Published in final edited form as:

Curr Opin Pharmacol. 2009 August ; 9(4): 419–426. doi:10.1016/j.coph.2009.06.002.

Anti-inflammatory drugs, antioxidants, and prostate cancer prevention

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Abstract

Prostate cancer may be the most common preventable cancer among men in the United States (US) and the rest of the developed world. Emerging insights into the molecular pathogenesis of prostate cancer suggest that damage to the prostate epithelium, potentially inflicted by a variety of exposures, triggers procarcinogenic inflammatory processes to promote disease development. In this milieu, the damaged epithelium may generate proliferative inflammatory atrophy (PIA) lesions, which may progress to prostatic intraepithelial neoplasia (PIN) or to prostate cancer. To attenuate prostatic carcinogenesis driven by chronic or recurrent prostate inflammation, rational chemoprevention has thus far featured anti-inflammatory drugs and antioxidants. Results from clinical trials of these approaches have been mixed, emphasizing the need for mechanistic studies of the contribution of inflammation to prostatic carcinogenesis, more extensive analyses of the pharmacology, including distribution of drugs into target tissue, and, rational development of biomarkers to identify patients that are most likely to respond to anti-inflammatory drugs and antioxidants (targeted chemoprevention), alone, or in combination (combination chemoprevention).

Introduction

Prostate cancer is the most common cause of cancer among men in the United States (US), accounting for ~25% of all cancers in men, with more than 186 000 prostate cancer diagnoses in 2008 [1]. Prostate cancer caused around 28 000 deaths in the US (~10% of cancer deaths), with disproportionate death rates among African-American men. New strategies for reducing prostate cancer incidence and mortality, and for eliminating disparities in prostate cancer outcomes, are needed.

At least 20% of all human cancers, and most epithelial cancers, likely arise in a tissue microenvironment dominated by chronic or recurrent inflammation triggered by environmental exposures such as infections, diet, and trauma. Prostate cancer appears to be no exception, and evidence is accumulating linking inflammation and prostate cancer from

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Financial disclosure: none.

pathological, molecular, genetic, and epidemiological perspectives [2•]. In this review, the mechanisms by which inflammatory processes contribute to prostatic carcinogenesis will be considered, with special attention to anti-inflammatory and antioxidant approaches to prostate cancer prevention.

Proliferative inflammatory atrophy (PIA) as a precursor to prostate cancer

Injury to the prostate epithelium, regardless of the source of the damage, elicits a stereotypical stress and regenerative response characterized by the emergence of proliferative inflammatory atrophy (PIA) or proliferative atrophy (PA) lesions, described by De Marzo *et al.* [3]. In PIA, epithelial cells fail to fully differentiate, leaving an atrophic appearance to the luminal epithelial cells, and instead, activate a number of stress signaling pathways, leading to high level expression of glutathione *S*-transferases (GSTA1, GSTP1, etc.), p16, p53, cyclo-oxygenase-2 (COX-2), and other markers. Typically, PIA lesions are associated with chronic inflammation of the prostate, and histological transitions between areas of PIA and high-grade prostate intraepithelial neoplasia (PIN), and between PIA and prostate cancer, have been observed. In the human prostate, the lesions are predominantly found in the peripheral zone of the prostate where most cancers arise. The relationship between PIA and prostate cancer is also quite compelling in animal models of prostate cancer. For example, in rats fed the ‘well-done’ meat carcinogen, 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP), mutations were induced in each prostate lobe, but a chronic inflammatory reaction leading to PIA appeared only in the ventral lobe, the lobe which also developed prostate cancer [4•].

In the human prostate, a striking heterogeneity of host inflammatory responses can be seen. The chronic inflammatory cells appear to be mostly composed of lymphocytes (70–80% T cells, 10–15% B cells), macrophages, and monocytes. These cells can secrete various inflammatory cytokines, including IL-6, IL-8, vascular endothelial growth factor (VEGF), and TNF- α , that could potentially contribute to the development and/or malignant behavior of prostate cancer. IL-17 is another cytokine produced by T_H17 cells, a subset of CD4⁺ T cells that is increasingly recognized for its contributions to inflammation and carcinogenesis generally [5•]. In a recent study by Narayanan *et al.* [6•], increased levels of various cytokines were seen in a rat model of prostate cancer triggered by *N*-methyl-*N*-nitrosourea (MNU) and testosterone; in this model, celecoxib appeared to attenuate prostate carcinogenesis.

Linkages between inflammation, PIA, and somatic epigenetic alterations

The most compelling molecular evidence for a mechanistic association between inflammation and prostate cancer is the appearance of somatic epigenetic alterations in PIA lesions that are reminiscent of those known to be present in prostate cancers. The best studied epigenetic alteration, hypermethylation of cytosine bases in the regulatory region of the gene encoding the π -class glutathione *S*-transferase (*GSTP1*), results in transcriptional silencing of the gene and enhanced susceptibility to a variety of carcinogenic genomic stresses. *GSTP1* hypermethylation, which is present in nearly all prostate cancers, can be detected in some 5% or more of PIA lesions. How such *de novo* methylation changes at

GSTP1 and at other genes arise is not well understood, but some sort of DNA methylation ‘catastrophe’ in response to inflammatory stimuli appears likely [7]. Curiously, the major genetic alterations reported in prostate cancer, featuring deletions/translocations generating fusion transcripts involving androgen regulated differentiation genes, such as *TMPRSS2*, and candidate oncogenes, such as those encoding ETS family transcription factors, appear to arise later than the epigenetic changes, becoming evident in PIN lesions [8•].

