The concept of prevention as a public health strategy for prostate cancer control

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Abstract

Prostate cancer is probably present for up to two decades before it becomes clinically evident. Recent improvements in early diagnostic procedures have resulted in an increasing number of men being diagnosed when they are still in the pre-clinical phase of their disease. Early detection, however, has yet to show that secondary prevention leads to any significant decrease in prostate cancer mortality.
It logically follows, therefore, that attention must now be directed to the primary prevention of prostate cancer or, at the very least, to restrain the development of the disease to its latent, slowly-growing indolent form. Men of all ethnic groups and from all parts of the world, have a high prevalence of latent prostate cancer. The proportion of these men who develop clinically significant disease does, however, differ widely among different races and in geographical locations. Although this geographical variability in the incidence of clinical cancer would seem most likely to be due to the effect of dietary components on the biological processes implicated in carcinogenesis, evidence of any real associations between specific constituents of a diet and prostate cancer has yet to be determined. Attention would seem to be shifting to the potentially protective effects of specific dietary components, taken as a form of supplementation, but with products that may often have an uncertain composition, unproven efficacy and are not yet monitored by the strict pharmaceutical regulations. Evidence-based research is indeed vital for the scientific evaluation of such dietary constituents, or any other substances that are being considered as chemo-preventive agents for prostate cancer.

Key words: prostate cancer, chemoprevention, phytoestrogen, bioactive dietary components; selenium.

Introduction

The natural history of prostate cancer is characterised by a 20-year, slow-growing development period from microscopic foci of early preneoplastic lesions, through a latent, indolent cancer phase and a 10-year pre-clinical, asymptomatic period, before the growth and progression of the disease to the malignant aggressive phenotype. Incidence rates for prostate cancer during this pre-clinical phase have increased dramatically, due to earlier diagnosis through the increased use of the serum prostate-specific antigen (PSA) test and the development of easy, painless biopsy procedures. The enthusiasm generated by these improvements to the fundamental diagnostic procedures brought a wave of clinical studies directed to the evaluation of earlier detection and population screening for prostate cancer. The initial

enthusiasm for secondary prevention has been somewhat tempered, however, especially in the field of population screening, by the modest decreases in mortality, an overenthusiastic reporting of local screening studies and the critical evaluation of cost/benefit implications of such programmes.

Prostate cancer has the highest incidence of any male cancer in the developed countries, with either the first or second highest cause of cancer mortality. This pre-eminence of prostate cancer amongst the male cancers is perceived as a global trend, as the men in developing countries achieve the expected increases in life expectancy. The high prevalence of prostate cancer makes it a costly chronic disease in the ageing male population and not least, a major public health concern.

There are three primary issues that must be addressed in dealing with the current endemic health problem of prostate cancer. The first centers on the control, or possible cure of clinical prostate cancer. It must be accepted, however, that despite the enormous progress being made in managing the disease, advanced prostate cancer remains incurable. Secondly, there is the clear need to identify and then cure the disease in its early, localised stage of development. There has been a silent consensus regarding early detection, essentially involving a critical evaluation of the consequences to the fully informed individual, of 'PSA testing' and the related diagnostic algorithms. Most experts now agree that population screening should wait for the final analysis of both the European Randomized Screening for Prostate Cancer (ERSPC) trial and the Prostate, Lung, Colorectal and Ovary (PLCO) cancer trial, currently in progress in Europe and the United States [1]. The third issue must be the serious consideration of the potential role of primary prevention, with a clear stated aim of either preventing the initiation and development of prostate cancer, or at least, restraining the progression of the disease to its latent, indolent form (Figure 1).

Particularly important, with regard to the concept of primary prevention, is that despite the high prevalence of early pre-cancerous lesions in the prostate glands of all men, independent of their country of origin, or ethnic background and up to 30% of all men, world-wide, manifesting latent cancer, relatively few of these lesions progress to clinical cancer [2]. Moreover, observational epidemiological evidence has consistently identified a high prevalence of the latent slow-growing prostate cancer, whereas and there are marked differences in the incidence of the clinical disease, differing substantially, according to race and geographical location. There are 100-fold differences between the prevalence of prostate cancer in the Afro-American males and the incidence in their counterparts in Asian countries (Figure 2). Interestingly, a familiar and widely accepted phenomenon, involves the migration of Chinese and Japanese people through Hawaii and then to mainland United States, when the incidence of prostate cancer in the migrants approaches that of the native American people in a few generations. This data and studies of the countries surrounding Mediterranean, direct attention the the probable relationship between diet and prostate cancer and the possibility that dietary constituents can restrain the progression of the latent cancer to the malignant phenotype [3, 4].

