Medical Research Archives

European Society of Medicine

OPEN ACCESS

Published: November 30, 2023

Citation: Moorthy, H., K., and Krishnamoorthy, A., 2023. The Myths and Realities of Prostate Cancer Chemoprevention – A Journey Through Scientific Evidences. Medical Research Archives, [online] 11(11). https://doi.org/10.18103/mra.v11i11.4645

DOI: https://doi.org/10.18103/mra.v11i11.4645

ISSN: 2375-1924

REVIEW ARTICLE

The Myths and Realities of Prostate Cancer Chemoprevention – A Journey Through Scientific Evidences

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ABSTRACT

The goals of primary chemoprevention of any disease include decreasing the incidence of disease, reducing treatment-related adverse events, cutting down the cost of treatment and bringing down the mortality due to the disease. Increased prevalence of prostate cancer and identification of large numbers of newly detected disease due to the availability of better screening measures, long latency of the disease and peculiar molecular basis of pathogenesis make prostate cancer an attractive target of chemoprevention. This article reviews the experimental and epidemiological data available from 1998 to 2023 on the effectiveness, safety and toxicity of various nutritional and other agents proposed to be used for prostate cancer chemoprevention either to reduce the incidence of this cancer and/or slow down the disease progression. No single agent has been categorically proved to be the best for chemoprevention of prostate cancer as of now. Although majority of studies do not propose adopting chemoprevention in the entire elderly men population, it may be ideal that the men at higher risk of contracting prostate cancer like those having positive family history would be the best choice for implementing chemoprevention.

Introduction

Prostate cancer is a common but very slow growing tumor of elderly men, constituting the second leading cause of cancer related deaths in American men. Identification of prostate specific antigen (PSA) as an ideal screening tool in the late 80s and early 90s has enabled the clinicians to identify this disease quite early and monitor its progress. It is a paradox that despite the increase in the incidence of the disease (or an increased identification of the disease), the mortality due to prostate cancer has actually decreased since 1992. This could be partly attributed to the availability of better treatment modalities, though the cost of the treatment has been high. Although indolent in early stages, once metastases develop, the symptoms and suffering due to prostate cancer become very annoying. The exact pathogenesis of prostate cancer is still elusive. But the relationship between prostate cancer and serum levels of testosterone has been clearly identified in epidemiological studies[1]. Advanced age, positive family history of the disease, African-American ethnicity, consumption of unhealthy diet and exposure to cadmium have all been identified as other risk factors of prostate cancer[2]. Though the frequency of prostate cancer increases exponentially with increase in age, the aggressiveness of the disease decreases as age advances.

In the early 90s, strategies for decreasing prostate cancer mortality mainly focused on pre-symptomatic detection of the disease and monitoring its progress using PSA assays in the blood. However it was soon identified that increased levels of serum PSA could occur fallaciously in benign prostatic hyperplasia, prostatitis and a variety of non-prostate cancer scenario also. Conversely, treatment with 5 alpha reductase inhibitors (5ARIs) was found to lower PSA levels by nearly 50%. Therefore newer methods for increasing the sensitivity and specificity of PSA as a screening tool are being evaluated and adopted.

The long latency period to manifest clinical symptoms, identification of various modifiable environmental factors contributing to the disease coupled with the urgent need to prevent the upstaging of the disease makes prostate cancer a hot focus for adopting chemoprevention. It is imperative that chemopreventive strategies should always outweigh the potential benefits against the risks and cost of the specific agents used for this purpose.

Scientific articles published during the period 1998 to 2023 pertaining to prostate cancer chemoprevention available in Google Search and PUBMED have been reviewed and analysed for arriving at conclusions regarding the efficacy of various agents proposed for this purpose.

Goals of chemoprevention

Carcinogenesis in humans is induced by genetic and epi-genetic changes at the molecular level leading to an imbalance in cellular proliferation, apoptosis, differentiation and senescence concurrent with disruption in the various pathways controlling these cellular processes. The whole process of carcinogenesis involves multi-level pathways with the precursor lesions that represent the intermediate stage between normal and malignant cells arising as early as 20 years before the appearance of clinical cancer.

