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Prostate cancer chemoprevention in men of African descent: current state of the art and opportunities for future research

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Abstract

Prostate cancer is the most frequently diagnosed malignancy in men. However, African American / Black men are 60% more likely to be diagnosed with and 2.4 times more likely to die from prostate cancer, compared to Non-Hispanic White men. Despite the increased burden of this particular malignancy, no evidence-based recommendation regarding prostate cancer screening exists for the high risk population. Moreover, in addition to screening and detection, high-risk African American men may constitute a prime population for chemoprevention. Early detection and chemoprevention may thus represent an integral part of prostate cancer control in this population. Importantly, recent research have elucidated biological differences in the prostate tumors of African American compared to European American men,. The latter may enable a more favorable response in African American men to specific chemopreventive agents that target relevant signal transduction pathways. Based on this evolving evidence, the aims of this review are three-fold. First, we aim to summarize the biological differences that were reported in the prostate tumors of African American and European American men. Second, we will review the single and multi target chemopreventive agents placing specific emphasis on targeting the pathways implicated in prostate carcinogenesis. And lastly, we will discuss the most promising multi-target nutraceutical chemopreventive compounds. Our review underscores the promise of chemoprevention in prostate cancer control, as well as provides justification for further growth and investment in this field to ultimately reduce prostate cancer morbidity and mortality in this high risk population of African American men.

Keywords

prostate cancer; African American / Black men; evidence-based chemoprevention; pharmaceutical compounds; nutraceutical compounds

Introduction

Prostate cancer (PCa) is the most frequently diagnosed malignancy in men with 241,740 new cases and 28,170 deaths estimated to occur in 2012 [1]. However, African American / Black men (AAM) are 60% more likely to be diagnosed with and 2.4 times more likely to

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die from PCa, compared to the Non-Hispanic White men (EAM) [2]. The etiology of increased susceptibility of AAM to PCa have not been elucidated, but is likely multifactorial involving genetic, biological, socio-cultural and lifestyle components [3–4].

Current PCa screening and treatment strategies are subject to intense debate. While Prostate Specific Antigen (PSA) screening test has not been shown to significantly reduce either PCa-specific or overall mortality, it has been linked to substantial overtreatment of clinically insignificant, potentially indolent tumors [5–6]. Taking into consideration all the evidence accumulated to date, U.S. Preventive Services Task Force (USPSTF) recommended against PSA-based PCa screening in asymptomatic men (grade D recommendation) [7]. However, USPSTF acknowledges that “no firm conclusions can be made about the balance of benefits and harms of PSA-based screening” in AAM due to “the absence of data that support a more favorable balance of risks and benefits”. In fact, the two major PCa screening trials (U.S. PLCO (Prostate, Lung, Colorectal, and Ovarian) Cancer Screening Trial [6] and the ERSPC (European Randomized Study of Screening for Prostate Cancer) [8] included mainly men of European descent (4.5% AAM in PLCO; even less in ERSPC), thus largely precluding meaningful conclusions pertaining to men of African descent specifically. Hence, no evidence-based recommendation regarding PCa screening exists for the high risk population of AAM at this time.

Given the aforementioned uncertainty in screening and early detection, alternative PCa control measures specific and effective for the high risk population of AAM, are urgently needed. As such, chemopreventive strategies deserve attention. Importantly, recent research have elucidated biological differences in the prostate tumors of AAM and EAM; these differences may make AAM even more susceptible to chemopreventive interventions using compounds, that have been shown to specifically target those pathways. Hence, in this manuscript, our aims are three-fold. First, we aim to summarize the biological tumor differences that were reported in the prostate tumors of AAM and EAM. Second, we will briefly review the single-target (pharmaceutical) prostate cancer chemopreventive compounds placing specific emphasis on targeting the aforementioned pathways. And lastly, we will discuss the most promising, in our opinion, group of multi-target nutraceutical chemopreventive compounds. Our review manuscript may be of interest to the specialists (including researchers, clinicians, and nutritionists) as well as the community (including consumer advocates, survivors and general public). The current review underscores the promise of chemopreventive intervention in PCa control in the high risk populations, as well as urges the cancer community to invest additional effort to further evaluate its public health benefits for the racially and ethnically diverse population of the United States.

1. Biological (functional) differences in prostate tumors of AAM and EAM

In this section, we discuss the biological differences reported in the prostate tumors derived from AAM and EAM. To keep our manuscript tailored towards the evidence-based chemoprevention strategies, we will only include the functional differences (such as altered protein expression) that may mediate differential tumor response to chemoprevention. The role of either genetic variation (such as single nucleotide polymorphisms or SNPs, and germline and tumor mutations), or organism-based changes (such as altered hormonal

expression) in PCa risk and progression, although important, is beyond the scope of this review. The general schematic of the broad molecular mechanisms that may be involved in the increased PCa aggressiveness in men of African descent is shown in the Figure 1. The authors would like to note that at this time, the evidence presented is still in its hypothesis-building stage. The published studies are largely sporadic, involving small sample sizes and/or limited number of genes and/or proteins studied. Nonetheless, this evidence may open new promising venues for PCa health disparity resolution. The authors hope that review of the available data will facilitate future research in this important public health topic.

1.1. Increased tumor proliferation

Prostate tumors derived from AAM were reported to over-express several signaling receptors that may mediate increased and uncontrollable cell proliferation. Shuch et al [9] observed that Epidermal Growth Factor Receptor (EGFR) over expression was significantly higher in AA versus EA prostate tumors (45% AA v 18% EA; $p = 0.0006$). Additionally, greater EGFR expression correlated with poorer prognostic characteristics such as higher Gleason score at diagnosis. EGFR is a membrane receptor that mediates cancer proliferation and progression by activating the Extracellular signal-regulated kinase (ERK), Phosphatidylinositol 3-kinase (PI3K) and Janus kinase/Signal Transducer and Activator of Transcription (Jack/Stat) pathways [10]. On the functional level, over expressed EGFR enables proliferation and metastasis, helps avoid cell cycle arrest and may confer chemo- and radio-resistance [11]. It is thus biologically plausible that prostate tumors originating from AAM tend to progress more rapidly and/or resist treatment more aggressively due to over-expressed EGFR. Interestingly, this feature may also enable better response of AAM to select compounds currently investigated for PCa prevention.

Gaston et al [12] have found that Androgen receptor (AR) protein expression was 22% higher in the benign prostate and 81% higher in the PCa of AA compared to EA men. In addition, malignant nuclei were 27% more likely to immunostain for AR in AA vs. EA men. The authors hypothesized that PCa may occur at a younger age and progress more rapidly in AAM compared to EAM due to racial differences in androgenic stimulation of the prostate. In concordance with these data, Kim et al [13] have reported that, in the multivariate models, AR expression was significantly higher in PCa samples obtained from AAM ($p = 0.006$). Similar finding was reported by Olapade-Olaopa [14] who found that although AR expression was similar in a normal prostate tissue, PCa epithelium of AAM demonstrated significantly higher AR density ($P = 0.0001$). AR is a cytoplasmic receptor that can be activated by a vast array of hormones (androgens, corticosteroids and growth factors among others) [15]. AR-mediated pathway is thought to be largely responsible for growth and proliferation of prostate cells; thus, its aberrant activation may support PCa growth [16–17]. AR-mediated signaling may enable proliferation of both an early (androgen sensitive) and later (androgen refractory) PCa [16]. Interestingly, AR expression may increase in response to low androgen levels in men that undergo androgen ablation as a treatment for advanced PCa [18]; however, the reviewed studies [12–14] were performed using the specimens from men with unaltered androgen levels. Since there is generally no difference in the androgen levels in AA and EA men [19–20], it appears plausible to suggest

that over-expressed AR in AAM indeed mediates more aggressive PCa proliferation and is not due to the hormonal differences. This feature may potentially be exploited for targeted PCa chemoprevention in AAM; however, additional research is needed to link the increased AR and EGFR expression in AAM to clinical indicators of aggressive disease, such as higher rates of relapse and/or worse survival.

1.2. Altered apoptosis

In a healthy organism, apoptotic stimuli are tightly balanced with the proliferation stimuli, hence maintaining a steady state between the two. Conversely, tumor cells develop various strategies to suppress or evade apoptosis [21]. In this venue, deVere White et al [22] have reported that localized prostate tumors obtained from AAM were significantly more likely to immunostain for an antiapoptotic protein B-cell lymphoma 2 (bcl-2), suggesting that perhaps higher bcl-2 expression may enable decreased apoptosis and higher tumor proliferation in AAM. Interestingly, Guo et al [23] have found that apoptosis in PCa cells was significantly higher in AA compared to EA men (11.6% vs. 4.2%, $P < 0.001$). The authors also report that anti-apoptotic protein bcl-2 was detected at significantly higher levels in tumors from EA than AA patients (40.8% vs. 31.6%, $p < 0.05$). Because there was no difference in the proliferation rates between the two races (as measured by the antigen Ki-67 expression), the authors hypothesized that higher apoptosis indices may be indicative of a more biologically aggressive prostate tumor behavior in AAM. While the sample size in both studies was relatively small, these reports provide preliminary evidence in support of the biological differences in the apoptotic mechanisms observed in the AAM and EAM. Additional research is required to elucidate these mechanisms, as well as determine the usefulness of these data for PCa chemoprevention.

1.3. Increased tumor metastasis capacity

Wallace et al [24] reported that several metastasis (AMFR, CXCR4, CCR7, and MMP9) related genes are differentially expressed in prostate tumors obtained from AA and EA men. Autocrine motility factor receptor, isoform 2 (AMFR) is a tumor motility-stimulating protein secreted by tumor cells. While it has not been studied in PCa specifically, AMFR is over expressed in human breast cancer and is negatively associated with patients' clinical outcome [25]. C-X-C chemokine receptor type 4 (CXCR4) related pathway had been shown to facilitate the ability of PCa cells (and perhaps, other cancers as well) to spread and "home" to bone [26]. C-C chemokine receptor type 7 (CCR7) is a member of the G protein-coupled receptor family that has been shown to play a role in lymph node metastasis [27]. There is some evidence that CCR7 expression in patients with PCa predicts metastases to lymph nodes [28]; however, the exact role of CCR7 in PCa in general and the racial disparity remain to be elucidated. Finally, Matrix metalloproteinase 9 (MMP-9) takes part in the breakdown and remodeling of extracellular matrix and is thus linked to PCa invasion and metastasis [29]. Kim et al [13] reported that Ki67 was significantly higher expressed ($p=0.02$) in the malignant prostate tissues of AAM, (compared to EAM) and the difference attained statistical significance ($p=0.007$) even in the multivariate analysis. Antigen Ki-67 is a nuclear protein that is strictly associated with, and may be necessary for cellular proliferation [30]. Yang et al [31] have reported that moderately differentiated PCa tumors from AAM were more likely to immunostain for Caveolin-1 (Cav-1) (39% and 17% in AA

and EA patients, respectively, $p=0.0048$). The authors have connected over-expression of Cav-1 to an early or accelerated seeding of prostate tumor cells into the blood or lymph circulation, thus possibly enabling rapid metastatic spread in AAM. Rosen et al [32] have recently reported significantly higher proportion of the ETS-related gene (ERG) positive prostate tumors in EA, compared to AA men (41.9% vs 23.9%, respectively, $p<0.0001$). In addition, the authors noted that in AAM, the higher grade tumors were predominantly ERG-negative. The authors suggested that the observed results may indicate biological differences in the AA and EA prostate tumors, and hypothesized that higher proportion of AA-derived prostate tumors (those that are ERG-negative) “use distinct genetic mechanisms for progression”. These data support the hypothesis that PCa may be biologically more aggressive in AAM that leads to increased tumor proliferation and metastasis capacity, specifically towards the two most common “homes” for PCa metastasis bone and lymph nodes. Identifying specific agents that target these pathways may provide a promising opportunity to evaluate novel agents for PCa chemoprevention in men of African descent. However, these data remain to be confirmed in the larger preclinical studies before it can be considered for a clinical application.