Principles of chemoprevention

A widely accepted axiom, passed down through the ages as an integral part of folk lore, inherent wisdom and tradition is that „an ounce of prevention is better than a pound of cure". Scientific evidence has been applied to this conventional wisdom to

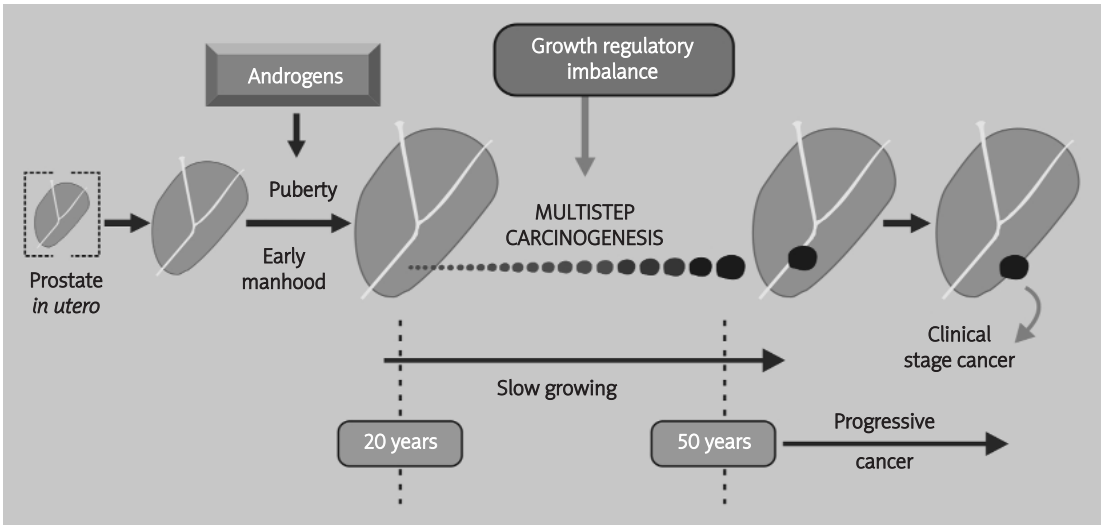

Figure 1. Natural history of prostatic cancer

counter various diseases. For example, modern medicine has had its share of success in the use of vaccination and new innovative drugs, to prevent the development of certain infectious diseases. Molecular genetics is expected to expand this field of endeavour, with cancers caused by infectious diseases, soon to be the target for new types of vaccines.

Equally clear and the concept behind many current, major international public relations programmes, is that improved nutrition, regular physical activity and an adequate socio-cultural environment, will provide substantial health benefits, enhance the quality of life and extend life expectancy. It would seem very reasonable that the prevention of disease, but cancer in particular, must be a major commitment for the oncoming years. The relatively long latent period between the initiation of cancer and the clinical manifestation of the disease emphasizes, quite distinctly, that the tissues have their own most effective capacity to restrain the processes of carcinogenesis. Evidence is accumulating, to indicate that dietary factors may well have an important regulatory role in enhancing these biological processes that are implicated in protecting the body from the development of clones of aggressive, malignant cancer cells from foci of early preneoplastic lesions.

Nonetheless, despite this more enlightened approach to disease prevention, it would seem that there remains a huge gap between perceived attitudes to preventive and curative medicine. One can be excused for believing that for many years, the perception of a substantial proportion of the medical community is that cancer only 'begins' when the disease can be clinically detected. Simply stated, people with early preneoplasia are not readily seen as being ill.

A scientific approach, an input from clinical and scientific research, is so essential to the efficacy of organised medicine and it is this approach that will ultimately help to close the gap between the preventive and curative aspects of medicine. At present, the extent of the dichotomy between prevention and cure results from the prevailing concept of healthcare. In a health-orientated, medicine-based

