

Anti-inflammatory activity of soy and tea in prostate cancer prevention

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Abstract

Prostate cancer is the leading cancer-related cause of death for men in the USA. Prostate cancer risk is significantly lower in Asian countries compared with the USA, which has prompted interest in the potential chemo-preventive action of soy and green tea that are more predominant in Asian diets. It has been proposed that chronic inflammation is a major risk factor of prostate cancer, acting as both an initiator and promoter. Specifically, the nuclear factor-kappa B (NF- κ B) pathway has been implicated as an important mediator between chronic inflammation, cell proliferation and prostate cancer. Dietary factors that inhibit inflammation and NF- κ B may serve as effective chemo-preventive agents. Recent studies have demonstrated that soy and green tea have anti-inflammatory properties, and may have the potential to block the inflammatory response during cancer progression. This minireview discusses the relationship between chronic inflammation and prostate cancer, emphasizing on the significance of NF- κ B, and further explores the anti-inflammatory effects of soy and green tea. Finally, we propose that dietary strategies that incorporate these bioactive food components as whole foods may be a more effective means to target pathways that contribute to prostate cancer development.

Keywords: soy, green tea, inflammation, prostate cancer, nuclear factor-kappa B

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Introduction

Prostate cancer is the most common type of cancer found in American men, accounting for 10% of male cancer-related deaths.¹ Risk factors of prostate cancer include age, family history, ethnicity and hormonal status, but there is compelling evidence to suggest that environmental factors, such as diet and lifestyle, play more important roles in prostate carcinogenesis than genetic predisposition.² The incidence of latent prostatic lesions in men appears uniform across Asian and Western countries, but prostate cancer outcomes and mortality rates are considerably higher in Western countries.³ Moreover, prostate cancer rates have been increasing gradually in major industrialized cities in Asia. For example, between 1978 and 1997, prostate cancer incidence has risen to more than double in Singapore.⁴ It has been postulated that westernization and specifically increased consumption of 'Western diets' could be contributing factors to the increased prostate cancer rate in these Asian cities. Some of the popular foods in Asian diet, such as soy and green tea, have been investigated for their anticancer properties, including their abilities to target inflammatory pathways as means to attenuate cancer development. The goal of this literature review is to examine the

interactions of green tea, soy and inflammation in prostate cancer development.

Chronic inflammation, nuclear factor-kappa B and prostate cancer

The connection between chronic inflammation and cancer was first noted by Virchow in 1863. He hypothesized that a combination of some classes of irritants, tissue injuries and associated inflammation enhanced cell proliferation and contributed to the origin of cancer. Chronic inflammation has been estimated to contribute to as much as one-third of all cancers,⁵ acting as both initiators and/or promoters in the carcinogenesis process. Cells that mediate inflammatory responses are major contributors of *in vivo* production of reactive oxygen species (ROS). Polymorphonuclear leukocytes (PMNs, which include neutrophils, eosinophils and basophils) and mononuclear phagocytes (monocytes and macrophages) produce superoxide, nitric oxide, hydrogen peroxide and hypochloric acid in attempts to defend against pathogens. High concentrations and the persistent presence of these ROS are mutagenic and can lead to

tissue damage. Furthermore, damaged tissues generate proliferation signals for cell growth and repair. Both increased ROS and cell proliferation contribute to the initiation and promotion of carcinogenesis, and in combination they provide an optimal microenvironment for tumorigenesis.

