Introduction

Prostate cancer is the second most common cause of male cancer death in the United States (1). The American Cancer society predicts that in 2003 there will be 220,900 new cases and 28,900 deaths from prostate cancer in the U.S. (12). 1 in 6 men will be diagnosed with prostate cancer in their lifetime and 1 in 32 will die from it (12). Due to the easily identifiable risk factors such as age and family history, there is a clear population that can be targeted and would benefit from chemopreventive compounds. Many foods are now being researched as functional foods that could be used for cancer prevention. The March 6, 2002 issue of the Journal of the American Cancer Institute reported findings on the diets of 47,365 participants ranging in age from 40-75 years that were followed for more than 12 years. (4,7,8) Men consuming two or more servings of tomato products per week had a 23% lower risk of overall prostate cancer and a 36% lower risk of metastatic prostate cancer over participants only consuming less then one serving of tomato products per month (7,8).

Tomatoes are a source of vitamins A and C, folate, potassium, calcium, iron, and carotenoids (6,7). Carotenoids are fat soluble pigments that give natural color to fruits and vegetables and are postulated to be phytochemicals related to cancer prevention in humans. Of the carotenoids in tomatoes, lycopene is the most abundant followed by γ-carotene, phytoene, and β-carotene. Lycopene is postulated to work as a chemopreventive agent through antioxidant properties. It has been found to be twice as powerful as beta-carotene is neutralizing free radicals (7). However other mechanisms of action such as modulation of intracellular communication, hormonal and immune system changes, and metabolic pathway alterations, are being researched and may also be involved (2,10). Tomato processing increases the bioavailability of lycopene to humans (10). Tomato paste or sauce was shown to have higher bioavailability then fresh tomatoes due to the change in bond isomers, decrease in physical size, and oil addition with processing (2).

Lycopene is thought to act on the prostate and prostate cancer in particular due to studies that have shown lycopene is concentrated in the prostate tissue and that levels of lycopene both in prostate tissue and blood are inversely related to prostate cancer (6,10). While lycopene is presently being researched and thought to be the major factor in tomatoes that leads to their chemopreventive capabilities, others postulate that it is not lycopene alone lowering prostate cancer risks and that more research needs to be done on tomatoes as a whole. The chemopreventive effects may be a complex combination of compounds working together, and that the whole fruit may be more beneficial then one purified component (6).

Recently the results of epidemiological studies aimed at showing if tomatoes have chemopreventive compounds that can reduce the risks of developing prostate cancer have been mixed and a small clinical study that was done to look at the effects of isolated lycopenes on prostate cancer progression and prevention showed promising correlations (1,2,7,8,10).

Epidemiologic Studies

The data presented from early epidemiologic studies suggests a correlation between prostate cancer and tomatoes however, due to the mixed results the subject still remains controversial. Six studies have shown a 30-40% reduction in prostate cancer risk associated with higher intakes of tomatoes and tomato products (4,8). Three other studies showed a similar reduction is risk but their results were not statistically significant (4,8). While seven other studies data did not support an association at all (4,8). The dietary-based studies were either retrospective in which prior diets of men with prostate cancer was compared to prior diets of men without cancer, or prospective, for which the study begins by measuring baseline diet and then men are followed for prostate cancer occurrence. Some of the differences in reported results may be due to several factors; the first of which being if a population consumes low levels of tomato products and/or lycopene, there may not be enough of a contrast between the high and low consumers to show differences in risk rates. (4,8). Also the dietary questionnaires may be a source of variability between studies. They may not all be adequate in capturing every relevant item such as processed tomato products including ketchup, tomato sauce, pizza, or salsa. In addition there may be inconsistencies in how the questions are interpreted and the bioavailability of lycopene varies markedly across different items (4,8,10,11).

The retrospective studies elicited mixed results. Schuman et al., a case control study of 223 participants with prostate cancer conducted in Minnesota reported that patients consuming high amounts of tomatoes and tomato products, >14 times per month, had a 30% lower risk of total prostate cancer then patients with low tomato consumption, <3 times per month (4,8,13). Another case control study, LeMarchand et al., done with a multiethnic population in Hawaii with 452 participants found that there was no correlation between tomato consumption and prostate cancer risks (4,8,14). However, in this study it appears that the most relevant bioavailable sources of lycopene, processed tomato products like tomato sauce, may not have been reported or accounted for. Kolonel et al., also provided a large multiethnic case-control study with 1619 participants in the U.S. and Canada, that did not show a correlation between tomato consumption and prostate cancer (4,8,15). This study may have been limited by the low response rate of 58% among controls (15).