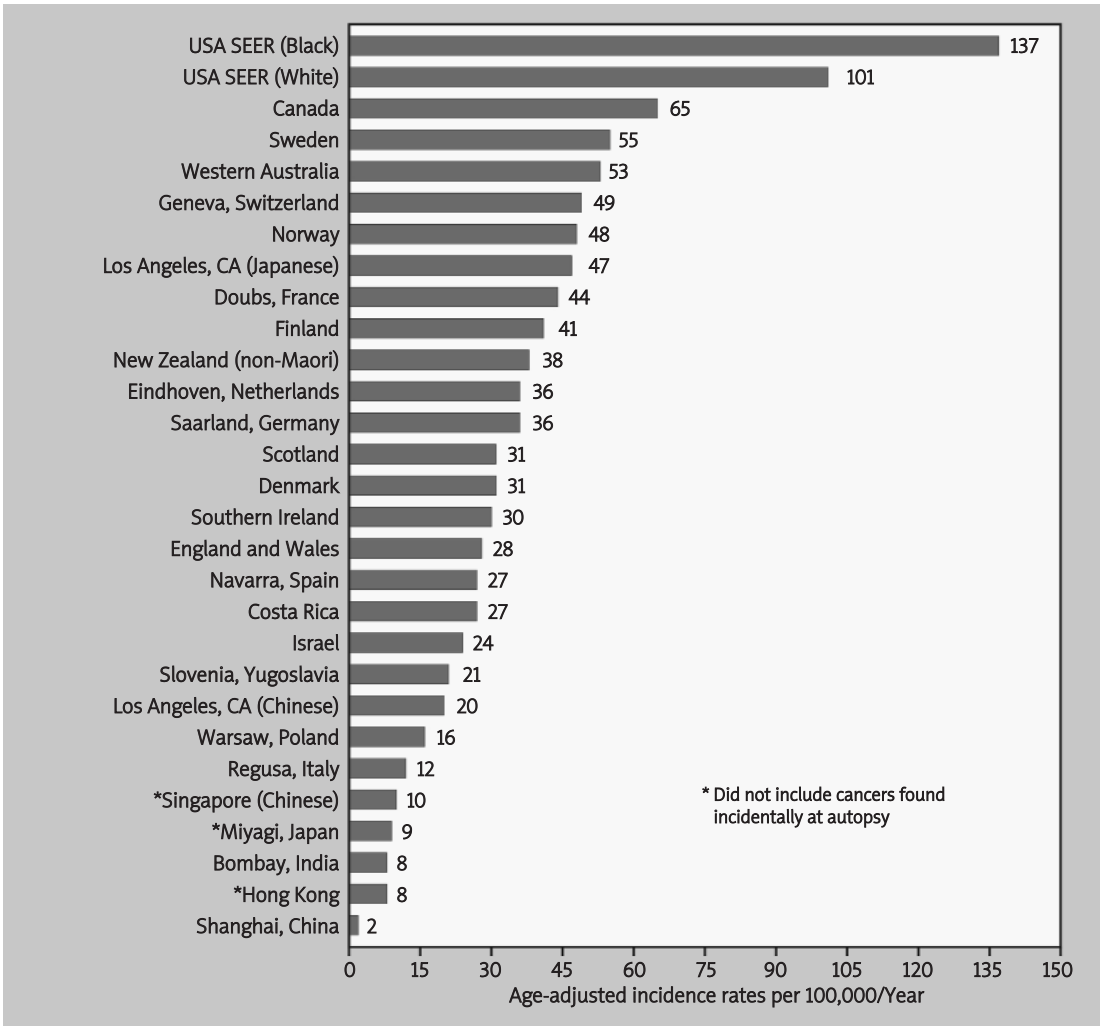

Figure 2. Geographical variation in the incidence of prostatic cancer.

Table I. Principles of chemoprevention

Questions to be posed when considering any particular cancer
• Does the cancer represent an important health problem?
• Does it have a recognized premalignant stage that can be evaluated?
• Is the natural history of the cancer well established and accepted?
• Would chemoprevention be effective in controlling this cancer?
• Is the form of chemoprevention considered acceptable and safe?

society, prevention should be inextricably interwoven with curative medicine, essentially in an integrated package. The alternative approach is one in which prevention is essentially a major aspect of public health, with medicine simply identified as one of a range of important activities. These two options have distinct medico-legal and financial implications.

Some of the principles on which chemoprevention programmes can be based, are summarised in the five questions posed in Table I. The first three questions obviously are answered in the affirmative. Prostate cancer is an important health-care problem, with a long pre-malignant state and a known natural history. However, the natural history of prostate cancer should be more thoroughly explored, and it is important that investigators effectively pursue the means of evaluating optimal endpoints for pre-clinical research.

It is difficult to judge the efficacy and possible side effects of chemopreventive agents, since few randomised trials, or even clinical studies to develop guidelines for data collection, have been completed and their results analysed. Moreover, diets, herbal remedies and phytotherapeutic agents are complex mixtures of various constituents, some obtained by a range of extraction procedures that have only been partially chemically defined [5].

All of these agents are considered to be complementary, or forms of alternative medicine (CAM), the distinction between the two, being seen as important. Alternative treatment is seen as equal to the standard forms of therapy, whereas complementary medicine is given in addition to standard treatment (Table II).

Table II. Potential agents for chemoprevention

• Dietary constituents	Isoflavonoids Flavonoids Lignans
• Trace elements	Selenium Zinc
• Vitamins/Antioxidants	Vitamin A Vitamin D Vitamin E Coenzyme Q_{10}
• Hormonal agents	5α-reductase inhibitors Phyto-oestrogens Growth Factors

Consumers often have a positive attitude toward such forms of treatment, simply because it is believed that they are 'natural' rather than 'chemical' and consequently, therefore, both purer and safer. There is also a medico-legal distinction between these products in the different countries. In the European Union, herbal products with therapeutic claims are marketed and regulated as drugs. Such products are considered dietary supplements in the United States. Most countries are now attempting to standardise the scientific and regulatory criteria that govern the marketing of these products [6].

In general, these substances are considered safe for human ingestion, a conclusion largely based on long-term traditional consumption. Their efficacy, however, remains unproven and dose responses are unknown. Although this relationship between diet and disease has become a field of enormous interest, clinical research is very limited and, to date, few appropriate clinical trials have been conducted. It is essential that such trials are instigated, properly designed and conducted for the benefit of public health. A recent International Union Against Cancer (UICC) survey disclosed that about one-third of the patients in both developed and developing countries, used various forms of CAM treatment [7]. It is not unreasonable to presume that certain adverse effects may ultimately be associated with dietary supplements, with PC-Spes capturing the imagination and also the headlines [8].

Potential agents for chemoprevention

Dietary components

The marked geographical differences in the incidence of clinical prostate cancer are most likely due to the influence of dietary components on the processes of carcinogenesis. The first 'causative theories' centred on the Western diet, which typically is high in animal fat and protein content and a low fibre intake. This concept generated the widely accepted belief that a higher consumption of vegetables and fruits, a greater intake of fibre from cereals and other whole-grain foods and a reduction in animal fat intake, should reduce the incidence of cancer. As such, the concept forms the basis of the advice offered through the Europe Against Cancer