Inflammation is implicated as a major risk factor for prostate cancer. Population studies have found an increased relative risk of prostate cancer in men with prior histories of prostatitis (inflammation of the prostate).⁶ Benign prostatic hyperplasia (BPH), which is a condition that often precedes and coexists with prostate cancer, demonstrates signs of inflammatory response. Specifically, almost all human BPH specimens showed inflammatory infiltration and high expression of pro-inflammatory cytokines, including interleukin-17 (IL-17) that promotes stromal growth and chronic inflammation.⁷ Interestingly, inflammatory pathways including the cyclooxygenase-2 (COX-2) and nuclear factor kappa B (NF- κ B) are over-expressed in human prostate adenocarcinomas compared with normal prostate tissues,^{8–10} and targeting these inflammatory pathways have shown promise as an intervention strategy for prostate cancer. Regular intakes of non-steroidal anti-inflammatory drugs (NSAIDs) appear to reduce prostate cancer growth by decreasing inflammation in the transgenic adenocarcinoma of the mouse prostate (TRAMP) model, and there is a correlation between long-term usage of NSAIDs and lower prostate cancer risk.^{11,12} The NF- κ B pathway has gained much interest in recent years because of its influence on many cellular responses that contribute to carcinogenesis, including regulation of cell cycle, cell proliferation, apoptosis and inflammation. The deregulation of NF- κ B pathway increases cell proliferation by up-regulating antiapoptotic protein, Bcl2,^{13,14} promoting angiogenesis,¹⁵ and inhibiting immune surveillance via production of immunosuppressive interleukins, such as IL-10.¹⁶ Thus, inflammation plays a major role in cancer etiology and may provide selective growth advantages for cancer cells. Targeting aberrant NF- κ B activation in cancer cells may restore deregulated cellular functions by inducing apoptosis and by decreasing uncontrolled cell proliferation and chronic inflammation; thus strategies to mitigate NF- κ B have important preventive or therapeutic values against cancer.

Constitutive activation of NF- κ B is responsible for numerous diseases.¹⁷ Potential toxicity associated with NF- κ B blockage leads to liver apoptosis,¹⁸ but the first link implicating NF- κ B as a possible target for chemoprevention was based on the recognition that c-Rel, which encodes an NF- κ B subunit, is the cellular homolog of the v-Rel oncogene. Upon stimulation, I κ B kinase (IKK) is activated. Activated IKK phosphorylates I κ B that is bound to NF- κ B and targets I κ B for poly-ubiquitination and degradation. Free NF- κ B homodimers and heterodimers then translocate into the nucleus and transactivate genes involved in inflammatory responses and cell proliferation.^{19,20} NF- κ B activity is negatively self-regulated by transcriptional up-regulation of its inhibitor, I κ B α . Initially, it was believed that I κ B α solely prevents nuclear localization of activated NF- κ B, but recent studies suggest that I κ B α also directly interacts with DNA-bound NF- κ B. I κ B α disassembles NF- κ B from DNA by changing conformation of p65 subunits, and

channels NF- κ B to the cytoplasm via its nuclear export signal.²¹ Furthermore, I κ Bs are controlled by upstream kinases, the IKKs via phosphorylation. The complexity of NF- κ B pathway suggests that total blockage of the NF- κ B in healthy cells is not ideal, but the multiple levels of regulation in the NF- κ B pathway provide many possible targets for chemoprevention in cancer cells.

Over-expression of NF- κ B promotes tumor growth through activations of genes responsible for inflammation, apoptosis and cell proliferation. For instance, NF- κ B controls expressions of cyclin D1, which influences cell growth and differentiation.^{21,22} NF- κ B also amplifies inflammatory signals, including COX-2 and pro-inflammatory cytokines, such as IL-6, by acting as a transcriptional activator.²³ Constitutive activation of IL-6 by NF- κ B has been implicated in prostate cancer progression.²⁴ Furthermore, NF- κ B intimately interacts with the homeostasis of steroid hormones. Androgen receptor (AR) expression antagonizes NF- κ B activity. Prostate cancer cell lines without endogenous AR expression, such as malignant PC3 cells, have constitutive NF- κ B activity, whereas cell lines that express AR (LnCap cells) have low basal NF- κ B activity.²⁵ Upon the loss of AR expression and androgen dependency, deregulation of NF- κ B becomes a major promoting factor for transformation of cancer cells to malignancy and poor prognosis. Many *in vitro* studies have shown that targeting NF- κ B was effective in inducing cell death in prostate cancer cells. Blocking NF- κ B activity in PC3 cells by transfection of mutant I κ B α suppresses angiogenesis and cell invasion.²⁶ Strategies utilizing I κ B α -super repressors or inhibitors of NF- κ B activity to sensitize prostate epithelial cells to chemotherapy have been deemed promising.^{27,28} Even though there are limited *in vivo* studies investigating the impact of NF- κ B in prostate cancer, these studies suggest that NF- κ B is a crucial mediator of tumorigenesis in several cancer models. Deletion of IKK β is associated with an increase in epithelial apoptosis during tumor promotion and a decrease in tumor incidence in a colitis-associated cancer mouse model.²⁹ Tumor necrosis factor α (TNF- α)-induced NF- κ B activation does not affect tumor initiation, but is essential for the promotion of hepatitis-induced hepatocellular carcinoma in mice.³⁰

