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Does Dietary Intervention Have an Effect on the Progression and Ultimately the Treatment of Prostate Cancer?

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ABSTRACT

OBJECTIVE: The objective of this systematic review is to determine whether or not dietary intervention has an effect on the progression and ultimately the treatment of Prostate cancer.

STUDY DESIGN: Review of three English language primary studies published in 2007, 2008, and 2009.

DATA SOURCES: Two randomized control trials and one cohort study studying the effects of dietary intervention on the progression of prostate cancer found using OVID and Medline.

OUTCOME MEASURED: Outcomes were measured by further progression or recurrence of prostate cancer. This was possible by looking at reduced tumor proliferation, reduced PSA levels, wt. changes, gene expression changes, food consumption, and number of events. The numbers of events of prostate cancer recurrence of progression were defined as the first of following events: prostate cancer death, metastases, biochemical recurrence, or initiation of a second treatment.

RESULTS: All three published studies included in this review provided evidence to suggest that post-diagnostic dietary intervention can have an effect in some way on the progression of prostate cancer.

CONCLUSIONS: The results of this review demonstrate that there is currently enough evidence to suggest that dietary intervention can possibly have an effect on the course or change the progression of prostate cancer after diagnosis and before treatment. Whether studies showed an increased risk of progression, or a reduction in tumor growth, there is enough information to establish a significant change in progression as a result of dietary influence. Because the results of the two RCT's and one Cohort study reviewed reported varying results as to what types of dietary interventions may play a specific role, more research is required to explore the definite types of food, amounts, and their mechanisms in influencing the outcome of prostate cancer before it can be considered as adjunct treatment.

KEY WORDS: Prostate, Prostate Cancer, Diet, Dietary Intervention, Reduction, Progression, Treatment

INTRODUCTION

Prostate cancer is a very common malignancy of the prostate gland, one of the structures that make up part of the male reproductive system. The disease is characterized on a basic level by changes in the DNA of the prostate cells, with the majority developing from gland cells usually leading to a relatively slow growing adenocarcinoma.[1] While the disease can affect men of all ages, the majority of men affected are over age 40, with 1 in 6 of all men affected in their lifetime. Prostate cancer is currently the 2nd leading cause of cancer death in American men, with approximately 2.1 million men currently living with prostate cancer in the US. This year about 217,730 new cases will be diagnosed with about 32,050 of those men dying. The disease is so common that has been shown that 70-90% of men by age 80 have prostate cancer at autopsy but were unaware before death. [1]

Because of its universal nature, prostate cancer is a disease that crosses over into many scopes of PA practice and is something that many practitioners must become familiar with treating and diagnosing. Currently available treatments can be effective, but depend on the extent of cancer spread, and are often expensive. The cumulative cost of treating prostate cancer is estimated to be, on average, $42,570 over 5 years of treatment.[2] The usual methods used to treat prostate cancer are observation with close monitoring, surgery via radical or robotic prostatectomy, radiation therapy via external beam radiation or internal brachytherapy, cryosurgery, hormone therapy, and chemotherapy.

Currently, the exact cause of prostate cancer is unknown, although there are known risk factors. Risk factors include African American race, family history, genetics, obesity, and diet. Because diet is a known risk factor for the disease, and is believed to have an influence on the development and progression of the disease, the prospect of adding something such as dietary

intervention to the treatment plan, if shown to be beneficial, could be a relatively simple and cost effective method for patients to bolster the care and slow the progression of prostate cancer.

OBJECTIVE

The objective of this systematic review is to determine whether or not dietary intervention has an effect on the progression and ultimately the treatment of prostate cancer.