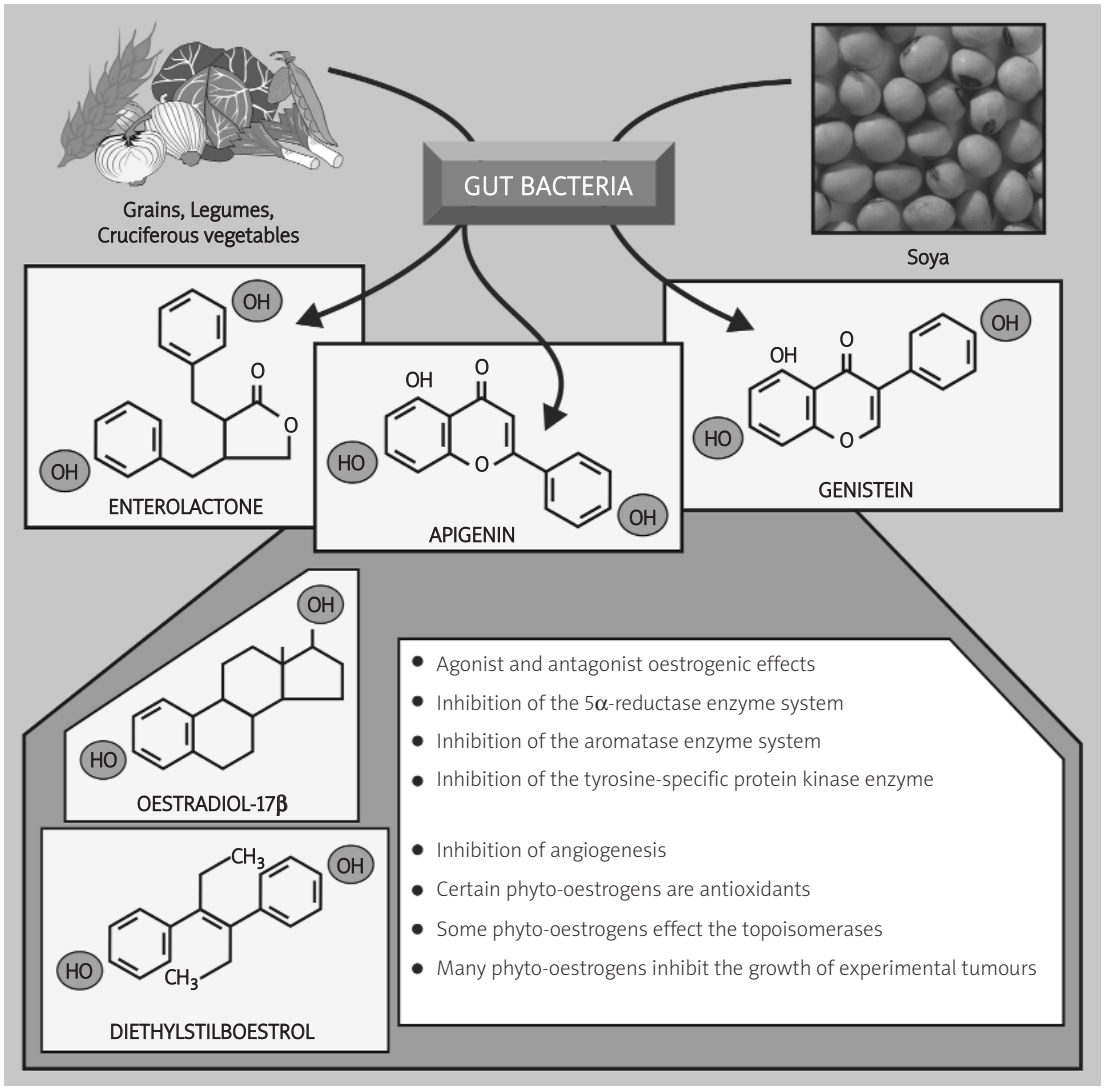

Figure 3. Phyto-oestrogens are produced by flora in the intestinal tract from conjugates in the food. The diagram illustrates the range of properties of the phyto-oestrogens and the approximate 10 angstrom separation of the hydroxyl groups similar to oestradiol

recommendations on nutrition. Although the association between such a general diet and cancer are presently considered somewhat equivocal for hormone-related cancers, such as those of breast and prostate, nevertheless, it is clear that these dietary recommendations provide health benefits for other chronic diseases and moreover, may not only increase life expectancy, but also improve quality of life for the ageing male [9].

Interest has now shifted to the protective aspects of specific dietary components, a concept first promulgated by Adlercreutz [10], with particular attention focused on the potential beneficial effects of isoflavonoids, flavonoids and lignans, referred to generally [11], as phytoestrogens (Figure 3). Soy protein is a major source of isoflavonoids, containing certain 'conjugates' that can be metabolized by enzymes of the normal microflora of the gut, to produce the genistein and daidzein. Since the soybean is an important dietary staple in Chinese, Japanese and many other traditional Asian cuisines, it is not surprising that Asians have higher concentrations of isoflavonoids in their plasma compared with Caucasians. The various diets of South American and Mediterranean countries, also have a high legume content.

Enterolactone and enterodiol are two principal, weakly estrogenic lignans, which are also formed from dietary precursors by their metabolism by intestinal microflora (Figure 3). Vegetarians and people from Mediterranean countries have high plasma concentrations of such lignans.