Host inflammatory response genes and prostate cancer risk

Several of the germline gene variants implicated in prostate cancer risk encode genes participating in host inflammatory responses to infection and other threats. Both *RNASEL*, which encodes a ribonuclease functioning in an interferon-inducible 2',5'-oligoadenylate-dependent RNA decay pathway that degrades viral and cellular RNA upon viral infection, and *MSRI*, which encodes subunits of a class A macrophage scavenger receptor capable of binding bacterial lipopolysaccharide and lipoteichoic acid, along with oxidized high and low density serum lipoproteins (oxidized HDL and LDL), have been implicated in hereditary prostate cancer syndromes.

In addition, genetic epidemiology studies have detected increased prostate cancer risks associated with polymorphic variants of *TLR4* and other toll-like receptor family genes, which are involved in signaling the production of various proinflammatory cytokines, *CD59/MIC1*, which regulates macrophage activation, *IL1RN*, which is involved in the regulation of interleukin-1 action, and IL-10, an anti-inflammatory cytokine [9]. Recent studies utilizing genome-wide analysis have identified few potential loci that increase susceptibility to prostate cancer, and appear promising as biomarkers to identify individuals at high risk for prostate cancer [10].

Inflammation, infection, and prostate cancer epidemiology

Various inflammatory stimuli, including sexually transmitted infections (STIs), dietary factors, exposure to estrogen, and urine reflux, have been implicated as potential environmental triggers of prostatic inflammation [2•]. Young men with sexually transmitted infections (STIs) have been reported to be more likely to have an increase in serum prostate-specific antigen (PSA) than men without STIs, suggesting that such infections can damage the prostate epithelium, leading to the leakage of PSA into the bloodstream, even at a young age. However, though a number of STIs have been correlated with prostate cancer incidence, a causal relationship has not been established. Recently, a novel retrovirus, XMRV (xenotropic murine leukemia virus related virus), was discovered in prostate tumors among men with genetic defects in *RNASEL*, hinting that an interaction between genetic susceptibility and environmental exposure might trigger and/or propagate prostatic inflammation [11].

Epidemiological studies have also observed an increased risk of prostate cancer among men with a history of prostatitis. A systematic review of 11 epidemiological studies found that men with a history of prostatitis had a 1.6 higher risk (95% CI: 1.0, 2.4) of prostate cancer [12], although this could partly be because of detection bias as patients with symptomatic prostatitis are more likely to visit a urologist and thus are more likely to be screened for

prostate cancer. Reflux of urine has been implicated to promote prostatic inflammation presumably by damaging the prostatic epithelium, and by stimulating the production of inflammatory cytokines via activation of NALP3 inflammasomes by prostatic calculi [13].

As for dietary factors, meat intake has long been associated with increased prostate cancer risk. Some of this risk may be explained by cooking practices: cooking meats at high temperatures, especially charbroiling fatty meats, can result in the generation of heterocyclic amines (HCAs), such as PhIP and others, as well as in polycyclic aromatic hydrocarbons (PAHs), which can each induce mutations, and cause cell and tissue damage [14]. In rats, PhIP is a known carcinogen which triggers epithelial cell damage, inflammation, PIA, and cancer selectively in the ventral prostate lobe [4•]. Diets rich in fruits and vegetables, particularly tomatoes (which contain antioxidants such as lycopene) and cruciferous vegetables (which contain chemoprotective isothiocyanates like sulforaphane) have been associated with a reduced risk of prostate cancer [15].

Aspirin, nonaspirin nonsteroidal anti-inflammatory drugs, and prostate cancer

Aspirin, and nonaspirin nonsteroidal anti-inflammatory drugs (NSAIDs), which act to attenuate inflammation by inhibiting cyclo-oxygenases (COXs), have received widespread attention as potential chemopreventive agents for a number of different cancers [16•]. Observational studies have found these agents to be inversely associated with total cancer incidence [17], and with cancer-related mortality [18], particularly for colorectal, upper gastrointestinal, breast, and prostate cancer [19]. Although aspirin and the nonaspirin NSAIDs broadly inhibit both COX isoforms, COX-1 and COX-2, newer drugs such as celecoxib and rofecoxib selectively block COX-2, providing anti-inflammatory activity but less of the adverse effects associated with COX-1 blockade such as gastrointestinal bleeding.

Preclinical studies using selective and nonselective COX inhibitors for prostate cancer prevention and treatment have generated confusing results. For example, although COX-2-selective inhibitors have been reported to induce apoptosis and reduce the growth of various human prostate cancer cell lines propagated as xenografts *in vivo*, whether this effect is a consequence of COX-2 inhibition in prostate cancer cells per se or in host cells in the prostate tumor microenvironment has not been established [20]. This nuance is especially important since COX-2 is not produced in human prostate cancer cells [21]. Of note, several previous studies purportedly demonstrating COX-2 expression in human prostate cancer cells used defective immunohistochemistry methods. The absence of COX-2 expression in human prostate cancer cases may be attributable to epigenetic silencing of COX-2 [22]. Another confounding phenomenon is that selective and nonselective COX inhibitors appear to also promote inactivation of Bcl-2, inactivation of Akt, reduction of NF-kappaB p65, downregulation of androgen receptor activity, upregulation of the p75 NTR tumor suppressor, and increase in detoxification enzyme GSTP1, all of which could contribute to potential tumor inhibitory effects.

Population-based studies of aspirin intake have hinted at a protective effect on prostate cancer risk. In a systematic review and meta-analysis involving 12 studies published before

January of 2003, Mahmud *et al.* ([23•], Table 1) found an inverse association between aspirin use and prostate cancer with an OR = 0.90 (95% CI: 0.82–0.99). More recent studies published after the systematic review have also tended to support an inverse association between aspirin and prostate cancer [24–26]. The inverse association between aspirin use and prostate cancer appears stronger for higher frequency use, for greater duration of use, among younger men, and for advanced prostate cancer.