1.4. Reduced expression of tumor suppressor genes

Reams et al [33] observed that the transcription elongation factor A-like 7 (TCEAL 7) expression in PCa tumor and in non-tumor tissue was higher in EA compared to AA men. The TCEAL7 gene modulates transcription in a promoter context-dependent manner. Since TCEAL 7 expression was shown to inhibit ovarian cancer cell lines growth [34], the authors speculate that increased expression of TCEAL 7 may correlate with increased suppression of PCa in EAM, but decreased prostate tumor suppression in AAM.

1.5. Summary of the Section 1

Taken together, these data suggests that there may be functional biological differences in the prostate tumors of AAM that may predispose them to a biologically more aggressive malignancy (Figure 1). At the same time, these data provide first provocative clues that AAM may be differentially (possibly even better) responsive to PCa chemopreventive intervention.. While the data looks promising, additional research is urgently needed to comprehensively elucidate and/or confirm the biological tumor differences, link them to the clinical indicators of disease aggressiveness, and explore their utility for PCa control in the exceptionally high-risk population of AAM.

2. PCa chemoprevention in AAM

Because of the present uncertainty with PCa screening and early detection strategies, especially in the high-risk populations such as AAM, alternative management strategies are needed. Importantly, PCa is an ideal malignancy from the chemoprevention point of view due to the high incidence, existence of well defined premalignant lesions, as well as a generally prolonged localized stage [35–36]. In this chapter, we will discuss the most promising single-target (pharmaceutical) and multi-target (nutraceutical) chemopreventive compounds that have been studied for PCa chemoprevention. We will focus on the pathways

that are being targeted, and will relate that information to the biological differences reported in the prostate tumors of AAM.

2.1 Single-target (pharmaceutical) PCa chemopreventive agents

5-alpha-reductase inhibitors are a class of synthetic anti-androgens that prevent the conversion of testosterone (T) into dihydrotestosterone (DHT) (androgen-dependent pathway) [37]. Only a small fraction of the total T (<5%) is converted into DHT; however, since DHT is several times more potent towards AR, it produces significant increase in prostate growth and proliferation [38]. It has thus been hypothesized that 5-alpha-reductase blockade may prevent PCa and/or delay its progression. Two 5-alpha-reductase inhibitors have been studied for PCa prevention: finasteride and dutasteride. While the drugs have been shown to reduce the total PCa incidence by approximately 24–30%, this reduction is largely due to decrease in the incidence of low grade, potentially insignificant cancers [39–40]. However, both drugs appear to significantly increase the risk for high-grade, potentially fatal PCa (Gleason score 8–10; odds ratios (OR) are 1.7 for finasteride and 2.06 for dutasteride) [39–40]. We note, however, that because casual and non-causal explanations for this association have been postulated [41–42], significant uncertainty on this subject remains, calling for additional investigations on this important subject. In addition, 5-alpha-reductase inhibitors are known to produce significant adverse side effects (some of which may persist after cessation of therapy), including sexual dysfunction, reduction or loss of libido, gynecomastia, and depression [43]. Because of the aforementioned reasons, U.S. Food and Drug Administration (FDA) does not recommend 5-alpha-reductase inhibitors for PCa prevention, and warns about the “increased risk of being diagnosed with a more serious form of PCa (high-grade PCa)” [44]. Of note, PCa chemopreventive trials did not include enough AAM to conduct separate analyses for that racial group. However, a study [45] concluded that when dutasteride was used for the treatment of benign prostate hyperplasia (BPH), the efficacy and safety profiles were similar in AA and EA men. Hence, although it is conceivable that 5-alpha-reductase inhibitors may be differentially active in AAM due to an overactive AR-mediated pathway, at this time there’s not enough evidence to support this claim. Thus, additional studies, involving sufficient numbers of AA-participants are required to establish the effectiveness of 5-alpha-reductase inhibitors for PCa chemoprevention in AAM.

Statins are a class of drugs widely prescribed to lower the blood cholesterol levels and hence prevent the cardiovascular disease [46]. Epidemiological studies have linked statins to a slightly albeit significantly reduced overall PCa incidence, with the marked reduction in the fatal, high grade disease (ORs of 0.69 for total, and 0.4 for high grade PCa) [47]. Brown et al [48] have reported that statins reduce the ability of PCa cells to migrate and invade, especially towards the bone marrow which is one of the primary metastatic site for PCa cells. This finding may be especially relevant to AAM since their PCa tends to demonstrate increased invasive capacities through mechanisms that are not fully understood. We note that the data on the PCa chemopreventive effectiveness of statins in AAM specifically are missing. In addition, statins’ use is associated with significant side effects, including myalgia and liver dysfunction, and the risk of any adverse event in the statin users was found to be elevated by 39% compared to a placebo group [49]. Thus, the safety concerns

significantly hamper the enthusiasm of testing statins for PCa prevention in otherwise healthy, high risk populations.

Metformin is a popular oral antidiabetic drug that was shown to prevent cardiovascular events without causing weight gain [50]. In addition to the type II diabetes, it is widely used and is effective for the management of other diseases associated with insulin resistance, such as polycystic ovarian syndrome (PCOS) [51]. From the point of cancer prevention, metformin can be viewed as a “hybrid” drug. Not only it lowers the concentration of potential cancer “ligands” in the bloodstream (such as glucose and insulin), but also acts within the cell suppressing the AMPK/mTOR/p70S6K1 pathway [52], including specifically in PCa cell lines [53]. More recently, IGFR and p53 mediated mechanisms of its anticancer action were reported [54]. Sparse epidemiological studies on metformin use and PCa risk have not been consistent. One study linked metformin use to a 44% decrease in PCa risk in EA, but not in AA men [55]; however, another study did not confirm the reduction in PCa risk in EA diabetics who took metformin [56]. The authors cautioned that the interplay between diabetes, obesity, metformin use and PCa has to be studied first before any conclusions can be made. Although metformin appears to be a relatively safe drug, its use has been linked to the gastrointestinal (GI) adverse events [57]. In addition, metformin (as well as any other antihyperglycemic drug) may be associated with increased lactic acidosis rates, although a comprehensive meta-analysis did not support this association [58]. Metformin is contraindicated for individuals with known liver, kidney or lung diseases which further limits its use in the aging non-diabetic population. Hence, at this time the long-term health effects of metformin must be studied more rigorously before it can be recommended for cancer prevention in AA or EA populations.

Non-steroidal anti-inflammatory drugs (NSAIDs)—Epidemiological studies have linked regular NSAIDs use to a significantly reduced PCa incidence (an average reduction of 10–40% dependent on the type of NSAID, duration and frequency of use) [59–63]. Interestingly, regular (at least 3 days a week) aspirin use for extended periods of time (1 year or longer) was associated with significantly reduced PCa risk in large prospective cohort studies [64–66]. A statistically significant protective association was observed in regular users who were of African and European descent with the magnitudes of association in the range of 0.75–0.9 (controlling for age, race, stage and the duration and frequency of use, and in some studies, for certain conditions such as heart disease), and was seen even at the doses as low as 75mg a day [65]. *In vitro* evidence suggests that NSAIDs exert the antiproliferative effect on PCa cells by inhibiting the cyclooxygenase (COX)-2 enzyme, as COX-2 up-regulation was linked to increased proliferation and angiogenesis [67]. Of note, prostate has high levels of COX-2 mRNA expression, with additional 3–4 times increase in malignant, compared to normal prostate tissue [64]. There is also evidence that NSAIDs may inhibit transcription of the AR and PSA genes [62], although this observation needs further research. Despite their promise as chemopreventive agents, NSAIDs cannot be recommended for cancer prevention due to serious and potentially fatal side effects of GI bleeding, renal failure and hepatotoxicity with overdose [68].

Summary of the section 2.1—In summary, although select single-agent pharmaceuticals demonstrate significant PCa preventive properties, the studies aimed to research the benefits of those compounds in AAM are missing. Using the published indirect evidence, the authors of this review hypothesize, that some pharmaceuticals demonstrate a potential to be more (such as statins) or less (such as metformin) beneficial in the high risk population of AAM. However, verification of this hypothesis will require thoroughly designed and well-powered studies. Unfortunately, anticancer properties of those agents are accompanied by toxicities that significantly limit their applicability for cancer prevention in healthy populations. At this time, additional research on the long-term adverse side effects and the balance of risks and benefits is needed to consider one or more of the aforementioned single-agent pharmaceuticals for cancer prevention in general, or specifically in the high-risk population of AAM.

2.2 Multiple-target (naturaceutical) PCa chemopreventive agents

Because of the significant toxicity profiles, observed with the use of single-target pharmaceutical compounds, scientific community is increasingly turning towards the multiple-target (naturaceutical) agents for cancer prevention. These promising compounds were shown to exert their anti-tumor properties by lightly modulating an umbrella of cellular pathways, rather than heavily influencing one pathway as is usually the case with pharmaceutical compounds. Because of this, nutraceuticals have fewer side effects and are generally well tolerated by healthy individuals [69]. In this section, we will review the most studied nutraceutical compounds currently being investigated for PCa prevention, focusing our attention on the potential benefits of the latter specifically in AAM.

Green tea catechins (GTCs) have been extensively studied for their potential beneficial health-related properties in cardiovascular [70], digestive [71], cognitive [72] and other [73] systems, and anti-cancerous properties against select human malignancies [74]. GTCs are among the most extensively studied nutraceutical chemopreventive compound for PCa. At this time, FDA states that “Green tea may reduce the risk of breast or prostate cancer, which the FDA has concluded that there is very little scientific evidence for this claim” [75]. Despite the known issues with GTCs administration, standardization and bioavailability [76], there are numerous documented beneficial effects of GTCs on PCa both *in vitro* and *in vivo*. We recommend the following detailed reviews for the in-depth description of the action of GTCs in PCa [76–78]. In relevance to our chosen mechanisms (Figure 1), GTCs were reported to exert the following select actions on PCa cells:

1. Reduce AR-mediated proliferation by inhibiting both the AR expression and transcriptional activity, and the 5 α -reductase activity;
2. Increase apoptosis by reducing bcl-2 expression;
3. Reduce invasiveness and metastasis by inhibiting MMP9 expression and activity.

Importantly, GTCs are generally well tolerated with only a few minor side effects, including GI upset, bloating and jitteriness that appear to be caffeine-related [79–80]. The majority of authors agree that, for generally healthy individuals, it was safe to take GTCs in the doses equivalent to 6 cups of green tea a day and up to 6 months. Unfortunately, despite the

increased promise for effectiveness in AAM and plethora of completed research, the authors could not find any studies in AAM. Hence, we conclude that at this time, the aforementioned studies are highly warranted.

