ARTICLE REVIEW

# Diet as a Risk Factors of Prostate Cancer: A Literature Review

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## ABSTRACT

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**Introduction** Prostate cancer is indeed a raising health problem in the world. As our life expectancy improves, the prevalence of prostate cancer may also increase. Diet is believed to be one of the common major risk factors contributing to the development of prostate cancer.

**Objective** This review aims to i) understand the effect of dietary habit towards risk of developing prostate cancer, ii) to summarize the published articles on risk of developing prostate cancer and iii) to provide information in designing the optimal diet for primary and secondary prostate cancer prevention.

**Methods** A search was conducted to review published studies on prostate cancer and diet through PubMed/MEDLINE, Google Scholar and Science Direct.

**Results** High intake of red meat, processed meat and dairy products were commonly linked to the prostate cancer while consumption of antioxidants and certain vitamins may give protective mechanism towards prostate cancer.

**Conclusions** Diet of low carbohydrates, n-3 PUFAs, colorful fruits and vegetables are still the best advice to counsel the patient while lifestyle of smoking and heavy alcohol intake should be avoided in preventing prostate cancer.

**Keywords** Prostate cancer - diet - literature review.

## INTRODUCTION

Data from the International Agency for Research on Cancer (IARC) reported that prostate cancer is the fourth most common cancer in both male and female sexes combined and ranked second most common cancer in men worldwide. In 2012 it is estimated that 1.1 million men were diagnosed with prostate cancer with estimated 307,000 deaths.[1] Common major identified risk factors for developing prostate cancer are increasing age more than 60 years old, close first or second degree family history of prostate cancer, and African-American race however recent studies showed that the incidence of prostate cancer is also increasing among immigrants for example immigrants to the United States of America from low incidence of prostate cancer countries like Japan and China that reported almost the same incidence rate of prostate cancer in their second generation compared to their native country.[2] It suggests that mixture of different cultures, lifestyle and dietary habits may influence the risk of developing prostate cancer. It is also well known that caloric excess will lead to increased cancer incidence in which it promotes cancer cell proliferation and tumour progression. This literature review aims to i) understand the effect of dietary habit towards prostate cancer and ii) summarize the published literature on risk of developing prostate cancer and iii) provide information in designing the optimal diet for primary and secondary prostate cancer prevention.

## METHODOLOGY

A search was conducted to examine published studies and articles on diet as risk factor of the prostate cancer through PubMed/MEDLINE, Google Scholar and Science Direct databases using keywords: “prostate cancer”, “prostate” and “diet”. For exploration on the burden itself, the keywords used were “meta analysis”, “systematic review”, “human”, “prevention” and “risk”. Boolean operator “OR” was applied in combining search keywords for study population, comparison, and outcomes, where “AND” was applied in the title and abstract. Full article texts then were reviewed for further analysis.

## RESULTS

*Red Meat and Saturated Animal Fat*

Many studies had reported that dietary habit of red meat consumption may relate to the increasing risk of prostate cancer incidence and mortality. Several mechanisms relate meats to the development of prostate cancer including formation of heterocyclic amines (HCA), polycyclic aromatic hydrocarbons (PAH) and N- nitroso compounds (NOC) that are found during processing and cooking of meats. It is believed that cooking practices of red meats with high temperatures of 150 – 300 degree Celcius which is the culturak dietary habit among African-American and Caucasian men actually induced the carcinogenic effect by creating heterocyclic aromatic amine and polycyclic aromatic hydrocarbon.[3] This was explained by Turesky et al when pyrolysis of the fats in the meat will generate PAHs when exposed to the high temperature which then become deposited on the meat while HCAs are formed from the reaction between creatine or creatinine, amino acids, and sugars that are found in muscle meats at high cooking temperatures while steaming, microwaving, and marinating are all known to produce less heterocyclic amines.[4] Another study by Rohrman et al showed that men who consumed more than 5 servings per week of processed meat had higher risk of prostate cancer compared to men who ate less than 1 serving per week while another a meta-analysis by Alexander et al in 2010 of 15 cohort studies concluded that there was no association observed between red meat consumption and the development of prostate cancer. [5,6] World Research Cancer and Fund (WCRF) reported that consumption of less than 500 grams of red meat per week is actually a significant factor for lowering the risk of aggressive prostate cancer (OR = 0.77; 95% CI: 0.61, 0.98).[7] This finding is also supported by a recent systematic review by Bylsma and Alexander in 2015 based on 26 publications from 19 different cohort studies conducted in the United States, Canada, Japan, and Europe involving over 700,000 male participants ranging from 6 to 22 years duration that reported that consuming fresh red meat or unprocessed lamb, pork and beef gave no significant association with the development of prostate cancer (RR = 1.06; 95 % CI: 0.97–1.16) while 11 prospective cohort studies reported that processed meat such as sausage, bacon, hot dogs or cured and salted meats estimated low risk of developing prostate cancer (RR=1.05; 95% CI :1.01–1.10).[8] Studies by Cross et al and Ferguson et al reported that in the processed meat, nitrite is often added as an antibacterial agent against *Clostridium botulinum* and also acts to produce the reddish color of processed meats. These nitrates and nitrites found in processed meats can lead to the formation of NOCs, which are produced when nitrites and nitrogen oxides react with secondary amines and N-alkylamides, a process that can occur endogenously in processed meat. [9,10]