Overall, both pharmacological and genetic strategies have provided strong support for the rationale of using agents that target inflammatory pathways as a cancer chemoprevention strategy. Importantly, many factors found in the diet also can target these pathways and possibly exert anti-inflammatory and cancer preventive properties.

Diet and prostate cancer

Human migration studies emphasize the importance of diet and lifestyle on prostate cancer development. For instance, first-generation Asian migrants (high soy and tea intake population) have a lower incidence of prostate and mammary cancers than subsequent generations of Asian Americans.³¹ Incidences of prostate cancer in Chinese (24 per 100,000), Japanese (29.6 per 100,000) and Filipino (56.8 per 100,000) men born in China, Japan and the Philippines were about half of those born in the USA (44.4, 42.2 and

111.3 per 100,000, respectively).² These observations have prompted studies to investigate and compare dietary components in the Asian diet, such as soy and green tea that may have cancer preventive properties. A typical soy-rich Japanese diet consists of 25–100 mg soy isoflavones/d (1 serving of traditional fermented soy food contains about 25 mg soy isoflavones), while the typical American diet contains about 1–3 mg soy isoflavones/d.³² The green tea consumption in Asian countries averages ~360–480 mL/d, whereas only 8% of the American population regularly consumes ~180 mL of green tea per day.³³ The different dietary intake levels of soy and green tea are hypothesized to contribute moderately to differences in prostate cancer outcomes between the two populations.

Various mechanisms for the anticarcinogenic properties of soy or green tea have been proposed. For instance, soy isoflavones, classified as phytoestrogens, act as both estrogen agonists and antagonists by differentially binding to estrogen receptor α or β ^{34,35} and/or altering enzymes involved in hormone metabolism.^{34–36} Soy isoflavones induce G2/M arrest and p21 expression in androgen-independent PC3 prostate cancer cells³⁷ and may act through hormone-independent pathways that target cell cycle or apoptotic mechanisms. Genistein is a known inhibitor of protein tyrosine kinase,³⁸ topoisomerase II,³⁹ and up-regulates p21 in various cancer cells.^{40–42} Green tea polyphenols, especially EGCG, exerts anticarcinogenic effects at multiple stages of carcinogenesis. EGCG is a strong antioxidant and effective inhibitor for carcinogen activation. EGCG induces cell cycle arrest, apoptosis and attenuates tumor promotion.⁴³ EGCG suppresses growth of human gastric cancer xenografts in mice through the inhibition of tumor invasion and metastasis by regulating expression of matrix metalloproteinases and vascular endothelial growth factor production.^{43,44} The role of EGCG in prostate cancer prevention and treatment are summarized by Stuart *et al.*⁴⁵ Among the various mechanisms, we favor the likelihood that inflammation, especially as dependent on the NF- κ B pathway, to be a target of inhibition by soy and green tea. Whether dietary soy or green tea has significant impacts on chronic inflammation and NF- κ B *in vivo* is still unclear and is an important area of future research. If increasing the consumption of soy or green tea may prevent prostate cancer development, these dietary recommendations would provide a more cost-effective and a safer chemo-preventive strategy than using pharmacological agents.

Green tea and prostate cancer

Green tea (*Camellia sinensis*) is one of the most widely consumed beverages, especially in Asia. It is different from black or Oolong tea by methods of processing. Green tea is prepared by pan-frying or steaming fresh leaves to heat inactivate oxidative enzymes followed by drying, whereas Oolong and black tea are prepared by additional steps of fermentation.