Isoflavones are phytoestrogens found in the soy beans. Select soy isoflavones (namely, geinstein and daidzein) have weak estrogenic properties [81] and thus have been reported to exert antiproliferative effects on PCa due to suppression of AR-signaling pathways [82–85]. Indeed, consumption of soy food appears to be associated with a 30% reduction in PCa risk in the epidemiological studies, which were primarily conducted in populations with diets traditionally high in soy [86]. Additionally, soy isoflavones supplementation (*Novasoy*®) was shown to either stabilize, or slow down the rising PSA in a multiracial cohort of untreated men diagnosed with PCa (a watchful waiting cohort), or those who have progressed following definitive treatment [87]. Soy isoflavones have reduced the side effects of radiation treatment for localized PCa, such as bowel and urinary problems and pain, resulting in the increased quality of life [88]. Soy isoflavones are known to influence multiple cellular pathways leading to aforementioned anticancerous effects; the authors recommend the following comprehensive review for detailed description of action of soy isoflavones on PCa [89]. Because down regulating the AR-mediated proliferation is thought to be one of the main mechanisms by which soy isoflavones exert its PCa chemopreventive action [82–85], it appears biologically plausible that AAM would have a different (and better) response to the intervention using this compound. Although no published data are available on soy isoflavones effectiveness specifically in AAM, there is a currently active phase II clinical trial of Purified Isoflavones in PCa (NCT01036321, Kumar P.I.), that aims to Compare its Safety and Effectiveness in AA and EA men. We hope that this timely chemopreventive trial would provide new insights on the action of purified soy isoflavones in AAM and EAM.

Available clinical data suggest that purified soy isoflavones are generally safe when consumed as food; however, when taken in higher concentrations as a supplement, they may produce thyroid toxicity, certain undesirable nutritional effects such as reduced iron adsorption [90] and estrogen-related effects such as reduced testosterone in men. However, these adverse events are very rare. A comprehensive meta-analysis suggests that there is no effect of soy isoflavones consumption on an array of reproductive hormones in healthy men [91], as well as no genotoxicity was observed in 20 PCa patients treated with purified soy isoflavones [92]. Soy isoflavones are well tolerated in human clinical trials [91; 93]; however, there are isolated reports of sexual dysfunction [94] and gynecomastia [95] in men followed heavy soy consumption. Although soy products and isoflavones are generally recognized as safe, further research into their efficacy in PCa prevention and treatment should continue.

Lycopene is a red-colored carotene with no recognized vitamin A activity and a potent antioxidant, found in certain red-colored vegetables and fruits, such as tomatoes (the main dietary source for the most people), red peppers and watermelon [96]. Numerous epidemiological, *in vitro*, *in vivo* and human studies offered mixed and inconclusive results [97] on the health benefits of lycopene. In response to a petition initiated by a company that intended to sell lycopene supplements, FDA issued the following statement: “Very limited

and preliminary scientific research suggests that eating one-half to one cup of tomatoes and/or tomato sauce a week may reduce the risk of PCa, which the FDA concludes that there is little scientific evidence supporting this claim” [98]. Even then, FDA warns that the PCa preventive benefit may be associated “with eating the whole tomatoes, perhaps because as yet undiscovered compounds (other than lycopene)”. Epidemiological studies of lycopene for PCa prevention face significant challenges and biases, including inaccurate dietary assessment and dose measurement, bioavailability and administration, inconsistent PSA-screening practices, and potential differences in the bioactivity and/or biological susceptibility to the compound among the subgroups of men [99]. Interestingly, the mechanistic effects of lycopene in prostate tissues have not been extensively studied (which, in our opinion, is surprising given the high number of epidemiological studies involving this compound). Biological PCa protective mechanisms appear to be related either to the antioxidative and anti-inflammatory [100–101] or apoptosis-inducing properties, such as ability to induce G0/G1 cycle arrest, apoptosis and delayed *in vivo* growth in different PCa cell lines [102–104]. Other mechanisms mediated by steroid hormones may also be involved [105]. Because PCa in AAM may demonstrate decreased apoptosis, lycopene might be more potent in men of African descent. Unfortunately, the number of AA participants in the major lycopene studies was small thus precluding a meaningful sub-analysis for that racial group. Smaller studies have shown that blood lycopene levels are generally lower in AA compared to EA men [106], and that lycopene administration leads to increased plasma lycopene concentrations in AAM [107]; however, the value of the aforementioned observations for PCa prevention remains to be established. Although lycopene is generally well tolerated and is considered safe in either its natural or synthetic form [108–109], the evidence of benefits must be established more definitively before lycopene can be recommended for PCa prevention in healthy individuals.

Curcumin is a naturally occurring plant-derived phenol and a component of a popular Indian spice turmeric and a powerful antioxidant, that has been extensively studied because of its beneficial health effects including antimicrobial/antifungal [110–111], hepatoprotective [112], neuroprotective [113], cardioprotective [114], anti-inflammatory [115] and anticancer properties [116]. Mechanistic effects of curcumin on PCa *in vitro* and *in vivo* are mainly antiproliferative (down regulated AR, EGFR and cyclin D expression, inactivated NFkB) and proapoptotic (down regulated bcl-xl, bcl-2 and surviving expression) [117]. Importantly, curcumin was shown to inhibit PCa growth (50% inhibition) and induce the caspase-dependent apoptosis and reduce lung metastases by 89% *in vivo* [118]. Taken together, this evidence indicates that curcumin exhibits robust multitargeted anticancer activity against PCa, which is described in detail in the following comprehensive reviews [119–121]. In relevance to our selected mechanisms that may be more active in AAM (Figure 1), curcumin has the following effects:

1. Suppresses proliferation by inhibiting AR and EGFR signaling;
2. Promotes apoptosis by suppressing the bcl-2 expression;
3. Reduces invasiveness by suppressing MMPs expression and activation.

Interestingly, curcumin is currently undergoing clinical trials in the prevention of colon [NCT00027495, Brenner P.I.] and colorectal [NCT00118989, Guerra P.I.] cancers. However, despite convincing and very encouraging preclinical data, chemopreventive clinical trials of curcumin in PCa are lacking. The authors are hopeful that future studies will fill this gap, directing specific effort on elucidating the action of curcumin in AAM.

Rare and mild curcumin side effects often manifest as a GI upset [122], although there is a recent report that curcumin is an active iron chelator and as such, may potentially lead to anemia in susceptible individuals [123]. While this aspect certainly warrants additional investigation, curcumin is generally considered safe even at the very high doses of up to 12 grams per day [122].

Omega-3 fatty acids are polyunsaturated essential fats commonly found in seafood (such as fish and squid) and some plant oils (such as flaxseed oil), that has been investigated for prevention of cancers, including PCa [124]. Currently, there are 7 trials registered at www.clinicaltrials.gov that investigate the action of omega-3 fatty acid in PCa, and 66 studies in all cancers combined. The reported mechanisms of omega-3 fatty acid anti-PCa action are suppressed AR-signaling and suppression of the Akt/mTOR pathway [125] and NF-kB-mediated signaling [126] – all of which may be especially relevant to PCa in AAM. However, comprehensive meta-analysis suggests that there is yet little evidence that omega-3 fatty acid is effective for cancer prevention [127]. Epidemiological and clinical studies aimed to tease out the effect of Omega-3 fatty acid on cancer are subjected to numerous biases, such as difficulties to accurately collect and report the data on omega-3 fatty acid consumption, and account for other possible confounders such as total fat consumption [128]. One study [129] reported the plasma fatty acid profiles in AAM and native Nigerian men; the authors noted that although Nigerians demonstrated the overall higher plasma omega-3 fatty acid concentrations, these data did not appear to correlate with PCa risk. In agreement with this evidence, Williams et al. [130] have reported that increasing dietary ratio of omega-6/omega-3 fatty acids correlated with higher PCa risk among EAM (Ptrend = 0.05), but not AAM. Hence, although omega-3 fatty acid is safe and may provide other health benefits (unrelated to cancer prevention), such as cardiovascular health [131–132], at present the evidence of its effectiveness for PCa prevention in AAM or EAM appears to be weak. The authors are hopeful that future studies (including the currently active clinical trials) will provide insights on the chemopreventive action of omega-3 fatty acid in cancer.

Vitamin D constitutes a group of fat-soluble steroids that in mammals can either be ingested from a limited variety of foods (such as fatty fish, eggs and mushrooms exposed to ultraviolet (UV) light) or synthesized from cholesterol under exposure to sunlight [133]. It was previously reported that vitamin D exhibits anti-inflammatory action in the prostate, thus preventing and/or slowing down PCa progression [134]. However the majority of studies do not support a casual association between PCa and vitamin D consumption and/or serum concentration overall [135–137], as well as in specifically in AAM [138–139]. Although AAM tend to have lower circulating vitamin D concentrations [140], available data [135–139] largely do not support the hypothesis that vitamin D lowers the risk of PCa. However, the number of vitamin D studies involving AAM is small; thus, additional

research is needed to reach a definitive conclusion in that particular population. Interestingly, a very recent study [141] supplemented men on active surveillance (diagnosed with low grade PCa) with a daily dose of 4000 IU vitamin D for one year. The authors reported that 55% of men showed a decrease in the number of positive cores or decrease in Gleason score, and concluded that patients with low-risk PCa under active surveillance may benefit from vitamin D supplementation. Although the number of patients was small and there was no control group, this preliminary finding is intriguing and, in our opinion, deserves further investigation.

Of note, adequate vitamin D consumption has a number of other health benefits (unrelated to PCa risk) such as bone health [133], and seems to be associated with slightly albeit significantly lower all-cause mortality [142]. As such, efforts should be taken to identify and resolve the vitamin D deficiencies.

Dietary Calcium has been implicated in PCa risk; however the directionality of the data is conflicting. Both positive [143], negative [144] and neutral [145–146] associations were reported. Interestingly, even the studies involving predominantly AA participants have been conflicting. One recent study [146] has reported that AAM with poor adsorption of calcium were at the 60% reduced PCa risk, compared to AAM who were the highest absorbers. Another study [144] reported that high dietary calcium intake was negatively associated with PCa, specifically in AAM (no association observed in EAM). Of note, both studies controlled for vitamin D intake and other major known confounders.

The underlying mechanistic pathways that can explain observed effects of calcium on PCa are unclear and may be related to the cellular calcium-dependent channel function [146]. Prostate cells, including malignant tissues, possess both the calcium-sensing receptor and calcium-dependent voltage-gated channels, which respond to an increase in calcium with an increase in proliferation and a decrease in apoptosis. More recent *in vitro* work with various PCa cell lines has also implicated Notch and Mapk signaling pathways [147–148]. However, the exact mechanistic pathways remain to be elucidated. The authors are hopeful that better understanding of the calcium effect on functioning of prostate cells on the cellular level will explain the apparent discrepancy in the data as well as provide improved understanding on the role of dietary calcium in PCa etiology specifically in AAM.

Selenium and vitamin E have been investigated for PCa prevention in healthy multiethnic cohort of men in one of the largest chemopreventive trials ever undertaken (SELECT; NCT00006392). However, the trial was stopped early since neither selenium, nor vitamin E or a combination of the aforementioned compounds provided PCa preventive benefit [149]. While the retrospective analysis revealed design flaws that might have affected the results [150], at present there is a consensus that the aforementioned compounds, in the formulations and doses used, do not prevent PCa in a multiethnic cohort of healthy men. Despite these findings, selenium and vitamin E remain attractive chemopreventive compounds. Specific limitations and future directions regarding each of these compounds are discussed below.

