Tomato, Broccoli, Soy and Reduced Prostate Cancer Risk: Whole Foods or Their Bioactive Components?

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ABSTRACT

Prostate cancer (PCa) is the second leading cause of cancer-related deaths in U.S. men. PCa is a slow-growing cancer; therefore, identifying dietary interventions to reduce the risk or progression of PCa could greatly impact public health. A growing body of evidence has identified several foods that may reduce the risk of PCa. Mechanistic studies have investigated individual bioactives from foods to identify their anticarcinogenic properties; however, it is also important to study the whole food. In rodent models of PCa, we have shown that consumption of whole tomato powder was more effective than lycopene alone in reducing PCa progression. In a transgenic mouse model of PCa, broccoli consumption significantly altered expression of genes involved in the epithelial-mesenchymal transition, which may be a mechanism by which broccoli intake has been associated with a reduced risk of aggressive PCa. Combinations of foods may be more protective than individual foods, but this should not be assumed, as antagonistic activity between bioactives has been suggested. We have investigated the combinations of tomato and broccoli and tomato and soy germ. Future diet and cancer research should continue to focus on whole foods and combinations of foods for better translation into recommendations for the public.

Key words: tomato, lycopene, broccoli, soy, prostate cancer

INTRODUCTION

In the United States, 1 in 6 men will develop prostate cancer (PCa) in their lifetime[1]. PCa mortality has been decreasing; however, this change is likely attributable to increased screening and early detection and not from dietary changes for reduction of PCa risk. In 1981, a landmark paper estimated that approximately 35% of cancer deaths could be prevented by a change in dietary habits[2].The 2007 report from the American Institute for Cancer Research and World Cancer Research Fund promotes a diet based on plant foods to reduce the risk of cancer[3], a recommendation based on the growing amount of scientific evidence on the health protective effects of fruits and vegetables.

WHOLE FOODS AND COMBINATIONS OF FOODS FOR REDUCTION OF PROSTATE CANCER RISK AND PROGRESSION

I. *Whole Foods vs. Dietary Bioactives*

Epidemiological evidence has identified several foods that may reduce cancer risk which has fueled research to identify the mechanisms by which these foods and their bioactive compounds may be protective. Only a few foods have been tested in animal models, and even fewer have been studied in human clinical trials. Instead, many studies have used a pharmacologic approach, testing a single bioactive at high doses, making it difficult to extrapolate these findings to a whole food. After an epidemiological study correlated tomato sauce, pizza, and tomato paste consumption, all good sources of lycopene, with reduced PCa risk[4], many studies then focused on pure lycopene, disregarding the fact that tomatoes are also a source of other nutrients and bioactive compounds. Our laboratory was the first to show that tomato powder was more effective than lycopene alone in reducing PCa development and progression[3,4]. In N-methyl-N-nitrosourea (NMU)-testosterone-treated rats, animals that consumed tomato powder-containing diets (13 mg lycopene/kg diet) had longer prostate cancer-free survival than animals fed diets containing lycopene beadlets (161 mg lycopene/kg diet) or placebo beadlets[5]. In the Dunning transplantable tumor rat model, consumption of diets containg tomato powder (13 nmol lycopene/g diet), but not lycopene alone (224 nmol lycopene or 23 nmol lycopene/gram diet) resulted in significantly reduced tumor weight compared to control fed rats. Our findings suggest that consumption of a whole food that contains an array of bioactives may be more protective against PCa than a single bioactive.

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II. *Broccoli and Prostate Carcinogenesis*

There is some epidemiological evidence to suggest that high intakes of cruciferous vegetables may reduce the risk of PCa[6]. Glucosinolates and isothiocyanates, found in cruciferous vegetables such as broccoli, may reduce PCa risk by inhibiting malignant transformation, alleviating inflammation, and inhibiting proliferation[7]. In the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial, men that consumed > 1 serving of broccoli per week had a 45% reduction in risk of developing aggressive PCa compared to men consuming < 1 serving of broccoli per month[8]. Our laboratory has previously demonstrated in the Dunning transplantable tumor model, that consumption of broccoli powder may be protective against the progression of PCa. Compared to the control group, rats consuming diets containing 10% broccoli powder had significantly reduced tumor weights, and tumors from broccoli fed animals had significantly reduced proliferation and increased apoptosis rates[9].