Many studies reported that a high calorie consumption of saturated animal fat is related to an increased risk of developing prostate cancer due to increasing testosterone levels. It was supported by studies of Pauwels et al that concluded that animal fat consumption per capita is positively associated with the incidence and mortality of prostate cancer with OR=1.6-2.9.[11]

A recent case control population based study by Aronson et al in 2010 among patients age less than 60 years old found a significant high risk of developing prostate cancer in high intake of total fat (OR = 2.53, CI 95%: 1.72-3.74), saturated fat

(OR = 2.49; CI 95%: 1.69-3.66), monounsaturated fat (OR = 2.69; CI 95%: 1.82-3.96), and polyunsaturated fat (OR = 2.34; CI 95%: 1.59--3.46). [12] Hence it is suggested that larger prospective studies are needed to show consistency of findings including method of cooking to understand further on the risk of developing prostate cancer from meat product.

*Dairy products*

Dairy products intake was closely related to health issues as it provides recommended dietary intake nutrient elements such as protein, fat, minerals and vitamins. It is believed that dairy products were beneficial for chronic diseases such as cancer for example element of casein which was proven to have potential anti mutagenic and anti-carcinogenic effects. The high consumption of dairy products such as milk may increase calcium intake and suppress the conversion of 25(OH) vitamin D to 1,25(OH)2 vitamin D, which has anti proliferative effects on human prostate cancer cells. Apart from the hypothesis that milk is a rich source of estrogens which is associated with hormone related prostate cancer, however the mechanism of action is poorly understood. A meta-analysis study by Huncharek in 2008 among 4 cohort studies showed no evidence of an association between calcium adjusted dairy products and the risk of prostate cancer (RR: 1.06; 95% CI: 0.92-1.22) and no association was observed between milk intake and the risk of prostate cancer in 11 homogeneous cohort studies (RR: 1.06; 95% CI: 0.91, 1.23).[13]

A systematic review from 11 studies by Lu et al in 2016 also stated that skim or low-fat milk intake was not associated with prostate mortality risk, with the pooled relative risk of 1.00 (95 % CI 0.75–1.33, p = 0.985). However whole milk intake in men contributed to significantly elevated prostate cancer mortality risk with the pooled relative risk, RR of 1.50 (95 % CI 1.03–2.17, p = 0.032). Thus, this meta-analysis study concluded that low total dairy products intake may have protective effect against cancer related death, however high dose of total dairy products did not have the protective effect against elevated prostate cancer mortality risk.[14] This was further supported by Yang et al. who demonstrated that among men with non-metastatic prostate cancer, post diagnostic dairy products intake increased prostate cancer-specific mortality risk and all-cause mortality risk.[15] This might be explained by the Giovannucci et al hypothesis in which that luxuriant calcium content in whole milk would increase the risk of prostate cancer by inhibiting the potential anti prostate carcinogenic nutrient 1,25-dihydroxyvitamin D.[16]