Selenium, administered in SELECT in the form of l-selenomethionine for the purposes of standardization and safety [151], was previously shown to reduce PCa incidence by 60% in smaller trial named Nutritional Prevention of Cancer (NPC) study [152]. Notably, NPC used different forms of selenium (selenite and selenium-enriched baker's yeast), and was conducted in a population with lower baseline serum selenium levels. The antitumor action of selenium is thought to be mediated via selenoproteins essential proteins that are synthesized using selenium. Similarly to other forms of selenium, selenomethionine was shown to provide selenium for selenoprotein biosynthesis [153]; however, it can be diverted from that pathway into general protein synthesis [154] thus potentially minimizing or negating the antitumor benefits provided by l-selenomethionine. Sub-analyses have revealed that antitumor effects of selenium supplementation are largely observed in persons who are deficient [155], suggesting that the anticancerous benefit could be observed only in people with inadequate baseline selenium levels. In addition, polymorphic forms of selenoproteins in different individuals also affect cancer risk [156]. Given the complexity of selenium biology, genetics and environment interactions, improved understanding of selenium biology in humans is needed before a definitive conclusion on its role in human carcinogenesis can be made.

Vitamin E (limited in SELECT to α -tocopherol, the most studies and biologically potent form of vitamin E) decreased PCa incidence by 32% in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study [157]. Additionally, it was shown to inhibit AR-mediated signaling in PCa cell lines [158]. Despite these exciting preliminary data, SELECT have demonstrated no benefit of Vitamin E supplementation for PCa prevention in a cohort of healthy diverse men. Notably, ATBC study involved current heavy (at least 5 cigarettes a day) smokers who have increased baseline oxidative stress levels [155], whereas SELECT participants did not. There is also emerging evidence that tocotrienols (a less studied group of vitamin E forms) have potent anti-PCa properties *in vitro* [159], raising concerns of whether the most appropriate vitamin E formulation was used in SELECT. Given the aforementioned considerations, it is imperative to obtain in depth understanding of biology, pharmaco-kinetics, and gene-environment interactions of any chemopreventive compound before embarking on the extensive, time consuming and costly human trials.

It is important to note that, although SELECT had one of the highest AAM participation rates (13%) of any large-scale cancer chemoprevention trial to date [151], the number of AA participants was too small to reach statistical significance for any of the outcomes studied. Nonetheless, it appears that the outcomes for AAM were similar to those reported for all men combined [160]. Since either of the precursor trials (ATBC and NPC) included very few AA participants, there are virtually no preclinical or clinical data on the effectiveness of Selenium or Vitamin E on PCa prevention in AAM. Given the attention these compounds have been receiving in the cancer prevention, the authors conclude that obtaining such data is highly warranted.

Conclusions—Evidence-based PCa control approaches offer the most promise to reduce the burden of cancer, especially in the high-risk populations. Currently there is a significant lack of clear and consistent screening and early detection guidelines. A number of single-target pharmaceutical compounds show promise for PCa prevention; however, their use in

healthy men is largely limited by the unacceptable toxicities. As opposite to the latter, multi-target nutraceuticals are usually viewed as safe and demonstrate broad anticancerous properties by affecting plethora of cellular antiproliferative and proapoptotic pathways. However, implementation of nutraceutical compounds for PCa prevention requires additional rigorous studies to establish their respective mechanism(s) of action, effective doses, safety profiles and subset(s) of men that are likely to benefit of the proposed intervention. The latter is especially true for the high-risk populations such as AAM, since the evidence of efficacy and safety in that population is currently lacking for many compounds (Table 1). The authors believe that further advancement in PCa chemoprevention cannot be possible without improved understanding of prostate tumor biology on the mechanistic levels, and are optimistic about the future of PCa chemoprevention specifically in the high-risk populations.

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References

1. Cancer Facts & Figures for African Americans 2011–2012. American Cancer Society; 2011.
2. Cancer Facts & Figures 2012. American Cancer Society; 2012.
3. Chornokur G, Dalton K, Borysova ME, Kumar NB. Disparities at presentation, diagnosis, treatment, and survival in African American men, affected by prostate cancer. *Prostate*. 2011; 71(9):985–997.10.1002/pros.21314 [PubMed: 21541975]
4. Powell IJ. Epidemiology and pathophysiology of prostate cancer in African-American men. *J Urol*. 2007; 177(2):444–449.10.1016/j.juro.2006.09.024 [PubMed: 17222606]
5. Ilic D, O'Connor D, Green S, Wilt TJ. Screening for prostate cancer: an updated Cochrane systematic review. *BJU Int*. 2011; 107(6):882–891.10.1111/j.1464-410X.2010.10032.x [PubMed: 21392207]
6. Andriole GL, Crawford ED, Grubb RL 3rd, Buys SS, Chia D, Church TR, Fouad MN, Gelmann EP, Kvale PA, Reding DJ, Weissfeld JL, Yokochi LA, O'Brien B, Clapp JD, Rathmell JM, Riley TL, Hayes RB, Kramer BS, Izmirlian G, Miller AB, Pinsky PF, Prorok PC, Gohagan JK, Berg CD. Mortality results from a randomized prostate-cancer screening trial. *N Engl J Med*. 2009; 360(13):1310–1319.10.1056/NEJMoa0810696 [PubMed: 19297565]
7. Moyer VA. Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2012; 157(2):120–134.10.7326/0003-4819-157-2-201207170-00459 [PubMed: 22801674]
8. Wolters T, Roobol MJ, Steyerberg EW, van den Bergh RC, Bangma CH, Hugosson J, Ciatto S, Kwiatkowski M, Villers A, Lujan M, Nelen V, Tammela TL, Schroder FH. The effect of study arm on prostate cancer treatment in the large screening trial ESRPC. *Int J Cancer*. 2010; 126(10):2387–2393.10.1002/ijc.24870 [PubMed: 19739124]
9. Shuch B, Mikhail M, Satagopan J, Lee P, Yee H, Chang C, Cordon-Cardo C, Taneja SS, Osman I. Racial disparity of epidermal growth factor receptor expression in prostate cancer. *J Clin Oncol*. 2004; 22(23):4725–4729.10.1200/JCO.2004.06.134 [PubMed: 15570072]
10. Ladanyi M, Pao W. Lung adenocarcinoma: guiding EGFR-targeted therapy and beyond. *Mod Pathol*. 2008; 21(Suppl 2):S16–22.10.1038/modpathol.3801018 [PubMed: 18437168]
11. Li C, Iida M, Dunn EF, Ghia AJ, Wheeler DL. Nuclear EGFR contributes to acquired resistance to cetuximab. *Oncogene*. 2009; 28(43):3801–3813.10.1038/onc.2009.234 [PubMed: 19684613]

12. Gaston KE, Kim D, Singh S, Ford OH 3rd, Mohler JL. Racial differences in androgen receptor protein expression in men with clinically localized prostate cancer. *J Urol.* 2003; 170(3):990–993.10.1097/01.ju.0000079761.56154.e5 [PubMed: 12913756]
13. Kim HS, Moreira DM, Jayachandran J, Gerber L, Banez LL, Vollmer RT, Lark AL, Donovan MJ, Powell D, Khan FM, Freedland SJ. Prostate biopsies from black men express higher levels of aggressive disease biomarkers than prostate biopsies from white men. *Prostate Cancer Prostatic Dis.* 2011; 14(3):262–265.10.1038/pcan.2011.18 [PubMed: 21519348]
14. Olapade-Olaopa EO, Muronda CA, MacKay EH, Danso AP, Sandhu DP, Terry TR, Habib FK. Androgen receptor protein expression in prostatic tissues in Black and Caucasian men. *Prostate.* 2004; 59(4):460–468.10.1002/pros.20014 [PubMed: 15065095]
15. Gelmann EP. Molecular biology of the androgen receptor. *J Clin Oncol.* 2002; 20 (13):3001–3015. [PubMed: 12089231]
16. Lattouf JB, Srinivasan R, Pinto PA, Linehan WM, Neckers L. Mechanisms of disease: the role of heat-shock protein 90 in genitourinary malignancy. *Nat Clin Pract Urol.* 2006; 3(11):590–601.10.1038/ncpuro0604 [PubMed: 17088927]
17. Sarkar FH, Li Y, Wang Z, Kong D. Novel targets for prostate cancer chemoprevention. *Endocr Relat Cancer.* 2010; 17(3):R195–212.10.1677/ERC-10-0074 [PubMed: 20576802]
18. Gregory CW, Johnson RT Jr, Mohler JL, French FS, Wilson EM. Androgen receptor stabilization in recurrent prostate cancer is associated with hypersensitivity to low androgen. *Cancer Res.* 2001; 61 (7):2892–2898. [PubMed: 11306464]
19. Rohrmann S, Nelson WG, Rifai N, Brown TR, Dobs A, Kanarek N, Yager JD, Platz EA. Serum estrogen, but not testosterone, levels differ between black and white men in a nationally representative sample of Americans. *J Clin Endocrinol Metab.* 2007; 92(7):2519–2525.10.1210/jc.2007-0028 [PubMed: 17456570]
20. Litman HJ, Bhasin S, Link CL, Araujo AB, McKinlay JB. Serum androgen levels in black, Hispanic, and white men. *J Clin Endocrinol Metab.* 2006; 91(11):4326–4334.10.1210/jc.2006-0037 [PubMed: 16912139]
21. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell.* 2011; 144(5):646–674.10.1016/j.cell.2011.02.013 [PubMed: 21376230]
22. de Vere White RW, Deitch AD, Jackson AG, Gandour-Edwards R, Marshall J, Soares SE, Toscano SN, Lunetta JM, Stewart SL. Racial differences in clinically localized prostate cancers of black and white men. *J Urol.* 1998; 159(6):1979–1982. discussion 1982–1973. [PubMed: 9598502]
23. Guo Y, Sigman DB, Borkowski A, Kyprianou N. Racial differences in prostate cancer growth: apoptosis and cell proliferation in Caucasian and African-American patients. *Prostate.* 2000; 42 (2):130–136. [PubMed: 10617870]
24. Wallace TA, Prueitt RL, Yi M, Howe TM, Gillespie JW, Yfantis HG, Stephens RM, Caporaso NE, Loffredo CA, Ambs S. Tumor immunobiological differences in prostate cancer between African-American and European-American men. *Cancer Res.* 2008; 68(3):927–936.10.1158/0008-5472.CAN-07-2608 [PubMed: 18245496]
25. Jiang WG, Raz A, Douglas-Jones A, Mansel RE. Expression of autocrine motility factor (AMF) and its receptor, AMFR, in human breast cancer. *J Histochem Cytochem.* 2006; 54(2):231–241.10.1369/jhc.5A6785.2005 [PubMed: 16204225]
26. Taichman RS, Cooper C, Keller ET, Pienta KJ, Taichman NS, McCauley LK. Use of the stromal cell-derived factor-1/CXCR4 pathway in prostate cancer metastasis to bone. *Cancer Res.* 2002; 62 (6):1832–1837. [PubMed: 11912162]
27. Shields JD, Fleury ME, Yong C, Tomei AA, Randolph GJ, Swartz MA. Autologous chemotaxis as a mechanism of tumor cell homing to lymphatics via interstitial flow and autocrine CCR7 signaling. *Cancer Cell.* 2007; 11(6):526–538.10.1016/j.ccr.2007.04.020 [PubMed: 17560334]
28. Heresi GA, Wang J, Taichman R, Chirinos JA, Regalado JJ, Lichtstein DM, Rosenblatt JD. Expression of the chemokine receptor CCR7 in prostate cancer presenting with generalized lymphadenopathy: report of a case, review of the literature, and analysis of chemokine receptor expression. *Urol Oncol.* 2005; 23(4):261–267.10.1016/j.urolonc.2005.02.004 [PubMed: 16018941]