The bioactive components of green tea include catechins, epigallocatechin-3-gallate (EGCG), epigallocatechin (EGC), epicatechin gallate (ECG) and epicatechin (EC) and

theaflavins (Figure 1). Catechins are especially concentrated in green tea, accounting for 30–40% of its dry weight.⁴⁶ During fermentation, most of the catechins are converted to oligomeric theaflavins and polymeric thearubigins in black tea.⁴⁷

Epidemiological studies suggest protective properties of green tea against the development of stomach,⁴⁸ lung,⁴⁹ pancreatic and colorectal,⁵⁰ and breast cancer.⁵¹ Most studies ascribe the beneficial effects of green tea to the most abundant catechin in green tea, EGCG. EGCG exerts anticarcinogenic effects at multiple stages of the carcinogenesis pathway. Noticeably, EGCG is a strong antioxidant and effective inhibitor of carcinogen activation. EGCG induces phase-II detoxifying enzymes, such as glutathione peroxidase and quinone reductase, cell cycle arrest and apoptosis. Moreover, the inhibitory effects of EGCG on inflammation and tumor promotion are well established.⁵² In particular, EGCG appears to target NF- κ B as a key mechanism of action. EGCG exerts pro-apoptotic effects through inhibition of NF- κ B *in vitro* by inducing kinase (NIK) and subsequent activation of the IKK/NIK signaling complex in human lung cancer cells.⁵³ In JB6 mouse epidermal cells, EGCG decreased phosphorylated-I κ B α ; hence blocking the degradation of NF- κ B inhibitor proteins,⁵⁴ and increased the ratio of the pro-apoptotic protein Bax to antiapoptotic protein Bcl-2.¹³ Importantly, the pro-apoptotic effects of EGCG appeared to specifically target tumor cells because while EGCG significantly decreased NF- κ B activation in epidermoid carcinoma (A431) cells, normal human epidermal

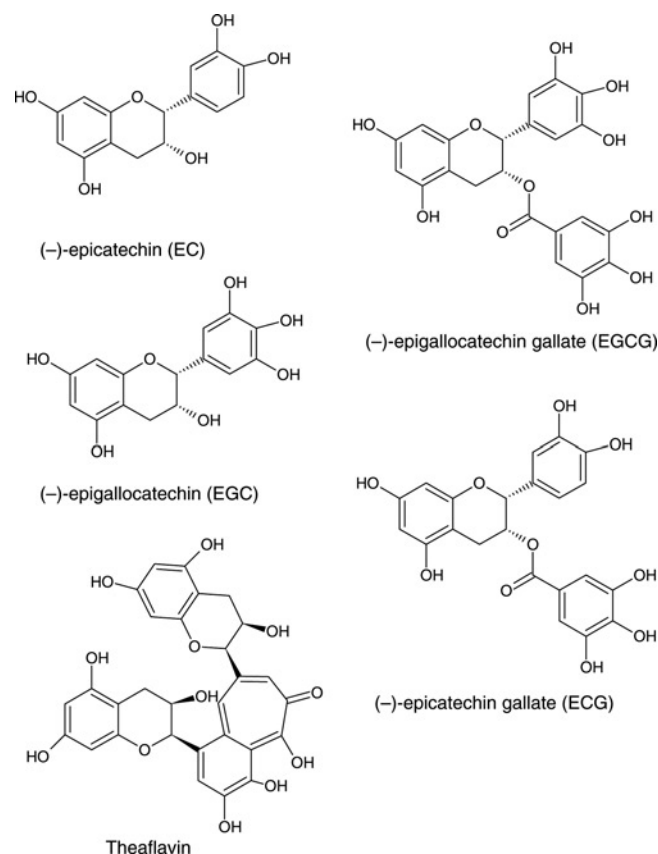


Figure 1 Chemical structures of primary green tea constituents

keratinocytes were unaffected.⁵⁵ EGCG suppressed abnormal over-production of pro-inflammatory mediators in mouse macrophage cells (RAW2647)⁵⁶ and *in vivo*, EGCG supplementation decreased downstream markers in the NF- κ B pathway, such as oncogene cyclin D, COX-2 and prostaglandin E₂ production and reduced N-nitrosomethylbenzylamine-induced esophageal tumors.²² One possible mechanism by which EGCG inhibits NF- κ B may be the attenuation of p-ERK activation and subsequent mitigation of NF- κ B and COX-2 *in vitro*.⁵⁷