Flavonoids, which are ubiquitous in nature, are polyphenolic compounds some of which contribute to the colour and flavour of fruits and vegetables. They constitute a vast and complex group of plant

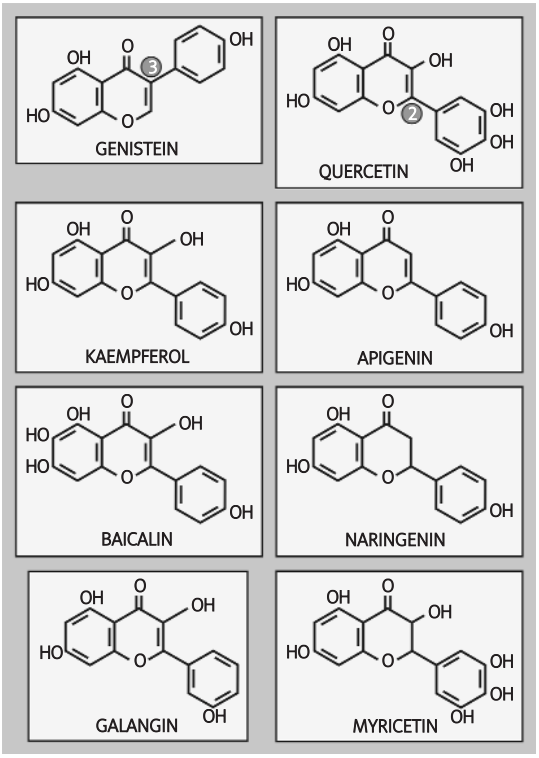

Figure 4. Structures of some of the flavonoids

constituents that are classified as flavones, flavonoids, flavonones, catechins and anthocyanidins. Major sources of flavonoids include onions, apples, tea, red wine and certain herbs. Some flavonoids, such as apigenin and kaempferol, also have weak oestrogenic activity (Figure 4) and many flavonoids are potent antioxidants.

Research has established that these phytoestrogens have an impressive range of biological activities (Figure 3). They may possibly influence biological processes in a multifactorial manner, at varying times throughout life, ranging from acting as antioxidants to expressing weakly agonistic and antagonistic oestrogenic activity. In many studies using animal cancer models, genistein has demonstrated significant anti-cancer activity, with a restraining effect on cell proliferation at the cellular level.

In the west, a substantial increase in the phyto-estrogen intake may offer health gains, although any dietary influence on the natural history of prostate cancer would be seen as multifactorial. Since the latent, indolent form of cancer is prevalent in all men from both East and West, any beneficial dietary constituent would appear to be directed to the prevention of the progression of latent cancer to the clinical malignant phenotype. A number of clinical trials are now in progress to determine the pharma-cokinetics, safety and efficacy of phytoestrogen treatment in men [12]. The majority of studies have reported beneficial effects in experimental carcinogenesis in animal studies, although a recent report indicated an enhanced growth of the Dunning R-3327-AT-1 rat prostate tumour, when a soy protein isolate was added to the diet [13]. The effect of a specific genistein preparaton would be of interest.

Lignans and flavonoids are non-nutritive components of vegetables, fruits and whole-grain products. A strong relationship has been shown between the intake of these dietary constituents and a decrease in the incidence of certain cancers, for example, cancers of lung, stomach, colon and pancreas. As mentioned previously, antioxidant activity has been and is still seen as a panacea for the prevention of many chronic diseases. In addition to their capacity to deal with the oxidative stress induced by free radicals, phyto-oestrogens stimulate the immune system, elicit oestrogenic activity, inhibit aromatase enzyme systems, induce SH-BG synthesis and may exercise a major cancer restraining action (Table III).

The influence of diet on disease most probably is multifactorial and at present, it is still difficult to determine the important bioactive components of a diet. The influence of food preparation and purification on these dietary constituents, as well as their effective doses, remains to be established. Clearly production and preparation of foods must play an important role in determining the biological activity of the constituents. Lycopene, however, may be the exception to this rule. Lycopene, which is the dominant carotenoid in the prostate gland, has potent

Table III. Selected activities of certain dietary constituents

Biological action	Components	Food sources
• Oestrogenic agonists and antagonists	Phyto-oestrogens	Soy, grain, beans
• Antioxidants	Carotenoids	Spinach, tomatoes, oranges
	Polyphenols	Grapes, nuts
	Catechins	Tea
	Flavonoids	Onions, fruits
• Immune stimulation	Peptides	Milk, wheat
• Detoxification	Glucosinolates	Cruciferous vegetables

antioxidant activity and it is the lycopene released by cooking and subsequent processing of tomatoes, which offers the health benefit. Raw tomatoes represent a poorer source. Certain biological properties reported for lycopene, are listed in Table IV. A number of clinical studies have suggested a positive relationship between lycopene intake, associated serum levels and a reduced risk of developing prostate cancer, although equivocal, conflicting results have also been published [14]. Larger randomised trials are to be conducted as soon as the optimal intake of lycopene has been determined.

Table IV. Biological properties of lycopene

• Potent antioxidant activity
• Regulation of cell-cell communication
• Suppression of protein phosphorylation
• Modulation of cytochrome P450
• Inhibition of IGF I signaling
• Immunomodulation

Trace elements

Selenium is a non-metallic trace element that is found predominantly in meat, poultry, grains and fish. The international recommendations for daily selenium intake range from 50 to 200 micrograms per day. Selenium acts as a catalyst in the glutathione-S-transferase (GST)π and catalase regulated removal of hydrogen peroxide from tissues. Hydrogen peroxidase is formed in tissues by the response of cells to free radicals. Since selenium enters the food chain when plants absorb it from the soil, it would seem likely that a balanced diet should be sufficient to maintain serum selenium to the 100-microgram level, necessary for optimal antioxidant activity. There is, however, a large variation in serum selenium levels in different regions and countries and low levels have been found in smokers, drinkers, elderly people with poor nutritional habits and pregnant women.

