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CANCER CHEMOPREVENTION (R AGARWAL, SECTION EDITOR)

A Perspective on Prostate Carcinogenesis and Chemoprevention

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Abstract In this perspective, modifiable carcinogenic factors for the prostate are summarized. This is followed by a discussion of how current knowledge about causation of prostate cancer and chemoprevention of prostate cancer can be used to develop preventive strategies. Prostate cancer is a slowly developing cancer which offers opportunities for preventive interventions. Only a few randomized clinical trials of prostate cancer prevention have been completed. The SELECT study with selenium and vitamin E did not find protective effects, but in two trials with 5α-reductase inhibitors risk was reduced about 25 %, showing that chemoprevention is possible and indicating that the androgen receptor is a suitable target. Besides smoking cessation and reduction of obesity, there are no known dietary or life style interventions that will have a major impact on prostate cancer risk. Inflammation of the prostate is an attractive target, and aspirin may be a promising candidate agent, but has not been addressed yet in preclinical and clinical studies. Antioxidants other than selenium and vitamin E are unlikely to be very effective and data on several dietary supplements are not encouraging. More candidate agents need to be identified and tested in relevant and adequate preclinical models and phase II trials that have predictive value for outcome of phase III randomized studies. Doing this will require a systematic approach comparing preclinical and clinical study outcomes to determine their predictive value of preventive efficacy.

Keywords Prostate cancer · Carcinogenesis · Chemoprevention · Antioxidants · Hormones

Introduction

The idea that cancer can be prevented implies that its causation is known, so that the causes can be eliminated (primary prevention such as smoking cessation); or that the mechanism by which causative factors act are understood so that they can be interfered with by chemopreventive or dietary interventions preventing development of cancer or preneoplastic lesions that may progress to cancer. For slowly growing and slowly progressing cancers, inhibition of growth and a delay of progression to more aggressive malignancy may also be effective. Prostate cancer is an example of such a slow developing cancer for which there is often a long period between development of the first malignant glands and the emergence of aggressive and fast growing tumors that are fatal. This explains why small cancers are found at autopsy in as many as 30 % of men between the ages of 30 and 60 years and as much as 45–75 % of men between 60 and 80 years [1, 2]. Thus, to prevent for prostate cancer, we must understand both causation and mechanism of growth and progression in order to create preventive strategies to interfere with the development of this malignancy, particularly fatal cancer.

A separate question is whether risk of prostate cancer is modifiable and prevention of progression is possible. The answer to this question is probably yes, but conclusive evidence is lacking. Studies of migrants from low risk to high risk countries, such as men moving from Japan to the USA, have shown that risk is highly modifiable in the high risk direction,

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implicating life style factors, probably diet, as major risk determinants [3]. However, there are no studies of men moving from high to low risk areas in the world. There have been only a few true prevention randomized clinical trials (RCTs) of prostate cancer, one with selenium and vitamin E in which no protective effects were found [4], and two studies with drugs that inhibit 5α-reductase which reduced risk by about 25 % [5], showing that prevention is possible.

Another issue is whether prostate cancer needs to be prevented and what type of prostate cancer should be prevented. Prostate cancer is diagnosed in about 230,000 annually, and approximately 30,000 men die from this malignancy every year in the USA; prostate cancer is thus the most prevalent malignancy and the second most common cause of cancer death in US men [6]. Clearly, this is a major human cancer. Although the majority of prostate cancers is not fatal, this malignancy still accounts for 10 % of all male US cancer deaths ahead of colorectal and pancreatic cancer [6]. Prevention of prostate cancer, particularly the aggressive and fatal form of this malignancy, is thus an important objective.

In this perspective, modifiable carcinogenic factors for the prostate will be summarized followed by a discussion of chemoprevention of prostate cancer and how current knowledge about causation of prostate cancer can be used to identify preventive strategies. There is no attempt to be complete or address many mechanistic issues; instead, the focus is on efficacy and relevance, on successes and failures, and on ways to move forward with chemoprevention.