EGCG appears to attenuate NF- κ B at different levels along the pathway *in vitro*. However, there are limited studies investigating the effects of green tea or green tea polyphenols on inflammation and prostate carcinogenesis *in vivo*. Most studies have focused on the effects of green tea on tumorigenesis. For example, one study showed that oral infusion of green tea polyphenols at human physiologically achievable concentrations inhibited prostate cancer development and distant-site metastasis in the TRAMP model.⁵⁸ They also showed that GTP infusion decreased IGF-1/IGFBP-3 ratio, a predictor in prostate cancer progression.^{58–61} These findings suggested that a green tea polyphenol mixture inhibited growth signaling, progression and invasion of malignant tumors. Another study using male athymic nude mice inoculated with human prostate cancer cells lines showed that EGCG supplementation significantly attenuated growth of both androgen dependent and independent tumors.^{62,63} Nevertheless, these studies had focused on progression and metastatic potentials of established prostate tumors, not the processes contributing to the initiation and promotion of prostate cancer, such as chronic inflammation. The complexity of hormonal signaling and balance in the prostate further complicated the story and rendered it very difficult to pinpoint a specific target for intervention. For example, the effects of green tea on prostate hormone homeostasis, inflammation and NF- κ B *in vivo* are still not clearly defined and are an important area for further research.

Soy and prostate cancer

Soy foods have been the subject of considerable investigation since the 1960s, largely due to the potential health effects of soy isoflavones. Soybeans are the only food to contain nutritionally relevant amounts of isoflavones. Soy isoflavones are classified as phytoestrogens, and have been suggested to modulate endogenous hormone homeostasis because their phenolic ring structures resemble estradiol and can bind to estrogen receptors, acting as either an estrogen agonist or antagonist.^{56,57} The primary isoflavones in soybeans are genistein (4',5,7-trihydroxyisoflavone), daidzein (4',7-dihydroxyisoflavone) and glycitein (4',7-dihydroxy-6-methoxyisoflavone) (Figure 2), and their respective β -glycosides, genistin, daidzin and glycitin. Isoflavones are phytoalexins, substances formed by the host plant tissue in response to environmental stimuli and possess properties that enhance the survival of the soybean. Therefore, isoflavone concentrations vary depending on environmental conditions; normally isoflavone levels increase with increasing environmental stresses.

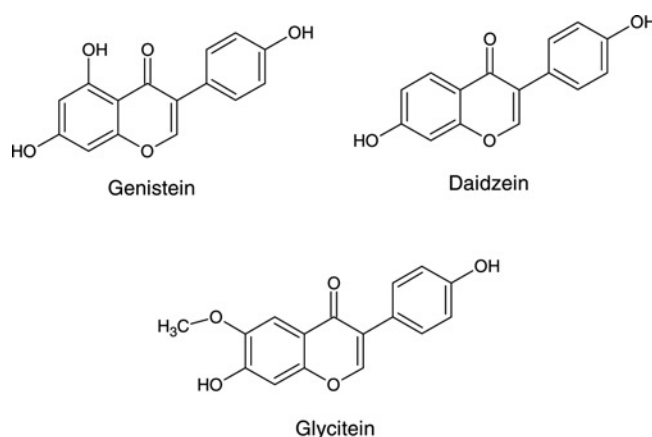


Figure 2 Chemical structures of primary soy isoflavones

Nevertheless, soybeans contain ~1.2–3.3 mg of isoflavones/g dry weight. Soy isoflavones exist predominantly as glycosides in soybeans, but fermentation and processing significantly alter the aglycone contents of soy products.³²