The beneficial role of selenium in protection against cardiovascular disease and prevention of cancer has been recognized for several decades. Five prospective epidemiological studies have addressed the relationship between selenium levels and prostate cancer risk. A clear association between prostate cancer risk and pre-diagnostic levels of toenail selenium content has been reported. Three of these studies, however, revealed non-significant trends for a reduction of prostate cancer, and one found no relationship between pre-diagnostic levels of selenium and prostate cancer [15]. Nonetheless, a most compelling study supporting the role of selenium as a chemopreventive agent, came from the secondary endpoints of the Nutritional Prevention of Cancer Study. In this double-blind clinical trial, 1312 patients with prior skin cancer, were randomized to receive either 200 micrograms a day of selenium yeast, containing 70% seleno-methionine, or placebo [16]. No reduction in the incidence of skin cancer was observed: however, when secondary endpoints were analysed, participants randomised to receive selenium had a significant reduction in total cancer incidence and mortality, as well as substantial decreases in the incidence of lung, colon and prostate cancers.

The Selenium and Vitamin E Cancer Prevention Trial (SELECT) is a phase III, randomised, double-blinded, placebo-controlled prospective trial now being conducted to evaluate the hypothesis that selenium (200 microgram/day), vitamin E (400 mg/day), or a combination of both, will reduce the incidence of clinical cancer in healthy males. Secondary endpoints include the incidence of total cancers, lung and colon cancers, cardiovascular events and overall survival. The Prevention of Cancer through Intervention with Selenium (PRECISE) study, is also a large randomised, double-blinded, placebo-controlled trial to evaluate the effects on identical endpoints, of three different doses of selenium versus placebo.

All of the doses of selenium are considered safe and/or within the range of optimal intake in healthy individuals. It is important that these large intervention studies finally settle the question of the health benefits of appropriate levels of selenium intake and the necessary daily dose, since there is already a large over-the-counter market promoting beneficial properties of selenium yeast for cardiovascular diseases and cancer.

Zinc is essential for the normal growth, reproduction and functional activities of all mammalian cells, including those of the prostate. The prostate contains the highest levels of zinc in the human body. It is secreted in prostate fluid and is concerned in citrate production. Accumulation of zinc in the secretory epithelial cells of the prostate is regulated by testosterone and prolactin. Malignant prostate cells lose their ability to accumulate high levels of zinc, an effect that is reported to promote prostate cancer progression [17]. However, several population-controlled studies have failed to show that zinc intake is protective against clinical prostate cancer. The prevailing evidence relating to the value of selenium and zinc in protecting against the development of prostate cancer, remains equivocal and inconclusive.

Vitamins A, D and E and Coenzyme Q_{10}

Epidemiological studies established to assess the protective capacity of dietary vitamins against cancer [18], have been fraught with difficulties. The reports of most studies have produced conflicting equivocal data. The results of a various trials to investigate the effect of beta-carotene supplementation on cancer incidence, have failed to support the promising

findings from observational studies. On the contrary, the Alpha-Tocopherol Beta-Carotene (ATBC) Cancer Prevention Study showed that when compared to placebo, supplementation with beta-carotene was associated with an increase in cancer at several sites, including the prostate [19]. However, men receiving vitamin E had a lower incidence of prostate cancer. Beta-carotene, a constituent of vegetables and fruit, is the major source of vitamin A in the human diet. Vitamin A is essential for normal cellular growth regulation, essentially limiting cell proliferation and promoting differentiation. Currently, there is no evidence that dietary supplementation with either beta-carotene or vitamin A, has any value in cancer chemoprevention.

Vitamin D_3 is produced in the skin, where 7-dehydrocholesterol is converted by solar ultraviolet radiation, to the provitamin D_3. In the final stage of metabolism, the hydroxylated D_3 is converted in the kidney to the biologically active metabolite 1,25 dihydroxyvitamin D_3, which suppresses cell proliferation and inhibits the expression of the C-myc-proto-oncogene.

Prostate cancer mortality rates in the United States are inversely related to sunlight exposure and low serum levels of vitamin D have been reported to associated with an increased risk for prostate cancer [20]. In a case-control study, a high intake of dietary products that provided an increased intake of calcium in addition to vitamin D, was associated with an increased risk for prostate cancer. A number of vitamin D analogues are under clinical development and dosing schedules are being explored in clinical trials to test the potential of vitamin D in preventing prostate cancer.

Vitamin E belongs to a class of lipid-soluble compounds known as tocopherols and tocotrienols. These compounds are concentrated in certain cell membranes and on lipoproteins, where they have major intra- and extra-cellular antioxidative activity. Vegetable oils and their derivatives are the main sources of vitamin E in the human diet. Alpha-tocopherol, the most active form of vitamin E, is predominant in human tissues and in the prostate. It exercises antioxidant, antiproliferative and antigrowth effects. Vitamin E also elicits other biological effects influencing intra-cellular signaling pathways, cell proliferation and the regulation of prostaglandin metabolism and cytokine-induced cell-mediated immunity. In addition, 50 mg/day of vitamin E has been reported to lower serum concentrations of testosterone and also vascular endothelial growth factor [21]. Although several trials have established the safety of vitamin E, evidence to support its effectiveness in preventing cancer, or cardiovascular disease, has been equivocal. It is hoped that the SELECT study, with a primary endpoint of the clinical diagnosis of prostate cancer, will provide this evidence.