*Fishery Product*

Fish is a one of the common sources of protein worldwide. There are many studies reported inverse associations between consumption of fish per capita and the incidence and mortality rates from prostate cancer. It is believed that intake of long-chain n_3 fatty acids in fishery products will inhibit the proliferations of prostate cancer cell and also facilitates in the reduction of testosterone concentration. A meta-analysis carried out by Szymanski in 2010 among 4 cohort studies involving 49 661 participants reported that there was an association between fish consumption and a significant 63% reduction in prostate cancer-specific mortality with RR: 0.37;95% CI: 0.18-0.74.[17] Studies by Berquin and Williams also found that ω-3 PUFAs, which are found primarily in cold water oily fish such as tuna, salmon and herring may slow growth of many tumors, including prostate. It suggests that poly-unsaturated fatty acids may induce anti-inflammatory, pro-apoptotic, anti-proliferative and anti-angiogenic pathways mechanisms.[18,19] However study by Larsson et al reported that the critical period for the dietary of n_3 fatty acid exposures should be during childhood or early adulthood as if exposure is obtained at middle or old age when cancer is diagnosed, the association between n_3 fatty acid intake and cancer might be missed. Besides that it is important to remember that the composition of the fat depends on the geographic area in which the fish live, the fish's diet, and seasonal variations and on environmental factors such as temperature, salinity, and the depth at which the fish live.[20]

*Acrylamide*

Acrylamide is a chemical produced naturally as a result of cooking starch-rich at high temperatures such as when baking or frying. It is also likely to be produced by grilling and roasting food. When carbohydrate rich foods are cooked at high temperature above 120 degree Celcius, amino acids can combine with reducing sugars to form a range of products. The amino acid asparagine, can combine with sugars to produce acrylamide. Higher temperature and longer cooking times will produce more acrylamide. It is believed that carcinogenesis of acrylamide mechanism is through its oxidization to glycidamide, a chemically reactive genotoxic metabolite that resulted in damaging and mutagenic effects on DNA. Acrylamide may also exert a carcinogenic role on selected body sites by affecting hormonal balances. A meta-analysis study by Pelucchi et al on 6 studies from 2006 till 2014 (3 case controls and 3 cohorts) involving 13,559 men reported that there was no significant risk of developing prostate cancer (RR=1.0: 95% CI, 0.85–1.04) for high versus low intake and 1.00 (95% CI, 0.98–1.01) for an increase of 10 mg/day. [21]

*Soy-based products*

Soy contains protein and phytoestrogens and is commonly consumed in East Asian countries. It has

important role in reducing the incidence of prostate cancer. Besides being a great source of protein, soy contains high levels of phytoestrogens comprising of four classes of compounds which are isoflavones, flavonoids, coumestans, and lignans. There are many studies especially on genistein that may compete with and inhibit endogenous estrogens from binding to the estrogen receptor, thereby inhibiting cellular proliferation in tumour. Several clinical studies suggest high soy consumption may give prevention against prostate cancer development such as isoflavonoids obtained from soy have been shown to inhibit the growth of both benign and malignant prostatic epithelial cells. It was proven by a meta-analysis by Hsu and Gupta in which men with identified risk of prostate cancer showed a significant reduction in the diagnosis of prostate cancer following administration of soy isoflavones (RR = 0.49, 95% CI: 0.26, 0.95).[22,23] A study of soy protein isolate consumption by Hamilton et al in 2007 in 58 men demonstrated an effect on androgen receptor expression that could be beneficial in preventing prostate cancer development.[24] It was later supported by study by Nagata et al 2007 however there was no significant effect on testosterone level as also mentioned by study by Van Die et al. [25,26]

However, the study on effect of isoflavones on diagnosed prostate cancer patients showed that no significant changes in prostate specific antigen (PSA) level. Messina et al had analyzed the results of 11 published trials to examine the effects of isoflavones on serum PSA levels in prostate cancer patients and healthy subjects. The study showed that there was a delayed PSA progression in prostate cancer patient but no affect serum PSA in healthy men.[27] The result is also supported by Hamilton et al where no significant changes in serum PSA was observed among 86 prostate cancer patients who were planned for prostatectomy after given isoflavones. Hence, it may be concluded that isoflavones may not play an important role in the reduction of prostate specific antigen levels reduction in prostate cancer patients or healthy men with identified risk of prostate cancer. [28]