Prostate Carcinogenesis

What is known about the causes of prostate cancer? The answer is not much. Even though the aforementioned migrant studies strongly suggest that dietary factors are very important risk determinants, major dietary risk factors have been elusive [7]. There are several important non-modifiable risk factors, such as age, race/ethnicity, familial history of prostate cancer, and still poorly defined genetic susceptibility, but these will not be discussed here because they do not offer preventive opportunities.

Dietary Factors

There is no strong evidence that high intake of meats or fat and low intake of fruits and vegetables increase risk [8–11] and that consumption of antioxidants, fish, or a Mediterranean diet would lower risk [12–14], while data on diary intake are mixed [9, 15, 16]. Thus, it is not clear which dietary factors have to be reduced in intake and which need to be consumed in increased amounts to prevent prostate cancer [17, 7]. Furthermore, it is not clear how these factors mechanistically act [18•]. Although many have proposed dietary guidelines to reduce prostate cancer rates [19], there is currently no real evidence to indicate that this approach has preventive results. The vast majority of data comes from epidemiological studies, and there are no published RCTs of diet modifications to reduce prostate cancer risk [20]. Obesity is a risk factor for fatal prostate cancer, and weight reduction may offer a way to modify prostate cancer mortality through dietary and energy expenditure approaches; however, this has not yet been tested in RCTs [21, 22].

Hormonal Factors

Hormones, particularly androgens and estrogens, have been widely considered involved in prostate carcinogenesis, but evidence from human studies, mostly from epidemiological studies, is either lacking or null [23, 24]. Nonetheless, the biology of prostate cancer strongly suggests that androgens and possibly estrogens are involved as causative factors [25•, 26, 27]. Indeed, treatment of rats with testosterone induces prostate carcinomas [28•]. If these steroid hormones act via their nuclear receptors, interventions that block their action may offer opportunities for prevention. But because these hormones have many essential functions, this approach may pose a risk of serious side effects. Other activities of steroid hormones may be involved as well. There is evidence that testosterone can have pro-oxidant properties [29, 30], and oxidative stress may thus be mechanistically involved.

Estrogen is formed in the male from androgens by the aromatase enzyme encoded by the CYP19 gene [31] in various tissues, including the prostate [32]. Because there are estrogen receptors in the prostate (both ER-α and ER-β) [33], there is plausibility for a biological effect of estrogen in the prostate and possibly prostatic carcinogenesis. 17β-Estradiol and estrone can be converted by CYP1B1 and CYP1A1 to 4- and 2-hydroxylated catecholestrogens, respectively, which can undergo redox cycling resulting in the formation of highly reactive estrogen-quinones and reactive oxygen species (ROS) [34, 35]. ROS can directly and indirectly damage DNA and cause mutations, and the estrogen-quinones can cause depurinating DNA adducts that can lead to mutations as well [35, 36]. Thus, it is plausible that testosterone can cause cancer of the prostate, acting via the androgen receptor and via conversion to estrogen activating estrogen receptors and inducing genotoxicity due to formation of reactive species.

Prostatitis

Prostatitis, inflammation of the prostate, has long been considered a risk factor for prostate cancer [37, 38]. Some recent studies support that notion [39•], whereas others do not [40, 41]. Inflammation results in generation of ROS which may cause DNA damage, aggravate the inflammatory process by causing tissue damage and release of inflammatory mediators,

and often causes increased cell proliferation as reaction of prostatic epithelium. Indeed, hyper-proliferation occurs in post-inflammatory atrophic acini in the prostate which lesion, proliferative inflammatory atrophy, has been associated with formation or preneoplastic and malignant lesions in the human prostate [39•].

Carcinogens

Exposure to specific carcinogens has not been associated with risk of prostate cancer in humans, but several structurally diverse chemical carcinogens have caused prostate cancer in laboratory animals, mostly rats; this occurs if the carcinogens are metabolically activated in the prostate [42–45], if the prostate is made susceptible by inducing cell proliferation at the time of carcinogen exposure [46, 47], or if a strong tumor promoting stimulus by androgens is given post-carcinogen exposure [48]. Recent evidence indicates that cigarette smoking, particularly heavy smoking, increases the risk of prostate cancer [49, 50]. Thus, overall exposure to carcinogenic chemicals may be a risk factor with susceptibility and tumor promotion by androgens as critical determinants.