29. London CA, Sekhon HS, Arora V, Stein DA, Iversen PL, Devi GR. A novel antisense inhibitor of MMP-9 attenuates angiogenesis, human prostate cancer cell invasion and tumorigenicity. *Cancer Gene Ther.* 2003; 10(11):823–832.10.1038/sj.cgt.7700642 [PubMed: 14605668]
30. Scholzen T, Gerdes J. The Ki-67 protein: from the known and the unknown. *J Cell Physiol.* 2000; 182(3):311–322.10.1002/(SICI)1097-4652(200003)182:3<311::AID-JCP1>3.0.CO;2-9 [PubMed: 10653597]
31. Yang G, Addai J, Ittmann M, Wheeler TM, Thompson TC. Elevated caveolin-1 levels in African-American versus white-American prostate cancer. *Clin Cancer Res.* 2000; 6 (9):3430–3433. [PubMed: 10999725]
32. Rosen P, Pfister D, Young D, Petrovics G, Chen Y, Cullen J, Bohm D, Perner S, Dobi A, McLeod DG, Sesterhenn IA, Srivastava S. Differences in frequency of ERG oncoprotein expression between index tumors of Caucasian and African American patients with prostate cancer. *Urology.* 2012; 80(4):749–753.10.1016/j.urology.2012.07.001 [PubMed: 22950997]
33. Reams RR, Agrawal D, Davis MB, Yoder S, Odedina FT, Kumar N, Higginbotham JM, Akinremi T, Suther S, Soliman KF. Microarray comparison of prostate tumor gene expression in African-American and Caucasian American males: a pilot project study. *Infect Agent Cancer.* 2009; 4(Suppl 1):S3.10.1186/1750-9378-4-S1-S3 [PubMed: 19208208]
34. Chien J, Staub J, Avula R, Zhang H, Liu W, Hartmann LC, Kaufmann SH, Smith DI, Shridhar V. Epigenetic silencing of TCEAL7 (Bex4) in ovarian cancer. *Oncogene.* 2005; 24(32):5089–5100.10.1038/sj.onc.1208700 [PubMed: 15870691]
35. Singh RP, Agarwal R. Mechanisms of action of novel agents for prostate cancer chemoprevention. *Endocr Relat Cancer.* 2006; 13(3):751–778.10.1677/erc.1.01126 [PubMed: 16954429]
36. Walsh PC. Chemoprevention of prostate cancer. *N Engl J Med.* 2010; 362(13):1237–1238.10.1056/NEJMe1001045 [PubMed: 20357287]
37. Aggarwal S, Thareja S, Verma A, Bhardwaj TR, Kumar M. An overview on 5alpha-reductase inhibitors. *Steroids.* 2010; 75(2):109–153.10.1016/j.steroids.2009.10.005 [PubMed: 19879888]
38. Rittmaster RS. 5alpha-reductase inhibitors in benign prostatic hyperplasia and prostate cancer risk reduction. *Best Pract Res Clin Endocrinol Metab.* 2008; 22(2):389–402.10.1016/j.beem.2008.01.016 [PubMed: 18471794]
39. Wilt TJ, MacDonald R, Hagerty K, Schellhammer P, Kramer BS. Five-alpha-reductase Inhibitors for prostate cancer prevention. *Cochrane Database Syst Rev.* 2008; (2):CD007091.10.1002/14651858.CD007091 [PubMed: 18425978]
40. Theoret MR, Ning YM, Zhang JJ, Justice R, Keegan P, Pazdur R. The risks and benefits of 5alpha-reductase inhibitors for prostate-cancer prevention. *N Engl J Med.* 2011; 365(2):97–99.10.1056/NEJMp1106783 [PubMed: 21675880]
41. Hong SK, Oh JJ, Lee S, et al. Association of 5a-Reductase Inhibitor Use and Pathological Features of Prostate Cancer in Men Undergoing Radical Prostatectomy. *Prostate.* 2012; 72:1187–1192. [PubMed: 22161951]
42. Kramer BS, Hagerty KL, Justman S, et al. Use of 5- α -Reductase Inhibitors for Prostate Cancer Chemoprevention: American Society of Clinical Oncology/ American Urological Association 2008 Clinical Practice Guideline. *J Clin Oncol.* 2009; 27(9):1502–16. [PubMed: 19252137]
43. Traish AM, Hassani J, Guay AT, Zitzmann M, Hansen ML. Adverse side effects of 5alpha-reductase inhibitors therapy: persistent diminished libido and erectile dysfunction and depression in a subset of patients. *J Sex Med.* 2011; 8(3):872–884.10.1111/j.1743-6109.2010.02157.x [PubMed: 21176115]
44. 5-alpha reductase inhibitor (5-ARSSs) may increase the risk of a more serious form of prostate cancer. FDA Drug Safety Communication. <http://www.fda.gov/Drugs/DrugSafety/ucm258314.htm>
45. Roehrborn CG, Ray P. Efficacy and tolerability of the dual 5alpha-reductase inhibitor, dutasteride, in the treatment of benign prostatic hyperplasia in African-American men. *Prostate Cancer Prostatic Dis.* 2006; 9(4):432–438.10.1038/sj.pcan.4500911 [PubMed: 16983393]
46. Taylor F, Ward K, Moore TH, Burke M, Davey Smith G, Casas JP, Ebrahim S. Statins for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev.* 2011; (1):CD004816.10.1002/14651858.CD004816.pub4 [PubMed: 21249663]

47. Farwell WR, D'Avolio LW, Scranton RE, Lawler EV, Gaziano JM. Statins and prostate cancer diagnosis and grade in a veterans population. *J Natl Cancer Inst.* 2011; 103(11):885–892.10.1093/jnci/djr108 [PubMed: 21498780]
48. Brown M, Hart C, Tawadros T, Ramani V, Sangar V, Lau M, Clarke N. The differential effects of statins on the metastatic behaviour of prostate cancer. *Br J Cancer.* 2012; 106(10):1689–1696.10.1038/bjc.2012.138 [PubMed: 22531631]
49. Silva MA, Swanson AC, Gandhi PJ, Tataronis GR. Statin-related adverse events: a meta-analysis. *Clin Ther.* 2006; 28(1):26–35.10.1016/j.clinthera.2006.01.005 [PubMed: 16490577]
50. Saenz A, Fernandez-Esteban I, Mataix A, Ausejo M, Roque M, Moher D. Metformin monotherapy for type 2 diabetes mellitus. *Cochrane Database Syst Rev.* 2005; (3):CD002966.10.1002/14651858.CD002966.pub3 [PubMed: 16034881]
51. Lord JM, Flight IH, Norman RJ. Metformin in polycystic ovary syndrome: systematic review and meta-analysis. *Bmj.* 2003; 327(7421):951–953.10.1136/bmj.327.7421.951 [PubMed: 14576245]
52. Martin-Castillo B, Vazquez-Martin A, Oliveras-Ferraro C, Menendez JA. Metformin and cancer: doses, mechanisms and the dandelion and hormetic phenomena. *Cell Cycle.* 2010; 9 (6):1057–1064. [PubMed: 20305377]
53. Clements A, Gao B, Yeap SH, Wong MK, Ali SS, Gurney H. Metformin in prostate cancer: two for the price of one. *Ann Oncol.* 2011; 22(12):2556–2560.10.1093/annonc/mdr037 [PubMed: 21421541]
54. Pierotti MA, Berrino F, Gariboldi M, Melani C, Mogavero A, Negri T, Pisanis P, Pilotti S. Targeting metabolism for cancer treatment and prevention: metformin, an old drug with multi-faceted effects. *Oncogene.* 2012.10.1038/ncr.2012.181
55. Wright JL, Stanford JL. Metformin use and prostate cancer in Caucasian men: results from a population-based case-control study. *Cancer Causes Control.* 2009; 20(9):1617–1622.10.1007/s10552-009-9407-y [PubMed: 19653109]
56. Azoulay L, Dell'Aniello S, Gagnon B, Pollak M, Suissa S. Metformin and the incidence of prostate cancer in patients with type 2 diabetes. *Cancer Epidemiol Biomarkers Prev.* 2011; 20(2):337–344.10.1158/1055-9965.EPI-10-0940 [PubMed: 21148757]
57. Bolen S, Feldman L, Vassy J, Wilson L, Yeh HC, Marinopoulos S, Wiley C, Selvin E, Wilson R, Bass EB, Brancati FL. Systematic review: comparative effectiveness and safety of oral medications for type 2 diabetes mellitus. *Ann Intern Med.* 2007; 147 (6):386–399. [PubMed: 17638715]
58. Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus: systematic review and meta-analysis. *Arch Intern Med.* 2003; 163(21):2594–2602.10.1001/archinte.163.21.2594 [PubMed: 14638559]
59. Nelson JE, Harris RE. Inverse association of prostate cancer and non-steroidal anti-inflammatory drugs (NSAIDs): results of a case-control study. *Oncol Rep.* 2000; 7 (1):169–170. [PubMed: 10601612]
60. Harris RE, Beebe-Donk J, Doss H, Burr Doss D. Aspirin, ibuprofen, and other non-steroidal anti-inflammatory drugs in cancer prevention: a critical review of non-selective COX-2 blockade (review). *Oncol Rep.* 2005; 13 (4):559–583. [PubMed: 15756426]
61. Mahmud S, Franco E, Aprikian A. Prostate cancer and use of nonsteroidal anti-inflammatory drugs: systematic review and meta-analysis. *Br J Cancer.* 2004; 90(1):93–99.10.1038/sj.bjc.6601416 [PubMed: 14710213]
62. Mahmud SM, Franco EL, Aprikian AG. Use of nonsteroidal anti-inflammatory drugs and prostate cancer risk: a meta-analysis. *Int J Cancer.* 2010; 127:1680–1691. [PubMed: 20091856]
63. Jafari S, Etminan M, Afshar K. Nonsteroidal anti-inflammatory drugs prostate cancer: a systematic review of the literature meta-analysis. *Can Urol Assoc J.* 2009 Aug; 3(4):323–330. [PubMed: 19672448]
64. Habel LA, Zhao W, Stanford JL. Daily aspirin use and prostate cancer risk in a large, multiracial cohort in the US. *Cancer Causes Control.* 2002; 13(5):427–434.10.1023/A:1015788502099 [PubMed: 12146847]

