the initiation or progression phase of the disease. Strong evidence exists that prostate cancer is already initiated at ages 30–35 [1]. Progression, as witnessed by worldwide incidence data, probably starts around the age of 50 years. Due to the very long natural history of the disease long observation times are required to reach the most suitable endpoint, prostate cancer mortality, and surrogate endpoints are therefore in common use.

Secondary prevention, screening for prostate cancer, will not be covered within this presentation.

Considering the increasing number of men who experience progression after potentially curative management of prostate cancer, tertiary prevention has become a major issue. The methodology is less demanding: clinical progression or progression identified by means of PSA can be utilised as an endpoint, although with some caution. Recruitment to studies is easy because of ignorance about the best management of patients with minimal disease and rising PSA. In line with the shorter duration trials, tertiary prevention can also address issues like dosage, treatment duration, proper participant selection, effectiveness in relation to available prognostic factors and others. It is an open question whether agents and regimens shown to be effective in tertiary prevention can also be considered to qualify for primary prevention or primary prevention trials.

Why prevention in prostate cancer?

The incidence and mortality of prostate cancer shows strong worldwide variations [2]. Prior to the PSA era, which has induced strong increases in the incidence of prostate cancer worldwide, the highest rates of incidence and mortality were found in African-Americans. The lowest rates were identified in Japan and other Asian countries. Ten to fifteen-fold differences in mortality rates have been reported. Racial predetermination is unlikely because of the results of the

so-called 'migrant studies'. These show that incidence and mortality rise in Japanese men who migrate from the mainland to Hawaii or to California [3]. Epidemiological investigations identify lifestyle, above all diet, as the major leads. Genetic predisposition is likely. A high rate of concurrence of prostate cancer in identical twins has been revealed [4]. However, the genetic mechanisms unraveled so far explain only a very small fraction of prostate cancer cases as being genetically pre-disposed. Lifestyle, and specifically what has been termed as the 'Western diet', is likely to induce prostate cancer [5]. Nutritional factors, such as meat, fat and dairy intake, which are common in Western diets, have been linked to a greater risk of the disease [6]. It is possible if not likely, however, that foodstuffs used in countries with a very low prostate cancer mortality are protective. These include plant-derived anti-oxidants and soy products which contains isoflavones such as daidzeine and genisteine, which have weak oestrogenic properties and may function as selective androgen receptor modulators (SARMS). For many of the epidemiological findings, mechanisms have not been established. It is possible, therefore, that the Western diet does not initiate or promote prostate cancer, but that the lower incidence and mortality rates in Far Eastern countries are due to the protective mechanism available in foods that are not commonly used in the West. This would allow the application of dietary supplements with a preventive action to Western populations without having to change their dietary habits.

A vegetarian diet, as is used in Eastern countries, was also shown to influence the levels of circulating androgens in men [7]. In addition, in a case-control study, Japanese men had lower serum testosterone levels than Dutch men [8]. This provides a link to the endocrine dependence of prostate cancer, which may play an important role in the phase of promotion to clinically relevant disease. Several food products have weak properties of 5 alpha-reductase (5AR) inhibition, which leads to a decrease of 5 alpha-dihydrotestosterone (DHT), the most important androgen in prostatic tissue. 5 alpha-reductase inhibitors (5ARIs) have been identified as important preventive agents and will be discussed later in this review.

Possible preventive mechanisms and agents

Up to now the approach of inhibiting the two known 5AR enzymes, type I and type II, which are responsible for synthesising DHT from testosterone in prostatic tissue and in peripheral tissues, has been the most studied and most effective approach. In men with benign prostatic enlargement the use of clinically available 5ARIs leads to a reduction in prostatic volume of around 30%, and serum PSA levels are reduced by 50 to 60%. The mechanism by which prostate cancer is prevented is subject to intense debate. The results and problems of the only completed clinical study, the prostate cancer prevention trial (PCPT), will be subject to more discussion [9,10].