Chemoprevention is defined as the use of natural or synthetic agents that reverse, inhibit or prevent the development of clinically evident cancer in cancer free individuals[3] or slow down the process to prevent cancers from becoming clinically significant[4]. The goal of chemoprevention is to decrease the incidence of a given cancer, simultaneously reducing treatment related side effects and mortality. Cancer prevention strategies can be of 3 types - primary, secondary and tertiary. Primary prevention targets the general population of healthy individuals at risk to prevent the development of cancer. Secondary prevention strategies target individuals with premalignant lesions preventing them from progressing to frank cancer or developing metastases. Tertiary prevention aims to prevent the development of second primary cancer in an already affected individual. The identification of the potential use of tamoxifen for prevention of breast cancer in high risk women[5] probably opened new vistas to develop agents with lower adverse effects for reducing the incidence of prostate cancer also by targeting healthy persons at risk of developing the cancer. Prostate carcinogenesis is a slow molecular process starting from changes in the normal appearing epithelium to dysplasia (low grade prostatic intraepithelial neoplasia or LGPIN), then to severe dysplasia (high grade prostatic intraepithelial neoplasia or HGPIN) and finally to invasive prostate cancer. The ubiquity, long lead time to development of clinically significant disease and the low mortality make prostate cancer ideal for chemoprevention[6,7]. The high lifetime risk of prostate cancer development, the mortality associated with treatment of established prostate cancer and the inability to eradicate life-threatening metastatic prostate cancer are also compelling reasons for the need to adopt prostate cancer chemoprevention. The clinical rationale for prostate cancer chemoprevention is based on the fact that the risk factors for prostate cancer (age, ethnicity and family history) cannot be modified; the biological rationale is that premalignant changes in prostate occur as early as 20- 30 years before appearance of cancer[8,9] and therefore there is a window of opportunity to intervene before a malignancy is established. This intervention may be by lifestyle modifications (dietary alterations, cessation of smoking, exercise) or by chemoprevention. Adoption of primary prevention strategy for prostate cancer would spare the burden of diagnosis and cure, reduce over-diagnosis and over-treatment associated with screening protocols, augment the benefits of use of more accurate screening tests and adoption of active surveillance. The chemopreventive agents proposed for prostate cancer can be classified as Nutritional Agents, Pharmaceutical Agents, Phytogenic Agents, Life Style Factor Modifications and Vaccines.

Nutritional agents

A variety of dietary nutrients have been identified to be associated with certain cancers involving lung, colon, breast and prostate[10,11]. Some of these agents have been proposed to be useful for chemoprevention of prostate cancer also in several clinical trials.

1. NUTRIENTS:

Carotenoids

A case-control study on the association between dietary factors and the incidence and

aggressiveness of prostatic cancer has shown a significant inverse correlation between prostate cancer risk and the consumption of vegetables and fruits (p=0.029)[12]. Lycopene is a red-orange, highly unsaturated, acyclic isomer of beta-carotene found primarily in tomatoes and tomato-derived products and in other red fruits and vegetables. Studies have found out that increased lycopene intake could confer antineoplastic activity due to its antioxidant properties, reducing the decrease risk of prostate cancer[13,14,15]. In the Alpha Tocoferol Beta Carotene Cancer Prevention Trial (ATBC) intended for lung cancer prevention among smokers, a statistically significant 32% reduction in prostate cancer incidence was observed on secondary analysis in group receiving αtocoferol 50 mg daily[16]. Though meta-analysis of observational data indicated no overall effect with low to moderate intake of lycopene, a potential effect was observed with higher intake of lycopene (RR 0.89, 95% CI 0.81-0.98)[17]. Interestingly, Kolonel et al found out that while the intake of vitamin A from plant sources was associated with decreased prostate cancer risk, the intake of vitamin A from animal sources was actually associated with increased risk probably due to the higher fat content available in the diet which had high animal vitamin A[18]. Consumption of at least two servings per week of tomato sauce could significantly decrease the risk of developing prostate cancer[19]. Due to the conversion of trans-form of lycopene found in fresh tomatoes into the cis-form which is much readily absorbed in humans during food processing, tomato paste and other processed tomato products were found to be more effective than fresh tomatoes in preventing prostate cancer[20].

Dietary Fat

The association between animal fat and its components and prostate cancer risk has been identified in many studies[21,22]. Populations with higher dietary fat intake were identified to have increased prostate cancer relative risks by a factor of 1.6-1.9[23]. Though the precise mechanism for promotion of carcinogenesis by dietary fat has not been understood, it has been identified that high fat diet could increase serum androgen levels and increase the plasma concentrations of fatty acids, which in turn inhibit the binding of gonadal steroids to sex hormone binding globulins[24]. Conversely, a low fat, high fiber diet could increase the fecal excretion of gonadal hormones, lower the serum androgen levels, thereby lowering the incidence of prostate cancer[25]. Lifestyle changes including exercise and diets low in saturated fatty acids with increased antioxidants and omega 3 acids have also been reported to prevent prostate cancer and comorbidities[26]. Consumption of oily fish and other food items rich in omega-3 fatty acids was also found to prevent the spread of carcinoma prostate[27]. The omega-3 fatty acids interfere with functions of omega-6, which is used as an energy source by cancer cells, thereby preventing the spread of cancer cells beyond the prostate.