Prospective studies also showed mixed results however, a greater number suggested a correlation between tomatoes and prostate cancer. Mills et al., in a cohort study of 14,000 Seventh Day Adventists showed that higher consumption of tomatoes, more than 5 servings a week, was statistically significantly related to lower levels of prostate cancer in men in a multivariate analysis (4,8,16). Schuurman et al., preformed a study in the Netherlands that did not report a correlation between tomato consumption and prostate cancer. However, processed tomato products were not included in this study and it also appears that the tomato consumption is so low in this population that it is not at levels that can be distinguished (4,8,17). The largest study to date was the Physician's Health Study conducted in male health professionals. Data was collected from 1986-1992 by way of dietary questionnaires that were sent out to cancer free men in 1986, 1988, 1990, and 1992. During 1986-1992, 773 new cases of prostate cancer were diagnosed (4,8). Of the 46 fruits and vegetables analyzed only four showed a significant association with decreased risk for prostate cancer. These were tomato sauce ($P<0.001$), tomatoes

($P<0.03$), pizza ($P<0.05$), and strawberries (4,8). Of the top four foods three of them were tomato products that are primary sources of lycopene. This study was then updated in 2002 and additional data was collected from 1992-1998. There were 47,365 participants and additional dietary questionnaires were given out in 1990,1994, and1998 (4,8). From 1986-1998 there were 2481 men who developed prostate cancer(4,8). The data from 1992-1998 confirmed previous findings that the increased consumption of tomatoes and tomato products were associated with lower risks for prostate cancer (4,8). Due to the superior study design, these results help to suggest the correlation between prostate cancer and tomatoes more then the previous studies. The Physician's Health Study exhibited a large study size, well educated participants that were professionals with a lower risk for question misunderstandings or wrong interpretations, and in addition prospective studies have a lower chance for bias then retrospective studies (8).

Epidemiologic studies have also been done aiming to show a correlation between levels of circulating lycopenes in the blood stream and the risk of prostate cancer. Serum levels are possibly a more reliable way to measure if there is a correlation between tomatoes and prostate cancers because, plasma levels of lycopene take into account absorption, metabolism, and accurate intake. They are not susceptible to memory errors as in diet recall studies and do not have associated problems with variability in questionnaire format or question interpretation. The results from theses studies have also been mixed. The first published report by Hsing et al., was based on serum from 25,802 patients in Washington County, Maryland in 1974 (4,8,18). It found 6.2% lower median levels of lycopene in men diagnosed with prostate cancer during a 13 year period, however the results were not statistically significant (4,8,18). The largest blood-based study was the Physician's Health Study using samples stored in 1982. 578 prostate cancer cases that occurred during the 13 years of the original study were used. 259 of those were classified as aggressive (4,8). The baseline lycopene levels were compared with age-matched cancer free controls. There was a reduction in risk of prostate cancer, especially for aggressive prostate cancer, in men with high levels of serum lycopene (4,8). However a study of Japanese-American men in Hawaii from 1971-1993 did not show an association between serum lycopene levels and prostate cancer risk (4,8,19). The inconsistent results with two studies showing a 25-50% decrease in prostate cancer risk with elevated lycopene serum levels and another study showing no correlation may be due to both racial differences and differences in lycopene exposure. The two cases suggesting positive correlations both were studying primarily white men where as the study in Hawaii was studying Japanese-American men. Therefore there may be a genetic or racial difference in prostate cancer's response to serum lycopene levels. In addition the levels of exposure to lycopene varied between the studies. The Maryland study reported 320ng/ml and the Physician's Health study showed 388ng/ml, whereas the Hawaii study only reported 134ng/ml of serum lycopene (4,8). The lower levels of exposure may have not been enough to show the chemopreventive effects of the tomatoes and/or lycopene.

Clinical Trial Studies

Due to the suggested correlation between tomatoes and prostate cancer in epidemiologic studies, the next step is to investigate the effects of lycopene in clinical trials. One such

study has been done on a small scale by Omar Kucuk. This study was aimed at determining if lycopene supplements containing tomato extracts would protect against prostate cancer (1,2,7). 26 men with localized prostate cancer that were scheduled to have radical prostatectomy in three weeks were randomly assigned to either receive lycopene supplements or a placebo (1,2). By the end of the three week time period mean plasma PSA levels had decreased by 18% in the lycopene group and increased by 14% with in the control group (1,2). Also 11 of the 15 patients (73%) in the lycopene group had tumors confined to the prostate, compared to only 2 of the 11 (18%) control patients (1,2). In addition, tumor size in 80% of the lycopene patients was measured at 4cc or less compared to only 45% of patient in the control group (1,2). While the results of this study suggest a correlation between tomatoes and prostate cancer this was a very small study and more large scale studies will need to be done to support and prove this correlation.