METHODS

All three studies used in this review required a population of men with diagnosed prostate cancer whether it was biopsy-confirmed or clinically localized. All interventions were strictly dietary and included methods such as the incorporation of flaxseed, a low-fat, low-glycemic load diet, or the consumption of processed and unprocessed red meat, poultry, fish, and eggs. Comparisons were made between control groups continuing with their usual diet and groups varying in their consumption of each food. The outcomes looked at included the progression of prostate cancer as well as the recurrence of prostate cancer, both which qualify as patient oriented evidence that matters (POEM). Studies included a RCT comparing men who began a flaxseed supplementation to men continuing their usual diet, a RCT comparing men who began a low-fat/low-glycemic load diet to men continuing their usual diet, and a cohort study looking at post-diagnostic consumption of processed and unprocessed red meat, poultry, fish, and eggs for 2 years.

A detailed search was completed by the author using key words such as prostate, prostate cancer, diet, dietary intervention, reduction, treatment, and progression. All articles were published in English and in peer-reviewed journals. All literature searches and the selection of studies for this review were performed by the author. Literature searches were performed for

articles via OVID, Medline and Cochrane databases and were selected based on relevance and that the outcomes of the studies mattered to patients. Inclusion criteria included studies that were randomized, controlled, prospective, and were based on patient oriented outcome. Studies were also chosen based on content including a demographic already diagnosed with prostate cancer. Under these criteria, two RCT's and one cohort study were selected and included in this review. The statistics used in these studies were p-values with a value of <0.05 being statistically significant and 95% confidence intervals.

OUTCOMES MEASURED

The primary outcome measured in all of the studies included was the status of the prostate cancer after some sort of a dietary intervention in terms of whether it got worse, slowed progression, or if it had previously been in remission, whether or not it returned. This was measured by looking for reduced tumor proliferation rates (indicating a slower growing tumor), reduced PSA levels (decrease between baseline and follow up levels indicating effective treatment), wt changes (kg), gene expression changes, food consumption (median values), and number of events. Numbers of events of prostate cancer recurrence or progression were defined as the first of the following: prostate cancer death, metastases, biochemical recurrence, or initiation of a second treatment.

RESULTS

The major characteristics of the trials used in this study are displayed in **Table 1**. Results pertaining to the primary outcome were presented as continuous data, not convertible to dichotomous format for all three studies. Test statistics provided included p-values and confidence intervals pertaining to the method of measuring the outcome in each individual study.

Table 1. Table of demographics of included studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Denmark-Wahnefried W (1)	RCT	161	36-73	Male w/ bx-confirmed prostatic CA electing prostatectomy as their primary treatment; at least 21 days from scheduled surgery; must be mentally competent; must be Eng. speaking/writing w/ telephone access	Recent flaxseed use and/or adherence to a diet < 30% kilocalories from fat; dietary supplements started w/in the past 3 mos; current abx use; hx of hormonal or other neoadjuvant therapies	7.5 %	Flaxseed Supplementation x 30 days: 10g days 1-3, 20g days 4-6, 30g days 7-30
Lin DW (2)	RCT	8	59-69	Men w/ clinically localized prostate CA who select radical prostatectomy; have ability to implement dietary change; have participated in an independent protocol that collected and stored 4 prostate tissue cores at the time of diagnostic prostate bx	No concurrent diseases requiring dietary modification; no current use of hormonal treatments; BMI >20kg/m2 and <35kg/m2	0	Initiation of Low-fat/low-glycemic diet: 20% energy from fat and total daily glycemic load <100
Richman EL (3)	Cohort Study	1294	Not specified	Men who had bx-proven prostate CA; men w/out recurrence or progression as of 2004-05 participating in the Cancer of the Prostate Strategic Urologic Research Endeavor; men must have completed the baseline Diet & Lifestyle CaPSURE survey between 4/2004 and 11/2005	Men with advanced or metastatic disease at dx; men w/ no treatment info.; men w/ no f/u beyond Diet & Lifestyle survey; men w/ prostate cancer that had progressed before they completed the surgery; men w/ unreasonable energy intake (<800 or >4200 kcal/d)	38	Post-diagnostic consumption of processed and unprocessed meat, fish, poultry, and eggs x 2 years

