

AD _____

Award Number: DAMD17-02-1-0101

TITLE: Dietary Phytoestrogens and Prostate Cancer Prevention

PRINCIPAL INVESTIGATOR: Mindy S. Kurzer, Ph.D.

CONTRACTING ORGANIZATION: University of Minnesota
Minneapolis, MN 55455-2070

REPORT DATE: May 2003

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

20030904 074

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503

1. AGENCY USE ONLY (Leave blank)		2. REPORT DATE May 2003	3. REPORT TYPE AND DATES COVERED Annual (15 Apr 2002 - 14 Apr 2003)	
4. TITLE AND SUBTITLE Dietary Phytoestrogens and Prostate Cancer Prevention			5. FUNDING NUMBERS DAMD17-02-1-0101	
6. AUTHOR(S) Mindy S. Kurzer, Ph.D.				
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) University of Minnesota Minneapolis, MN 55455-2070 E-Mail: mkurzer@umn.edu			8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012			10. SPONSORING / MONITORING AGENCY REPORT NUMBER	
11. SUPPLEMENTARY NOTES				
12a. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited			12b. DISTRIBUTION CODE	
13. ABSTRACT (Maximum 200 Words) The main objective of this project is to evaluate the effects of soy phytoestrogen consumption on reproductive hormones and prostate tissue markers of cell proliferation and androgen action in men at high risk of prostate cancer. The hypothesis is that alteration of endogenous hormones is a mechanism by which soy phytoestrogens prevent prostate cancer. A randomized parallel arm study will be performed, in which 90 men at high risk of prostate cancer will be randomized to receive one of three dietary supplements for six months: 1) soy powder containing phytoestrogens; 2) phytoestrogen-free soy powder; or 3) phytoestrogen-free milk powder. Urine and blood will be collected at 0, 3 and 6 months, for evaluation of prostate cancer risk factors, including serum hormones (testosterone, dihydrotestosterone, androstenedione, dehydroepiandrosterone, estradiol, estrone, 3 α , 17 β -androstenediol glucuronide, sex hormone binding globulin) and prostate specific antigen, as well as urinary estrogen and phytoestrogen metabolites. Before and after the intervention, prostate biopsies will be performed to evaluate prostate tissue expression of apoptosis (TUNEL assay, Bax, Bcl-2), proliferation (Ki67, PCNA) and androgen receptor density. At this point, seven subjects have begun the feeding study and biological samples have been collected, processed and stored.				
14. SUBJECT TERMS Prostate cancer, phytoestrogen			15. NUMBER OF PAGES 6	
			16. PRICE CODE	
17. SECURITY CLASSIFICATION OF REPORT Unclassified	18. SECURITY CLASSIFICATION OF THIS PAGE Unclassified	19. SECURITY CLASSIFICATION OF ABSTRACT Unclassified	20. LIMITATION OF ABSTRACT Unlimited	

Table of Contents

Cover.....	1
SF 298.....	2
Table of Contents.....	3
Introduction.....	4
Body.....	5
Key Research Accomplishments.....	6
Reportable Outcomes.....	6
Conclusions.....	6
References.....	none
Appendices.....	none

INTRODUCTION

The low risk of prostate cancer in Asia is thought to be due to dietary factors, including soy consumption. Studies showing an inverse association between prostate cancer risk and urinary excretion of soy phytoestrogens suggest that phytoestrogens contribute to the cancer-preventive effects of soy. One mechanism by which soy phytoestrogens are thought to be cancer-preventive is *via* reduction of endogenous sex hormones known to stimulate prostate cell growth. Despite the interest in soy phytoestrogens for prevention of prostate cancer, there have been no studies in men to evaluate the effects of soy phytoestrogen consumption on sex steroids and prostate tissue biomarkers, and no studies evaluating effects of phytoestrogen metabolism on sex steroids in men.

The main objective of this project is to evaluate the effects of soy phytoestrogen consumption on reproductive hormones and prostate tissue markers of cell proliferation and androgen action in men at high risk of prostate cancer. The underlying hypothesis is that alteration of endogenous hormones is a mechanism by which soy phytoestrogens prevent prostate cancer.