Soybeans and soy food

The daily diet of Southeast Asian men contain up to 50 times more plant products including soy compared to their Western counterparts and demonstrates a heartening 10-fold lower incidence of prostate cancer and its mortality[28]. Jacobsen et al also identified that higher consumption of soy milk lowered the risk of prostate cancer by 70%[29]. Several

natural anti-carcinogens (such as protease inhibitors, phytates, phytosterols, saponins, lignans and isofavones) have been identified in soybeans[30,31]. Isoflavones are converted to compounds that possess weak estrogenic and anti-estrogenic properties by the intestinal bacteria, while the phytoestrogens found in soy products increase serum sex hormone binding globulin via increased hepatic synthesis. This reduces the bioavailability of testosterone. Isofavonoids may weakly bind to the androgen hormone receptors in the prostate thereby interfere with androgenic stimulation of prostate cells [32]. The isoflavone namely genistein, has been found to have antiproliferative, estrogenic and antiestrogenic effects in prostate cancer cells[33,34]. Meta-analysis of two studies conducted in men with identified risk of prostate cancer found a significant reduction in prostate cancer incidence following administration of soy isoflavones (RR=0.49, 95 CI 0.26-0.95)[35,36].

Green Tea

The polyphenol, Epigallo calechin-3-Gallate (EGCG) contained in green tea have been proposed to have chemopreventive effects[37] and hence higher intake of green tea, as practiced in Asian countries could reduce the incidence of prostate cancer. *In vitro* studies using prostate cancer cell cultures and other gene expression experiments also confirmed that the polyphenolic constituent of green tea could inhibit cell growth and deregulate the cell cycle[38]. Yang et al reported that EGCG potentially and specifically inhibited the chymotrypsin like activity of the proteasome *in vitro* by 50%) at an inhibitory concentration of 86 – 194 nmol/litre which is the same concentrations found in the serum of green tea drinkers[39]. A clinical trial[40] in which patients were randomized to receive either black or green tea before prostatectomy has shown that there is significant uptake of green tea polyphenols in the prostatic tissue This was evidenced by the fact that the prostatectomy specimen in patients who had consumed green tea had decreased nuclear staining of NF-κB This can form the basis for future clinical studies which may further decode the association between green tea and prostate cancer.

2. VITAMINS AND MICRONUTRIENTS:

Vitamin E

The α-tocopherol which is the most prevalent chemical form of vitamin E found in vegetable oils, seeds, grains, nuts and other foods has been found to be a potent antioxidant which could prevent cancers like lung cancer[41]. Various studies have found out that the incidence of prostate cancer and prostate cancer mortality were reduced by administration of α-tocopherol and vitamin E could also prevent progression of latent tumors to more invasive disease[42,43]. The antioxidant property of vitamin E could prevent the propagation of free radical damage in biologic membranes and to critical cellular structures like DNAs and proteins. Vitamin E may also protect by enhancing immune function and lower protein kinase C activity, a cellular signal transducer that regulates cell proliferation. The recommended dose of α-tocopherol for prevention of prostate cancer has been suggested as $\leq$ 150 IU/day[44]. Conversely, some other studies suggested an inverse relation between blood α-tocopherol levels and prostate cancer risk[45].

Vitamin D

Men with higher levels of serum calcium have been found to have four to five fold elevated

risk of metastatic prostate cancer[14,46]. Therefore it was postulated that vitamin D could have chemopreventive role in prostate cancer, reducing the risk of lethal cancer by 57% (0R=0.43, 95% CI 0.24-0.76)[47]. Calcitriol, which is the active metabolite of vitamin D could inhibit growth of both primary cultures of human prostate cancer cell lines by altering cell cycle progression and initiating apoptosis. The current recommended dose of vitamin D for cancer prevetion is 10 µgram/day[48]. Exposure to sunlight has been found to increase body levels of Vitamin D and calcium. More potent calcitriol analogues having lesser side effects have been developed[49] for therapeutic purposes to reduce the toxicity of using higher doses of vitamin D.

Selenium

In vitro studies have shown that selenium found in many vegetables and grains has antioxidant activity could inhibit the growth of prostate tumor cells[50]. Administration of selenium was found to be more effective for chemoprevention in men with low baselines levels of PSA (<4 ng/ml) and low baseline plasma selenium concentrations. Interestingly, a randomized placebo-controlled clinical trial done using a daily supplementation of 200 micrograms of selenium rich yeast for skin cancer demonstrated a statistically significant reduction of prostate cancer incidence by 63%[51].