Anti-oxidants are second in line on the list of candidates for chemoprevention of prostate cancer. Their potential effectiveness is based on the working hypothesis that residual oxygen species (ROS), mainly super-oxide which accumulates in the aging body, may play an important role in prostate cancer pathogenesis. Anti-oxidants catalyse the process of transforming super-oxide to O_2 and to water at several levels. Selenium, one of the anti-oxidants under study, catalyses glutathione paroxydase, an enzyme important in the removal of hydrogen peroxide. Food products with anti-oxidant activity include green tea containing flavonoids, red wine (quercitine), vitamin E, selenium and lycopene, the red colour of the tomato and other substances from vegetables.

The mechanism of action of the isoflavonoids in soy products is not entirely clear. They function as SARMs but may have additional poorly identified activities. Dietary components which show weak 5AR inhibition include serenoa repens, a substance derived from berries and leaves of the small American palm with the same name. The extracts are also named saw palmetto.

Selected phase II studies

Uncontroversial proof of effectiveness has not been established for any of the dietary substances and mechanisms mentioned.

- Selenium and vitamin E have been the study components of one of the largest trials ever conducted, the SELECT trial [11]. This trial was discontinued on September 2, 2008 after a safety monitoring committee review. No difference between the three study arms, including a placebo arm, were found at an interim analysis; however, there were side-effects including a higher chance of developing diabetes mellitus with the use of selenium [12]. The choice of selenium and vitamin E was based on two randomised studies in which prostate cancer was not

the primary endpoint but which showed reductions in prostate cancer incidence and mortality.

- The study of selenium was conducted as part of the Harvard-based Health Professionals Cohort Study [13]. This study was a randomised controlled double blind trial of 200 μg selenium/day in men and women with prevention of squamous cancer of the skin as the endpoint. It included 1312 men. Among secondary endpoints was prostate cancer incidence. The trial was obviously conducted prior to the PSA era and cancer incidence was incidence of clinical cancer. At a 6.5-year median follow-up 13 cases of prostate cancer were detected on the selenium and 35 on the control arm translating into a relative risk of 0.37 favouring selenium.
- The study which provided the basis for including vitamin E into the SELECT trial was an open randomised study of 29,133 male smokers with the main endpoint of lung cancer incidence and mortality. After a median follow-up of 6.1 years there was a 32% decrease in prostate cancer incidence and a 41% decrease in prostate cancer mortality; no effect on lung cancer was seen. A dosage of 50 mg of alpha tocopherol was used. The differences seen were statistically significant [14].

Unfortunately, hard data to confirm this secondary evidence will probably never be obtained.

- The story around lycopene is even more complicated. The incidence and mortality of prostate cancer has additionally been lower in Southern-European countries than in the North. This was attributed to their frequent use of tomatoes (and of olive oil) as well as to higher vitamin D levels due to more sun exposure). Lycopene, the red colour of the tomato, is one of the most active antioxidants used in nutrients. A wealth of small clinical and experimental studies have been conducted. A study by Limpens and colleagues compared two different dosages of vitamin E and/or lycopene to the combination of both drugs in a human prostate cancer line in nude mice. The combination of lycopene and vitamin E suppress tumour growth in a statistically significant way [15]. A very complete review of lycopene and prostate cancer has recently become available. This review confirms contradictory findings obtained in small clinical studies with the use of experimental models [16]. A large case control study was conducted in connection with the Prostate, Lung, and Colorectal Cancer Prevention Trial (PLCO). The frequent use of tomato products did not relate to significantly higher lycopene serum levels or lower rates of prostate cancer [17,18]. A recent review by the US Food and Drug Administration (FDA) found only very limited evidence to support an association between tomato consumption and reduced risk of prostate cancer [19]. However, in an editorial, Giovannucci pointed out that the reviewed studies for a large part may have been biased by the increasing use of PSA and the detection of prostate cancer. Almost all studies in which a risk reduction by lycopene and some of the other potentially protective substances is found relate to the pre-PSA era [20].

