

SERUM SELENIUM AND THE RISK OF PROSTATE CANCER

A Research Project by

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Bachelor's of Science in Biology, Newman University, 2005

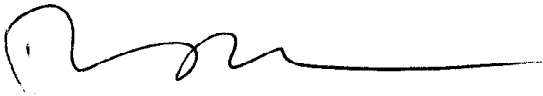
Submitted to the Department of Physician Assistant
and the faculty of the Graduate School of
Wichita State University
in partial fulfillment of
the requirements for the degree of
Master of Physician Assistant

May, 2007

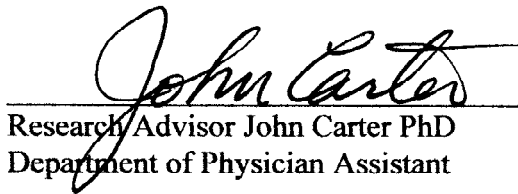
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We hereby recommend that the research project prepared under our supervision by Graduate Chelsea Stancoff-Hon entitled Serum Selenium and the Risk of Prostate Cancer be accepted as partial fulfillment for the degree of Master of Physician Assistant.

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4-25-07
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ACKNOWLEDGEMENT

I would like to express my gratitude to my professor and research advisor, Dr. John Carter Ph.D, for his guidance on this project. Thank you for your help and being so flexible with my hectic schedule through PA school. I also wanted to thank my husband Kyle and my parents David and Debi for their patience, for believing in me, and for their love and support.

ABSTRACT

Introduction: The purpose of this study is to investigate the relationship of serum selenium levels and the risk of developing prostate cancer. It has been documented that antioxidants reduce the incidence of cancer by eradicating free radicals that damage DNA, thus increasing the risk of cancer. Selenium is a component of the antioxidant enzyme glutathione peroxidase, whose role in cancer prevention has been controversial in the last 40 years. *Methodology:* A systematic review of evidence-based literature was performed utilizing the following search engines: MEDLINE FirstSearch, ArticleFirst, dissertations, and Paper's First and a bibliographic search of selected articles. MeSH (medical subject heading terms) and text words utilized in this study include: serum, selenium, prostate, neoplasia, risk, nutrition, adenocarcinoma, male, prostatic intraepithelial neoplasm, and prostatic neoplasia. *Results:* The results of the evidence-based literature results are consistent with the epidemiologic studies available at this time. The best quality evidence suggests that higher selenium levels decrease a man's risk of developing prostate cancer. However, because of unaccounted for confounders including family history of prostate cancer and educational level, it is not recommended that providers prescribe selenium as preventive medicine combating prostate cancer. Nevertheless, individuals who have a higher intake of selenium may benefit from its protective effects.

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INTRODUCTION

A systematic, evidence-based literature review was performed looking for an association between the risk of prostate cancer and serum selenium in men of different races, cultures and regions. Prostate cancer is the most common cancer in American men. It is also the second leading cause of cancer death, after lung cancer; however, the etiology of the disease is unknown. The prevalence of microscopic or latent prostate tumors is similar in most countries, but clinical prostate cancer morbidity and mortality are extremely different in various geographic regions among various ethnic or racial groups^{1,2}. The epidemiology of prostate cancer is quite complicated because there are few recognized risk factors that are associated with the disease. Risk factors which may be relevant include: family history, age, country, race, testosterone deficiency, and diet³. Significant dietary factors include a high consumption of red meat and dairy products, as well as a diet high in fat.

Prostate cancer may be found as nodules in the prostate at the time of a digital rectal exam (DRE). Most prostate cancers are diagnosed, however, due to the elevation of serum prostate specific antigen (PSA). PSA is a glycoprotein produced in the cytoplasm of benign as well as malignant prostatic cells; its level correlates to the amount of prostate tissue, benign or malignant³.

Antioxidants are nontoxic compounds that have been shown to reduce the incidence of cancer. Their function is to eradicate free radicals that damage DNA, which in turn can cause cancer. The most widely known, highly effective antioxidants include vitamin E, Beta-carotene, and lycopene. Selenium is an element in the antioxidant enzyme glutathione peroxidase; its role in cancer prevention has been somewhat

controversial over the last 40 years. Selenium has many functions in the body. It is present in the active site of many enzymes which may encourage apoptosis of cancer cells; it improves the body's immune system by causing the formation of natural killer cells, it restrains the prostaglandins that cause inflammation, and it may induce P450 enzymes in the liver that detoxify carcinogenic molecules. Lastly, selenium, at high doses can decrease the rate of tumor growth in humans¹.

LITERATURE REVIEW

It has been reported that the prevalence of cancer can be reduced by the consumption of the nontoxic antioxidants. Some antioxidants such as Alpha- and Beta-carotene, lycopene, and vitamin C have been found to reduce the incidence of total cancers, especially lung, prostate and stomach as well as oral pre-cancers⁴. Antioxidants can be obtained from dietary supplementation and from dietary components (Brazilian nuts, tuna, beef, turkey, cottage cheese and eggs) and green tea phenols⁵. The cancer risk reduction is usually around 0.6; however, it can be up to 3-fold in the elderly and in those that smoke⁴. Antioxidants have two different types of actions. The first is scavenging for free⁴ radicals which reduce damage to DNA, which is the most well known mechanism. The second action is where selenium becomes important. Work done by Seo *et al.* found evidence that selenomethionine (SeMet), which is the form of selenium that is reported to be the major component of dietary selenium, has the role listed previously as well as a new one⁶. SeMet undergoes an intermolecular transulfuration reaction to form selenocysteine. The two proteins are contained in this molecule are glutathione peroxidase and thioredoxin reductase. Both of these proteins are known for their antioxidant properties, as well as maintaining the redox balance in cells. Their activities

are extremely dependant on the concentration of selenium in the cellular environment. Thioredoxin reductase is also instrumental in the conversion of ribonucleotides to deoxyribonucleotides, which are required for DNA synthesis and for regulating numerous transcription factors⁷. Ref-1 is a substrate for reduction by the thioredoxin reductase system⁶.