The association between nonaspirin NSAIDs and prostate cancer in population studies is more varied. The systematic review by Mahmud *et al.* (Table 1) found that nonaspirin NSAIDs were inversely associated with prostate cancer (OR = 0.87, 95% CI: 0.61, 1.23), although this finding was not statistically significant ($P = 0.43$) and substantial heterogeneity was evident between studies ($P = 0.005$). More recent studies have continued to describe mixed results [24,26,27]. One major unresolved issue that might add clarity to the population studies concerns the fraction of ingested aspirin or of the different nonaspirin NSAIDs appearing in prostate tissues and/or the lumens of prostate glands (the location of many of the inflammatory cells). Careful pharmacological studies, using drugs like aspirin and desipramine as model agents, have suggested that factors such as hydrophobicity, pH– pK_a partitioning, and metabolism, might affect the propensity of drugs to pass into the prostate and seminal vesicles [28]. For protection against prostatic carcinogenesis, drugs that are incapable of accumulating in the prostate at sufficient concentrations to attenuate inflammation are unlikely to be of great benefit.

While there have been large clinical trials evaluating the effect of aspirin on colorectal cancer incidence, and on total cancer incidence among women [29], there has been no randomized clinical trial testing the effect of aspirin on prostate cancer incidence. Three trials have reported the results of celecoxib as therapy for prostate cancer [30–32], but it is difficult to derive meaningful conclusions from these trials as they were stopped early because of safety concerns (Table 1). Furthermore, a planned large randomized prostate cancer prevention trial of another COX-2 selective inhibitor rofecoxib was abandoned when rofecoxib was pulled from the market out of a concern for increased cardiovascular risks seen in a different trial. The only informative data have been generated in pursuit of a randomized clinical trial of celecoxib, given at a dose of 400 mg twice daily to men ($n = 64$) with prostate cancer in a four-week to six-week period before radical prostatectomy. In this trial, the selective COX-2 inhibitor showed very little, if any, effect on prostate tissues removed at surgery (unpublished data with Carducci M, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore). Specifically, the drug had no effect on the appearance or extent of PIA lesions, indicating that epithelial damage and associated inflammation was not attenuated.

When considered together, the basic, preclinical, epidemiological, and limited clinical trial evidence supports further study of the protective effects of aspirin and nonaspirin NSAIDs against prostate cancer development. Identifying subpopulation of patients that are most likely to respond to NSAIDs, based on biomarker profile, and utilizing NSAIDs as targeted therapies is most likely to optimize success. Given the potential gastrointestinal adverse effects of NSAIDs, combination with proton pump inhibitors also appears to be an attractive

option [16•]. On the other hand, given the serious cardiovascular adverse effects, there should be little enthusiasm to focus such efforts on selective COX-2 inhibitors.

Statins and prostate cancer

Statins inhibit the enzyme 3-hydroxy-3-methylglutarylcoenzyme A (HMG-CoA) reductase involved in the cholesterol synthesis pathway. The drugs can be classified as hydrophilic (atorvastatin, fluvastatin, pravastatin, rosuvastatin) versus lipophilic (lovastatin and simvastatin), based on solubility in water or lipids, respectively. While statins are predominantly used in clinical practice to lower cholesterol to reduce cardiovascular disease risk, recent studies have raised the possibility of chemopreventive potential of these drugs for various cancers, including prostate cancer.

At relatively high concentrations, statins induce G1 cell cycle arrest, trigger apoptosis, and reduce the growth of human prostate cancer cells, an action thought to reflect inactivation of Ras and Rho GTPases involved in the regulation of the cell cycle [33]. Whether the drugs accomplish any of these actions at clinically relevant doses is not clear. Statins have also been reported to have anti-inflammatory properties likely mediated by the modulation of endothelial nitric oxide synthase, peroxisome proliferator-activated receptors (PPARs), and other targets.

At first glance, epidemiological studies assessing the relationship between statins and prostate cancer have shown mixed results regarding the effects on prostate cancer incidence. However, it should be noted that studies that do not control for PSA testing the results are subjected to detection bias. On the one hand, statin users tend to be more health conscious and more likely to undergo PSA screening more than the counterparts. On the other hand, the initiation of statins can result in decline in PSA levels itself [34]. Interestingly, the studies that controlled for PSA testing have consistently demonstrated an inverse association between statin use and advanced prostate cancer [35–38,39•]. The reduction has been reported to occur with both lipophilic and lipophobic statins, to be more prominent after five years or greater duration of use, and to provide a synergistic benefit when combined with NSAID use.

Four systematic reviews of randomized controlled trials (RCTs) have evaluated the efficacy of statins in the prevention of prostate cancer in recent years, and all of them found no association between statins and prostate cancer [40–43]. However, the systematic reviews did not assess the efficacy of statins on advanced prostate cancers, and the median follow-up of the trials was less than five years. Moreover, prostate cancer was a secondary outcome in most of the clinical trials and is subject to detection and reporting bias. A recent systematic review by Bonovas *et al.* [44•] combined data from 13 observational (6 cohort and 7 case–control studies) and 6 randomized control trials, and found no evidence between statin use and total prostate cancer incidence among either RCTs or the observational studies (Table 1). However, statin use was inversely related to advanced prostate cancer among observational studies (relative risk (RR) = 0.77 with a 95% CI of 0.64–0.93).

Thus, while the literature on efficacy of statins for chemoprevention for prostate cancer is heterogeneous, these agents do appear promising. Similar to NSAIDs, the development of

biomarkers that predict response to statins, and facilitate their use as targeted therapy would ensure rational utilization of these therapies as chemopreventive agents. Combination of NSAIDs and statins as combined chemopreventive agents also appears to be an attractive option.