A dietary supplement containing most of the known potentially preventive agents has been designed and tested clinically. In a setting of tertiary prevention the study revealed a 2.6 fold prolongation of PSA doubling time in comparison to placebo with the use of a self designed supplement [21].

Plant-derived products containing substances with weak 5AR inhibitory activities will not be discussed further. Their mechanism of action, although at a lower level of activity, is likely to be comparable to those synthetically produced 5ARIs which are, and have been, subject to extensive studies in preventive settings.

Phase III studies

The most important study in prostate cancer is the Prostate Cancer Prevention Trial (PCPT) which randomised 18,882 eligible men to receive either placebo or finasteride for a period of 7 years. At entry, men had to have a PSA level of less then 3.0 ng/ml, a negative rectal examination and no evidence of prostate cancer. Biopsies were taken as a result of yearly check-ups if PSA rose above 4 ng/ml or if rectal examination became abnormal. All participants were supposed to undergo an 'end of study prostate biopsy'. The study showed a 24.8% reduction in the prevalence of prostate cancer over a 7-year period. However, there was also a 15% (37% versus 22%) higher prevalence of high-grade prostate cancer in the finasteride group. An additional unexpected finding was the very high prevalence of 24.4% of prostate cancer in the control group. This figure is about six times higher than the lifetime prevalence of prostate cancer prior to the PSA era.

This trial has resulted in a large number of publications reviewing various aspects which will be the subject of the more complete review in the educational book. Several publications have dealt with the possible reasons for the increase in poorly differentiated disease

in the finasteride arm. In a recent comprehensive study a modelling approach was used to adjust for four biases that were identified in the original analysis of the PCPT trial. This also took account of the findings in 500 cases who underwent radical prostatectomy and in whom poorly differentiated cancer was found more frequently in the placebo arm than in the finasteride arm [22]. This resulted in a non-significant difference in the prevalence of high-grade cancer between the placebo arm (4.2%) and the finasteride arm (4.8%, $P = 0.12$) [23]. Whether these recent findings will lead to the acceptance of finasteride as a chemopreventive agent in the US and around the World remains an open question at this time.

Dutasteride is another, competing, 5ARI. A phase III trial utilising this drug against placebo, the Reduce trial, is still ongoing [24]. Final results are expected during the year of 2009. Dutasteride is a dual 5ARI which inhibits type 2 and type 1 of this enzyme which is mainly located in peripheral tissues. Several tertiary prevention studies are in the process of being carried out with dutasteride. These include the so called REDEEM study, conducted in men who are candidates for active surveillance and the ARTS study which addresses the situation of rising PSA after unsuccessful potentially curative management.

Conclusions

The scientific interest in identifying preventive mechanisms and agents that could be applied to prostate cancer has experienced an important growth in recent years. However, this has not led to more clarity with respect to the effectiveness of food products. One dietary supplement was shown to prolong PSA doubling time in a small randomised cross-over study. Experimental and clinical data available so far on food products are contradictory, which is best shown with the example of lycopene.

The 5ARI finasteride has been shown to reduce prostate cancer incidence in a randomised study by 24.8% over a 7-year period. The initially described increase in the rate of high-grade cancer has been identified as an artifact after correcting for identifiable biases in the original evaluation.

Large clinical trials in a primary and tertiary preventive setting are ongoing with the use of the 5ARI dutasteride. The results will be known during the year of 2009. Considering the developments around finasteride and the expected proof of effectiveness of dutasteride, it is likely that 5ARIs will, in the future, play an important role as preventive agents in prostate cancer. Proper indications are in the process of being worked out. Appropriate risk stratifications will be necessary to avoid the haphazard treatment of a large fraction of the entire male population just by age.

Conflict of interest statement

None declared.

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