The Selenium and Vitamin E Cancer Prevention Trial (SELECT) was a prospective, randomized, double blind, placebo-controlled prevention trial which evaluated the role of vitamin E and selenium supplementation in preventing prostate cancer[52]. This study involved 35, 533 men 55 years of age or older (or 50 years and older if they were African-American). They were randomized to receive one of four treatments Selenium 200 mg/day plus vitamin E placebo, vitamin E 400 IU/day plus selenium placebo, selenium plus vitamin E and double placebo. At a median follow-up of 5.46 years compared with the placebo group, the hazard ratio for prostate cancer was 1.04 in the selenium only group, 1.13 in the vitamin E only group and 1.05 in this selenium plus vitamin E group. None of the differences was statistically significant. The Physicians health study also ascertained that vitamin E given every other day could not prevent prostate cancer[53].

The beneficial effects of vitamins and micro nutrients on reducing prostate cancer risk was not conclusively observed in many other randomized trials also[53,54]. However, a meta-analysis which looked into the relationship between circulating vitamin D levels and mortality in prostate cancer found that patients with a higher vitamin D level had reduced mortality[55]. It may be prudent to say that these agents might have cancer preventive activity in individuals who have specific deficiency of these micronutrients and vitamins, but may not be of benefit to those who are nutritionally replete.

Pharmaceutical agents

5 ALPHA REDUCTASE INHIBITORS

Testosterone is converted to the more potent dihydrotestosterone, which has been implemented as the principal androgen responsible for normal and hyperplastic growth of prostate[56]. Of the two isoenzymes which convert testosterone to dihydrotestosterone, 5-alpha-reductase (5ARI) type 2 is present in normal and hyperplastic

prostate tissue, whereas type 1 is overexpressed in prostate cancer cells. Therefore 5ARIs have been considered as target for chemoprevention of prostate cancer. *In vitro* studies also showed that inhibition of 5ARI could retard the growth of previously established prostate cancer lines[57,58]. The role of finasteride, which is 5ARI type 1 as a chemopreventive agent was established in the critical analysis of the Prostate Cancer Prevention Trial (PCPT) study by Goetzl and Holzbeierlein[59]. Finasteride could reduce prostate cancer prevalence by up to 24.8% (95% CI 18.6-30.6) compared to the placebo arm on 7 yrs of follow up in cancers with Gleason Score of 6 or less. However it was also observed that while finasteride inhibited low grade tumors and even reduced urinary symptoms and risk of urinary retention, there was an increase of 27% in potentially lethal high grade tumors (RR 1.27; 95% CI 1.07–1.5) requiring more aggressive therapy. Therefore the regular use of finasteride for prostate cancer prevention was cautioned[37].

It has been observed that the dual (type 1 and 2) 5ARI, dutasteride suppressed serum dihydrotestosterone levels significantly more than finasteride in men with benign prostatic hyperplasia[60]. The Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial[61] was aimed to study the effect of dutasteride 0.5 mg/day in men with an increased risk of developing prostate cancer in a high risk population of men with PSA between 2.5-10 ng/ml and a negative initial prostate biopsy. After 4 years of follow up, a 23% reduction in overall prostate cancer incidence was reported compared to those who received placebo, but there was not much effect on cancer with Gleason Score 7 or more. Dutasteride was used as an adjuvant treatment in the REDEEM trial of 302 men with Gleason 5-6 cancer managed by active surveillance[62]. After 3 years of follow up, a 38% reduction in disease progression (HR 0.62, 95% CI 0.43-0.89) was reported with dutasteride but no metastatic disease or prostate cancer related deaths were reported in either group.

It is interesting to analyze the results of review of all biopsy specimens from the PCPT and REDUCE trials by the Oncology Drug Advisory Committee of FDA. The FDA reassessment showed a significant increase in Gleason 8-10 cancers across both trials (RR 1.7, 95% CI 1.2-2.3) suggesting that one additional man would be diagnosed with high grade prostate cancer to avert 3 to 4 low grade cancers for every 150 to 200 men treated with 5ARI[63].

It is debatable whether 5ARIs should be used by all men at risk of prostate cancer or only by those at highest risk. Several cost utility analyses have however suggested that chemoprevention with 5ARI may be cost effective only in populations at high risk[64,65,66]. However the long term follow up of the PCPT and several cohort studies have demonstrated no impact or long term mortality in men taking 5ARIs. None of the available 5-ARIs have been approved by the European Medicines Agency (EMA) for chemoprevention.

It may be noteworthy that while using 5ARIs as chemopreventive agents for prostate cancer, the other benefits of using finasteride in improving the sensitivity of PSA and DRE for prostate cancer detection and reducing the risk of prostatitis, acute urinary retention and need for surgical intervention should also be

taken into serious consideration[67,68]. These beneficial effects would be obtained only at the cost of the adverse effects of finasteride on sexual and erectile functions and other endocrine effects. Larger trials with a longer follow-up would be the need of the hour to assess the effectiveness of 5ARI for prevention of aggressive prostate cancer before a definite conclusion could be drawn.