Antioxidants and prostate cancer

Chronic inflammation is associated with oxidative stress and free radical production, which can damage genomic DNA and enhance the development of prostate carcinogenesis, particularly in the presence of androgens [45]. Men with deficiencies in antioxidant enzymes, such as polymorphisms in *OGG1*, encoding an enzyme necessary for oxidized DNA damage repair, or in *SOD2*, encoding manganese superoxide dismutase, a mitochondrial enzyme that protects cell from oxidative damage, have been found to have a higher risk of prostate cancer. While various antioxidants have been proposed to have chemopreventive properties, vitamin E (various tocopherols), and selenium have received great attention for the prevention of prostate cancer. Selenium is postulated to decrease oxidative damage to DNA, to promote apoptosis, and to inhibit prostate cancer cell proliferation [46]. Vitamin E has been reported to attenuate lipid peroxidation, to induce cell cycle arrest via upregulation of p27, and to inhibit prostate cancer growth.

Low levels of selenium, as well as of tocopherols, have been associated with higher risk of prostate cancer in multiple observational studies [47–50]. The inverse association has predominantly been observed for advanced prostate cancers, usually becomes apparent after at least five years of supplementation, and is higher among men with baseline PSA level greater than 4 ng/dl [49,51].

In the 1990s, two large randomized controlled chemoprevention trials reported that alpha-tocopherol and selenium supplementation, reduced the incidence of prostate cancer [52,53]. Similar results were seen in other trials [54,55], and in a systematic review of these trials [56•]. However, two recent large randomized controlled trials, Selenium and Vitamin E Cancer Prevention Trial (SELECT) and Physicians' Health Study II failed to confirm these findings [57•,58•], as outlined in Table 1. SELECT, the largest chemopreventive trial conducted to date, reported that selenium alone (HR = 1.04 with 99% CI of 0.87–1.24), vitamin E alone (HR = 1.13 with 99% CI of 0.95–1.35), or their combination (HR = 1.05 with 99% CI of 0.88–1.25) had no effect on prostate cancer incidence [57•]. Similarly, in the Physician Health II study, vitamin E (HR = 0.97 with 95% CI of 0.85–1.09), or vitamin C (HR = 1.01 with 95% CI of 0.92–1.10) had no effect on prostate cancer incidence [58•].

Why did the two recent trials fail to detect the protective effects of antioxidant supplementation against prostate cancer development seen in earlier studies? First, the NPC trial, which found selenium supplementation to reduce the incidence of prostate cancer, targeted a population thought to be nutritionally deficient in selenium. In this trial, as was predicted by epidemiological studies, the beneficial effects of selenium in reducing prostate cancer were predominantly restricted to men with low plasma selenium concentrations [59]. Similarly, the ATBC trial, which found vitamin E supplementation to reduce prostate cancer incidence, targeted male smokers, known to have lower vitamin E levels [52]. Thus, it is

possible that the negative results from SELECT were due to the administration of supplements to a nutritionally replete (rather than deficient) population. In fact, a recent follow-up of the General Population Nutrition Intervention Trial found that people who received factor D (50 µg selenium, 30 mg vitamin E, and 15 mg beta-carotene) had lower overall mortality (HR = 0.95, 95% CI = 0.91–0.99; $P = .009$), particularly among those younger than 55 years [60]. Second, SELECT may have used the incorrect supplement preparations. For example, gamma-tocopherol may provide a greater benefit than the alpha-tocopherol used for SELECT [48]. In the SELECT study, the serum levels of gamma-tocopherol actually declined with alpha-tocopherol supplementation. The selenium used for SELECT, L-selenomethionine, was not the selenium used in the NPC trial, which gave high-selenium yeast. Finally, the data from several large cohort studies have suggested that reduction in prostate cancer that might be associated with vitamin E and selenium supplementation would be predominantly seen for advanced prostate cancers, and would be most evident after at least five years of supplementation [49,51]. In SELECT, the majority of prostate cancers detected were low-grade, early-stage tumors.

For now, the benefits of antioxidant supplementation for the prevention of prostate cancer are not established. Hopefully, future analyses of SELECT may detect men, with either low antioxidant levels or specific genetic vulnerability, who might benefit from targeted use of supplements. Until then, the consistent finding that the consumption of vegetables rich in antioxidant micronutrients is associated diminished prostate cancer risk suggests that antioxidant intake might better be accomplished via dietary modulation than by supplement pills [61].

Conclusions

The pathogenesis of human prostate cancer, featuring the emergence of a chronic or recurrent inflammatory state in the prostate in response to epithelial damage, likely occurs over many decades. Rational prostate cancer prevention strategies must involve a combination of primary prevention against exposures, such as to HCAs and PAHs in charbroiled meats, which inflict prostate epithelial damage, and of therapeutic approaches for interference with the procarcinogenic inflammatory processes that drive cancer development.

Anti-inflammatory drugs and antioxidants may be capable of attenuating prostate cancer pathogenesis after a prolonged use, particularly advanced cancers, but for these agents to be effective they need to get to the prostate tissue and inhibit inflammation and/or oxidant damage, and thus pharmacodynamic studies, besides efficacy studies, should also be developed. While aspirin, and statins appear promising as chemopreventive agents, development of biomarkers that predict response to these therapies, and facilitate their use as targeted therapies, alone or in combination, would ensure rational and effective utilization of these therapies as chemopreventive agents.

Acknowledgements

Financial support: none.