65. Garcia Rodriguez LA, Gonzalez-Perez A. Inverse association between nonsteroidal anti-inflammatory drugs and prostate cancer. *Cancer Epidemiol Biomarkers Prev.* 2004; 13 (4):649–653. [PubMed: 15066932]
66. Jacobs EJ, Rodriguez C, Mondul AM, Connell CJ, Henley SJ, Calle EE, Thun MJ. A large cohort study of aspirin and other nonsteroidal anti-inflammatory drugs and prostate cancer incidence. *J Natl Cancer Inst.* 2005; 97(13):975–980.10.1093/jnci/dji173 [PubMed: 15998950]
67. Basler JW, Piazza GA. Nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 selective inhibitors for prostate cancer chemoprevention. *J Urol.* 2004; 171(2 Pt 2):S59–62. discussion S62–53. 10.1097/01.ju.0000107839.06670.27 [PubMed: 14713756]
68. Rainsford KD. Profile and mechanisms of gastrointestinal and other side effects of nonsteroidal anti-inflammatory drugs (NSAIDs). *Am J Med.* 1999; 107(6A):27S–35S. discussion 35S–36S. [PubMed: 10628591]
69. Amin AR, Kucuk O, Khuri FR, Shin DM. Perspectives for cancer prevention with natural compounds. *J Clin Oncol.* 2009; 27(16):2712–2725.10.1200/JCO.2008.20.6235 [PubMed: 19414669]
70. Kuriyama S, Shimazu T, Ohmori K, Kikuchi N, Nakaya N, Nishino Y, Tsubono Y, Tsuji I. Green tea consumption and mortality due to cardiovascular disease, cancer, and all causes in Japan: the Ohsaki study. *Jama.* 2006; 296(10):1255–1265.10.1001/jama.296.10.1255 [PubMed: 16968850]
71. Koo MW, Cho CH. Pharmacological effects of green tea on the gastrointestinal system. *Eur J Pharmacol.* 2004; 500(1–3):177–185.10.1016/j.ejphar.2004.07.023 [PubMed: 15464031]
72. Mandel SA, Avramovich-Tirosh Y, Reznichenko L, Zheng H, Weinreb O, Amit T, Youdim MB. Multifunctional activities of green tea catechins in neuroprotection. Modulation of cell survival genes, iron-dependent oxidative stress and PKC signaling pathway. *Neurosignals.* 2005; 14(1–2): 46–60.10.1159/000085385 [PubMed: 15956814]
73. Cabrera C, Artacho R, Gimenez R. Beneficial effects of green tea—a review. *J Am Coll Nutr.* 2006; 25 (2):79–99. [PubMed: 16582024]
74. Boehm K, Borrelli F, Ernst E, Habacher G, Hung SK, Milazzo S, Horneber M. Green tea (*Camellia sinensis*) for the prevention of cancer. *Cochrane Database Syst Rev.* 2009; (3):CD005004.10.1002/14651858.CD005004.pub2 [PubMed: 19588362]
75. Letter Updating the Green Tea and Risk of Breast Cancer and Prostate cancer Health Claim. 2012. <http://www.fda.gov/Food/LabelingNutrition/LabelClaims/QualifiedHealthClaims/ucm301644.htm>
76. Connors SK, Chornokur G, Kumar NB. New insights into the mechanisms of green tea catechins in the chemoprevention of prostate cancer. *Nutr Cancer.* 2012; 64(1):4–22.10.1080/01635581.2012.630158 [PubMed: 22098273]
77. Singh BN, Shankar S, Srivastava RK. Green tea catechin, epigallocatechin-3-gallate (EGCG): mechanisms, perspectives and clinical applications. *Biochem Pharmacol.* 2011; 82(12):1807–1821.10.1016/j.bcp.2011.07.093 [PubMed: 21827739]
78. Lee AH, Fraser ML, Meng X, Binns CW. Protective effects of green tea against prostate cancer. *Expert Rev Anticancer Ther.* 2006; 6(4):507–513.10.1586/14737140.6.4.507 [PubMed: 16613539]
79. Pisters KM, Newman RA, Coldman B, Shin DM, Khuri FR, Hong WK, Glisson BS, Lee JS. Phase I trial of oral green tea extract in adult patients with solid tumors. *J Clin Oncol.* 2001; 19 (6):1830–1838. [PubMed: 11251015]
80. Chow HH, Cai Y, Hakim IA, Crowell JA, Shahi F, Brooks CA, Dorr RT, Hara Y, Alberts DS. Pharmacokinetics and safety of green tea polyphenols after multiple-dose administration of epigallocatechin gallate and polyphenon E in healthy individuals. *Clin Cancer Res.* 2003; 9 (9): 3312–3319. [PubMed: 12960117]
81. Vincent A, Fitzpatrick LA. Soy isoflavones: are they useful in menopause? *Mayo Clin Proc.* 2000; 75(11):1174–1184.10.4065/75.11.1174 [PubMed: 11075748]
82. Pihlajamäki P, Zhang FP, Saarinen L, Mikkonen L, Hautaniemi S, Janne OA. The phytoestrogen genistein is a tissue-specific androgen receptor modulator. *Endocrinology.* 2011; 152(11):4395–4405.10.1210/en.2011-0221 [PubMed: 21878517]
83. Horie S. Chemoprevention of prostate cancer: soy isoflavones and curcumin. *Korean J Urol.* 2012; 53(10):665–672.10.4111/kju.2012.53.10.665 [PubMed: 23136625]

84. Kumar NB, Krischer JP, Allen K, Riccardi D, Besterman-Dahan K, Salup R, Kang L, Xu P, Pow-Sang J. A Phase II randomized, placebo-controlled clinical trial of purified isoflavones in modulating steroid hormones in men diagnosed with localized prostate cancer. *Nutr Cancer*. 2007; 59(2):163–168.10.1080/01635580701432678 [PubMed: 18001210]
85. Kumar NB, Kang L, Pow-Sang J, Xu P, Allen K, Riccardi D, Besterman-Dahan K, Krischer JP. Results of a randomized phase I dose-finding trial of several doses of isoflavones in men with localized prostate cancer: administration prior to radical prostatectomy. *J Soc Integr Oncol*. 2010; 8 (1):3–13. [PubMed: 20205984]
86. Yan L, Spitznagel EL. Meta-analysis of soy food and risk of prostate cancer in men. *Int J Cancer*. 2005; 117(4):667–669.10.1002/ijc.21266 [PubMed: 15945102]
87. Hussain M, Banerjee M, Sarkar FH, Djuric Z, Pollak MN, Doerge D, Fontana J, Chinni S, Davis J, Forman J, Wood DP, Kucuk O. Soy isoflavones in the treatment of prostate cancer. *Nutr Cancer*. 2003; 47(2):111–117.10.1207/s15327914nc4702_1 [PubMed: 15087261]
88. Ahmad IU, Forman JD, Sarkar FH, Hillman GG, Heath E, Vaishampayan U, Cher ML, Andic F, Rossi PJ, Kucuk O. Soy isoflavones in conjunction with radiation therapy in patients with prostate cancer. *Nutr Cancer*. 2010; 62(7):996–1000.10.1080/01635581.2010.509839 [PubMed: 20924975]
89. Perabo FG, Von Low EC, Ellinger J, von Rucker A, Muller SC, Bastian PJ. Soy isoflavone genistein in prevention and treatment of prostate cancer. *Prostate Cancer Prostatic Dis*. 2008; 11(1):6–12.10.1038/sj.pcan.4501000 [PubMed: 17923857]
90. Mennen LI, Walker R, Bennetau-Pelissero C, Scalbert A. Risks and safety of polyphenol consumption. *Am J Clin Nutr*. 2005; 81 (1 Suppl):326S–329S. [PubMed: 15640498]
91. Hamilton-Reeves JM, Vazquez G, Duval SJ, Phipps WR, Kurzer MS, Messina MJ. Clinical studies show no effects of soy protein or isoflavones on reproductive hormones in men: results of a meta-analysis. *Fertil Steril*. 2010; 94(3):997–1007.10.1016/j.fertnstert.2009.04.038 [PubMed: 19524224]
92. Mityk W, Craciunescu CN, Fischer L, Jeffcoat RA, Koch MA, Lopaczynski W, Mahoney C, Crowell J, Paglieri J, Zeisel SH. Lack of significant genotoxicity of purified soy isoflavones (genistein, daidzein, and glycitein) in 20 patients with prostate cancer. *Am J Clin Nutr*. 2003; 77 (4):875–882. [PubMed: 12663286]
93. Kumar NB, Krischer JP, Allen K, Riccardi D, Besterman-Dahan K, Salup R, Kang L, Xu P, Pow-Sang J. Safety of purified isoflavones in men with clinically localized prostate cancer. *Nutr Cancer*. 2007; 59(2):169–175.10.1080/01635580701432660 [PubMed: 18001211]
94. Siepmann T, Roofeh J, Kiefer FW, Edelson DG. Hypogonadism and erectile dysfunction associated with soy product consumption. *Nutrition*. 2011; 27(7–8):859–862.10.1016/j.nut.2010.10.018 [PubMed: 21353476]
95. Martinez J, Lewi JE. An unusual case of gynecomastia associated with soy product consumption. *Endocr Pract*. 2008; 14 (4):415–418. [PubMed: 18558591]
96. Clinton SK. Lycopene: chemistry, biology, and implications for human health and disease. *Nutr Rev*. 1998; 56 (2 Pt 1):35–51. [PubMed: 9529899]
97. Ilic D, Forbes KM, Hammad C. Lycopene for the prevention of prostate cancer. *Cochrane Database Syst Rev*. 2011; (11):CD008007.10.1002/14651858.CD008007.pub2 [PubMed: 22071840]
98. Qualified Health Claims: Letter Regarding Tomatoes and Prostate Cancer (Lycopene Health Claim Coalition) (Docket No. 2004Q-0201). 2004. <http://www.fda.gov/Food/LabelingNutrition/LabelClaims/QualifiedHealthCare/ucm072767.htm>
99. Wei MY, Giovannucci EL. Lycopene, Tomato Products, and Prostate Cancer Incidence: A Review and Reassessment in the PSA Screening Era. *J Oncol*. 2012; 2012:271063.10.1155/2012/271063 [PubMed: 22690215]
100. Heber D, Lu QY. Overview of mechanisms of action of lycopene. *Exp Biol Med (Maywood)*. 2002; 227 (10):920–923. [PubMed: 12424335]
101. Kucuk O, Sarkar FH, Djuric Z, Sakr W, Pollak MN, Khachik F, Banerjee M, Bertram JS, Wood DP Jr. Effects of lycopene supplementation in patients with localized prostate cancer. *Exp Biol Med (Maywood)*. 2002; 227 (10):881–885. [PubMed: 12424329]