Epidemiological studies suggest that consumption of soy foods is associated with lower risk of prostate cancer.⁶⁴ The plasma and serum phytoestrogen concentrations in Japanese men are at least 10-fold higher than their Caucasian counterparts in the UK.^{36,65} The protective properties of soy against prostate cancer are not only apparent for the low-intake populations; even among Japanese men with relatively high soy intake compared with Caucasians, higher soy consumption was associated with a decrease in localized prostate cancer.⁶⁶ Such observations led to hypotheses that soy or components in soy exerts anticancer effects, and most have attributed these effects to soy isoflavones, especially genistein.⁵² The anticarcinogenic effects of genistein are summarized in several reviews.^{67,68} Soy constituents modulate several steroidogenic enzymes important for hormone homeostasis, such as 5 α -reductase,⁶⁹ aromatase,³⁶ 17 β -hydroxysteroid oxidoreductase³⁵ and cytochrome P450.³⁴ Furthermore, dietary genistein decreases AR expression,^{70,71} thus limiting the contribution of AR deregulation in prostate carcinogenesis. Daily consumption of soy grits decreases prostate specific antigen (PSA) levels and the free/total PSA ratio in prostate cancer patients,⁷² and total and free testosterone concentrations are also inversely correlated with soy intake in Japanese men.⁷³ Soy isoflavones also act through hormone-independent pathways. Genistein is a known inhibitor of protein tyrosine kinase³⁸ and topoisomerase II,³⁹ and inhibits angiogenesis and cancer cell proliferation.^{74–77} In prostate cancer, soy isoflavones induce cell cycle arrest in prostate cancer cells.³⁷ Soy constituents, especially isoflavones, appear to target different stages of the carcinogenesis pathway.

Previous studies have looked at anti-inflammatory effects of soy in different inflammatory diseases and organ systems. Soy protein and isoflavones have been suggested to act as antioxidants and exert beneficial effects on vascular reactivity.⁷⁸ Genistein regulates immune function in mice by modulating humoral and cell-mediated immunity.⁷⁹ Obese Zucker rats fed soy proteins enriched with isoflavones

showed significant lower plasma TNF- α and IL-1 β levels and protections against lipid oxidation in the liver.⁸⁰ Soy decreased UVB-induced COX2 expression and skin damage in mice,⁸¹ and decreased NF- κ B, nitric oxide and prostaglandin E₂ pathways in neuronal and immune cells.^{82,83} *In vitro*, genistein inhibits constitutive NF- κ B/Ap-1 activities in breast cancer cells⁸⁴ and prostate cancer PC3 cells. Similar to EGCG, inhibitory effects are cancer cell-specific because non-tumorigenic prostate epithelial cells, CRL2221, are not affected by genistein.^{85,86} This ability to target cancerous cells is highly desirable for chemo-preventive agents. *In vivo*, Yatkin et al.^{87,88} found that dietary soy (7.61% extracted and toasted soy protein and 4.25% soy oil) decreased inflammatory foci in the prostate and marginally decreased development of obstructive voiding in Noble rats. In contrast to other established effects of soy, the anti-inflammatory effects of soy constituents in prostate carcinogenesis are relatively understudied.

Our lab has also utilized the Noble rat model to study the combined effects of dietary soy and green tea on inflammation and prostate cancer development. Eighty to 100% of Noble rats develop hormone-induced prostate intraepithelial neoplasia (PIN) after 36 weeks of testosterone and estradiol treatments, and PIN lesions in the Noble rats were useful intermediate endpoints in assessing efficacy of chemo-preventive agents.⁸⁷ The prostates in the Noble rats are also characterized by inflammation prior to tumor development.⁸⁹ The slow progression and distinctive stages of disease progression observed in this model mimics the human condition, and the model can be a useful tool for understanding the intricate relationships among chronic inflammation, hormonal microenvironment, prostate carcinogenesis and the efficacies of cancer-preventive agents in attenuating these processes. Using this model, we have found that dietary supplementation of both green tea and soy effectively inhibited NF- κ B activation, decreased inflammation and decreased hyperplasia incidence in the prostate of hormone-treated Noble rats. The combination of soy and green tea suppressed NF- κ B p50 binding activity and protein levels via induction of I κ B α . Soy and green tea also decreased prostate inflammatory infiltration, increased Bax/Bcl2 ratio and decreased protein expression of TNF- α , IL-6 and IL1- β compared with control. Soy and tea attenuated prostate malignancy by decreasing prostate hyperplasia. These effects were not apparent in groups treated with soy or tea alone (unpublished data). More *in vivo* studies are needed to establish their anti-inflammatory and antioxidative properties in the prostate, but both tea and soy appear to interfere with cellular signaling pathways that modulate inflammation and cell proliferation, deeming it a promising chemo-preventive agent against prostate cancer.