References and recommended reading

Papers of particular interest published within the period of review have been highlighted as:

- of special interest

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, Thun MJ. Cancer statistics, 2008. *CA Cancer J Clin.* 2008; 58:71–96. [PubMed: 18287387]
2. De Marzo AM, Platz EA, Sutcliffe S, Xu J, Grünberg H, Drake CG, Nakai Y, Isaacs WB, Nelson WG. Inflammation in prostate carcinogenesis. *Nat Rev Cancer.* 2007; 7:256–269. [PubMed: 17384581] Comprehensive review article on the role of inflammation in prostate carcinogenesis.
3. De Marzo AM, Platz EA, Epstein JI, Ali T, Billis A, Chan TY, Cheng L, Datta M, Egevad L, Ertoy-Baydar D, et al. A working group classification of focal prostate atrophy lesions. *Am J Surg Pathol.* 2006; 30:1281–1291. [PubMed: 17001160]
4. Nakai Y, Nelson WG, De Marzo AM. The dietary charred meat carcinogen 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine acts as both a tumor initiator and promoter in the rat ventral prostate. *Cancer Res.* 2007; 67:1378–1384. [PubMed: 17264317] Study evaluating the molecular mechanisms contributing to PhIP induced prostate cancer in rats.
5. Sfanos KS, Bruno TC, Maris CH, Xu L, Thoburn CJ, DeMarzo AM, Meeker AK, Isaacs WB, Drake CG. Phenotypic analysis of prostate-infiltrating lymphocytes reveals TH17 and Treg skewing. *Clin Cancer Res.* 2008; 14:3254–3261. [PubMed: 18519750] Study evaluating role of TH17 in prostate carcinogenesis.
6. Narayanan NK, Nargi D, Horton L, Reddy BS, Bosland MC, Narayanan BA. Inflammatory processes of prostate tissue microenvironment drive rat prostate carcinogenesis: preventive effects of celecoxib. *Prostate.* 2009; 69:133–141. [PubMed: 18819100] Study evaluating the role of inflammatory cells and cytokines in prostate carcinogenesis.
7. Yegnasubramanian S, Haffner MC, Zhang Y, Gurel B, Cornish TC, Wu Z, Irizarry RA, Morgan J, Hicks J, DeWeese TL, et al. DNA hypomethylation arises later in prostate cancer progression than CpG island hypermethylation and contributes to metastatic tumor heterogeneity. *Cancer Res.* 2008; 68:8954–8967. [PubMed: 18974140]
8. Mosquera JM, Perner S, Genega EM, Sanda M, Hofer MD, Mertz KD, Paris PL, Simko J, Bismar TA, Ayala G, et al. Characterization of TMPRSS2-ERG fusion high-grade prostatic intraepithelial neoplasia and potential clinical implications. *Clin Cancer Res.* 2008; 14:3380–3385. [PubMed: 18519767] Study evaluating the presence of TMPRSS2-ERG gene fusions among prostatic intraepithelial neoplasia lesions as predictor of aggressive prostate cancer.
9. Wang MH, Helzlsouer KJ, Smith MW, Hoffman-Bolton JA, Clipp SL, Grinberg V, De Marzo AM, Isaacs WB, Drake CG, Shugart YY, et al. Association of IL10 and other immune response- and obesity-related genes with prostate cancer in CLUE II. *Prostate.* 2009; 69:874–885. [PubMed: 19267370]
10. Thomas G, Jacobs KB, Yeager M, Kraft P, Wacholder S, Orr N, Yu K, Chatterjee N, Welch R, Hutchinson A, et al. Multiple loci identified in a genome-wide association study of prostate cancer. *Nat Genet.* 2008; 40:310–315. [PubMed: 18264096]
11. Dong B, Kim S, Hong S, Das Gupta J, Malathi K, Klein EA, Ganem D, Derisi JL, Chow SA, Silverman RH. An infectious retrovirus susceptible to an IFN antiviral pathway from human prostate tumors. *Proc Natl Acad Sci U S A.* 2007; 104:1655–1660. [PubMed: 17234809]
12. Dennis LK, Lynch CF, Torner JC. Epidemiologic association between prostatitis and prostate cancer. *Urology.* 2002; 60:78–83. [PubMed: 12100928]
13. Sfanos KS, Wilson BA, De Marzo AM, Isaacs WB. Acute inflammatory proteins constitute the organic matrix of prostatic corpora amylacea and calculi in men with prostate cancer. *Proc Natl Acad Sci U S A.* 2009; 106:3443–3448. [PubMed: 19202053]
14. Felton JS, Knize MG, Wu RW, Colvin ME, Hatch FT, Malfatti MA. Mutagenic potency of food-derived heterocyclic amines. *Mutat Res.* 2007; 616:90–94. [PubMed: 17161439]
15. Cohen JH, Kristal AR, Stanford JL. Fruit and vegetable intakes and prostate cancer risk. *J Natl Cancer Inst.* 2000; 92:61–68. [PubMed: 10620635]