Considering the serious side effects associated with other androgen blockers like flutamide, bicalutamide and nilutamide, their regular use for prostate cancer prevention should be condemned in the asymptomatic healthy population[69].

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit cyclo-oxygenase (COX) enzyme and thereby reduce the synthesis of endogenous prostaglandins. It has been observed that COX-2 isoenzyme expression is 3-5 times greater in patients with prostate cancer which could be responsible for increased angiogenesis, tumorigenesis and prostate cancer growth[70,71]. Drugs such as aspirin, sulindac and ibuprofen have been reported to have prostate cancer chemopreventive activity and hence regular intake of these NSAIDs, particularly aspirin actually could reduce the risk of prostate cancer by upto 1%[72,73]. Case control and cohort studies using aspirin in which prostate cancer was a secondary end point suggested a small but consistent reduction in disease incidence of about 10%[74].However a meta-analysis of randomised control trials reported a large but non-significant reduction in mortality in patients taking aspirin regularly (19%, p=0.12) compared to controls who did not take regular aspirin; however the drug may not be benefit in patients with aggressive tumors[75]. Thorat MA and Cuzick J also reported a 16% reduction (HR 0.84, 95% CI 0.96-1.02) in lethal prostate cancers (cancer death or metastasis) when aspirin was taken regularly compared to those who did not take the drug[76].These studies were undertaken in individuals at average risk of prostate cancer with or without cardiovascular risk factors, and not in high risk individual with tumors of Gleason's score 7 or above.

The potential advantages of using COX-2 inhibitors as chemopreventive agents should be outweighed against the potential side effects of long term use of these drugs on other body systems.

SELECTIVE ESTROGEN RECEPTOR MODULATORS

Once the role of estrogens in the pathogenesis of prostate cancer was identified[77], there has been a significant interest in testing selective estrogen receptor modulators (SERMs) as preventive drugs for this disease. It has been observed that there was a lower incidence of prostate cancer in cultures with diets rich in phytoestrogens[33]. Toremifine citrate is a modulator of estrogen receptors (ER) and FDA had approved this drug for treatment of breast cancer. *In vitro* studies have shown that low dose toremifine selectively inhibited ER α in prostate cancer cells, which is a mediator for growth-stimulatory signal transduction and also has a direct antiproliferative effect through ER β However a randomised trial conducted in 1467 men with HGPIN failed to show a reduction in prostate cancer incidence at 3

years among those receiving toremifine citrate 20 mg daily vs placebo, even among high risk groups[78].

METFORMIN

There is ample evidence to show the link between obesity, metabolic syndrome and high circulating insulin levels with the development of various cancers including prostate cancer. However the results of various studies on the risk of prostate cancer in men using metformin have been mixed with some showing no effect at all whereas some others suggested benefit[79,80,81].

STATINS

The role of statins which are widely used as cholesterol lowering drugs, preventing cancers by inhibition of inflammation and angiogenesis, altering steroid-hormone biosynthesis or metabolism, cell cycle regulation or promoting apoptosis has been hypothesized[82]. A meta-analysis of 27 observational studies conducted by Barsal et al concluded that statin use reduces overall risk of prostate cancer by about 7% and risk of higher grade or advanced cancer by 20%[83].

OTHER POSSIBLE AGENTS

Dietary factors like vitamin C, vitamin B_1, vitamin B_2, niacin, zinc, protein and carbohydrates have not been found to have substantial association with prostate cancer[84]. There are weak evidences on use of non-classic antioxidant agents including the polyphenols, the isothiocyanates, difluromethylornithine, oltipraz and N-acetyl cysteine as potential chemopreventive agents[85,86].

Phytogenic agents

Phytoestrogens have been found to have potential activity on prostatic epithelial cells. They increase the serum concentration of sex hormone binding globulin (SHBG) and subsequently decrease progesterone, inhibit tyrosine kinase and topoisomerase and thereby decrease DNA synthesis, decrease the effect of free radicals through antioxidant properties, inhibit cytochrome P 450 activation, inhibit neoangiogenesis and inhibit intra prostatic 5ARIs and aromatase[87]. The major categories of phytoestrogens includes isoflavanoids (Genistein, Daidzein), flavanoids (Quercetin) and lignans (Enterolactone). The first 2 groups are found in vegetables such as beans, peas (especially soy) and fruits. Lignans also occur in grains, cereals and linseeds.

It has been observed in laboratory studies that many naturally occurring chemotherapeutic agents including silibinin, inositol hexaphosphate, hecursin, apigenin, acacetin and epigallocatechin-3 gallate have all been found to be of use in the management of prostate cancers[88]. *In vitro* and *in vivo* preclinical models identified the potential ability of the extract of pomegranate from the tree *Punica granatum*, which possessed strong anti-oxidant and anti-inflammatory properties, to inhibit human prostate cancer cell growth[89]. Similarly grape seed extract which promotes caspase 3 and caspase 9 mediated apoptosis has been found to inhibit growth and even induce apoptotic death of human prostate cancer cells in culture[90].