'Whole food' approaches for cancer prevention

More studies in recent years have started to take a 'holistic' instead of a 'reductionist' approach in searching for effective disease-preventive agents. Consuming a food instead of a supplement containing high levels of a specific bioactive component from that food may be more effective in

preventing disease. This approach has become a more appealing and economic consideration for disease prevention. Different components of a whole food may work synergistically together, or form specific food matrix effects that provide greater benefits, which are omitted when using only a single component of whole food. In addition, high levels of a specific individual bioactive agent may also elicit toxicity.

Many *in vitro* studies with soy isoflavones and green tea polyphenols have used concentrations of soy isoflavones and green tea polyphenols to inhibit cell growth in prostate cancer cells that are beyond physiological levels and higher than attainable from diet (50–100 μ mol/L soy isoflavones; $\geq$ 100 μ mol/L EGCG).^{84,85,90–93} High levels of dietary genistein and daidzein had a stimulatory effect on MCF-7 breast cancer tumor growth in ovariectomized athymic mice.^{94,95} There is also emerging evidence that suggests that acute administration of high levels of soy isoflavones had no protective effects against other hormonal cancers such as breast cancer in postmenopausal women.^{96–98} Therefore, the timing and dosing of soy isoflavone supplementation may be a critical determining factor for its beneficial effects. Similarly, EGCG at high concentrations may also elicit adverse effects. High levels of EGCG were shown to produce hydrogen peroxide, and its pro-oxidant activity inhibited gap junction communication in rat liver cells, which was linked to carcinogenesis.^{99,100}

On the contrary, lower dosages of a combination of bioactive compounds as a whole food may eliminate the possible toxicity and induce additional/synergistic effects among them. Previous studies have demonstrated that dietary lycopene, one of the bioactive components of tomatoes, is effective in reducing prostate cancer. Interestingly, a diet supplemented with whole tomato product (dried tomato powder) was more effective in reducing prostate cancer mortality than dietary supplementation with equivalent levels of lycopene alone.¹⁰¹ These results indicated that other compounds in tomatoes, such as folate, vitamin C, β -carotene or phenolic compounds, may enhance the beneficial effects of lycopene. In addition, combinations of soy isoflavones appear to be more effective in inhibiting prostate cancer cell growth than individual soy isoflavones, genistein or daidzein treatments alone.¹⁰² Results from our *in vitro* studies found that soy extract, containing soy isoflavones and other bioactive compounds, induced significantly higher percentage of cells undergoing apoptosis than genistein or daidzein alone at equal concentrations. Soy extract did not induce cell cycle arrest or apoptosis in non-cancerous BPH-1 cells, whereas both genistein and daidzein induced apoptosis.¹⁰³ These findings further suggest that individual isoflavones may have cytotoxicity in non-cancerous cells, and supported the whole-food based approach to prostate cancer prevention.

Whole foods contain multiple antioxidants and nutrients that may target various points of the carcinogenesis pathway. For example, soy contains several compounds besides isoflavones that have been suggested to have anticarcinogenic effects, such as saponins and protease inhibitors,^{104–106} and green tea contains vitamin C and other phytochemicals. These compounds may target different