The specific aims of this study are to compare the effects of consumption of phytoestrogen-containing soy protein, phytoestrogen-free soy protein, and milk protein, on risk factors for prostate cancer (endogenous hormones, prostate specific antigen, prostate tissue markers of cell proliferation and hormone action), in men at high risk for prostate cancer. Comparing the three groups will enable us to distinguish the specific effects of soy phytoestrogens from effects caused by other soy components. A randomized parallel arm study will be performed, in which 90 men at high risk of prostate cancer will be randomized to receive one of three dietary supplements for six months: 1) soy powder containing 1 mg phytoestrogens/kg body weight; 2) phytoestrogen-free soy powder; and 3) phytoestrogen-free milk powder. Urine and blood will be collected at 0, 3 and 6 months, for evaluation of serum hormones (testosterone, dihydrotestosterone, androstenedione, dehydroepiandrosterone, estradiol, estrone, 3α , 17β -androstenediol glucuronide, sex hormone binding globulin) and prostate specific antigen, as well as urinary estrogen and phytoestrogen metabolites. Before and after the intervention, prostate biopsies will be performed to evaluate prostate tissue expression of apoptosis (TUNEL assay, Bax, Bcl-2), proliferation (Ki67, PCNA), and androgen receptor density.

Data from *in vitro*, animal and epidemiological studies suggest that androgens and estrogens play a role in prostate carcinogenesis. Soy phytoestrogens have been shown to alter sex steroids in women in a potentially beneficial direction, yet such studies in men have not been reported. Studies of the hormonal effects of soy phytoestrogens in men will contribute to our knowledge of the cancer-preventive mechanisms of soy phytoestrogens, and may lead to dietary recommendations for prevention of prostate cancer.

BODY

According to the original statement of work, the following tasks were to be performed during the first year of this project:

Task 1: Hire and train staff, coordinate with Veteran's Administration and Fairview-University Hospital staff, establish all study protocols (months 0-2)

Task 2: Perform feeding study on cohort #1 (30 men)

- Recruit 30 men at high risk of prostate cancer (cohort #1) and randomize into three intervention groups: phytoestrogen-containing soy protein, phytoestrogen-free soy protein, or milk protein
- Perform feeding study; process and store serum, urine and biopsy slides
- Analyze samples from cohort #1: serum hormones and SHBG by RIA; serum free and total PSA by ELISA; urine estrogen metabolites and phytoestrogens by GC-MS; biopsy slides by immunohistochemistry

Although the grant officially began on April 15, 2002, final approval from the DOD IRB was not received until January 2003. As a result, we were not able to begin the project until February 2003. Between April 2002 and January 2003, the following tasks were accomplished:

- Obtained approval from three institutional review boards: the Minneapolis VA Medical Center, where we are recruiting subjects and collecting biological samples; the University of Minnesota; and the Department of Defense.
- Finalized the study design
 - Chose all protein powders for intervention (offer sugared and sugar-free)
 - Finalized biological endpoints
 - Finalized subject inclusion/exclusion criteria
 - Ordered research materials
- Designed all research forms
 - Subject handbook
 - Subject recording calendars
 - Physician orders
 - Lab and clinic protocols
- Developed collaboration between Veteran's Hospital and University of Minnesota's research lab
 - Arranged regular meetings
 - Disseminated correspondence among investigators and technicians
- Conducted orientation sessions
 - Presented study hypothesis, design, dietary protocol, and collection procedures
 - Coordinated clinical visits for study participants
 - Maintained rapport with subjects
- Developed protocols for sample collection, processing and storage

Since February 2003, ten men have qualified for the study. Nine of these men were oriented and signed consent forms, and seven have begun the feeding study. Two of the men who were oriented withdrew from the study due to difficulties with the protocol (limiting alcohol intake and maintaining body weight). We hope to increase the rate of recruitment by using sugar-free protein powders to accommodate type II diabetics and investigating additional recruitment sites. We anticipate that recruitment will increase as retirees return to Minnesota from having spent the winter in warmer climates.

KEY RESEARCH ACCOMPLISHMENTS

- Received IRB approval from three institutions: The VA Medical Center, the University of Minnesota, and the Dept. of Defense
- Developed successful collaboration with researchers at the VA Medical Center
- Trained staff
- Planned and developed protocols for all aspects of the study
- Successfully recruited first seven subjects and began feeding study
- Developed methods for collecting, processing, and storing biological samples, and performed them successfully with the first group of subjects

REPORTABLE OUTCOMES

None at this time

CONCLUSIONS

The human feeding study has successfully begun and biological samples have been processed and are being stored as stated in the study design. At this point there are no reportable data from which to draw conclusions.

REFERENCES

None

APPENDICES

None