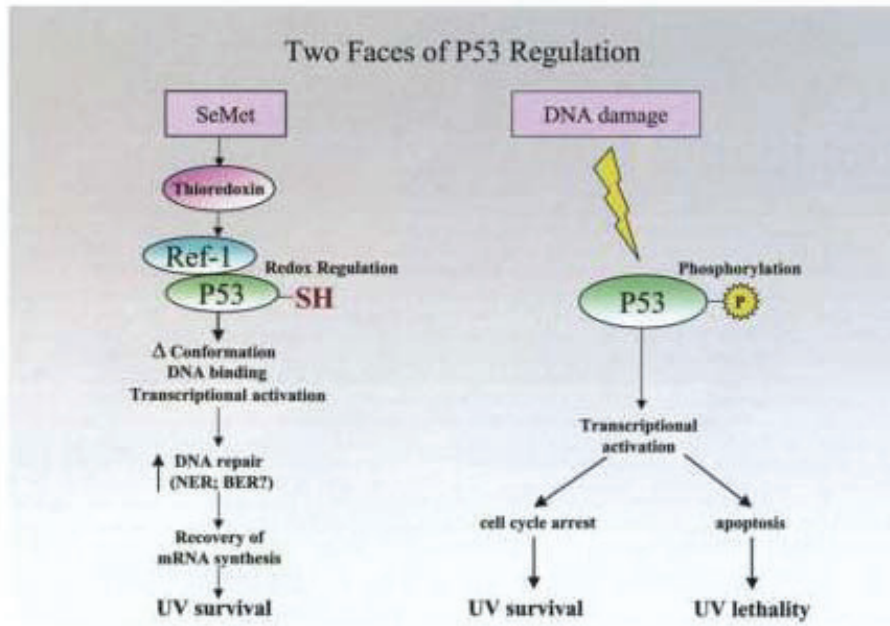


Figure 1⁸

Selenomethionine activates P53 by way of this pathway. It was speculated that this in turn activates Ref-1's ability to change the redox state of P53 cysteines. P53 set in motion by SeMet increases DNA excision repair. Unlike the activation of P53 by phosphorylation, SeMet does not induce apoptosis when DNA damage activates this cycle⁸.

There are several unknown factors regarding selenium, such as whether or not selenium is a chemopreventive of cancer. The largest ongoing chemoprevention study ever to be performed began in August 2001. The selenium and Vitamin E Cancer

Prevention Trial (SELECT) randomized 32,400 men 50-55 years and older to selenium, vitamin E, both, or placebo for 7-12 years and from 435 sites across the United States, Canada, and Puerto Rico. The results of this trial will not be known until 2012. This trial should answer the question regarding whether dietary supplementation is related to a decreased risk of prostate cancer. The available literature points to yes (supplementation of selenium does decrease the risk of prostate cancer). The SELECT trial is based on information obtained from two trials, the Alpha-Tocopherol, Beta-Carotene (ATBC) Cancer Prevention Trial, a double-blinded placebo controlled trial of male smokers in Finland, and the selenium skin cancer trial⁹. The ATBC Cancer Prevention Study revealed up to a 32% reduction in prostate cancer and the selenium and skin cancer trial reduced the occurrence of prostate cancer by 63%^{9, 10}. However, the appropriate dosage seems to be a major issue. Other unanswered questions regarding selenium include: (1) Does a low serum selenium level put men at higher risk for prostate cancer? (2) Do low serum selenium levels put male smokers at higher risk for prostate cancer? (3) Are those that live in an area with poor soil selenium at an increased risk? (4) Are individuals of different races or ethnic backgrounds at a higher risk for prostate cancer?

PURPOSE OF STUDY

The purpose of this study is to determine whether or not the scientific literature indicates that serum selenium affects the risk of prostate cancer.

METHODOLOGY

The design of this study is a systematic review of evidenced-based medicine. A review of the literature was done using a combined search of MEDLINE FirstSearch,

ArticleFirst, dissertations, and Paper's First using the following subjects:

1. *serum AND selenium AND prostate cancer*
2. *prostate cancer AND risk AND selenium*
3. *prostate cancer AND nutrition AND selenium*
4. *prostate AND adenocarcinoma AND selenium*
5. *prostatic intraepithelial neoplasm AND selenium*
6. *male AND selenium AND risk AND neoplasm*
7. *prostatic neoplasia AND selenium*
8. *male AND selenium*

Other searches were performed using the same search terms but in the following search engines:

1. Cambridge Scientific Abstracts (CSA)
2. Info Trac Web
3. LexisNexis Academic
4. SilverPlatter Web SPIRS
5. Wilson Web
6. Complementary and Alternative Medicine (CAM) on PubMed

MeSH (medical subject heading terms) and text words utilized in this study include: serum, selenium, prostate, neoplasia, risk, nutrition, adenocarcinoma, male, prostatic intraepithelial neoplasm, and prostatic neoplasia. Potentially missed articles were searched in the reference section of each obtained article and from reviews of this topic. All applicable articles were then retrieved based on consensus among authors and searching the reference lists of those articles for potentially relevant articles.

Articles were used from the years 1977-2005. There were no articles on this subject found before the year 1977, thus the reason for this start date.

Inclusion and exclusion criterion were used to select which studies would be incorporated in this evidenced based literature review. Men between the ages of 45 and 75, that currently had not been diagnosed with any other type of cancer besides prostate cancer at the onset of the trial, and the evidence level of the article had to be a Level 1 or

Level 2 article to be included in this review. Exclusion criterion used included African American men, because of their higher rates of prostate cancer, articles that were low in evidence and those articles that used selenium in a cocktail of nutrients or antioxidants.

Three levels of evidence were used to classify each study. Level 1 evidence is based on randomized controlled trials and large meta-analysis studies. Studies that are considered to be Level 2 studies are nonrandomized controlled studies, clinical cohort studies, and case-controlled studies with nonbiased selection of study participants. Level 3 includes case series, and non-controlled case studies.