Several studies[91,92,93] have shown the therapeutic potential of the phytochemical named curcumin as a prostate cancer preventive agent, which is the active constituent of turmeric widely used as a spice in Indian cooking. Curcumin has anti-inflammatory, anti-oxidant and anti-tumour properties[94]. Curcumin could probably induce

apoptosis in both androgen-dependent and androgen-independent prostate cancer cells, inhibit proliferation and angiogenesis of LNCaP prostate cancer cells, reduce tyrosine kinase activity of epidermal growth factor receptor and deplete the protein.

The anti-microbial, anti-inflammatory and anti-oxidant properties of sanguinarine, an alkaloid derived from the bloodroot plant *Sanguinaria canadensis,* has been well documented. Sanguinarine could also cause cell cycle blockade and apoptosis of human prostate carcinoma cells via modulation of cyclin kinase inhibitor-cyclin-cyclin dependent kinase machinery[95], independent of the androgen status.

Encouragingly, it has been proposed that consumption of red wine, unlike other alcoholic beverages, might be protective against prostate cancer[96]. Every additional glass of red wine drunk per week showed statistically significant 6% decrease in relative risk of prostate cancer and men drinking 4-7 glasses per week were almost 25% less likely to have the disease (a relative risk reduction of 48%). Resveratrol is a naturally occurring plant antibiotic found in grape skins and red wine which has anti-oxidant activity, anti-platelet aggregation effect, anti-atherogenic property, estrogen-like growth promoting effect, growth-inhibiting activity, immunomodulation and cancer preventive effect. Resveratrol metabolizes into the anti-leukemic agent piceatannol, which may be responsible for the cancer preventive properties of resveratrol.

Consumption of at least five servings of cruciferous vegetables such as broccoli and cauliflower every week has been identified to significantly decrease the risk of developing prostate cancer[97]. The naturally occurring isothiocyanate, sulforaphane is the active chemopreventive component present in broccoli and other cruciferous vegetables contributing to the anti-cancer potential.

Capsaicin, the active hot ingredient in red chilly peppers, is a biologically active molecule that targets various prostate cancer pathways. The inhibitory capacity of capsaicin in prostate cancer growth, cell cycle arrest and induction of apoptosis has been studied in animal models[98].

Quercetin (3,3′,4′,5,7 pentahydroxy flavone) is a bioactive plant derived flavonoid abundant in fruits and vegetables particularly in onions, apples, red wine and tea. Daily human intake ranges from 10-100mg of quercetin. Quercetin antagonises prostate cancer by reducing androgen receptor expression, induces apoptosis, inhibits angiogenesis and suppresses proliferation[99,100]. *In vitro* and *In vivo* studies have confirmed the inhibitory capacity of quercetin on prostate cancer cells via various mechanisms namely inhibition of phosphatidylinositol 3-kinase signaling pathway, regulation of ERK-1/2/JNK/MAPK signaling pathway, reversal of epithelial to mesenchymal transition and invasiveness induced by epidermal growth factor, NF-$_K$B mediated transcriptional activity, reduction of heat shock protein 90,70,72 expression, down regulation of matrix metalloproteinases 2 and 9 proteins, inhibition of CYP1 cytochrome P450 enzyme and fatty acid synthase activity and ErbB2 and ErbB3 expression in prostate cancer cell lines[101]. This has rekindled the interest of researchers to use this molecule for chemoprevention of prostate cancer in animal experiments[102,103,104]. However clinical trials

confirming the definite therapeutic and preventive effects of quercetin on human prostate cancer are still awaited.

With the identification of chemopreventive effect of phytogenic agents, there have been many decoctions made of extract of various plant components popularized for prostate cancer chemoprevention. One such decoction is Zyflamend, which is a unique herbal preparation composed of 10 potency assured herbal extracts: rosemary (*Rosmarinus officianalis*), turmeric (*Curcuma longa*), ginger (*Zingiber officinale*), basil (*Ocimum basilicum*), green tea (*Camellia sinensis*), Japanese knotweed (*Polygonum cuspidatum*), Chinese goldthread (*Soptis* spp), barberry (*Berberis* spp), Oregano (*Origanum vulgare*) and Chinese or Baikal skullcap (*Scutellaria baicalensis*) which is found to have non selective COX inhibitory activity, able to induce apoptosis of prostate cancer cells that lack COX-2 expression[105]. However clinical and scientific studies on prostate cancer chemoprevention using such phytogenic decoctions are limited.