In the multisite, randomized control trial included by Demark-Wahnefried et al, prostate cancer patients scheduled at least 21 days before prostatectomy were randomly assigned to either control or a dietary intervention arm.[3] After an average of 30 days on either the flaxseed or control diet, Demark-Wahnefried et al reported prostate cancer tumor proliferation rates as well as baseline and follow up PSA levels (**Table 2**). When looking at results in **Table 2**, TPR's (tumor proliferation rates) were significantly lower in the flaxseed, or experimental arm. The TPR of the control arm at the end of the study was 3.23, while the TPR for the experimental arm was 1.66. The significance of this difference was demonstrated through a statistically significant

p-value of 0.0013 (<0.05). Significant PSA changes between baseline and follow up for either study arm were not observed in this study. The results of this study demonstrate a control baseline PSA of 5.3 with a 95% CI (2.42-3.92) with a follow up level of 4.9 with a 95% CI (3.5-6.2), whereas the experimental arm baseline is 6.2 with a 95% CI (4.8-7.7) and follow up level is 6.4 with a 95% CI (5.0-7.0). The changes in PSA level after intervention from median baseline to median follow up demonstrated a p–value of 0.286 that is not statistically significant when comparing both arms of the study (Table 2).

In the randomized control trial by Lin et al, men who were newly diagnosed with prostate cancer were randomly assigned to either a "standard American" diet control arm which consisted of men continuing on their usual diet, or an experimental one including a low-fat/low-glycemic load.[4] In this study, the average weight change was reported for both arms. As seen in **Table 2**, a post-intervention weight change of -5.3kg in the experimental group was noted, while a weight change of only 0.8g was reported for the control group. A p-value for the weight change between the two groups was found to be 0.02 and statistically significant with a 95% CI (1.6-10.5). Gene expression was measured using cDNA microarray hybridization confirmed with quantitative reverse transcription-PCR. This data was also reported in both groups after the course of the study. For the control arm, no differences in transcript expression of genes were found to be statistically significant. In the experimental arm, it was reported that 23 (0.46%) of 5711 cDNAS with measurable expression were significantly altered, and although a p-value was not stated, it was reported to be <0.05 and statistically significant (Table 2).

In the Cohort study by Richman et al, men with biopsy-proven prostate cancer were selected and their diets were followed for 2 years.[5] Associations between consumption levels of four meat groups and eggs and relative risk of progression of prostate cancer were analyzed.

Groups included processed and unprocessed red meat, fish, poultry, and eggs. Richman et al reported their data by breaking down each food group into quartiles and quantiles based on what food type and how much of each was being consumed. The number of events within each quartile and quantile was recorded with number of events being defined as prostate cancer deaths, bone metastases from prostate cancer, biochemical recurrence, or initiation of secondary treatment. Because the data was broken down in this fashion, and provided in a very different manner than the RCT's included, a separate results table for this Cohort study was created as **Table 3**. The total number of events for each quartile/group can be seen in **Table 3.** After data was collected, poultry data was found to be border-line and that category was thus broken down and reanalyzed as poultry with skin and poultry without skin groups. It is important to note that individualized number of events for that division was not given. Relative risks of progression were calculated by comparing the risk of progression for men in the upper quantiles relative to men in the lowest quantile. Hazard ratios were calculated with a 95% CI for comparison of the highest with the lowest quantile and p-values for each were analyzed. Of all the groups, the p-values found to be statistically significant were those from the poultry with skin and egg groups. In the poultry with skin group, a p-value of 0.003 (<0.05) was found to be statistically significant with a HR (95% CI) of 2.26 (1.36-3.76). Data showed that men in the highest tertile of poultry with skin had more than double the risk of prostate cancer progression compared to men in the lowest tertile. Data also shows in the egg group, a p-value 0.05 was found to be statistically significant with a HR (95% CI) of 2.02 (1.10-3.72). This data represented an observed significant 2-fold increased risk of prostate cancer progression among men in the highest quartile of egg intake compared with men in the lowest (Table 3).