*Selenium*

Selenium is one of the trace elements but has proven to induce apoptosis, inhibit cellular proliferation and inhibit angiogenesis. Study by Chan et al in 2005 claimed that selenium may reduce the incidence of prostate cancer up to 50–65% with high versus low selenium levels.[29] Generally selenium can be found in plant such as cereal and tubers or seafood and eggs, and could bring good regards in small quantities. Few epidemiologic studies had shown lower rate of prostate cancer mortality in countries and regions with selenium rich soils. Study by Clark et al reported that men receiving supplemental selenium showed protective effect towards the incidence of prostate cancer (RR 0.37, 95% CI, 0.18–0.71; p=0.002) and a follow-up from this study showed that the incidence of prostate cancer persisted towards the end of the study (RR 0.48, 95% CI 0.28–0.80). However, the protective effect of selenium on prostate cancer was restricted to men with the lowest plasma selenium concentration at baseline, which indicates potential confounding due to selenium deficiency. This finding is best supported by a meta-analysis by Clark *et al.* in the years 1996, 1998 and Duffield-Lillico *et al.* 2003 who reported an approximately 50% reduction of risk of developing prostate cancer with a daily 200 μg selenium supplement, particularly in men with low selenium levels.[30-32] In 2006, a meta-analysis of 20 epidemiological studies by Brinkman et al showed a significant increase in the incidence of prostate cancer in men with low selenium levels.[33] However there is always a conflicting issue of selenium intervention in preventing prostate cancer as it is very difficult to assess the selenium element in daily diet.

*Cranberry*

Generally cranberry fruit contains several types of components and elements which are believed to be able to give good impact and health benefits. These include vitamins C, E, K, saccharides, flavan-3-ols, flavonols, anthocyanins, anthocyanidins, proanthocyanidins and triterpenoids, which are believed to possess anti-bacterial, anti-viral, anti-oxidant, anti-inflammatory, anti-angiogenic and anti-cancer activities. A case control study by Studenta in 2016 involving 64 respondents who were assigned into two groups of placebo and a daily dose of 1500mg dry cranberry fruit powder 21 days before prostatectomy had reported a decrease in serum prostate specific antigen (PSA) by 22.5% in the cranberry group, whereas the concentration increased by 0.9% in the placebo group over the study period.[34] Another study by Vidlar reported that daily intake of 1500 mg cranberry powder for 6 months significantly reduced total prostate-specific antigen (PSA) that was elevated from chronic non-bacterial prostatitis, and/or benign prostate hyperplasia. It is believed that cranberry proanthocyanidin enriched fraction inhibited matrix metalloproteinase-2 and -9 (MMP) activity through the induction and/or inhibition of specific temporal MMP regulators that inhibit tumor cell invasion and metastasis. It is suggested that cranberry extract of flavonols, proanthocyanidins or triterpenoids, are associated with biological alteration of cell targets and may be protective for prostate cancer.[35] However there are still limited studies on the element in different settings.

*Lycopene*

Lycopene is commonly found in tomatoes that contain carotenoid that is believed to have inhibited

oxidative damage to cellular macromolecules, increased gap junctional intercellular communication, and prevented oxidative DNA damage. It is recommended that two to four servings of tomato per week may reduce 35% risk of developing prostate cancer. It was proven by Giovannucci et al, Darlington et al and Peters et al in their multi centered cohort studies in which they stated that consumption of tomato product and lycopene may reduce the risk of prostate cancer development. It is believed that lycopene intake was associated with protective effect of developing prostate cancer (RR=0.79, 95% CI=0.64-0.99, for high versus low quintile of intake).[36-38] This findings was also similar to the meta-analysis by Etminan et al from 11 case–control and ten cohort studies which found an association between lycopene intake and a decreased risk of developing prostate cancer.[39] In summary, the evidence available to date suggests that a high versus low intake of foods containing lycopene decreases the risk of prostate cancer, where cooked produced may be more potent than raw products.