SYSTEMATIC REVIEW OF THE LITERATURE

Level 1 Evidence

Very few Level 1 studies have been performed to investigate the association between serum selenium and the risk of prostate cancer. There have only been two randomized controlled trials; neither of which studied prostate cancer as a primary endpoint. Both of these studies also were from the same trial, the Nutritional Prevention of Cancer Trial. Clark performed a double-blind randomized controlled trial observing the association between the incidence of prostate cancer with selenium supplementation.¹¹ Patients were eligible for this study if they had a previous history of basal cell carcinoma or squamous cell carcinoma, no report of internal malignancies five years prior to this trial, and at least a five year life expectancy. A total of 974 men were randomized to a daily 200 microgram selenium supplement or a placebo. The trial began in 1983, and by 1990, several secondary endpoints were added to the trial including mortality from any cause including cancer and the incidence of lung, colon and prostate cancer. Patients were followed every six months. At each visit to the clinic, the

participants were questioned to identify the incidence of illness and the use of prescription drugs. The participants were also required to give a sample of blood for selenium analysis and to screen for toxicity. The first blood sample after randomization was also used for the determination of preliminary prostate specific antigen (PSA) levels.¹¹ There were 13 cases of prostate cancer in the selenium treated group and 35 cases in the placebo controlled group which is a relative risk of 0.37 and a P-value of 0.002 and a 63% reduction in the secondary endpoint of prostate cancer. Clark also calculated a second figure based on the 843 patients that had an initially normal PSA level ($\leq 4\text{ng/mL}$). Following a two year treatment lag, there were 16 cases with diagnosed prostate cancer in the placebo group and only four in the selenium treated group.¹¹ Because of the significant reductions and the other positive health benefits that the selenium treated group experienced, the “blinded” phase of the trial was stopped early.

The second study based on the Nutritional Prevention of Cancer Trial was done to present the results of the end of the blinded treatment which lasted until January 1996. It studied baseline plasma selenium status as well as selenium supplementation and the incidence of prostate cancer.¹² There was an average follow-up time of 7.6 years. There were 42 cases of prostate cancer diagnosed in the placebo group and 22 in the participants provided with a selenium supplement. There was no statistical significance in the clinical stage or incidence of advanced prostate cancer between the two groups. Among men with an initial PSA level of $\leq 4\text{ng/mL}$ there was a 65% reduction in prostate cancer. There was no difference between the selenium supplemented group and the control group when the participant’s PSA was above 4ng/mL .¹² Duffield-Lillico divided

the men into three groups according to his preliminary serum selenium, ≤ 106.4 , 106.8-123.2 and > 123.2 ng/mL. Selenium supplementation had the greatest effect on the men in the lowest tertile of baseline plasma selenium concentrations. There were 22 cases in the placebo group and nine cases in the selenium supplemented group at $P < 0.05$.¹²

Meta-analysis studies are also of the utmost importance when examining the effects of selenium on the incidence of prostate cancer. The first meta-analysis by Schrauzer examined the effects of selenium on 10 different Type A cancers (intestine, rectum, prostate, breast, ovary, leukemia, lung, pancreas, skin and bladder).¹³ Cancer incidence, mortalities, dietary trace element intakes, and white population, were compiled using the studies of Segi et al., Lilienfeld, and Mason respectively.¹³ Dietary intakes were calculated from reported average concentrations of the elements in major food items and per-capita food consumption data published by the Food and Agriculture Organization of the United Nations for selected countries. There was an inverse relationship between serum selenium concentrations and prostate cancer as well as other Type A cancers such as intestine, rectum and breast. The study concluded that selenium has anti-carcinogenic properties in not only prostate cancer but in other cancers as well.¹³

The second meta-analysis was performed by Etminan from 1996 to May 2005. It studied the observation that selenium intake may prevent the risk of developing prostate cancer.¹⁴ Etminan conducted a systematic search of MEDLINE, Embase and The Cochrane Library using the following terms as text words and medical subject heading terms: neoplasm, diet, nails, prostatic neoplasms, prostate cancer, selenium, serum, and dietary supplements. Studies that were included in this meta-analysis had to have a clear diagnostic criteria for prostate cancer; had to have explicitly described exposure to

selenium; provided odds ratios or relative risks and 95% confidence intervals or provided enough data to allow the researchers to calculate those numbers; and discussed methods of adjustment for potential confounders. The data was then abstracted from the included studies by using a standardized data abstraction sheet by two self-sufficient reviewers.¹⁴ No randomized-controlled trials met the inclusion criteria stated above. Sixteen studies were included in the analysis. There were eleven cohort and five case-control studies. Etminan separated the studies into three groups based on intake of selenium, any intake of selenium, moderate intake, and high intake. Any intake was defined as the average between the first and third quartile; moderate intake was defined as intake between the second and fourth quintile and the second and third quartile, and high intake was defined as intake corresponding to fourth quartile or the fifth quintile. The lowest level of intake was used as the reference group.¹⁴

Level 2 Evidence

Cohort Studies

Of the Level 2 articles there were only three cohort studies. The first by Ozmen compared the concentration of trace metals, iron, vitamins and lipid peroxidation in patients with prostate cancer. All participants in the trial were patients who routinely visited the Department of Urology, First Medical Centre in Turkey. Levels of vitamins A, C and E, iron, nickel, zinc, cobalt, copper, and selenium were collected in 20 male patients with prostate cancer and 21 men who were age and sex matched controls.¹⁵ Statistical analyses were conducted using SPSS software and statistical significance was defined as $P < 0.05$. Patients with prostate cancer had significantly ($P < 0.01$) lower serum

levels of vitamins A and E, Zinc and selenium when compared with the control group participants.¹⁵

The second cohort study found in the literature was “The Association between Baseline Vitamin E, Selenium, and Prostate Cancer in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study”. The sample population was taken from the Alpha-Tocopherol, Beta-Carotene (ATBC) study that was conducted in Finland between 1985 and 1993. The ATBC study was a randomized, double-blinded, placebo controlled trial of 29,133 male smokers between the ages of 50 and 69. It was performed to determine whether daily supplementation with alpha-tocopherol, beta-carotene or both would cause a reduction in the incidence of lung or other cancers.¹⁶ There were nine years of follow-up; during that time, 317 men developed prostate cancer. In this cohort Hartmann looked at base-line levels of selenium and Vitamin E and those men who did/did not contract prostate cancer. There was statistical significance in the positive association between selenium supplement use and prostate cancer.¹⁶ However, Hartman takes this finding with some concern, because vitamin/supplement users have been found to be less obese, more physically active, and better educated.¹⁷ This study had several strengths, with the strongest being that the participants did not have prostate cancer at the beginning of the study and a fairly large number of men contracted prostate cancer during this study, unfortunately.¹⁶