Table 2. Methods of measure and results for study arms with statistical analysis of significance

Study	Methods of Measure	Control Results	Intervention Results	SS
Demark-Wahnefried et al	TPR PSA levels at Baseline and at F/U	TPR = 3.23, 95% CI (2.42-3.92) Baseline PSA = 5.3, 95% CI (3.7-5.8) F/U PSA = 4.9, 95% CI (3.5-6.2)	TPR = 1.66, 95% CI (1.13-2.64) Baseline PSA = 6.2, 95% CI (4.8-7.7) F/U PSA = 6.4, 95% CI (5.0-7.0)	TPR p-value = 0.0013* PSA Changes p-value = 0.286, NS
Lin et al	Post Intervention Weight Change (kg) Gene Expression Changes	Wt = 0.8kg No differences in transcript expression	Wt = -5.3kg 23 (0.46%) of 5711 cDNAs were altered	Diff in wt change = 6.1kg, 95% CI (1.6-10.5), p-value = 0.02* Control: gene expression p-value NS Intervention: gene expression p-value is <0.05* (exact p-values not given)
Richman et al	Number of Events	**See Table 3	**See Table 3	**See Table 3

TPR = Tumor Proliferation Rates, PSA = Prostate Specific Antigen, f/u = follow up, CI = Confidence Interval, * = statistically significant (p-value <0.05), SS = statistical significance, NS = not significant, **Note: Data for Richman et al provided in Table 3

Table 3. Statistical Analysis of Number of Events in each food group & quartile (Richman et al)

Cohort Study – Richman et al	Quartile 1 Number of events	Quartile 2 Number of events	Quartile 3 Number of events	Quartile 4 Number of events	P value, HR
Processed Red Meat	29/310	32/372	21/275	45/337	p-value = 0.18, HR (95% CI) = 1.30 (0.78,2.17)
Unprocessed Red Meat	30/324	38/371	26/296	33/303	p-value = 0.65, HR (95% CI) = 0.95 (0.55,1.66)
Fish	36/348	21/275	34/324	36/347	p-value = 0.46, HR (95% CI) = 1.13 (0.70,1.84)
Poultry	33/380	24/224	35/344	35/346	*p-value for poultry w/ skin = 0.003, HR (95% CI) = 2.26 (1.36, 3.76) p-value for poultry w/out skin= 0.87
Eggs	24/319	27/267	51/532	25/176	*p-value = 0.05, HR (95% CI) = 2.02 (1.10,3.72)

HR = Hazard Ratio, CI = Confidence Interval, *p-value = significant as defined as <0.05

Compliance to each diet was measured differently for each study. In the RCT by Demark-Wahnefried et al, compliance was encouraged by having participants keep logs of daily intakes and by having participants return any unused packets of flaxseed to monitor usage.

Adherence to the diet was also supported by noting higher lignin intakes and expression within urine and seminal fluid. In the RCT by Lin et al, dietary compliance was encouraged by weekly scheduled telephone calls between participants and the study nutritionist provided, as well as additional weekly unscheduled and blinded telephone interviewers making 24h dietary recalls. Methods to ensure compliance were not mentioned for the Cohort Study by Richman et al.

In mentioning the safety of these studies, Demark-Wahnefried et al was the only study to mention side effects. They reported that throughout the study there was a lack of, or only mild side effects reported for participants involved in flaxseed supplementation. Several participants in this study were noted to report symptoms of low libido or erectile dysfunction, however no differences were ultimately observed between the control and experimental arm for this or any other side effect. Other studies included failed to mention any adverse side effects of dietary change and all indicated that the interventions were tolerated sufficiently well.

DISCUSSION

The articles used in this review demonstrate that dietary intervention in many areas after the diagnosis of prostate cancer may play a role in its progression. While there are many aspects of dietary intervention discussed in this paper, and while much more research needs to be done on the subject and how it may someday be used as co-treatment, the prospect for knowledge on how diet can influence the progression of prostate cancer is vast. Exploring this research is important because the dietary methods of intervention examined in these studies are easily accessible, cost effective, and readily available for patients everywhere who have been recently diagnosed with prostate cancer.