Coenzyme Q_{10} is a naturally occurring coenzyme with antioxidant and membrane-stabilising activities. It protects cells from chemically-induced apoptosis by acting as an antioxidant in mitochondria [22]. Coenzyme Q_{10} has heamatopoietic and phagocytic activity and stimulates the host defense system against chemically-induced tumours and infection. A few clinical studies have described unexpected remissions of prostate cancer in men receiving Coenzyme Q_{10}. Information from an ongoing phase III study is needed for further evaluation of the possible effectiveness of this coenzyme in the prevention of prostate cancer.

It may be concluded that certain dietary constituents, trace elements, vitamins and other antioxidants, may well play a potentially protective role against cancer in general and prostatic cancer in particular. The relationship is, however, complex and it remains the responsibility of the medical and scientific community to identify and evaluate the biological activity and potential effectiveness of the important dietary constituents in the midst of media hype that promotes a large range of various supplements. Before these constituents can be included in our therapeutic armamentarium, their precise biological role must be defined and their safety, required dosage and possible effectiveness must be established. To achieve this end, investigators will need to conduct a step-by-step evaluation, differentiating between dietary sources and supplements. As a simple example, one study showed that neither the amount, nor type of alcohol consumed, was associated with the risk of prostate cancer [23]. Resveratrol, which is a constituent of red wine and with a range of potentially beneficial properties, induced caspase-mediated apoptosis in another study [24].

Hormonal agents

Androgens drive the growth and development of the pubertal prostate. Dihydrotestosterone (DHT) and not testosterone, is the predominant male androgenic hormone within the prostate, exercising its biological action (Figure 5) through the mediation of the androgen receptor (AR). Any adverse physiological or pathological changes would impact on the prostate gland by enhancing sensitivity to DHT, thereby increasing cellular proliferation, or alternately, decreasing apoptosis. Androgens, however, do not cause prostate cancer, although castration early in life, prevents the subsequent development of prostate cancer.

It is reasonable to presume that 5α-reductase inhibitors, anti-androgens, possible both, drugs which repress androgen stimulation, could be valuable chemopreventive agents. Several phase II and phase III studies offer some degree of support, reporting an effect of anti-androgens on various appropriate biomarkers in prostate tissue. The most important of the studies is the Prostate Cancer Prevention Trial

(PCPT). Following seven years of therapy with either finasteride, or placebo, all patients were followed until a biopsy could be performed. Whereas the toxicity profile has been reported, the final study results are not expected to be available until 2005, although interim reports that chemoprophylaxis with finasteride may do more harm than good.

It is well recognised that physiologic doses of oestrogens enhance the biological effects of androgens and that an imbalance in the androgen-oestrogen status appears to be responsible for prostate hyperplasia. The newly identified oestrogen receptor-β (ERβ) has a high affinity for oestradiol and is the principal oestrogen receptor localised in the epithelial cells of the prostate [25]. Oestradiol will therefore influence intraprostatic signaling pathways through ERβ, probably restraining the positive effect of ERα on the up-regulation of AR expression. The oestradiol signaling pathways appear complex, with homodimers, possibly heterodimers, associating with ERE recognition sites on the genome (Figure 6), cross-talking with signaling pathways driven by growth regulatory factors, as well as influencing growth through their influence on AP-1 signaling.

This fine balance between androgens and oestrogen, which is created during early adolescence and puberty, would seem to be susceptible to oestrogen imprinting signals already induced in prostate tissue in utero, which can increase the propensity to develop cancer later in life. Oestrogen imprinting in utero may explain the higher incidence of prostate cancer in Afro-American men, since their mothers can have plasma oestradiol concentration up to 40% higher than Caucasian-American mothers [26]. Since such oestrogen imprinting appears to have a major impact on the IGF-network, the IGF family of growth factors and their receptors would appear to be implicated in these events. If prenatal imprinting induces a predisposition to prostate cancer, a complex multifactorial picture emerges, centred on oestrogen-mediated events. The influence of phytoestrogens on these complex events remains to be elucidated, but the evidence that TGF-β1 expression is regulated by oestrogens suggests a more important role for oestrogens in the prostate than hitherto had been accepted. It may be that mepartricin, which is a semisynthetic derivative of a polyene antibiotic, may offer substantial health benefits by interfering with the entero-hepatic circulation of oestrogens and thereby decreasing plasma oestrogen levels.