mechanisms that become deregulated during the development of cancer, such that some nutrients act as antioxidants while others target cell proliferation or angiogenesis (Figure 3). Furthermore, combination of different foods can provide novel chemo-preventive strategies. Zhou *et al.*¹⁰⁷ showed that combination of soy phytochemical concentrates and green tea reduced angiogenesis, IGF-1 and estrogen-dependent breast and prostate tumorigenicity in mice.¹⁰⁸ Using the Noble rat model, we demonstrated that dietary soy and green tea in combination decreased prostate inflammation and precancerous lesions via attenuation of NF- κ B and downstream apoptotic pathways *in vivo*.¹⁰⁹ Soy or green tea alone did not demonstrate similar effects, suggesting that the interactions between soy and green tea provided additional benefits against prostate cancer. This study suggests that interactions among several foods may potentiate the activities of any single supplement. Furthermore, the most effective strategy for the prevention of prostate cancer may involve enhancing the entire antioxidant/anti-inflammation/antiproliferative network. Whole foods are more efficacious than single nutrient supplements because they contain an array of nutrients and phytochemicals that can target a wide range of biological functions and cellular pathways that are deregulated during cancer development. Furthermore, little is known about the metabolism of these phytochemicals and how they influence each other *in vivo*. It is possible that the nutrient bioavailability and metabolism interactions between phytochemicals within the food matrix are important for prostate cancer prevention. The precise mechanisms by which combining foods provide additional beneficial effects still need to be elucidated. In addition to targeting multiple pathways, combination of foods may provide additional beneficial effects by improving bioavailability of active compounds. Very few studies attempt to undertake the daunting task of understanding

synergism and interactions among nutrients and phytochemicals, but studies focusing on these subjects will be crucial for establishing dietary recommendations in the future.

Conclusion

Diet and nutrition contribute to prevention of most chronic diseases and are a major focus of prostate cancer research. In the USA, prostate cancer is the most prevalent non-cutaneous cancer in men and one of the leading causes of cancer-related deaths. In contrast, men from Asian countries have a 10–15-fold lower rate of prostate cancer than US men. Migration studies further emphasize the impact of diet and lifestyle. Moreover, there is a gradual increase of prostate cancer rate in major industrialized cities in China, reflecting that greater extent of westernization and adaptation of western diet is associated with increased prostate cancer risk.⁴ These observations have prompted studies in recent years to investigate and compare different dietary components in the Asian diet that may have cancer preventive properties such as soy and green tea. Studies support using soy and green tea as possible chemo-preventive strategies against prostate inflammation and carcinogenesis. Apoptosis and inflammatory pathways, such as the NF- κ B pathway, are key pathways of regulation by soy and green tea in attenuation of prostate carcinogenesis. More studies focusing on *in vivo* food matrix or food combinations are required for public dietary recommendations, but increasing both soy and green tea consumption may have the potential to help reduce prostate cancer incidence and health-care cost in the USA.

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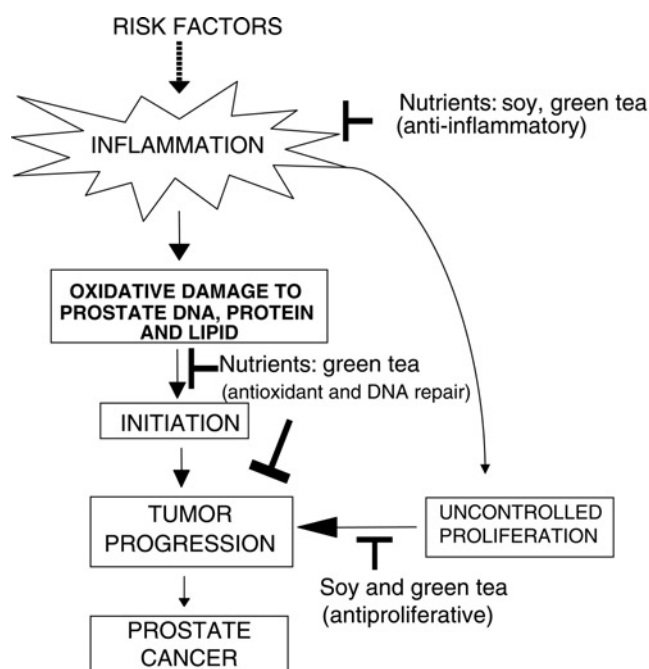


Figure 3 Schematic of the whole-food approach with soy and green tea

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