Lifestyle factors modification

EXERCISE

Exercise is one of the modifiable lifestyle therapies that appear to offer many benefits and relatively minimal side effects. Lack of exercise has been linked to increased prostate cancer risk. Significantly lower risk of prostate cancer was observed in veterans who exercised regularly[106] compared to those who did not. These authors also observed a significantly better quality of life, lesser fatigue, lower PSA levels and delay in initiating ADT by 2 years in those who exercised regularly. They also had significantly lower serum insulin and insulin like growth factor (IGF1), higher IGF binding protein (IGFBP1) and a lower risk of high grade disease compared to less active or sedentary prostate cancer patients.

There are many ways in which regular exercise could inhibit the risk of prostate cancer[107,108,109,110,111]. These include demodulation of circulating growth factors and sex steroid hormones, improvement in myokine and adipokine profiles, better immune function and androgen receptor adaptation, reduction in systemic inflammation and oxidative stress, changes in tumor vascularisation, modification of expression of regulatory genes and alteration of telomeres. Strenuous exertion (activity that requires an energy expenditure 6 or more times the resting metabolic rates), vigorous activity of more than 3 hrs per week and brisk walking of 7 hrs or more per week all have been reported to reduce incidence of prostate cancer risk.

OBESITY

Obesity has been reported to contribute to prostate cancer progression in several ways including alterations in leptin and adiponectin, increase in IGF1, decrease in IGF binding proteins 1 & 2, lowering sex hormone binding protein and thereby increasing oestrogen, increase in systemic inflammation and oxidative stress and increase in insulin levels[112]. A meta-analysis estimated that a 5 Kg/m^2 increase in body mass index (BMI) increased the risk for prostate cancer mortality by 20%[113] and a 0.1 unit increase in waist/hip ratio also was associated with a similar increase[114]. Therefore it is important to

maintain healthy optimum weight in patients who are at risk of prostate cancer.

SMOKING

Although prostate cancer is not closely linked to smoking unlike other cancers, literature suggests that smoking may promote the development of more aggressive cancer and increase disease specific mortality[115,116]. Therefore quitting smoking may reduce the risk of prostate cancer, while contributing to obvious other health benefits.

SEXUAL LIFE

A prospective study[117] was conducted looking into the relationship between ejaculation frequency and risk of prostate cancer. With a good sample size and long follow up, the results were encouraging. Men who have increased frequency of ejaculation (with or without partners) were found to have a lower incidence of prostate cancer

Vaccines

Administration of vaccines is a form of primary prevention of disease. With better genetic understanding of cancers, the development of anti-tumor vaccines have also advanced greatly.

The initial vaccine related studies in prostate cancer were done by injecting rat models with prostate cancer cell lines and the resulting immune response being studied[118]. These approaches were known as GVAX. Subsequent clinical trials of the same showed benefit in castrate sensitive[119] and castrate resistant prostate cancer[120]. Following this, randomized trials were carried out, the results of which showed a higher death rate among patients receiving vaccines when compared to standard docetaxel chemotherapy[121]. This resulted in a brief period of halt in the development of such vaccines. This hiatus was followed by the development of antigen specific vaccines (as opposed to the non-antigen specific nature of GVAX).

The anticancer vaccines immunologically activate the specific tumor-associated antigens (TAA) or tumor-specific antigens (TSA). These antigens then trigger the body's immune response by binding to costimulatory molecules localized on immune cells[122]. The dendritic cells play an important role in the antigen cross presentation and the mechanisms of actions of such vaccines. The various TAA in prostate cancer include PCA3, PAP, PSA and PSMA[123].

Polypeptide vaccines make use of synthesized polypeptides with antigenic properties. KRM-20 is an example of such a peptide vaccine[124]. DNA vaccines act by utilising the antigenic properties of naked plasmid DNA. The most important RNA vaccine is the mRNA vaccine platform, which combines the immunological characteristics of live attenuated vaccine, the expression of endogenous antigens and the immunological characteristics of T cell induction and inactivated vaccine, such as determined composition and safety[125]. The dendritic cell (DC) vaccines are composed of DCs loaded with tumor antigens.

Sipuleucel-T is currently the only active cellular immune product vaccine which has been approved for the treatment of CRPC[126]. Sipuleucel-T mainly includes peripheral blood monocytes activated by PAP and GM-CSF recombinant fusion protein *in vitro*, including antigen presenting cells. PAP is an enzyme secreted by the prostate and is highly expressed in metastatic prostate cancer and is

the target of sipuleucel-T[127]. In a phase III trial conducted in 2010, sipuleucel-T showed a survival benefit in asymptomatic or minimally symptomatic mCRPC patients. The study had a median follow-up of 34 months, the median survival was 25.8 months in the sipuleucel-T group compared to 21.7 months in the placebo group, with a HR of 0.78 (p = 0.03). There was no PSA decline observed and the PFS was similar in both arms. The overall tolerance of the therapy was also good[128]. The EAU 2023 treatment guidelines for prostate cancer[129] includes sipuleucel-T as a first line therapy for metastatic castrate resistant prostate cancer.