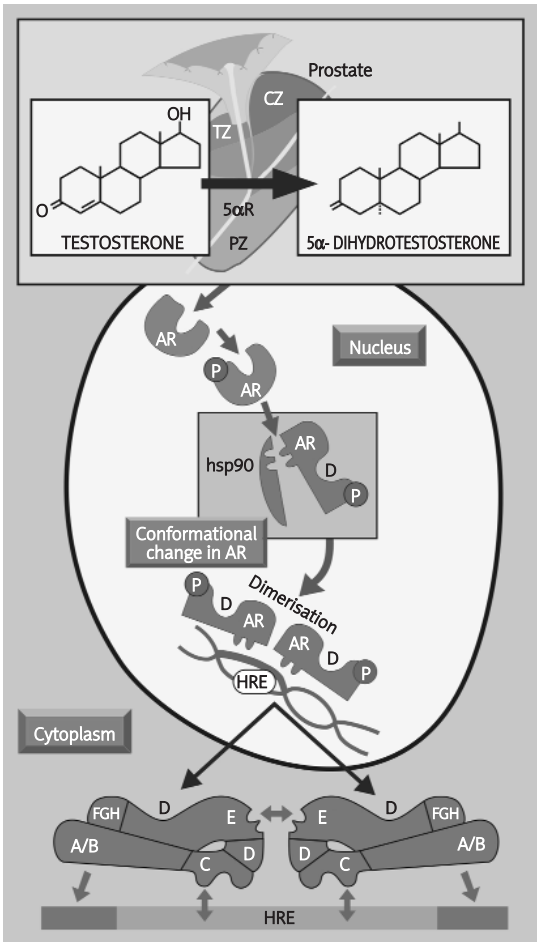

Figure 5. A simple illustration of DHT action

Conclusions

Despite the overwhelming circumstantial evidence that a regular intake of vegetables and fruits is good for health in general and may prevent some cancers, the five portions a day concept, scientific evidence that such dietary change will prevent prostate cancer is weak. The same conclusion may also be drawn for use of the chemopreventive agents such as the trace elements, vitamins and hormonal agents that have been studied.

One solution for this complex problem would be to establish a complete database, limited to report the negative side effects as well as any evidence-based proof of activity, for all the appropriate dietary components. Clearly, proof of efficacy must depend largely on randomised prospective trials, although it is essential that clinicians recognise the tested components that have identified chemical structures and an accepted, if not well established pharmacological dose. Although this is developing well in the case of genistein, for example, possibly selenium and certain vitamins, it will be far more difficult to achieve with the more complex plant or fruit extracts. Reliable and accepted clinical and scientific endpoints would greatly enhance the outcome of these trials.

It is hoped that the current chemoprevention trials of hormonal agents will provide a great deal of relevant data, since the studies have rigorous designs, a prerequisite for studies of medical drugs. One continuing enigma is the role of the immensely

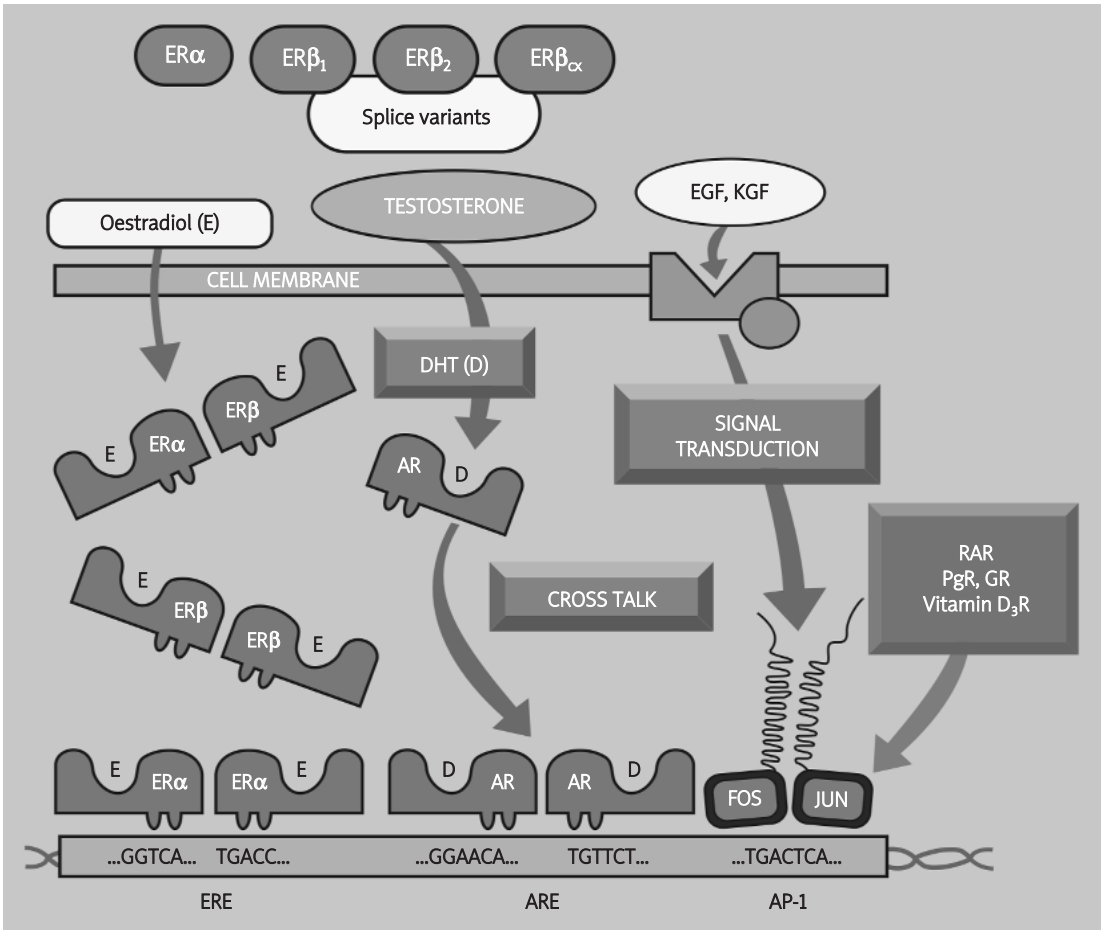

Figure 6. A simple portrayal of the crosstalk between steroid and growth factor signaling pathways

interesting phytoestrogens in this in vivo model. Much work remains to be done; however, current in vivo and clinical research endeavors assessing chemoprevention in prostate cancer will certainly increase interest and, it is to be hoped, result in substantial health benefits.

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