Chemoprevention

In the previous section, hormonal factors and prostatitis have been identified as possible targets for chemoprevention as well as avoidance of carcinogen exposure, including smoking, and bodyweight reduction as potential ways to reduce risk. However, one should keep in mind that the population-attributable risk of smoking is probably not high (<10 %) [49] and that of obesity is not clear [21]. Nonetheless, avoidance of smoking and obesity will result in fewer deaths from prostate cancer, in addition to a much larger benefit in terms of reduction of lung cancer, cardiovascular disease, and metabolic syndrome.

Hormonal Targets

Antiandrogens that block the androgen receptor are very effective in preventing prostate cancer in rats treated with a prostate-targeted carcinogen and chronic testosterone administration [51], but are not acceptable for use in men because of side effects. Instead, intracellular levels of the active testosterone metabolite 5α-dihydrotestosterone (DHT) can be reduced by treatment with inhibitors of 5α-reductase which mediates DHT formation. In two RCTs with 5α-reductase inhibitors (finasteride and dutasteride) [52, 53], a 25 % reduction of men diagnosed with prostate cancer [5]. However, because these treatments only reduced low grade prostate cancer and slightly increased risk of high grade cancer, the FDA did not approve them for prevention of prostate cancer [54], and they are not widely used of label for this purpose.

Two estrogen receptor blocking agents were not active against prostate cancer; toremifene was not active in a RCT [55], and tamoxifen was inactive in rats treated with a prostate-targeted carcinogen and chronic testosterone administration [51]. No studies have attempted to specifically interfere with the genotoxic affects of estrogen, and this remains an unexplored potential chemoprevention target [25•]; ROS as targets are discussed below.

Inflammation and ROS as Targets

Clearly, inflammatory processes and the formation of ROS are attractive targets for chemoprevention. Dietary antioxidants targeting ROS, however, have not been active and in some cases even harmful. Selenium in the form of selenomethionine and vitamin E in the form of α-tocopherol did not prevent prostate cancer in the large SELECT trial of men with low PSA (<4.0 ng/ml) [4]. Both agents actually increased risk of prostate cancer slightly, selenium only in a subset of subjects [56•, 57•]. Selenomethionine did not affect risk of progression to prostate cancer in men with high grade prostatic intraepithelial neoplasia (PIN) [58], and selenized yeast did not affect risk in men with elevated PSA or other high risk indicators who were negative on biopsy [59]. Selenomethionine and selenized yeast were also negative in studies with rat models of prostate cancer [60, 61]. In one of these studies, α-tocopherol increased the incidence of prostate cancer, similar to the results of SELECT [60]. We found that selenium at physiological concentrations increased cell proliferation in LNCaP prostate cancer cells in vitro, but inhibited proliferation at higher doses [62]. These findings can be interpreted as consistent with a postulated U-shaped dose response for selenium and cancer preventive effects [63]. We did not find a reduction of oxidative stress and preneoplastic lesions in the prostate of rats fed selenomethionine and minimal effects on antioxidant enzymes [64]; this is consistent with the null effects observed in abovementioned animal studies and clinical trials with selenium supplementation. The baseline selenium status of the subjects involved in RCTs may be of particular importance relevant to whether selenium prevents prostate cancer or is harmful [65]. Baseline vitamin E status may also affect selenium efficacy [57•]. The current evidence for another strong antioxidant, lycopene, to prevent prostate cancer is also weak [66, 67], although intake of tomato products appears to be protective [9].

The potential for some antioxidants to increase rather than reduce risk of prostate cancer, as was found for selenium and vitamin E in the SELECT trial and for vitamin E in a rat study, is disconcerting and may be a risk associated with antioxidants in general. In a recently published study of lung cancer in transgenic mice, *N*-acetylcysteine and vitamin E both

increased tumor progression and cancer-related mortality [68]. The findings from this study suggest that disruption of the balance between ROS formation, DNA damage, and the p53-related DNA damage response may be responsible for this. It is conceivable that there are optimal antioxidant doses for preventive activity. Higher doses may cause tumor promotion or pro-oxidant activity; such doses may be tumor type- and antioxidant-specific and dependent on "base-line" antioxidant status and degree of pre-existing DNA damage or mutations. This notion would be in line with the abovementioned U-shaped dose response for selenium and prostate cancer preventive activity.