The current use of vaccines in prostate cancer is only for advanced stage disease. The combination of such vaccines with androgen deprivation therapy has also been proposed due to a synergy between their actions[130]. Combination of vaccines with other therapies is an area of active research and the future holds promise for the treatment of this disease. However the development of vaccines for primary prevention of prostate cancer is still in infancy stage.

Concerns and future of prostate cancer chemoprevention

Though prevention of prostate cancer seems to be novel and attractive option, identification of suitable pharmacologic and nutritional preventive strategies for prostate cancer still remains a challenge. The other major obstacles ahead of popularizing various agents for chemoprevention include the difficulty in identifying the ideal patient and the high cost of treatment, outweighed against the actual benefit of preventing this indolent and very slowing cancer. Larger randomized clinical trials conducted over long duration and development of specific biomarkers of carcinogenesis tailored to the agent under investigation may be needed before there is a large scale clinical development of chemopreventive agents. Identification of prostatic intraepithelial neoplasia (PIN), which is an intraluminal proliferation of secretory cells of the prostate duct-acinar system[131] has been highlighted to be of potential use to identify patients who are at risk of developing future cancer prostate. There are common genetic alterations in PIN and prostate cancer namely gain of chromosome 7, loss of 8p, gain of 8q and loss of 10q, 16q and 18q[132]. While the predictive value of low grade PIN for malignancy is not clear, high–grade PIN is suspected to be the precursor for prostate cancer because of the similarities in histologic diagnosis. There are some speculations to suggest that other histological changes such as metaplasia and atrophy may also be important precursors for prostate cancer. However the identification of precursor and premalignant conditions by employing invasive methods like prostate biopsy and its regular follow up by repeating the procedure for instituting chemoprevention are questionable.

Androgen Receptor (AR) plays a key role as a transcriptional factor in prostate development and carcinogenesis. By combining chromatin immunoprecipitation (ChIP) with tiling microarrays (ChIP-chips), the androgen target genes that are directly regulated by AR in LNCaP cells have been indentified[133]. This could probably enable us to extend our knowledge of the diversity of androgen

genetic network and steroid action in prostate cancer cells, identification of the target group for chemoprevention and selection of best chemopreventive agent. Controversy still exists regarding the endpoint of chemoprevention, whether it is the prevention of death, regression of intraepithelial neoplasia or the decline in prostate specific antigen[23]. One interesting study by Uzzo et al.[134] showed that a high proportion of men at risk for prostate cancer self-initiated nutritional therapies in the form of various nutritional, vitamin and mineral supplements. A cost effective pharmacologic medically oriented translational science strategy would also be the future of chemoprevention. The concept of replication-competent adenovirus mediated suicide gene therapy in which an oncolytic adenovirus armed with chemo-radiosensitizing genes is combined with intensity modulated radiotherapy (IMRT) and used to destroy tumour cells experimentally[135] provided a beacon of hope to provide a potential long term benefit to patients with carcinoma of prostate. However further development of these strategies have not attained the required pace to categorically establish the efficacy of chemoprevention of prostate cancer.

Conclusions

A journey through the scientific evidences spanning 25 years have revealed that prostate cancer prevention is neither a myth nor a reality. Though the efficacy of some of the chemopreventive agents showed a beacon of hope, the long term follow up using these agents failed to stand the test of time. The most important hurdles for adopting chemoprevention for prostate cancer include identification of the ideal target population and the ways to monitor the progress of the disease, which currently centers upon PSA and its derivatives. Probably the men at higher risk of contracting prostate cancer like those having positive family history would be the best choice for implementing chemoprevention, as their acceptability and willingness for follow up would also be better compared to the general population. At this time, no single agent has been categorically proved to be the best for chemoprevention of prostate cancer. It may be worthwhile adopting a public health approach for prevention of prostate cancer including

i. changes in dietary practices – increased consumption of fruits, vegetables, more fiber, fish oils and carotenoids and reducing carbohydrates and charbroiled meat
ii. calories restriction with obesity control and quitting smoking
iii. enhanced physical activity, stress reduction and good sexual practice
iv. early detection of precancerous lesions such as PIA (proliferative inflammatory atrophy, which is now considered as the earliest precursor lesion for prostate cancer), IEN (intraepithelial neoplasia) and early cancer particularly in men who are at risk of prostate cancer.

Conflict of Interest Statement:

None

Funding Statement:

None

Acknowledgement Statement:

None

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