The third cohort study by Brandt was based in the Netherlands among 58,279 men.¹⁸ The NCLS (Netherlands Cohort Study) was initiated with a baseline mailed questionnaire on usual diet and potential confounding circumstances, and provided toenail clippings. A “case-cohort” approach was used. This is where cases come from the

entire cohort and the controls come from a random “subcohort” that can be used for multiple disease endpoints.¹⁸ Toenail selenium analysis was performed by the Interfaculty Reactor Institute at Delft University and the statistical analysis was done using the Stata statistical software package. Toenail selenium levels were classified into quintiles according to the distribution in the subcohort group. The mean toenail selenium level in the case group was 0.530 ug/g. The control group’s mean selenium was 0.547 ug/g. The cases were also divided according to the year of follow-up. Earlier diagnosed cases did not have significantly lower selenium levels when compared to the cases that were diagnosed in later years. There was an inverse association between selenium levels and prostate cancer risk in all age groups. The age-adjusted relative ratio was 0.69 when comparing the highest and lowest selenium quintile. Reduced risk of prostate cancer was mainly in the highest three quintiles and for current and ex-smokers.¹⁸ Brandt states that the reason that the relative risk in this study is different than the relative risks of 0.4-0.5 in other studies¹⁹⁻²¹ is because of the relatively small amount of exposure in the Netherlands compared to the United States.¹⁸

Case-control Studies

By far, the most studies done comparing selenium and prostate cancer risk are case-control studies in twelve articles. The first case-control study is a study of British men and nail selenium. The study included white men, who could speak English and who were competent enough to complete a diet interview. Cases were identified by searching appropriate medical records and cancer registries throughout Oxfordshire, West Berkshire and Leeds. Diagnosis date was identified as the date on the histopathology report. Cases were classified as advanced if there was radiologic or histopathologic

evidence of local lymph node invasion and/or metastases to the bone or soft tissue. Controls were taken from a general practitioners patient list. Controls and cases were matched on age and region of residence. One control was matched for each case. Each participant completed a questionnaire that included questions about age, anthropometric, smoking and other lifestyle factors as well as a “semiquantitative” food-frequency questionnaire that assessed intake of 83 food items. Participants were asked to provide nail clippings. These clippings were kept in envelopes and marked with an identification number. Selenium content was assayed using instrumental neutron activation analysis techniques. The mean nail selenium concentration was significantly different by region with the highest being those individuals from Oxfordshire and the lowest in the participants from Leeds. Smoking was associated with a 14% lower selenium level than non-smokers. Selenium concentration was not associated with prostate cancer risk. However, men in the highest quartile of selenium nail concentration had a non-significant, 22% reduced risk of developing advanced prostate cancer compared with participants in the lowest selenium quartile. The strengths of this study are the large number of subjects and controls and the ability to categorize cancers into localized and advanced disease. This study’s limitation is that the cases already had cancer and the cancer itself or its treatment may affect the nutritional status and thus the selenium levels.

The second is a case-control study by Brooks looking at pre-diagnostic plasma selenium levels and the risk of developing prostate cancer. All men selected for this study have been enrolled in the Baltimore Longitudinal Study of Aging (BLSA), which is an ongoing long-term longitudinal study on aging. This is being conducted by the National Institute on Aging.²² In 1991, prostate cancer diagnosis was added to the BLSA

medical records. Participants return every two years for follow-up visits in which they are evaluated by an urologist, given a digital rectal exam and a (PSA) test. Males with PSA levels greater than 4.0 ng/mL and/or a suspicious digital rectal exam underwent a transrectal ultrasound prostate biopsy. There were 52 men with diagnosed prostate cancer who had an available plasma sample. The cases included 18 men with clinically localized disease, three advanced disease and 31 with unknown disease stage. Control participants were matched for age, weight, height, race, smoking status and alcohol consumption.²² Plasma selenium levels were divided into quartiles. Statistical significance was set at $P < 0.05$ and the statistical analysis was done with commercial software.²² Brooks found that compared with the lowest selenium quartile, the odds ratios with 95% confidence interval were 0.15, 0.21 and 0.24 for the second, third and fourth quartiles respectively. Age did not correlate with prostate cancer risk because it was matched with controls; however, it was related to lower selenium levels. Plasma selenium levels before diagnosis was found to be inversely correlated with prostate cancer risk. The lowest quartile of plasma selenium had a four to five-fold increase in incidence when compared to the higher three quartiles. Brooks concluded that low plasma selenium levels may indicate those men who are at an increased risk for developing prostate cancer and those men that selenium supplementation may be beneficial, especially men that are increased in age.²²

A nested case-control study by Coates used two employee groups in Washington state. The blood samples were collected by the Washington State Department of Social and Health Services and the Northwest Lipid Research Center. There were 156 in the total case group and of those, only 37 were included in the study of prostate cancer.²³

Controls were chosen from the same two employee groups and were matched with the cases based on employer, age, sex, race, and year and season of blood draw.²³ Coates found that there was no appreciable association between overall cancer risk, or prostate cancer only risk.²³ However, this study had several limitations. The most important being the small number of cases and controls. Almost twenty percent of the identified cases could not be studied because of a lack of a blood sample, which could have resulted in bias. Also the means of identifying cancer cases was calculated by an underestimate of about fifteen percent.²³ These three factors make for a weak study.

Another case-control study was performed by Ghadirian and the staff at the Research Center at the University of Montreal. In this study, 404 prostate cancer cases and 202 controls were matched for age (+/-) five years, and for residence between the years 1989 and 1993.²⁴ Cases were identified in the five major teaching hospitals in the Montreal area. Controls were identified from a random-digit dialing method that was developed from a previous study performed by the same author. A total of 326 toenail samples were collected from the study subjects no more than three months after a diagnosis of cancer was made, and a total of 120 toenails were collected from the control group. Toenail selenium concentrations were calculated by neutron activation analysis and then compared with a standard that was measured using the same conditions.²⁴

Ghadirian found that in general, there were higher selenium levels in those men who did not smoke than in those that did. However, there was not a significant difference in the toenail selenium level in prostate cancer cases and the control group.²⁴ The strength of this study is the use of toenail selenium levels which represents a semi-long-term dietary intake of selenium. The weakness of this study is the control group.