102. Tang L, Jin T, Zeng X, Wang JS. Lycopene inhibits the growth of human androgen-independent prostate cancer cells in vitro and in BALB/c nude mice. *J Nutr.* 2005; 135 (2):287–290. [PubMed: 15671228]
103. Hantz HL, Young LF, Martin KR. Physiologically attainable concentrations of lycopene induce mitochondrial apoptosis in LNCaP human prostate cancer cells. *Exp Biol Med* (Maywood). 2005; 230 (3):171–179. [PubMed: 15734720]
104. Ivanov NI, Cowell SP, Brown P, Rennie PS, Guns ES, Cox ME. Lycopene differentially induces quiescence and apoptosis in androgen-responsive and -independent prostate cancer cell lines. *Clin Nutr.* 2007; 26(2):252–263.10.1016/j.clnu.2007.01.002 [PubMed: 17337101]
105. Kumar NB, Besterman-Dahan K, Kang L, Pow-Sang J, Xu P, Allen K, Riccardi D, Krischer JP. Results of a Randomized Clinical Trial of the Action of Several Doses of Lycopene in Localized Prostate Cancer: Administration Prior to Radical Prostatectomy. *Clin Med Urol.* 2008; 1:1–14. [PubMed: 20354574]
106. Vogt TM, Mayne ST, Graubard BI, Swanson CA, Sowell AL, Schoenberg JB, Swanson GM, Greenberg RS, Hoover RN, Hayes RB, Ziegler RG. Serum lycopene, other serum carotenoids, and risk of prostate cancer in US Blacks and Whites. *Am J Epidemiol.* 2002; 155 (11):1023–1032. [PubMed: 12034581]
107. van Breemen RB, Sharifi R, Viana M, Pajkovic N, Zhu D, Yuan L, Yang Y, Bowen PE, Stacewicz-Sapuntzakis M. Antioxidant effects of lycopene in African American men with prostate cancer or benign prostate hyperplasia: a randomized, controlled trial. *Cancer Prev Res (Phila).* 2011; 4(5):711–718.10.1158/1940-6207.CAPR-10-0288 [PubMed: 21430075]
108. Trumbo PR. Are there adverse effects of lycopene exposure? *J Nutr.* 2005; 135 (8):2060S–2061S. [PubMed: 16046742]
109. Michael McClain R, Bausch J. Summary of safety studies conducted with synthetic lycopene. *Regul Toxicol Pharmacol.* 2003; 37 (2):274–285. [PubMed: 12726756]
110. De R, Kundu P, Swarnakar S, Ramamurthy T, Chowdhury A, Nair GB, Mukhopadhyay AK. Antimicrobial activity of curcumin against *Helicobacter pylori* isolates from India and during infections in mice. *Antimicrob Agents Chemother.* 2009; 53(4):1592–1597.10.1128/AAC.01242-08 [PubMed: 19204190]
111. Martins CV, da Silva DL, Neres AT, Magalhaes TF, Watanabe GA, Modolo LV, Sabino AA, de Fatima A, de Resende MA. Curcumin as a promising antifungal of clinical interest. *J Antimicrob Chemother.* 2009; 63(2):337–339.10.1093/jac/dkn488 [PubMed: 19038979]
112. O'Connell MA, Rushworth SA. Curcumin: potential for hepatic fibrosis therapy? *Br J Pharmacol.* 2008; 153(3):403–405.10.1038/sj.bjp.0707580 [PubMed: 18037917]
113. Ringman JM, Frautschy SA, Cole GM, Masterman DL, Cummings JL. A potential role of the curry spice curcumin in Alzheimer's disease. *Curr Alzheimer Res.* 2005; 2 (2):131–136. [PubMed: 15974909]
114. Srivastava G, Mehta JL. Currying the heart: curcumin and cardioprotection. *J Cardiovasc Pharmacol Ther.* 2009; 14(1):22–27.10.1177/1074248408329608 [PubMed: 19153099]
115. Chainani-Wu N. Safety and anti-inflammatory activity of curcumin: a component of tumeric (*Curcuma longa*). *J Altern Complement Med.* 2003; 9(1):161–168.10.1089/107555303321223035 [PubMed: 12676044]
116. Bar-Sela G, Epelbaum R, Schaffer M. Curcumin as an anti-cancer agent: review of the gap between basic and clinical applications. *Curr Med Chem.* 2010; 17 (3):190–197. [PubMed: 20214562]
117. Aggarwal BB. Prostate cancer and curcumin: add spice to your life. *Cancer Biol Ther.* 2008; 7 (9):1436–1440. [PubMed: 18769126]
118. Hong JH, Ahn KS, Bae E, Jeon SS, Choi HY. The effects of curcumin on the invasiveness of prostate cancer in vitro and in vivo. *Prostate Cancer Prostatic Dis.* 2006; 9(2):147–152.10.1038/sj.pcan.4500856 [PubMed: 16389264]
119. Maheshwari RK, Singh AK, Gaddipati J, Srimal RC. Multiple biological activities of curcumin: a short review. *Life Sci.* 2006; 78(18):2081–2087.10.1016/j.lfs.2005.12.007 [PubMed: 16413584]

120. Shenouda NS, Zhou C, Browning JD, Ansell PJ, Sakla MS, Lubahn DB, Macdonald RS. Phytoestrogens in common herbs regulate prostate cancer cell growth in vitro. *Nutr Cancer*. 2004; 49(2):200–208.10.1207/s15327914nc4902_12 [PubMed: 15489213]
121. Teiten MH, Gaascht F, Eifes S, Dicato M, Diederich M. Chemopreventive potential of curcumin in prostate cancer. *Genes Nutr*. 2010; 5(1):61–74.10.1007/s12263-009-0152-3 [PubMed: 19806380]
122. Dadhaniya P, Patel C, Muchhara J, Bhadja N, Mathuria N, Vachhani K, Soni MG. Safety assessment of a solid lipid curcumin particle preparation: acute and subchronic toxicity studies. *Food Chem Toxicol*. 2011; 49(8):1834–1842.10.1016/j.fct.2011.05.001 [PubMed: 21571027]
123. Jiao Y, Wilkinson Jt, Di X, Wang W, Hatcher H, Kock ND, D'Agostino R Jr, Knovich MA, Torti FM, Torti SV. Curcumin, a cancer chemopreventive and chemotherapeutic agent, is a biologically active iron chelator. *Blood*. 2009; 113(2):462–469.10.1182/blood-2008-05-155952 [PubMed: 18815282]
124. Berquin IM, Edwards IJ, Chen YQ. Multi-targeted therapy of cancer by omega-3 fatty acids. *Cancer Lett*. 2008; 269(2):363–377.10.1016/j.canlet.2008.03.044 [PubMed: 18479809]
125. Friedrichs W, Ruparel SB, Marciniak RA, de Graffenried L. Omega-3 fatty acid inhibition of prostate cancer progression to hormone independence is associated with suppression of mTOR signaling and androgen receptor expression. *Nutr Cancer*. 2011; 63(5):771–777.10.1080/01635581.2011.570892 [PubMed: 21667400]
126. Cavazos DA, Price RS, Apte SS, de Graffenried LA. Docosahexaenoic acid selectively induces human prostate cancer cell sensitivity to oxidative stress through modulation of NF-kappaB. *Prostate*. 2011; 71(13):1420–1428.10.1002/pros.21359 [PubMed: 21360560]
127. MacLean CH, Newberry SJ, Mojica WA, Khanna P, Issa AM, Suttrop MJ, Lim YW, Traina SB, Hilton L, Garland R, Morton SC. Effects of omega-3 fatty acids on cancer risk: a systematic review. *Jama*. 2006; 295(4):403–415.10.1001/jama.295.4.403 [PubMed: 16434631]
128. Sala-Vila A, Calder PC. Update on the relationship of fish intake with prostate, breast, and colorectal cancers. *Crit Rev Food Sci Nutr*. 2011; 51(9):855–871.10.1080/10408398.2010.483527 [PubMed: 21888535]
129. Ukoli FA, Fowke JH, Akumabor P, Oguike T, Taher KA, Murff HJ, Amaefuna ER, Kittles R, Ahaghotu C, Osime U, Beech DJ. The association of plasma fatty acids with prostate cancer risk in African Americans and Africans. *J Health Care Poor Underserved*. 2010; 21(1 Suppl):127–147.10.1353/hpu.0.0242 [PubMed: 20173289]
130. Williams CD, Whitley BM, Hoyo C, Grant DJ, Iraggi JD, Newman KA, Gerber L, Taylor LA, McKeever MG, Freedland SJ. A high ratio of dietary n-6/n-3 polyunsaturated fatty acids is associated with increased risk of prostate cancer. *Nutr Res*. 2011; 31(1):1–8.10.1016/j.nutres.2011.01.002 [PubMed: 21310299]
131. Riediger ND, Othman RA, Suh M, Moghadasian MH. A systemic review of the roles of n-3 fatty acids in health and disease. *J Am Diet Assoc*. 2009; 109(4):668–679.10.1016/j.jada.2008.12.022 [PubMed: 19328262]
132. Marik PE, Varon J. Omega-3 dietary supplements and the risk of cardiovascular events: a systematic review. *Clin Cardiol*. 2009; 32(7):365–372.10.1002/clc.20604 [PubMed: 19609891]
133. Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. *Am J Clin Nutr*. 2004; 80 (6 Suppl):1678S–1688S. [PubMed: 15585788]
134. Schwartz GG. Vitamin D and intervention trials in prostate cancer: from theory to therapy. *Ann Epidemiol*. 2009; 19(2):96–102.10.1016/j.annepidem.2008.03.007 [PubMed: 18619854]
135. Gilbert R, Martin RM, Beynon R, Harris R, Savovic J, Zuccolo L, Bekkering GE, Fraser WD, Sterne JA, Metcalfe C. Associations of circulating and dietary vitamin D with prostate cancer risk: a systematic review and dose-response meta-analysis. *Cancer Causes Control*. 2011; 22(3):319–340.10.1007/s10552-010-9706-3 [PubMed: 21203822]
136. Manson JE, Mayne ST, Clinton SK. Vitamin D and prevention of cancer--ready for prime time? *N Engl J Med*. 2011; 364(15):1385–1387.10.1056/NEJMp1102022 [PubMed: 21428761]
137. Ahn J, Peters U, Albanes D, Purdue MP, Abnet CC, Chatterjee N, Horst RL, Hollis BW, Huang WY, Shikany JM, Hayes RB. Serum vitamin D concentration and prostate cancer risk: a nested