Certainly, these studies have their limitations. The study by Demark-Wahnefried et al was only an average of 30 days, which could have limited the potential for more extensive and thorough data over a longer period of time. In the study by Lin et al, a major limitation was the small sample size of 8, as well as a small number of genes that were analyzed within the prostate epithelium. Another important limitation point is that those participating in the experimental arm lost a significant amount of weight compared to those on the control diet simply from the change from their baseline. It might be possible that the effects the researchers are assuming are from dietary influence are more linked to the actual reduction in body mass as a result of the change in diet. In the study by Richman et al, limitations included a short follow-up, small number of prostate deaths or metastases, and lack of pre-diagnostic dietary data. Because men were recruited after diagnosis of prostate cancer, the dietary information of participants and its influence prior to the study could not be examined. It is possible that a lack of dietary data prior to the study could lead to a misrepresentation of the patient's overall dietary history and thus the strength of its influence.

CONCLUSION

In conclusion, the studies reviewed demonstrate that there is evidence to show that dietary intervention can have an effect on the progression of prostate cancer. Although more research needs to be done to investigate the specific nature of this link, and what other types of food play a role, at this time there is enough evidence to support an association between a change in diet and some change in the course or progression of prostate cancer.

At this time, it appears that flaxseed supplementation post-diagnostically in prostate cancer is safe and associated with biological changes, which may protect against the progression

of prostate cancer. Hope that initiation of flaxseed into one's diet after diagnosis can potentially slow down the progression appears promising at this time. However, while it appears that flaxseed supplementation has been associated with a reduction in tumor proliferation rates (or in other words, has been shown to slow the rate of tumor growth), there has not been a significant association found between flaxseed in one's diet and a change in PSA level at this time. Because of the inconclusive data on the effects of flaxseed on PSA levels and other measurements involved with tracking the progress of prostate cancer treatment, future studies need to investigate further the exact mechanism and influence this supplementation has on the prostate epithelium growth.

Results for consumption of poultry with skin and eggs after diagnosis demonstrated a positive association between these food groups and a 2-fold increased risk of progression among men with localized disease based on an increased number of events in those populations. Although, it appears that data supports this increased risk, the exact mechanism needs to be explored further, as well as the specific amount that is associated with this risk in the future alongside a more extensive dietary history.

Lastly, the study looking at the incorporation of a low-fat/low-glycemic diet showed a statistically significant effect of dietary change, and ultimately a significant change in weight, on gene expression within prostate epithelium. The implementation of this diet seemed to be associated with significant genetic changes in expression within the cancerous tissue of the prostate. At this time, because it's hard to decipher whether or not the genetic changes that occurred were due to the diet itself or instead the resultant weight change, the data is inconclusive as to whether or not this specific diet specifically can change the progression of cancer. Instead, the data supporting gene expression change as a result of changes in diet simply

opens up the door to study the link between diet, prostate cancer, and obesity. Because the changes could be more due to the reduction in body mass and because it is difficult to say at this time if the genetic changes truly have an effect on the course of the cancer, more research also needs in the area of gene expression usage in general as a measure of cancerous change.

In conclusion, while it appears there is enough evidence to establish a link between changing one's diet and altering the progression of prostate cancer, more research needs to be done to definitively determine what types of dietary intervention can potentially slow down or alternatively worsen the progression of prostate cancer and how it can be used as adjunct treatment in the future. If a more direct link or mechanism can be established, it's possible that dietary intervention may be the basis for co-treatment or even long-term prevention of prostate cancer in the future. Further studies are warranted to evaluate more specific effects of dietary intervention on the progression of prostate cancer and how it can possibly be incorporated into a treatment plan.

Future studies would benefit from larger sample sizes, longer studies, more in depth pooling of genes from participants, investigation into the worth of genetic expression changes as a reflection of changes in cancer status, and more extensive information on each participants' dietary history. This might prove to be more helpful in terms of reflecting the long term influences of diet on each patient, as well as representing a greater number of people and thus prostate cancer in general more accurately.

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