

SOY ISOFLAVONE SUPPLEMENTATION AND BIOCHEMICAL RECURRENCE AFTER CURATIVE TREATMENT FOR LOCALIZED PROSTATE CANCER

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ABSTRACT

Background: Despite an abundance of soy interventions, the effect of soy isoflavones prior to curative treatment for localized prostate cancer on biochemical recurrence has not been evaluated.

Objective: To determine if short-term supplementation with soy isoflavones prior to curative treatment delays or prevents biochemical recurrence in men with localized prostate cancer.

Design: Electronic medical record reviews were conducted in February 2013 to gather follow-up data on men ($n = 86$) previously enrolled in the Role of Isoflavones in Prostate Cancer study. Data collected included demographics, treatment modalities and complications, clinical and pathological staging, Gleason score, body mass index (BMI), comorbidities, prostate-specific antigen (PSA), PSA recurrence, time to recurrence, and death status. Fisher Exact test was used to compare rates of biochemical recurrence. Mann-Whitney U test was used to compare time to recurrence. Time to event analyses were performed using Kaplan-Meier plots with Log-rank test applied to assess statistical significance. Logistic regression analysis using PSA recurrence (yes/no) as a response was used adjusting for age and race.

Results: Sixty-six men were included in the final analysis. $p < 0.05$ was considered statistically significant. Overall rate of recurrence was 9%, with a rate of 9.3% in the soy group and 8.8% in the placebo group ($p = 0.63$). Mean time to recurrence overall was 33 ± 22 months, with 27 ± 26 months in the soy group and 40 ± 20 months in the placebo group ($p = 0.53$). There was no difference in survival times to biochemical recurrence or death between groups.

Conclusion: Short-term supplementation with soy isoflavones prior to curative treatment for localized prostate cancer was not found to significantly affect biochemical recurrence in this study.

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CHAPTER I: INTRODUCTION

Geographic variations in prostate cancer incidence suggest an environmental influence on development of the disease. Epidemiological studies show a lower incidence of prostate cancer in Asian populations compared to Western populations, though prostate cancer incidence and mortality is increasing in Asian countries as diet becomes Westernized (1,2). Likewise, studies show a rising incidence of prostate cancer among Japanese and Chinese men who migrate to the U.S. (2,3), suggesting some nutritional component is responsible for the environmental influence on prostate cancer.

Soy and soy isoflavones are nutritional components that may explain geographic variations in prostate cancer rates. Case-control studies in Japan find soy isoflavone consumption to be associated with a decreased risk of prostate cancer, possibly due to initiation of cancer cell apoptosis and tumor growth inhibition via effects on the cell cycle (4). Soy isoflavone consumption in Asian countries typically ranges from 25-50 mg/day versus a typical intake of 2-3 mg/day in the U.S. (5). Isoflavones may offer benefits for prostate health beyond cancer prevention to include cancer recurrence following treatment. Supplementing men with soy isoflavones concurrently with radiation therapy has led to a decrease in urinary, sexual, and intestinal side effects and may even enhance the effect of radiation therapy, but the long-term effects on biochemical recurrence have not been evaluated (6).

Biochemical recurrence is determined through serial measurements of prostate-specific antigen (PSA) and is managed with androgen deprivation therapy, radical prostatectomy, and/or radiation therapy. Side effects of androgen deprivation therapy include increased fat deposition, osteoporosis, and sexual dysfunction; side effects of prostatectomy

and radiation therapy include incontinence, bowel dysfunction, and erectile dysfunction.

Identifying a method to prevent or delay biochemical recurrence after curative treatment can help circumvent the negative side effects of current treatment options and reduce prostate-specific mortality.

Statement of purpose

The question addressed by this research study was as follows: does soy isoflavone supplementation prior to curative treatment for localized prostate cancer delay biochemical recurrence? To address this question, the study focused on the following aims:

1. To compare the rate of biochemical recurrence (defined as prostate-specific antigen [PSA] ≥ 0.2 ng/mL for radical prostatectomy; PSA nadir + 2 ng/mL for radiation therapy) and the length of time to recurrence in the treatment versus placebo group. I hypothesize that the rate of biochemical recurrence in the treatment group will be lower than that of the placebo group and that the length of time to recurrence will be greater in the treatment group than in the placebo group.
2. To compare rate and time to biochemical recurrence after stratification by treatment type (radical prostatectomy versus radiation therapy) in the treatment and placebo groups. I hypothesize that men supplemented with soy isoflavones who underwent prostatectomy will have lower rates and longer time to recurrence than men in the placebo group and men supplemented with isoflavones who were treated with radiation therapy.