- case-control study. *J Natl Cancer Inst.* 2008; 100(11):796–804.10.1093/jnci/djn152 [PubMed: 18505967]
138. Park SY, Cooney RV, Wilkens LR, Murphy SP, Henderson BE, Kolonel LN. Plasma 25-hydroxyvitamin D and prostate cancer risk: the multiethnic cohort. *Eur J Cancer.* 2010; 46(5): 932–936.10.1016/j.ejca.2009.12.030 [PubMed: 20064705]
 139. Tseng M, Giri V, Watkins-Bruner D, Giovannucci E. Dairy intake and 1,25-dihydroxyvitamin D levels in men at high risk for prostate cancer. *Cancer Causes Control.* 2009; 20(10):1947–1954.10.1007/s10552-009-9389-9 [PubMed: 19578936]
 140. Tseng M, Giri V, Bruner DW, Giovannucci E. Prevalence and correlates of vitamin D status in African American men. *BMC Public Health.* 2009; 9:191.10.1186/1471-2458-9-191 [PubMed: 19534831]
 141. Marshall DT, Savage SJ, Garrett-Mayer E, Keane TE, Hollis BW, Horst RL, Ambrose LH, Kindy MS, Gattoni-Celli S. Vitamin D3 supplementation at 4000 international units per day for one year results in a decrease of positive cores at repeat biopsy in subjects with low-risk prostate cancer under active surveillance. *J Clin Endocrinol Metab.* 2012; 97(7):2315–2324.10.1210/jc.2012-1451 [PubMed: 22508710]
 142. Autier P, Gandini S. Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled trials. *Arch Intern Med.* 2007; 167 (16):1730–1737. [PubMed: 17846391]
 143. Halthur C, Johansson AL, Almquist M, Malm J, Gronberg H, Manjer J, Dickman PW. Serum calcium and the risk of prostate cancer. *Cancer Causes Control.* 2009; 20(7):1205–1214.10.1007/s10552-009-9342-y [PubMed: 19377857]
 144. Williams CD, Whitley BM, Hoyo C, Grant DJ, Schwartz GG, Presti JC Jr, Iraggi JD, Newman KA, Gerber L, Taylor LA, McKeever MG, Freedland SJ. Dietary calcium and risk for prostate cancer: a case-control study among US veterans. *Prev Chronic Dis.* 2012; 9:E39. [PubMed: 22239754]
 145. Huncharek M, Muscat J, Kupelnick B. Dairy products, dietary calcium and vitamin D intake as risk factors for prostate cancer: a meta-analysis of 26,769 cases from 45 observational studies. *Nutr Cancer.* 2008; 60(4):421–441.10.1080/01635580801911779 [PubMed: 18584476]
 146. Rowland GW, Schwartz GG, John EM, Ingles SA. Calcium intake and prostate cancer among African Americans: Effect modification by vitamin D receptor calcium absorption genotype. *J Bone Miner Res.* 2011; 26(5):505–515.10.1002/jbmr.505
 147. Mamaeva OA, Kim J, Feng G, McDonald JM. Calcium/calmodulin-dependent kinase II regulates notch-1 signaling in prostate cancer cells. *J Cell Biochem.* 2009; 106(1):25–32.10.1002/jcb.21973 [PubMed: 19021144]
 148. Sun B, Zhang X, Yonz C, Cummings BS. Inhibition of calcium-independent phospholipase A2 activates p38 MAPK signaling pathways during cytostasis in prostate cancer cells. *Biochem Pharmacol.* 2010; 79(12):1727–1735.10.1016/j.bcp.2010.02.005 [PubMed: 20171194]
 149. Lippman SM, Klein EA, Goodman PJ, Lucia MS, Thompson IM, Ford LG, Parnes HL, Minasian LM, Gaziano JM, Hartline JA, Parsons JK, Bearden JD 3rd, Crawford ED, Goodman GE, Claudio J, Winkquist E, Cook ED, Karp DD, Walther P, Lieber MM, Kristal AR, Darke AK, Arnold KB, Ganz PA, Santella RM, Albanes D, Taylor PR, Probstfield JL, Jagpal TJ, Crowley JJ, Meyskens FL Jr, Baker LH, Coltman CA Jr. Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *Jama.* 2009; 301(1):39–51.10.1001/jama.2008.864 [PubMed: 19066370]
 150. Ledesma MC, Jung-Hynes B, Schmit TL, Kumar R, Mukhtar H, Ahmad N. Selenium and vitamin E for prostate cancer: post-SELECT (Selenium and Vitamin E Cancer Prevention Trial) status. *Mol Med.* 2011; 17(1–2):134–143.10.2119/molmed.2010.00136 [PubMed: 20882260]
 151. Lippman SM, Goodman PJ, Klein EA, Parnes HL, Thompson IM Jr, Kristal AR, Santella RM, Probstfield JL, Moynour CM, Albanes D, Taylor PR, Minasian LM, Hoque A, Thomas SM, Crowley JJ, Gaziano JM, Stanford JL, Cook ED, Fleschner NE, Lieber MM, Walther PJ, Khuri FR, Karp DD, Schwartz GG, Ford LG, Coltman CA Jr. Designing the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *J Natl Cancer Inst.* 2005; 97(2):94–102.10.1093/jnci/dji009 [PubMed: 15657339]
 152. Clark LC, Combs GF Jr, Turnbull BW, Slate EH, Chalker DK, Chow J, Davis LS, Glover RA, Graham GF, Gross EG, Krongrad A, Leshner JL Jr, Park HK, Sanders BB Jr, Smith CL, Taylor

- JR. Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized controlled trial. Nutritional Prevention of Cancer Study Group. *Jama*. 1996; 276 (24):1957–1963. [PubMed: 8971064]
153. Papp LV, Lu J, Holmgren A, Khanna KK. From selenium to selenoproteins: synthesis, identity, and their role in human health. *Antioxid Redox Signal*. 2007; 9(7):775–806.10.1089/ars.2007.1528 [PubMed: 17508906]
154. Hatfield DL, Gladyshev VN. The Outcome of Selenium and Vitamin E Cancer Prevention Trial (SELECT) reveals the need for better understanding of selenium biology. *Mol Interv*. 2009; 9(1): 18–21.10.1124/mi.9.1.6 [PubMed: 19299660]
155. Klein EA. Selenium and vitamin E: interesting biology and dashed hope. *J Natl Cancer Inst*. 2009; 101(5):283–285.10.1093/jnci/djp009 [PubMed: 19244172]
156. Platz EA, Lippman SM. Selenium, genetic variation, and prostate cancer risk: epidemiology reflects back on selenium and vitamin E cancer prevention trial. *J Clin Oncol*. 2009; 27(22): 3569–3572.10.1200/JCO.2009.22.2117 [PubMed: 19528369]
157. Heinonen OP, Albanes D, Virtamo J, Taylor PR, Huttunen JK, Hartman AM, Haapakoski J, Malila N, Rautalahti M, Ripatti S, Maenpaa H, Teerenhovi L, Koss L, Virolainen M, Edwards BK. Prostate cancer and supplementation with alpha-tocopherol and beta-carotene: incidence and mortality in a controlled trial. *J Natl Cancer Inst*. 1998; 90 (6):440–446. [PubMed: 9521168]
158. Zhang Y, Ni J, Messing EM, Chang E, Yang CR, Yeh S. Vitamin E succinate inhibits the function of androgen receptor and the expression of prostate-specific antigen in prostate cancer cells. *Proc Natl Acad Sci U S A*. 2002; 99(11):7408–7413.10.1073/pnas.102014399 [PubMed: 12032296]
159. Yap WN, Chang PN, Han HY, Lee DT, Ling MT, Wong YC, Yap YL. Gamma-tocotrienol suppresses prostate cancer cell proliferation and invasion through multiple-signaling pathways. *Br J Cancer*. 2008; 99(11):1832–1841.10.1038/sj.bjc.6604763 [PubMed: 19002171]
160. Selenium and Vitamin E Cancer Prevention Trial (SELECT). <http://www.cancer.gov/newscenter/qa/2008/selectqa>

Figure 1.

An overview of the molecular mechanisms that may be involved in the increased PCa aggressiveness in AAM. References are shown in the text.

Table 1

The most studied PCa chemopreventive compounds with the summaries of their mechanisms of action, effectiveness in AAM and EAM, side effects, references and the author's interpretation on the overall usefulness for men of African descent. The numbers denote a compound that was either shown, or has a potential to be: (1) more effective in AAM compared to EAM; (2) equally effective in AAM and EAM; (3) less effective in AAM compared to EAM; (4) no evidence-based conclusion can be made at this time.

Compound	Mechanism of action	Effectiveness in AAM and EAM	Side effects	Ref
Single-target pharmaceutical compounds				
5-alpha-reductase inhibitors (2)	Inhibits 5-alpha-reductase, an enzyme that converts T into DHT. Since DHT is more potent towards AR, this inhibits AR-mediated signaling	Clinical trials did not include enough AAM to achieve statistical significance. However, efficacy and safety appear similar in AA and EA men with BPH	Sexual dysfunction, reduction or loss of libido, erectile problems, gynecomastia, and depression	37–45
Statins (1)	Reduce invasiveness and ability to migrate specifically to bone marrow	May be more effective in AAM due to effective suppression of invasiveness. However, no data of any kind (<i>in vitro</i> , <i>in vivo</i> or clinical) are available specifically for AAM	Myalgia and liver dysfunction	46–49
Metformin (3)	Dual: 1. Lowers potential “cancer ligands” such as insulin and glucose; 2. Suppresses the AMPK/mTOR/p70S6K1 pathway and IGFR and p53 mediated mechanisms	Epidemiological studies largely do not find PCa chemopreventive benefits in AAM. While the reasons are unknown, may be due to confounding by diabetes, obesity and PCa – a relationship that is poorly understood	GI upset; lactic acidosis (controversial). Overall, appears to be relatively safe in healthy individuals.	50–58
NSAIDs (2)	Inhibits COX-2 enzyme that leads to reduced inflammation, proliferation and angiogenesis	Aspirin appears to be equally protective in AAM and EAM; no data for other NSAIDs	GI bleeding and hepatotoxicity in case of overdose	59–68
Multiple-target nutraceutical compounds				
GTCs (1)	Reduce AR-mediated proliferation; Increase apoptosis by reducing bcl-2 expression; reduce invasiveness and metastasis by inhibiting the MMPs among others	Although biologically promising for AAM (Figure 1), no data of any kind (<i>in vitro</i> , <i>in vivo</i> or clinical) are available specifically for AAM	Very mild and likely caffeine-related, including bloating and jitteriness.	70–80
Isoflavones (1)	Suppress AR-mediated signaling due to mild estrogenic action, among others	Data obtained mostly from people with diets high in soy. Although biologically promising for AAM, no data are yet available specifically for AAM. A phase II clinical trial of Purified Isoflavones in PCa that aims to compare its Safety and Effectiveness in AA and EA men is underway	Generally well-tolerated, but research should continue	81–95
Lycopene (4)	G0/G1 cycle arrest, apoptosis and delayed <i>in vivo</i> tumor growth through the mechanisms not well understood	Cause-effect studies involving AAM are lacking. Some evidence suggests lower levels of lycopene in AAM; however, the relevance of this observation for PCa prevention remains unclear	None noted, generally recognized as safe	96–109
Curcumin (1)	Suppresses proliferation by reduced AR and EGFR signaling; promotes apoptosis by suppressing the bcl-2 expression; reduces invasiveness by suppressing MMPs expression and activation	Although biologically promising for AAM (Table 1), no data of any kind (<i>in vitro</i> , <i>in vivo</i> or clinical) are available specifically for AAM	Generally recognized as safe; however, might lead to mild GI upset	110–123

Compound	Mechanism of action	Effectiveness in AAM and EAM	Side effects	Ref
Omega-3 fatty acids (3)	Suppression of the AR-signaling, the Akt/mTOR pathway and NF-kB-mediated signaling	Epidemiological studies largely <u>do not</u> find PCa chemopreventive benefits in AAM. However, biological reasons for this are unknown	None noted, generally recognized as safe	124–132
Vitamin D (4)	Unknown; perhaps attributed to anti-inflammatory properties	Although the topic is debated,, available data largely do not support the hypothesis that vitamin D lowers the risk of PCa	None noted, generally recognized as safe	133–142
Calcium (4)	May be related to the cellular calcium-dependent channel function; Notch and Mapk signaling	Studies in AAM are very conflicting perhaps due to potential confounding related to calcium and vitamin D absorption and circulating levels. More research is needed	None noted, generally recognized as safe	143–148
Selenium (4) Vitamin E (4)	Likely mediated via selenoproteins Inhibited AR signaling and/or general anti-inflammatory properties	Data is conflicting in general, and absent in AAM. Research should continue using different sub-populations as well as various formulations and dosages to elucidate the true chemopreventive potential	Selenium: selenosis if taken 400mcg/day Vit. E: none noted, generally recognized as safe	149–160