They were not matched for race and there was only a 30% compliance of the group. The low compliance rate is significant because not every case had a matched control.

Another article showing no significance between selenium and prostate cancer was a study done by Gary Goodman. He analyzed the serum selenium concentration in 235 prostate cancer cases and 450 from a previous trial, the Carotene and Retinol Efficacy Trial (CARET).²⁵ CARET was a multicenter randomized, double-blind, placebo-controlled, lung cancer chemoprevention trial. As a part of CARET, Goodman collected and stored serum on all participants preceding randomization and then yearly or every other year. Serum samples chosen for the analysis of prostate cancer were three or more years prior to the diagnosis of the neoplasia. Controls were matched to the cases by randomization year, age, smoking status, exposure population (asbestos workers or cigarette smokers), and year of blood draw. The follow-up time for the control group was greater than or equal to that of the case group at the time of cancer diagnosis.²⁵ Serum selenium was analyzed by flameless atomic absorption using the Perkin-Elmer 5000 and univariate statistics were used to describe the distribution. Statistical significance was set at $P < 0.10$. No statistical difference in serum selenium was seen in the control group versus the case group in any quartile or subgroup of the populations.²⁵

This was an excellent study because of the size of the CARET. It allowed Goodman to not only observe selenium levels in current smokers and ex-smokers, but also selenium levels in participants from different areas of the country. It was found that there is no correlation between soil selenium levels and serum selenium levels of the population from the same area.²⁵ This study was not ideal because it only examined smokers and ex-smokers which in general have lower selenium levels than the non-

smoking population²⁶. Goodman does acknowledge that this type of study has no bearing on whether supplementation of selenium would have an effect on the risk of prostate cancer.²⁵

It has been shown that oral supplementation can raise serum selenium levels.⁹ Helzlsouer conducted a study from a population of 10,500 male residents of Washington County, Maryland. The men were encouraged to donate blood for a campaign nicknamed “CLUE II” which was based on the slogan “Give us a clue to cancer and heart disease.”¹⁹ Medical histories, smoking status, height and weight were taken at the time of blood donation. Blood was drawn by trained personnel, and each participant was asked to mail in a nail clipping from the big toe. There was an 86% nail return rate.¹⁹ All males used in this case-study were older than 45 years old. Cases of prostate cancer were identified by linking the list of CLUE II participants with the Washington County Cancer Registry as well as the Maryland Cancer Registry. A self-report of cancer was also sent out to which there was a 69% return rate. 119 of the men that had returned toenail clippings were identified as having primary prostate cancer. For each case two controls were selected based on age, race, and date of participation in the CLUE II program within three weeks.¹⁹ The toenail clippings were sent to the University of Missouri, Columbia, and were assayed for selenium by neutron activation analysis. Blood samples were sent to be assayed for alpha-tocopherol and gamma-tocopherol at the Department of Biomedical Research, Our Lady of Mercy Medical Center, Bronx, New York. The results of this part of the study will not be discussed. Statistical analysis was based on a 95% confidence interval. Helzlsouer found that there was a statistically protective effect of higher levels of selenium for those men in the top four-fifths of the distribution

compared to the men in the bottom one-fifth of the distribution.¹⁹ This study was strong because of the large sample size and the use of outside laboratories allowed for a randomized study.

A longitudinal study was performed on 40,000 Finnish men and women who were participants in the Social Insurance Institution's Mobile Clinic Health Examination Survey in Finland. This survey conducted multi-phasic screening exams in various parts of Finland. A questionnaire was given that asked about occupation, past and present illnesses, medication, pregnancies, and smoking status. Body height and weight were measured at the time of the questionnaire. Incidences of cancer were identified by the Finnish Cancer Registry.¹⁷ Two controls per case were selected by matching sex, municipality, and age. The serum samples were analyzed randomly; serum selenium was determined by a graphite furnace atomic absorption spectrometric method. Statistical analyses were based on the conditional logistic model. The mean serum selenium level of all male cancer cases was statistically significantly lower than that of the male controls. The cancer sites that were included were lung, prostate, stomach, and colorectum.¹⁷ This study is weak because it lumps all cancers in one group and does not focus on prostate cancer alone.

A study performed by Kornitzer in Belgian was very similar to the Finnish study and had the same results.²⁷ A prospective case-control study of a sample of the Belgian male and female population was performed by randomly selecting 201 cases from all cancer deaths during a 10 year mortality follow-up of a large age, and sex stratified sample of the total Belgian population. Cases were matched for age and gender; there were 603 control subjects. Conditional logistic regression was used for both univariate

and multivariate analyses to test the association between baseline characteristics of study participants and cancer mortality.²⁷ The confidence interval was set at 95%. Serum selenium was separated into tertiles based on the controls' distribution. It was found that the highest tertile had a significantly lower incidence of cancer. Cancer sites included lung, mouth, stomach, gall bladder, colorectum, pancreas, prostate, brain, bladder, kidney, and lymphoma, leukemia and Hodgkin's lymphoma.²⁷ Like the Finnish study, this was a very weak study to support the research of prostate cancer and selenium because there were only seven cases of prostate cancer in the entire study.

Li performed a study based on the Physicians' Health Study. The Physicians' Health Study was a randomized, double-blind, placebo-controlled trial of aspirin and beta-carotene among healthy males physicians aged 40-84 years. Li's study concentrated on the reports of prostate cancer that occurred during the 13 years of follow-up.² Participants completed two mailed questionnaires and then were randomly assigned to a study arm. Blood samples were collected at baseline. When a participant reported the diagnosis of prostate, cancer hospital records and pathology reports were obtained and stage was determined based on the Gleason score and to the modified Whitmore-Jewett classification scheme. Cases diagnosed with stage C or D were considered to have advanced cancer. For each case, one control subject was selected from the men who had provided a baseline blood sample, had not had a prostatectomy or reported a diagnosis of prostate cancer and the time of diagnosis of the case.² Controls were matched for age, and smoking status. Selenium concentrations were determined by instrumental neutron activation analysis using the Se-77m isotope at the University of Missouri Research Reactor Center, Columbia, Missouri.² The confidence interval was set at 95%.