CHAPTER II: REVIEW OF LITERATURE

INTRODUCTION

Prostate cancer is projected to affect 238,590 U.S. men and lead to cancer-specific mortality in approximately 12% of these men in 2013 (7). In a Swedish cohort study of 6,849 men, 80-90% of prostate cancer diagnoses were identified as localized cases (8), and more than 75% of men with localized disease will undergo radical prostatectomy or radiation therapy (9,10). Data show approximately 30% of men managed with a curative intent will experience prostate cancer recurrence (11–13), ranging from 20-40% (14).

This review examines the effect of soy and soy isoflavone interventions on prostate cancer biomarkers with an emphasis on biochemical recurrence.

BACKGROUND

PSA in diagnosis and monitoring

PSA is a serine protease (15) that increases in instances of benign prostatic hyperplasia, inflammation, infection, and prostate cancer (16,17). The advent of PSA as a tool for screening after 1988 (18) led to an increase in prostate cancer diagnoses, 90% of which are localized or regionalized cases that would not have been detected previously (19,20). Though PSA is generally recognized as a poor marker for prostate cancer due to its lack of specificity and false positive and negative results, it is still widely used for screening and detection (21). PSA velocity and PSA doubling time (PSADT) are types of PSA kinetics used for monitoring PSA over time. PSADT in particular may be useful for stratifying the risk of cancer progression in men who have undergone radical prostatectomy (22), while preoperative PSA concentrations may predict biochemical progression and metastases post-prostatectomy (11,17).

Curative treatment options

Treatment options for localized prostate cancer consist of radical approaches, primarily radical prostatectomy and/or radiation therapy (11), conservative approaches such as watchful waiting (WW) or active surveillance (AS), and neoadjuvant or adjuvant hormonal therapy (23). Radical prostatectomy and radiation therapy are administered with a curative intent and will be emphasized in this review.

Radical Prostatectomy

Radical prostatectomy consists of complete removal of the prostate and seminal vesicles using either a retropubic, laparoscopic, or robotic approach and is typically performed on men who have a life expectancy >10 years (23,24). Radical prostatectomy is the gold standard for intermediate- to high-risk prostate cancer due to lower rates of metastases, prostate cancer-specific mortality, and overall death compared to watchful waiting (23,25), but the procedure carries significant risk. Adverse effects of the procedure may include major bleeding, incontinence, bowel dysfunction, and impotence (24), though symptoms may improve gradually throughout the first year post-operation (26). A recent review of evidenced found that robotic-assisted radical prostatectomy led to improved outcomes, faster physical recovery, and improved, though not significantly, biochemical recurrence-free survival (27).

Radiation Therapy

Radiation therapy includes external beam radiation and brachytherapy. External beam radiation is administered directly to the entire prostate (24). Treatment lasts approximately 6-7 weeks, during which the patient may receive neoadjuvant hormonal therapy to shrink the prostate through androgen deprivation (23,24). Radiation therapy is

most often used in men >65 years who have a greater risk of metastases (23). Side effects of external beam radiation include cystitis, hematuria, incontinence, erectile dysfunction, and secondary malignancies (24).

Brachytherapy involves the placement of radioactive seeds directly in the prostate (23,24). The seeds contain iodine or cesium and are placed permanently, typically in amounts of 80-100 seeds (23). Risks of brachytherapy are often less significant than those of radical prostatectomy or external beam radiation, but patients may still experience aggravated urinary tract symptoms, urinary retention, hematuria, erectile dysfunction, and rectal inflammation (24). Brachytherapy is better suited for less aggressive cancers and men whose prostate volume is <50 cm³ (23,24).

Biochemical recurrence of prostate cancer

Definition and criteria

Following curative treatment, PSA is measured every 3 months to monitor for biochemical recurrence and observe trends in PSA over time (11). Definitions of biochemical recurrence differ by treatment. Due to the removal of all prostatic tissue in radical prostatectomy, recurrence is defined as a single post-operation PSA ≥ 0.2 ng/mL (22). Since the prostate remains intact following radiation therapy, PSA will still be present at low concentrations. As a result, biochemical recurrence is defined as PSA nadir + 2 ng/mL (28).