*Vitamins*

Vitamin is a main liposoluble antioxidant of the human organism. Vitamin E consists of tocopherols and tocotrienols which are the major source of vitamin E in the diet. The relationship between vitamin E nutrition and prostate cancer risk has been investigated in many epidemiologic studies. It showed controversial results in which 7 of 14 case control studies showed an inverse association between blood levels of tocopherols and prostate cancer risks. α-tocopherols supplementation was found to be significantly associated with lower incidence of prostate cancer and higher serum α-Tocopherol was associated with a reduced risk of prostate cancer. The World Cancer Research Fund International (WCRF) expert panel examined a total of six cohort studies, 14 case control studies and one ecological study regarding dietary/serum vitamin E, and concluded that there is a 'probable' association between vitamin E intake and a decreased risk of prostate cancer (WCRF, 2007). One note of caution is that a vitamin E consumption of over 400 IU was found to increase all-cause mortality.[40]

Vitamin D acts as a regulatory hormone for multiple cell activities in the human body. The activated form of vitamin D 1,25-OH2 vitamin D can potentially play a role in cancer pathogenesis. It was supported by Shui et al who concluded that higher 25(OH)D levels were associated with a 57% reduction in the risk of lethal prostate cancer (OR=0.43, 95% CI=0.24-0.76) while study by John Mullin et al demonstrated a significant inverse association between ultra violet radiation and prostate cancer risk.[41-42] It also was proven by Barnett et al. when he managed to correlate cancer incidence and environmental exposure including exposure to sunlight and concluded that vitamin D production in the skin reduced the risk of several solid tumors, including prostate cancer. [43]

*Alcohol Consumption*

Alcohol consumption in daily lifestyle is one of the common major risk factors for human cancers. Alcohol consumption is generally measured in drinks per day, with a common drink of alcohol containing about 15 grams of ethanol irrespective of the type of beverage consumed such as beer, wine and liquor, straight or mixed. Study by Rizos et al stated that there is a relationship between heavy alcohol intake and cancer including prostate cancer. Evidence suggests that the effect of alcohol is modulated by polymorphisms in genes encoding enzymes for ethanol metabolism such as alcohol dehydrogenases, folate metabolism and DNA repair.[44] Meta-analysis study by Rota et al reported that there was a significant relationship between prostate cancer risk and number of alcohol intake with relative risk increased from 1.05 for one alcoholic drink per day to 1.21 for four alcoholic drinks per day.[45]

*Smoking*

It is well known that smoking is one of the risks of many cancer progressions. One of the major studies about smoking and prostate cancer carried out by Health Professionals Follow-up Study involving 524 prostate cancer specific deaths reported that smoking was associated with approximate 60% increased risk of prostate cancer mortality (HR 1.61, 95% CI: 1.11–2.32) and biochemical recurrence (HR 1.61, 95% CI 1.16–1.22). A meta-analysis study by Huncharek et al based on 24 prospective cohort studies enrolling 21 579 prostate cancer participant evaluated the relationship between smoking and prostate cancer. There was a statistically significant increase of risk in former smoker (RR=1.09; 95% CI=1.02, 1.16) with current smokers had an increased risk of fatal prostate cancer (RR=1.14; 95% CI=1.06, 1.19). The study also stated that those heavy smokers had 24% - 30% higher risk of death compared to non-smokers.[46] However a recent cohort study by Neuhouser et al in 2007 found a decrease in the risk of advanced prostate cancer in smokers with high dairy consumption.[47]

## CONCLUSION

In conclusion, the diet risk factor that may affect the incidence and progression of prostate cancer remains unclear. However based on many meta-analyses been done the objective to have fundamental idea about the dietary risk of prostate cancer may give benefit in providing the best understanding on prostate cancer prevention. Diet which consists of low carbohydrates, n-3 PUFAs, colorful fruits and vegetables is still the best advice

to counsel the patient while lifestyle of smoking and heavy alcohol intake should be avoided. Hence careful choice of diet and good cooking methods are recommended other than increased consumption of antioxidant which may play a role in reducing the burden of prostate cancer.

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