Prediagnostic selenium levels were inversely associated with the risk of advanced prostate cancer in the 5th versus the 1st quintile.² There are some limitations to this study; one being that selenium was based only on a single assessment. However, this is the design of all the studies available at this time, and blood reasonably reflects long-term selenium intake. This study was strong because it used prediagnostic selenium levels, so the presence of a prostate tumor could not affect the selenium level.

Lipsky performed a prospective study of 150 men, 70 of which had recently diagnosed, untreated prostate cancer. Toenail samples were collected from each case and control subject. Selenium levels were assayed using inductively coupled plasma dynamic reaction cell mass spectrometry after microwave-assisted closed vessel digestions. The Wilcoxon test was used to statistically compare the two groups.²⁸ No correlation was found between selenium level and prostate cancer cases and the control subjects. Furthermore, there was no association between selenium level and age, BMI, or smoking status.²⁸ There were several limitations to this study. One is that the measurement of selenium was taken at the time of diagnosis. Controls and cases were not matched, and evaluation of height and weight were not measured only asked in the questionnaire.

Nomura conducted a nested–case control study among Japanese-American men to investigate the relation of serum selenium levels to prostate cancer risk.²⁰ The Honolulu Heart Program examined 8006 Japanese-American men between the ages of 45-68 years old. Six years after the initial screening, 6,860 of these men returned and were re-examined and a blood sample was obtained. These men were asked to name their brothers. This led to 2,553 additional participants.²⁰ There were 360 cases of prostate cancer diagnosed. Each case was matched with one control subject. Controls were

matched for age within one year, and whether they were members of the original cohort group, or the 2,534 brothers. Analysis was performed at Cornell University, Ithaca, New York. Selenium was determined by automated electrothermal atomic absorption spectrophotometry using pyrolytically coated graphite tubes on an instrument electrodeless discharge lamp and automatic Zeeman-effect background correction. Binomial probability test was used for statistical analysis. A confidence interval of 95% was used.²⁰ There was an inverse association of advanced prostate cancer and selenium levels. This inverse association was most noticeable in smokers versus non-smokers.²⁰ This study is strong because of the large number of men; however, only using Japanese-American men could skew the results because that group has one of the lowest prostate cancer risks.

Salonen also performed a study on Finnish men and women investigating whether low serum selenium concentrations are associated with an excess risk of cancer. The study included 8,311 men and women aged 31-59 years who had no previous history of cancer. Selenium concentration was determined by the graphite furnace atomic absorption spectrometric method after a simple dilution procedure. For each case, a control was matched for sex, age, smoking history, and serum total cholesterol concentration. Relative risks of cancer were calculated by using the paired-sample odds ratio with a confidence interval set at 95%.²⁹ There was an association between serum selenium and cancer risk. The interesting thing is that these are dissimilar even when the residual differences in tobacco consumption and serum cholesterol and in four other possible confounding factors were controlled.²⁹ This is a strong study because of the

investigations of serum cholesterol and smoking status. However, for the present paper on prostate cancer, it is weak because of the small number of prostate cancer cases at 10.

An investigation of the racial disparity in prostate cancer incidence in the United States was performed by Vogt. It is a population-based case-control study comparing selenium levels in prostate cancer cases and subjects in both African-American and Caucasian individuals. Due to the increased incidence of prostate cancer in African-Americans, this group of individuals has been excluded from this evidence based research project. However, the Caucasian portion of the study will be used. There were 502 cases and 721 control subjects that successfully completed the interview phase. Cases were matched from age, race, and region. Blood was drawn from each participant and was analyzed for total selenium by neutron activation at the Massachusetts Institute of Technology Nuclear Reactor Laboratory. The SAS system was used for all statistical analyses which were 2-tailed with an $\alpha=0.05$.³⁰ There was an inverse association between prostate cancer risk and serum selenium when comparing the highest to lowest quartiles.³⁰ A limitation of this study is that the samples were drawn after the diagnosis of the disease which could have affected the serum selenium levels.