16. Cuzick J, Otto F, Baron JA, Brown PH, Burn J, Greenwald P, Jankowski J, La Vecchia C, Meyskens F, Senn HJ, Thun M. Aspirin and non-steroidal anti-inflammatory drugs for cancer prevention: an international consensus statement. *Lancet Oncol.* 2009; 10:501–507. [PubMed: 19410194] International consensus statement on the role of NSAIDs for chemoprevention.
17. Jacobs EJ, Thun MJ, Bain EB, Rodriguez C, Henley SJ, Calle EE. A large cohort study of long-term daily use of adult-strength aspirin and cancer incidence. *J Natl Cancer Inst.* 2007; 99:608–615. [PubMed: 17440162]
18. Bardia A, Ebbert JO, Vierkant RA, Limburg PJ, Anderson K, Wang AH, Olson JE, Vachon CM, Cerhan JR. Association of aspirin and nonaspirin nonsteroidal anti-inflammatory drugs with cancer incidence and mortality. *J Natl Cancer Inst.* 2007; 99:881–889. [PubMed: 17551148]
19. Harris RE, Beebe-Donk J, Doss H, Doss DB. Aspirin, ibuprofen, and other non-steroidal anti-inflammatory drugs in cancer prevention: a critical review of non-selective COX-2 blockade. *Oncol Rep.* 2005; 13:559–583. [PubMed: 15756426]
20. Narayanan BA, Narayanan NK, Pittman B, Reddy BS. Adenocarcinoma of the mouse prostate growth inhibition by celecoxib: downregulation of transcription factors involved in COX-2 inhibition. *Prostate.* 2006; 66:257–265. [PubMed: 16175586]
21. Zha S, Gage WR, Sauvageot J, Saria EA, Putzi MJ, Ewing CM, Faith DA, Nelson WG, De Marzo AM, Isaacs WB. Cyclooxygenase-2 is up-regulated in proliferative inflammatory atrophy of the prostate, but not in prostate carcinoma. *Cancer Res.* 2001; 61:8617–8623. [PubMed: 11751373]
22. Yegnasubramanian S, Kowalski J, Gonzalgo ML, Zahurak M, Piantadosi S, Walsh PC, Bova GS, De Marzo AM, Isaacs WB, Nelson WG. Hypermethylation of CpG islands in primary and metastatic human prostate cancer. *Cancer Res.* 2004; 64:1975–1986. [PubMed: 15026333]
23. Mahmud SM, Tanguay S, Bégin LR, Franco EL, Aprikian AG. Nonsteroidal anti-inflammatory drug use and prostate cancer in a high-risk population. *Eur J Cancer Prev.* 2006; 15:158–164. [PubMed: 16523013] Systematic review of aspirin as chemopreventive therapy for prostate cancer.
24. García Rodríguez LA, González-Pérez A. Inverse association between nonsteroidal anti-inflammatory drugs and prostate cancer. *Cancer Epidemiol Biomarkers Prev.* 2004; 13:649–653. [PubMed: 15066932]
25. 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; 97:975–980. [PubMed: 15998950]
26. Platz EA, Rohrmann S, Pearson JD, Corrada MM, Watson DJ, De Marzo AM, Landis PK, Metter EJ, Carter HB. Nonsteroidal anti-inflammatory drugs and risk of prostate cancer in the Baltimore Longitudinal Study of Aging. *Cancer Epidemiol Biomarkers Prev.* 2005; 14:390–396. [PubMed: 15734963]
27. Dasgupta K, Di Cesar D, Ghosn J, Rajan R, Mahmud S, Rahme E. Association between nonsteroidal anti-inflammatory drugs and prostate cancer occurrence. *Cancer J.* 2006; 12:130–135. [PubMed: 16630404]
28. Cao YJ, Caffo B, Choi L, Radebaugh CL, Fuchs EJ, Hendrix CW. Noninvasive quantitation of drug concentration in prostate and seminal vesicles: improvement and validation with desipramine and aspirin. *J Clin Pharmacol.* 2008; 48:176–183. [PubMed: 18094213]
29. Cook NR, Lee IM, Gaziano JM, Gordon D, Ridker PM, Manson JE, Hennekens CH, Buring JE. Low-dose aspirin in the primary prevention of cancer: the Women's Health Study: a randomized controlled trial. *JAMA.* 2005; 294:47–55. [PubMed: 15998890]
30. Carles J, Font A, Mellado B, Domenech M, Gallardo E, González-Larriba JL, Catalan G, Alfaro J, Gonzalez Del Alba A, Nogué M, et al. Weekly administration of docetaxel in combination with estramustine and celecoxib in patients with advanced hormone-refractory prostate cancer: final results from a phase II study. *Br J Cancer.* 2007; 97:1206–1210. [PubMed: 17955053]
31. Pruthi RS, Derksen JE, Moore D, Carson CC, Grigson G, Watkins C, Wallen E. Phase II trial of celecoxib in prostate-specific antigen recurrent prostate cancer after definitive radiation therapy or radical prostatectomy. *Clin Cancer Res.* 2006; 12(7 Pt 1):2172–2177. [PubMed: 16609031]
32. Smith MR, Manola J, Kaufman DS, Oh WK, Bubley GJ, Kantoff PW. Celecoxib versus placebo for men with prostate cancer and a rising serum prostate-specific antigen after radical prostatectomy and/or radiation therapy. *J Clin Oncol.* 2006; 24:2723–2728. [PubMed: 16782912]