Anti-inflammatory drugs have not been tested for preventive activity against prostate cancer in humans, but there are some animal studies indicating that the COX-2 inhibitors celecoxib and sulindac have chemopreventive effects [69], but the NSAID non-selective COX inhibitor piroxicam was negative (McCormick & Bosland, unpublished data). For aspirin, there are meta-analysis data of observational studies that suggest a preventive effect [70–72], but there are no results from RCTs or animal studies. Because of the lower safety concerns for aspirin compared to celecoxib, it is likely that human studies of the chemopreventive activity of aspirin will be undertaken [73].

Dietary Supplements and Drugs

Besides antioxidants, dietary supplements that are commonly taken include vitamin D and calcium. Vitamin D has been proposed to prevent prostate cancer, but recent epidemiologic data suggest that this may not be the case or that there is a U-shape dose response relationship between plasma vitamin D and risk of prostate cancer [74]. In any case, vitamin D toxicity limits its potential use as a chemoprevention agent [75]. Calcium supplements may be prostate cancer enhancing at high doses and should probably not exceed 1,000 mg per day [9]. The association between calcium and prostate cancer may be the reason for milk consumption to be associated with increased risk of this malignancy and modulation of vitamin D metabolism by calcium may be the underlying mechanism [76, 77]. Silibinin derived from the milk thistle plant has a range of anti-cancer activities and is particularly active against prostate cancer [78]. This agent is being developed for testing in human clinical trials, and milk thistle extract has been tested for carcinogenic and toxic effects in animals and is largely safe [79].

Berries, especially black raspberries, have been shown to possess anticancer activity against gastrointestinal diseases including cancer in experimental animals and humans [80, 81]. These berries are very rich in antioxidant compounds, such as ellagic acid and various anthocyanins that also affect carcinogen metabolism and a number of signaling pathways [81]. In unpublished studies, we used two different rat models to test the prostate cancer chemopreventive activity of freeze dried black raspberries mixed into the diet up to 10 % by weight, but found no preventive efficacy. This was surprising, because we could detect the anthocyanin metabolite protocatechuic acid in prostate tissue of rats fed diets containing black raspberries. We also did not find any in vitro growth inhibitory activity of protocatechuic acid and the anthocyanin cyanidin-3-rutinoside, while ellagic acid was growth inhibitory only at concentrations unattainable in vivo. However, ellagic acid reduced prostate cancer development in a SV40 T antigen transgenic prostate carcinogenesis rat model [82].

Soy consumption is associated with a modest reduction in risk of prostate cancer [83, 84•], and it has been proposed to have prostate cancer preventive properties because of its richness in isoflavones with anti-cancer activity, particularly genistein [85]. Genistein inhibits growth of human prostate cancer cells that have wild type androgen receptor. However, it stimulates growth at physiologically attainable concentrations in cell lines that carry certain androgen receptor mutations, such as LNCaP cells; these mutations can arise in tumors that have become castration resistant after failing to respond to hormone ablation therapy [86]. Although there are several studies that have examined the effect of soy supplements on PSA [87, 88], there are only two that have studied effects on cancer development. We did not find reduction or delay of biochemical recurrence after radical prostatectomy in a RCT of men at high risk for recurrence given a daily supplement of soy protein isolate [89]. Fleshner et al. [90] did not find an effect on progression from high-grade PIN to prostate cancer in a RCT of men consuming a mixture of soy protein and vitamin E plus selenium (forms of vitamin E and selenium were not specified). Thus, there is no current evidence from clinical trials that soy prevents prostate cancer.

Green tea and its extracts contain several compounds that have a range of anti-cancer activities [91]. A green tea catechin mixture reduced the number of men with high-grade PIN developing prostate cancer in a small RCT [92, 93]. However, a RCT with presurgical administration of a similar mixture, polyphenon E, indicated absence of effects on markers of proliferation, apoptosis, and angiogenesis in prostate tissue and low bioavailability of tea catechins to the prostate [94]. We did not find protective activity of green tea extract on chemical-hormonal induction of prostate cancer in rats (unpublished results). Although more clinical studies are ongoing [95], it seems unlikely at present that green tea provides a substantive amount of protection against prostate cancer development.