Recently, our lab utilized the transgenic adenocarcinoma of the mouse prostate (TRAMP) model to determine if consumption of standard broccoli, or a broccoli high in indole-glucosinolates would alter prostate carcinogenesis. When the broccoli plant tissue is disrupted, myrosinase will hydrolyze glucosinolates into bioactive compounds such as indole-3-carbinol. Treatment of broccoli with the plant stress hormone methyl-jasmonate (MeJa) significantly increased the plants' levels of glucosinolates: glucobrassicin, neoglucobrassicin, and gluconasturtiin[10]. We hypothesized that a broccoli higher in bioactive indole-glucosinolates would be more effective in reducing prostate carcinogenesis than a standard broccoli. Male TRAMP mice (n = 99) were randomized into 3 diet groups at 5 - 7 weeks of age: AIN-93G control, 10% standard broccoli powder, or 10% MeJa broccoli powder. Diets were consumed until 20 weeks of age. Compared to the control, broccoli feeding did not significantly alter pathologic score, proliferation, or apoptosis in the prostate, and these endpoints were not significantly different between broccoli powders[10].

Despite no differences in incidence of primary PCa; further analyses of gene expression in the prostate suggest that broccoli consumption may reduce the risk of metastasis by inhibiting the epithelial-mesenchymal transition (EMT) in PCa (unpublished data). This is important because men do not die from primary PCa, but from complications of metastasis when the cancer cells invade other tissues, primarily bone. In epithelial cancers, such as PCa, cancer cells may undergo EMT which enables the cell to acquire a more invasive phenotype[11]. EMT involves the loss of epithelial cell proteins such as E-cadherin and increased expression of mesenchymal cell proteins such as N-cadherin and vimentin. In clinical cases of PCa, low E-cadherin expression and high N-cadherin expression has been correlated with cancer progression, cancer-specific death, and skeletal metastasis[12]. In TRAMP mice with well-differentiated carcinoma, the mRNA expression ratio of E-cadherin to N-cadherin in the prostate was significantly increased 3.0 to 3.5 fold by standard broccoli and MeJa broccoli consumption, respectively, compared to the control group. mRNA expression of Snail, Slug, and Twist, major transcription factors involved in EMT signaling, were not significantly altered by broccoli feeding. Although the mechanism of altered cadherin expression was not elucidated, based on the predictive value of E-cadherin and N-cadherin expression in clinical cases of PCa, our findings suggest that broccoli consumption may reduce the risk of aggressive and metastatic PCa.

III. *Combinations of Foods*

People consume complex diets, yet there is limited research on the interactions and protective effects by consumption of multiple foods. Whole foods and combinations of foods and bioactives may be more protective due to the presence of multiple phytochemicals that may have additive or synergistic bioactivity[13-15]. In the Dunning transplantable tumor model, our laboratory found that the combination of 10% tomato powder and 10% broccoli powder was more effective in reducing tumor growth in rats than when these foods were consumed individually[9]. The added protection against PCa by combinations of foods or bioactives has been seen in other animal trials. In the Noble rat model, the combination of dietary soy and tea, but not soy or tea alone, was effective in reducing inflammation and hyperplasia in the prostate[16]. However, since foods are a complex matrix composed of a mixture of nutrients and bioactives, it should not be assumed that all interactions between foods and bioactives will be positive. In a small phase II clinical trial in men with PCa, supplementation with lycopene was significantly more effective in stabilization of prostate specific antigen (PSA) than a combination of lycopene and soy isoflavone supplementation, suggesting a negative interaction between these bioactives[17]. Interestingly, we have seen that combined consumption of soy germ and tomato powder reduced tissue accumulation of tomato carotenoids but increased urinary soy isoflavone excretion in male rats, supporting an interaction between these foods[18].

Our lab is interested in the potential interactions between dietary soy and tomato products and if these interactions impact their ability to alter prostate carcinogenesis. Four-week old male TRAMP mice (n = 118) were randomized to consume experimental diets: AIN-93G control, 10% tomato powder (TP), 2% soy germ (SG), or 10% tomato powder + 2% soy germ (TP + SG) until 18 weeks of age. Compared to the control group, consumption of any of the three dietary interventions resulted in a non-significant reduction of prostate-seminal vesicle (P-SV) complex weight (unpublished data). Prostate pathology grading and staging of cancer is underway. Our results with P-SV weights suggest that dietary interventions with soy germ or tomato may reduce PCa burden in TRAMP mice. Mice consuming TP + SG had significantly lower serum lycopene levels than mice con-

suming TP alone (unpublished data), suggesting an interaction between TP and SG that alters lycopene bioavailability. Potential interactions between foods that alter bioavailability or bioactivity require further investigation.

CONCLUSIONS

Due to the high incidence of PCa in the United States, identifying optimal dietary interventions for prevention and reduction of PCa progression would substantially impact public health. Studies utilizing individual bioactives provide important insight into potential mechanisms by which foods containing these compounds may be protective. However, future research should continue to investigate whole foods and combinations of foods to provide findings that could be more directly translated into clinical trials and recommendations to the public.

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