33. Hoque A, Chen H, Xu X. Statin induces apoptosis and cell growth arrest in prostate cancer cells. *Cancer Epidemiol Biomarkers Prev.* 2008; 17:88–94. [PubMed: 18199714]
34. Hamilton RJ, Goldberg KC, Platz EA, Freedland SJ. The influence of statin medications on prostate-specific antigen levels. *J Natl Cancer Inst.* 2008; 100:1511–1518. [PubMed: 18957682]
35. Boudreau DM, Yu O, Buist DS, Miglioretti DL. Statin use and prostate cancer risk in a large population-based setting. *Cancer Causes Control.* 2008; 19:767–774. [PubMed: 18322813]
36. Flick ED, Habel LA, Chan KA, Van Den Eeden SK, Quinn VP, Haque R, Orav EJ, Seeger JD, Sadler MC, Quesenberry CP Jr, et al. Statin use and risk of prostate cancer in the California Men's Health Study cohort. *Cancer Epidemiol Biomarkers Prev.* 2007; 16:2218–2225. [PubMed: 17971519]
37. Jacobs EJ, Rodriguez C, Bain EB, Wang Y, Thun MJ, Calle EE. Cholesterol-lowering drugs and advanced prostate cancer incidence in a large U.S. cohort. *Cancer Epidemiol Biomarkers Prev.* 2007; 16:2213–2217. [PubMed: 17971518]
38. Murtola TJ, Tammela TL, Lahtela J, Auvinen A. Cholesterol-lowering drugs and prostate cancer risk: a population-based case-control study. *Cancer Epidemiol Biomarkers Prev.* 2007; 16:2226–2232. [PubMed: 18006910]
39. Platz EA, Leitzmann MF, Visvanathan K, Rimm EB, Stampfer MJ, Willett WC, Giovannucci E. Statin drugs and risk of advanced prostate cancer. *J Natl Cancer Inst.* 2006; 98:1819–1825. [PubMed: 17179483] Large epidemiological study evaluating the role of statins as chemopreventive agent for prostate cancer, after controlling for confounding by PSA.
40. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, Kirby A, Sourjina T, Peto R, Collins R, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet.* 2005; 366:1267–1278. [PubMed: 16214597]
41. Bjerre LM, LeLorier J. Do statins cause cancer? A meta-analysis of large randomized clinical trials. *Am J Med.* 2001; 110:716–723. [PubMed: 11403756]
42. Browning DR, Martin RM. Statins and risk of cancer: a systematic review and metaanalysis. *Int J Cancer.* 2007; 120:833–843. [PubMed: 17131313]
43. Dale KM, Coleman CI, Henyan NN, Kluger J, White CM. Statins and cancer risk: a meta-analysis. *JAMA.* 2006; 295:74–80. [PubMed: 16391219] Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study Group. The effect of vitamin E and beta-carotene on the incidence of lung cancer and other cancers in male smokers. *N Engl J Med.* 1994; 330:1029–1035. [PubMed: 8127329]
44. Bonovas S, Filioussi K, Sitaras NM. Statin use and the risk of prostate cancer: a metaanalysis of 6 randomized clinical trials and 13 observational studies. *Int J Cancer.* 2008; 123:899–904. [PubMed: 18491405] Systematic review of statins as chemopreventive therapy for prostate cancer.
45. Ames BN, Wakimoto P. Are vitamin and mineral deficiencies a major cancer risk? *Nat Rev Cancer.* 2002; 2:694–704. [PubMed: 12209158]
46. Waters DJ, Shen S, Cooley DM, Bostwick DG, Qian J, Combs GF Jr, Glickman LT, Oteham C, Schlittler D, Morris JS. Effects of dietary selenium supplementation on DNA damage and apoptosis in canine prostate. *J Natl Cancer Inst.* 2003; 95:237–241. [PubMed: 12569146]
47. Brooks JD, Metter EJ, Chan DW, Sokoll LJ, Landis P, Nelson WG, Muller D, Andres R, Carter HB. Plasma selenium level before diagnosis and the risk of prostate cancer development. *J Urol.* 2001; 166:2034–2038. [PubMed: 11696701]
48. Helzlsouer KJ, Huang HY, Alberg AJ, Hoffman S, Burke A, Norkus EP, Morris JS, Comstock GW. Association between alpha-tocopherol, gamma-tocopherol, selenium, and subsequent prostate cancer. *J Natl Cancer Inst.* 2000; 92:2018–2023. [PubMed: 11121464]
49. Li H, Stampfer MJ, Giovannucci EL, Morris JS, Willett WC, Gaziano JM, Ma J. A prospective study of plasma selenium levels and prostate cancer risk. *J Natl Cancer Inst.* 2004; 96:696–703. [PubMed: 15126606]
50. Yoshizawa K, Willett WC, Morris SJ, Stampfer MJ, Spiegelman D, Rimm EB, Giovannucci E. Study of prediagnostic selenium level in toenails and the risk of advanced prostate cancer. *J Natl Cancer Inst.* 1998; 90:1219–1224. [PubMed: 9719083]
51. Kirsh VA, Hayes RB, Mayne ST, Chatterjee N, Subar AF, Dixon LB, Albanes D, Andriole GL, Urban DA, Peters U, et al. PLCO Trial. Supplemental and dietary vitamin E, beta-carotene, and