Pomegranate juice or extracts have been studied because of their richness in antioxidant compounds and anti-cancer effects [96]. Despite two encouraging small phase II studies [97, 98], a larger randomized study with pomegranate extract given to men before radical prostatectomy did not find any effects on relevant intermediate biomarkers, despite uptake in

the prostate of a metabolite found in pomegranate [99]. On the other hand, pomegranate juice and ellagic acid found in that juice reduced prostate cancer development in a SV40 T antigen transgenic prostate carcinogenesis rat model [82].

Vitamin E is the generic term for a family of naturally occurring tocopherols. Although α-tocopherol does not appear to provide protection against prostate cancer development (see above), other tocopherols, particularly γ-tocopherol and possibly δ-tocopherol, may have protective activity [100, 101]. Future studies are necessary to sort this out.

Resveratrol and curcumin have not been tested as yet in RCTs or even relevant animal models [102•]. The diabetes drug metformin and cholesterol-lowering statins have been proposed as potential candidate agents largely on the basis of epidemiological data, but RCT results and data from relevant preclinical models are lacking [102•, 103••].

Research Needs

The field of prostate cancer chemoprevention has been in crisis ever since the failure of SELECT and the refusal by the FDA to approve 5α-reducase inhibitors for use to prevent this malignancy. In part, this is the result of (1) the lack of effective approaches to identify agents with low toxicity but considerable promise to be efficacious, (2) uncertainty about which in vivo models are most predictive of outcomes in RCTs, (3) difficulties in conducting phase II trials, in terms of both accrual problems and lack of information about predictive value of intermediate biomarkers that should be the hallmark of such trials, and (4) absence of a systematic evaluation of outcomes of animal models, Phase II trials, and definitive phase III RCTs. All four of these aspects will require a substantive research effort to resolve, and unless such a systematic effort is undertaken, progress will remain spotty and probably largely unsuccessful.

Of note, human prostate cancer cell models used to test agents may help identify potentially promising compounds, but are not appropriate chemo*prevention* models because they represent advanced prostate cancer, and the TRAMP mouse model is no longer considered an appropriate model of adenocarcinoma of the prostate since it develops neuroendocrine tumors [104].

Concluding Remarks

The above summary of carcinogenesis and chemoprevention of prostate cancer indicates that we know too little about avoidable causes of prostate cancer that can be used to develop preventive strategies and that progress on chemoprevention, including dietary supplements, has to date been largely unsuccessful. Besides examining the effects on prostate cancer risk of smoking cessation and efforts to reduce the prevalence of obesity and increase healthy dietary habits, it will be important to continue a focus on dietary supplements that emerge as potential candidate prostate cancer chemoprevention agents. Dietary supplements are often not very toxic and typically have multiple mechanisms of action, particularly in the case of supplements that are extracts or other mixtures such as green tea and soy protein.

Although studies with antioxidants have been unsuccessful to prevent prostate cancer (see above), there are some agents that have some promise in this regard and need to be studies in more detail such as γ- and δ-tocopherols and the methyl selenium compounds methylseleninic acid and Se-methylselenocysteine [105, 106]. Aspirin in particular may offer some promise given its ability to interfere with colon cancer formation and its already wide use to prevent clotting [107]. However, more candidate agents need to be identified and tested in relevant and adequate animal models and phase II trials that have predictive value for outcome of phase III RCTs. Given the uncertainty of how to identify such agents and which animal models and phase II trial designs are most appropriate, much more systematic research is needed to move forward with chemoprevention of prostate cancer. Although recent failures has dampened enthusiasm for prostate cancer chemoprevention, developing effective strategies prevention needs to remain a high priority in view of the considerable prevalence and mortality of this malignancy in the USA, Europe, and elsewhere in world.

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Compliance with Ethics Guidelines

Conflict of Interest Maarten C. Bosland, Nur Özten, Jillian N. Eskra, and Abeer M. Mahmoud declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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