Conclusion

The epidemiologic data gathered to date suggests an inverse correlation between tomato or tomato product consumption and the risk of prostate cancer. While there have been studies that do not support this correlation, they have either been done with in populations that consume levels of lycopene too low to show differences between high and low consumers or they have not included the most relevant bioavailable sources of lycopene in processed tomato products. The largest and best structured Physician's Health Study showed a strong correlation between tomato consumption, lycopene serum blood levels, and reduced risk of prostate cancer (2,7). Clinical trials allow researchers to study the effects of isolated chemical components, such as lycopene, administered in cancer positive patients prior to surgery. This then permits the possible therapeutic effects of a particular compound to be examined in both tumor progression and at molecular levels. This type of information would help researchers to determine chemopreventative molecular modes of action on tumor cells. Clinical trials would also allow food components to be researched as possible means of both non-toxic treatment and prevention. In addition to testing compounds present in tomatoes individually, the combined affects of the tomato as a whole should also be investigated. Therefore the future direction of research should be in larger clinical trials that could definitively prove the correlation between increased tomato consumption and lower risks for prostate cancer.

References:

1. Kucuk, Omer. Chemoprevention of prostate cancer: *Cancer and Metastasis Reviews* 21:111-124, 2002.
2. Hadley CW, Miller EC, Schwartz SJ, Clinton SK. Tomatoes, lycopene, and prostate cancer: progress and promise: *Experimental Biology and Medicine* 227:869-880, 2002.

3. Kucuk, Omer. Cancer chemoprevention: *Cancer and Metastasis Reviews* 21: 189-197, 2002.
4. Giovannucci, Edward. A review of epidemiologic studies of tomatoes, lycopene, and prostate cancer. *Experimental Biology and Medicine* 227:852-859, 2002.
5. National Cancer Institute. Division of Cancer Prevention http://www3.cancer.gov/prevention/mtdppc/summary.html
6. Diegler RG, Vogt, TM. Tomatoes, lycopene, and risk of prostate cancer. *Pharmaceutical Biology* 40:59-69, 2002.
7. Cancer Therapies, holistic online. http://www.holistic-online.com/cancer/cancer_tomatoes-and-cancer.htm
8. Giovannucci E, Rimm EB, Lui Y, Stampfer MJ, Willett WC. A prospective study of tomato products, lycopene, and prostate cancer risk. *Journal of the National Cancer Institute*Vol.94, No.5:391 -398, 2002.
9. Astaxanthin, Biochemical Properties. http://www.astaxanthin.org/carotenoids.htm
10. Minorsky. Lycopene and the prevention of prostate cancer: the love apple lives up to its name. *Plant Physiology* 130(3):1077.
11. Nishino H, Murakoshi M, Ii T, Takemura M, Kuchide M, Kanazawa M. Carotenoids in cancer chemoprevention. *Cancer and Metastasis Reviews* 21:257-264, 2002.
12. American Cancer Society, prostate cancer statistics. http://www.cancer.org/docroot/CRI/content/CRI_2_4_1X_What_are_the_key_statistics_for_prostate_cancer_36.asp

13. Some selected features of the epidemiology of prostatic cancer: Minneapolis-St. Paul, Minnesota case-control study, 1976-1979. In: Magnus K, Ed. Trends in Cancer Incidence: Causes and Practical Implications. Washington, DC: Hemisphere Publishing, pp345–354, 1982.
14. Le Marchand L, Hankin JH, Kolonel LN, Wilkens LR. Vegetable and fruit consumption in relation to prostate cancer risk in Hawaii: a reevaluation of the effect of dietary ß-carotene. *Am J Epidemiol* 133**:**215–219, 1991.
15. Kolonel LN, Hankin JH, Whittemore AS, Wu AH, Gallagher RP, Wilkens LR, John EM, Howe GR, Dreon DM, West DW, Paffenbarger RS Jr. Vegetables, fruits, legumes and prostate cancer: a multiethnic case-control study. *Cancer Epidemiol Biomarkers Prev* 9**:**795–804, 2000.
16. Mills PK, Beeson WL, Phillips RL, Fraser GE. Cohort study of diet, lifestyle, and prostate cancer in Adventist men. *Cancer* 64**:**598–604, 1989.
17. Schuurman AG, Goldbohm RA, Dorant E, van den Brandt PA. Vegetable and fruit consumption and prostate cancer risk: a cohort study in The Netherlands. *Cancer Epidemiol Biomarkers Prev* 7**:**673–680, 1998.
18. Hsing AW, Comstock GW, Abbey H, Polk BF. Serologic precursors of cancer. Retinol, carotenoids, and tocopherol and risk of prostate cancer. *J Natl Cancer Inst* 82**:**941–946, 1990.
19. Nomura AMY, Stemmermann GN, Lee J, Craft NE. Serum micronutrients and prostate cancer in Japanese Americans in Hawaii. *Cancer Epidemiol Biomarkers Prev* 6**:**487–491, 1997.

20. Hadley CW, Clinton SK, Schwartz SJ. The consumption of processed tomato products enhances plasma lycopene concentrations in association with reduced lipoprotein sensitivity to oxidative damage. *J. Nutr.* 133:727-732, 2003.
21. Park, Eun Jung and Pezzuto, John M. Botanicals in cancer chemoprevention. *Cancer and Metastasis Reviews* 21:231-255, 2002.