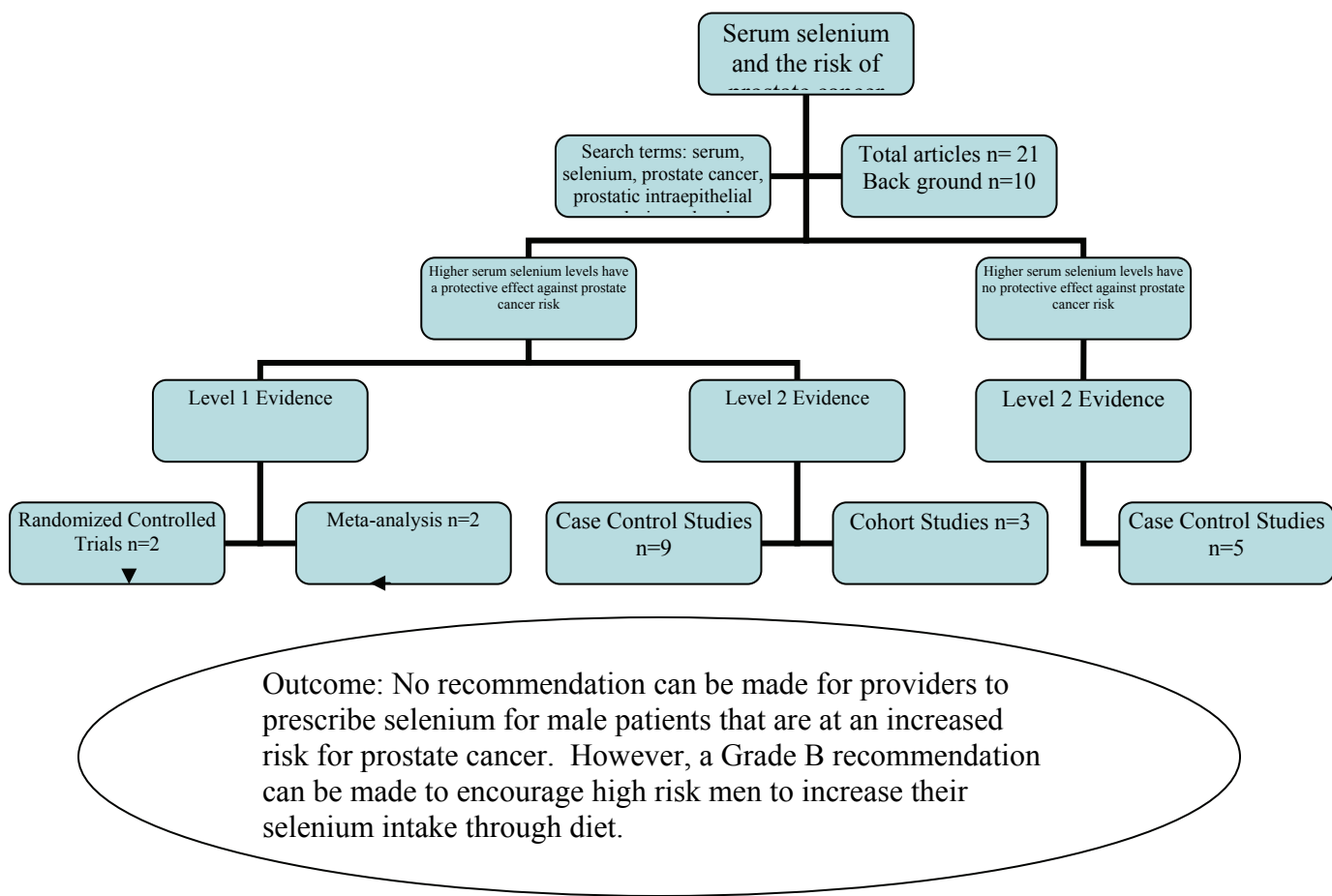
DISCUSSION

Evidence in the Literature:

The results of this systematic review of the literature are consistent with the results of other epidemiologic studies. A majority of the above studies suggest that higher serum selenium levels decrease a man's risk of developing prostate cancer. There were four Level 1 studies that showed a protective effect of selenium and eleven Level 2 studies that shared those same results. The strength of the association was similar for

both cohort studies and case-control studies although, results from the cohort studies are generally more vigorous as exposure is measured in a more objective fashion than case-control studies. The literature also showed a dose-response trend. The men with the lowest amount of serum selenium had the highest incidence of cancer.

Figure 2 Research Flow Diagram



Weaknesses in the Literature:

There needs to be a larger number of randomized controlled trials to decide the exact role of selenium and selenium supplementation in developing prostate cancer. The potential for confounding is present in each of the Level 2 studies. Each of these studies included control for potential confounders such as age, race and geography. However, there were two very important confounders that none of the studies accounted for: the first is family history of prostate cancer. The second was education level. Those men with higher education levels may be more health conscious and use dietary supplementation of antioxidants as a preventative measure for all types of cancer including prostate cancer.

Gaps in the Literature:

Currently there is research under way to determine the amount of supplemental selenium that should be recommended to provide a protective effect against contracting prostate cancer.

CONCLUSION

To date, the Level 1 evidence-based literature supports the protective effect of selenium in the risk of developing prostate cancer. There are also eleven good quality Level 2 studies that support this theory. However, the possibility of confounding factors that may have skewed the result cannot be excluded.

The SELECT trial is an ongoing randomized trial designed to answer whether selenium has a protective role in preventing prostate cancer.⁹ Until the publication of these results, it is not recommended that clinicians prescribe selenium for prostate cancer

prevention. However, those who have an elevated intake in selenium may benefit from its protective effects.

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APPENDICES

APPENDIX 1

Level 1: Randomized controlled clinical trials and high quality meta-analysis					
Author	Title of Article	N	Type of study	Results	Study Quality
Clark	Decreased Incidence of Prostate Cancer with Selenium Supplementation: Results of a Double-Blind Cancer Prevention Trial	479	Double-blind, placebo controlled, randomized trial.	The selenium-treated group had a lower incidence of prostate cancer (63%) and total cancer as well as mortality	1
Duffield-Lillico	Selenium Supplementation, Baseline Plasma Selenium Status and Incidence of Prostate Cancer: an Analysis of the Complete Treatment Period of the Nutritional Prevention of Cancer Trial	457	Randomized Controlled Trial	Participants with low baseline serum selenium levels had higher incidence of prostate cancer	1
Etminan	Intake of Selenium in the Prevention of Prostate Cancer: a Systematic Review and Meta-Analysis	5883	Meta-analysis	Selenium intake may reduce the risk of prostate cancer. "Results confirm the need for large randomized controlled trials"	1
Schrauzer	Cancer Mortality Correlation Studies-IV: Associations with Dietary Intakes and Blood Levels of Certain Trace Elements, Notably Se-Antagonists		Meta-analysis	Inverse correlation between blood Se concentration and the incidence of prostate cancer.	1

Level 2: Nonrandomized clinical trials, low-quality randomized controlled trials, clinical cohort studies, and case-controlled studies with non-partial selection of study participants.					
Author	Article Title	N	Type of Study	Results	Study Quality
Allen	A Case-Control Study of Selenium in Nails and Prostate Cancer Risk in British Men	300	Population-based case-control study	Nail selenium concentration was not significantly related to prostate cancer risk. Men in the highest quartile of nail selenium had a slightly lower risk of advanced prostate cancer compared to those in the lowest quartile.	2
Brandt	Toenail Selenium and the Subsequent Risk of Prostate Cancer: A Prospective Cohort Study	1,211	Prospective Cohort	With a 95% confidence interval the risk of prostate cancer was inversely proportionate to toenail selenium levels. This relationship was seen in all quartile but especially in the lowest. It was also most relevant in cases in which the participants were either current or ex-smokers	2