- vitamin C intakes and prostate cancer risk. *J Natl Cancer Inst.* 2006; 98:245–254. [PubMed: 16478743]
52. Clark LC, Combs GF Jr, Turnbull BW, Slate EH, Chalker DK, Chow J, Davis LS, Glover RA, Graham GF, Gross EG, et al. Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin: a randomized controlled trial. *J Am Med Assoc.* 1996; 276:1957–1963.
53. The Alpha-Tocopherol Beta Carotene Cancer Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. *N Engl J Med.* 1994; 330:1029–1035. [PubMed: 8127329]
54. Hercberg S, Galan P, Preziosi P, Bertrais S, Mennen L, Malvy D, Roussel AM, Favier A, Briançon S. The SU.VI.MAX study: a randomized, placebo-controlled trial of the health effects of antioxidant vitamins and minerals. *Arch Intern Med.* 2004; 164:2335–2342. [PubMed: 15557412]
55. Li H, Li HQ, Wang Y, Xu HX, Fan WT, Wang ML, Sun PH, Xie XY. An intervention study to prevent gastric cancer by micro selenium and large dose of allitridum. *Chin Med J.* 2004; 117:1155–1160. [PubMed: 15361287]
56. Bardia A, Tleyjeh IM, Cerhan JR, Sood AK, Limburg PJ, Erwin PJ, Montori VM. Efficacy of antioxidant supplementation in reducing primary cancer incidence and mortality: systematic review and meta-analysis. *Mayo Clin Proc.* 2008; 83:23–34. [PubMed: 18173999] Systematic review of antioxidants (beta carotene, vitamin E and selenium) as chemopreventive agents.
57. Lippman SM, Klein EA, Goodman PJ, Lucia MS, Thompson IM, Ford LG, Parnes HL, Minasian LM, Gaziano JM, Hartline JA, et al. 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; 301:39–51. [PubMed: 19066370] Large randomized controlled trial (SELECT study) evaluating the efficacy of vitamin E and selenium as potential chemopreventive agents for prostate cancer.
58. Gaziano JM, Glynn RJ, Christen WG, Kurth T, Belanger C, MacFadyen J, Bubes V, Manson JE, Sesso HD, Buring JE. Vitamins E and C in the prevention of prostate and total cancer in men: the Physicians' Health Study II randomized controlled trial. *JAMA.* 2009; 301:52–62. [PubMed: 19066368] Large randomized controlled trial (Physician Health II study) evaluating the efficacy of vitamin E and vitamin C as potential chemopreventive agents for prostate cancer.
59. Duffield-Lillico AJ, Slate EH, Reid ME, Turnbull BW, Wilkins PA, Combs GF Jr, Park HK, Gross EG, Graham GF, Stratton MS, et al. Selenium supplementation and secondary prevention of nonmelanoma skin cancer in a randomized trial. *J Natl Cancer Inst.* 2003; 95:1477–1481. [PubMed: 14519754]
60. Qiao YL, Dawsey SM, Kamangar F, Fan JH, Abnet CC, Sun XD, Johnson LL, Gail MH, Dong ZW, Yu B, et al. Total and cancer mortality after supplementation with vitamins and minerals: follow-up of the Linxian General Population Nutrition Intervention Trial. *J Natl Cancer Inst.* 2009; 101:507–518. [PubMed: 19318634]
61. Ames BN, Gold LS, Willett WC. The causes and prevention of cancer. *Proc Natl Acad Sci U S A.* 1995; 92:5258–5265. [PubMed: 7777494]

Table 1

Summary of clinical trials and systematic reviews assessing the efficacy of anti-inflammatory drugs for the reduction of prostate cancer

Author	Intervention	Study type	Sample size	Results	Comments
Mahmud <i>et al.</i> [23•]	Aspirin	Systematic review of observational studies (OS)	12 238	OR: 0.90 (95% CI: 0.82–0.99)	5 retrospective and 12 prospective studies. The inverse association was even stronger for advanced prostate cancer
Mahmud <i>et al.</i> [23•]	NSAIDS	Systematic review of OS	12 238	OR: 0.87 (95% CI: 0.61–1.24)	5 retrospective and 12 prospective studies. There was substantial heterogeneity between studies ($P = 0.005$)
Pruthi <i>et al.</i> [31]	Celecoxib (400 mg daily)	Phase II	40	28% had decline in PSA after 3 months, 20% stabilization of PSA, and 43% slowing of their PSA doubling time	Slope of rise in PSA showed flattening after celecoxib treatment, as compared to pretreatment, and the effect persisted till 18 months
Smith <i>et al.</i> [32]	Celecoxib (400 mg daily, versus placebo)	Phase II, randomized controlled trial (RCT)	78	Significantly lower mean PSA velocity (3.4% decrease) in celecoxib arm, as compared to placebo (3% increase), and significantly higher post-treatment PSA doubling time (40% in celecoxib arm as compared to 20% in placebo arm)	Study stopped early because of general concerns about the cardiovascular safety of selective COX-2 inhibitors
Carles <i>et al.</i> [30]	Celecoxib (400 mg twice daily), with weekly docetaxel and estramustine twice daily	Phase II	48	37% had complete remission or partial remission, 47% showed stable disease, and 16% progressed. Median time to progression was 7.1 months and median overall survival was 19.2 months	Median survival similar to the 18.4-month median overall survival seen with docetaxel-based chemotherapy, administered with estramustine or prednisone
Bonovas <i>et al.</i> [44•]	Statin	Systematic review of OS and RCT	40 178 for RCT, 1 678 614 for OS	RR for RCTs: 1.06, 95% CI: 0.93–1.20; RR for OS: 0.89, 95% CI: 0.65–1.24; for advanced prostate cancer; RR = 0.77, 95% CI: 0.64–0.93	13 observational (6 cohort and 7 case-control studies) and 6 randomized control trials. Only observational studies had data on advanced prostate cancer
Bardia <i>et al.</i> [56•]	Selenium, vitamin E	Systematic review of RCT	104 196	Selenium: RR = 0.54, 95% CI: 0.33, 0.89; vitamin E: RR = 0.82, 95% CI: 0.67, 0.99	Prostate cancer results based on 1 RCT for selenium, and 4 for vitamin E
Lippman <i>et al.</i> [57•]	Selenium (200 µg/d from L-selenomethionine), vitamin E (400 IU/d of <i>all rac-α</i> -tocopheryl acetate), both, or placebo	RCT	35 533	Selenium alone HR: 1.04, 99% CI: 0.87–1.24; vitamin E alone HR: 1.13, 99% CI: 0.95–1.35; combination HR: 1.05, 99% CI: 0.88–1.25	Median overall follow-up was 5.4 years. Preparation of the selenium used (L-selenomethionine) was different from that of the NPC trial (high-selenium yeast)
Gaziano <i>et al.</i> [58•]	Vitamin E (400 IU every other day) or vitamin C (500 mg daily)	RCT	14 641	Vitamin E HR: 0.97, 95% CI: 0.85–1.09; vitamin C HR: 1.01, 95% CI: 0.92–1.10	Mean follow-up was 8.0 years

OR = odds ratio, RR = relative risk, HR = hazard ratio; RCT = randomized control trial, OS = observational study.