Author	Title of Article	N	Type of study	Results	Study Quality
Brooks	Plasma Selenium Level Before Diagnosis and the Risk of Prostate Cancer Development	148	Case-control	Higher selenium was associated with a lower risk of developing prostate cancer especially in the lowest quartile of selenium (range=8.2-10.7 ug/dL). However it also showed a lower risk in the other 3 quartiles. Selenium also decreased with age.	2
Coates	Serum Levels of Selenium and Retinol and the Subsequent Risk of Cancer	37	Nested case-control study	These findings suggest that serum levels of selenium have no appreciable effect on the risk of prostate cancer	2
Ghadirian	A Case-Control Study of Toenail Selenium and Cancer of the Breast, Colon, and Prostate	232	Case-control	No association between toenail selenium and prostate cancer	2
Goodman	Predictors of Serum Selenium in Cigarette Smokers and the Lack of Association with Lung and Prostate Cancer Risk	232	Case-control	No detection between toenail selenium and prostate cancer. There was also no association with selenium levels and Gleason score (pathological stage)	2

Author	Title of Article	N	Type of Study	Results	Study Quality
Hartman	The Association Between Baseline Vitamin E, Selenium and Prostate Cancer in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	29,133	Trial-based cohort	There were 317 cases of prostate cancer. These participants had lower intakes of total energy as well as selenium. There was a high correlation between supplemental selenium pretrial and lower incidence of prostate cancer. However, there was also more supplementation of other vitamins and supplements.	2
Helzlsouer	Association Between alpha-Tocopherol, gamma-Tocopherol, Selenium, and Subsequent Prostate Cancer	N=350	Nested case-control	Participants with lower serum selenium levels had an increased risk of prostate cancer especially in the top four-fifths of the distribution when compared to the bottom one-fifth (P=0.002)	2
Knekt	Serum Selenium and Subsequent Risk of Cancer Among Finnish Men and Women	N=3093-(men and women)	Case-control longitudinal study	Developing cancer at several sites (lung, prostate, stomach) was associated with a lower serum selenium level (P<0.001)	2

Author	Type of Article	N	Type of Study	Results	Study Quality
Kornitzer	Serum Selenium and Cancer Mortality: a Nested Case-Control Study within an age- and sex-stratified sample of the Belgian adult population	N=139	Nested Case-control	Low serum selenium has an inverse correlation with prostate cancer and cancer mortality in male subjects.	2
Li	A Prospective Study of Plasma Selenium Levels and Prostate Cancer Risk	N=586	Nested case-control with in the Physicians ' Health Study	There was an inverse association between baseline plasma selenium levels and risk of advanced prostate cancer. This suggests that higher levels of selenium may slow prostate cancer tumor progression.	2
Lipsky	Selenium Levels of Patients with Newly Diagnosed Prostate Cancer Compared with Control Group	N=150	Prospective Case-control	There was no correlation found between toenail selenium levels and prostate cancer. The prostate cancer patients in this study were newly diagnosed, but not yet treated.	2
Nomura	Serum Selenium and Subsequent Risk of Prostate Cancer	N=9345	Nested case-control study	Serum selenium was inversely related to the risk of prostate cancer in this study. The association was strongest for the patients whose tumor extended beyond the prostate gland. The inverse association was mainly in current and past smokers.	2

Author	Title of Article	N	Type of Study	Results	Study Quality
Ozmen	Comparison of the Concentration of Trace Metals (Ni, Zn, Co Cu and Se), Fe, vitamins A, C and E, and lipid peroxidation in patients with prostate cancer	N=20	Case-control retrospective cohort	Serum levels of selenium were significantly lower in patients with prostate cancer when compared with controls (p<0.001)	2
Salonen	Association Between Serum Selenium and the Risk of Cancer	N=27	Case-control	There was an inverse relationship between serum selenium levels and prostate cancer even when the confounding factors of tobacco consumption and serum cholesterol were controlled	2
Vogt	Serum Selenium and Risk of Prostate Cancer in U.S. Blacks and Whites	N=502	Population based, case-control study	Inverse association between serum selenium and risk of prostate cancer. Reduction of risk is apparent with a serum selenium level above 0.135ug/ml. There was a stronger inverse relationship among those men with non-aggressive disease than among the men with aggressive disease. The inverse relationship is very strong for older men and those who were current or past smokers.	2

Author	Title of Article	N	Type of Study	Results	Study Quality
Yoshizawa	Study of Prediagnostic Selenium Level in Toenails and the Risk of Advanced Prostate Cancer	N=51529	Prospective cohort	There was an association between contracting prostate cancer and lower selenium levels, as well as an association between advanced prostate cancer and lower selenium levels.	2

APPENDIX 2

Excluded Articles			
Author	Article Title	Type of Study	Reason for Exclusion
Drasch	Selenium/Cadmium Ratios in Human Prostates	Human supplementation trials	This study looks at a relationship between Cadmium which is a known carcinogen and selenium.
Fleshner	Diet, Androgens, Oxidative Stress and Prostate Cancer Susceptibility	Review Article	Low levels of evidence.
Karunasinghe	DNA Stability and Serum Selenium Levels in a High-Risk Group for Prostate Cancer	Case-control cohort	The study was designed to investigate DNA damage in high risk patients. Not to investigate the effects of selenium on risk or incidence.
Kim	Changes in Serum Proteomic Patterns by Presurgical alpha-Tocopherol and L-Selenomethionine Supplementation in Prostate Cancer	Randomized-Controlled trial	Men in the study already had prostate cancer.
Kranse	Dietary Intervention in Prostate Cancer Patients: PSA Response in a Randomized Double-Blind Placebo-Controlled Study	Double-blind placebo-controlled study	This study does not look at prostate cancer only PSA levels and it does not look at selenium alone, but in combination with several other antioxidants.
Nyman	Selenium and Selenomethionine Levels in Prostate Cancer Patients	Cross-sectional study	Men enrolled in the study already had prostate cancer.
Ringstad	Serum Selenium Concentration Associated with Risk of Cancer	Nested case-control study	This study looks at all types of cancer and not exclusively prostate cancer. It found that patients with fatal cancer had a lower selenium level than the control group.

Author	Title of Article	Type of Study	Results
Vogt	Serum Selenium and Risk of Prostate Cancer in U.S. Blacks and Whites	Population based case-control study	This study was excluded due to its study of African American men because African American men already are at a higher risk for prostate cancer.

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