Biochemical recurrence is estimated to occur in approximately one third of men (11–14,29). One study of 5,277 men from the CaPSURE database found greater incidence of recurrence in radiation therapy patients versus radical prostatectomy patients (63% vs. 23%, respectively) (29), which is consistent with previous reports of 15%-33%

for radical prostatectomy (30,31), but slightly higher than data for radiation therapy (37%-48%) (32,33). Higher rates of biochemical recurrence after radiation therapy suggest an incomplete elimination of malignant cells compared to prostatectomy.

Natural history of biochemical recurrence

Time to biochemical recurrence varies by treatment. One study reported mean times of 34 months in prostatectomy patients and 38 months in radiation therapy patients (29). Additional studies reported median time to recurrence of 19-40 months after prostatectomy (13,14,22,34) and 34-41 months after radiation therapy, though some patients also received androgen deprivation therapy after primary treatment (34). A retrospective study focusing on obese men ($\text{BMI} \geq 30 \text{ kg/m}^2$) found a median time to recurrence after radical prostatectomy of only 10 months and a significantly higher PSA nadir, leading to the conclusion that men with a $\text{BMI} \geq 30 \text{ kg/m}^2$ have a greater risk of biochemical recurrence post-prostatectomy (35). These results are supported by previous studies that also find higher rates of recurrence in U.S. men with a $\text{BMI} \geq 30 \text{ kg/m}^2$ (36), though obesity does not appear to predict recurrence in Asian men (37,38). Finally, a review of sixteen studies of men who completed primary treatment found a 21% increase in the risk of biochemical recurrence for each 5 kg/m^2 increase in BMI (39).

Salvage treatment

Patients with biochemical recurrence have several treatment options, consisting of adjuvant androgen deprivation therapy administered immediately or delayed until metastases (14), or salvage therapy, which includes prostatectomy, radiation therapy, or cryotherapy (11). Due to the androgen dependence of most prostate tumors, the diminishing of androgens in the body leads to tumor shrinkage and subsequent

improvement of symptoms (24). In cases of failed androgen deprivation therapy, the cancer is referred to as castration-resistant (24). Side effects of androgen deprivation therapy include hot flashes, osteoporosis, increased fat storage, sexual dysfunction, loss of libido, and increased cardiovascular morbidity (11). Androgen deprivation therapy is the most common treatment for biochemical recurrence (11), with one study reporting 60% and 94% of men receiving treatment after prostatectomy and radiation therapy, respectively (29). A recent study of U.S. veterans found 3%, 11%, and 21% mortality rates from prostate cancer recurrence at 5, 10, and 15 years (40). Since the majority of men will die of causes unrelated to their prostate cancer, it is important that the benefits of salvage treatment outweigh the risks (11). Even better, however, would be the identification of a safe, non-toxic approach to help prevent or delay biochemical recurrence.

Soy and soy isoflavones

One novel approach to delaying or preventing biochemical recurrence is the use of soy and soy isoflavones. Soy foods contain a class of phytochemicals known as phytoestrogens, which exert both estrogenic and anti-estrogenic effects on the body (41,42). Major classes of phytoestrogens include isoflavones, flavones, coumestans, lignans, and stilbenes (41), but the primary phytoestrogens of interest to prostate cancer are isoflavones (43). There are multiple pathways by which soy isoflavones are thought to affect prostate tumors in addition to their hormonal effects, mainly through induction of apoptosis and cell differentiation, inhibition of cell proliferation and angiogenesis, and exertion of antioxidant properties (44–46). The interest in soy and prostate cancer started with epidemiological studies that found lower incidence of prostate cancer in Asian men,

who are known to consume more soy than men in the U.S. (2) and have plasma and serum phytoestrogen concentrations 10 times greater than amounts found in the Western populace (47–49). Furthermore, rates of biochemical recurrence may be lower in Asian countries than in Western countries, with one study reporting 23.6% of men in Japan experiencing recurrence after external beam radiation (50), which is slightly lower than the 33% seen in the U.S. for all treatments.

Soy isoflavones exist in a combination of two forms: the unconjugated aglycone form, consisting of genistein, daidzein, and glycitein, or the sugar-conjugated glucosidic form, which includes genistin, daidzin, and glycitin (42,49). Glucoside conjugates are not bioavailable until the glucoside is digested, thereby releasing the aglycone form for absorption (51). Isoflavone content of soybeans varies depending on the growing environment, but each soybean contains approximately 1.2-3.3 mg isoflavones per gram of dry weight (49). In individuals with a daidzein-metabolizing phenotype, gut bacteria further metabolize daidzein to equol, a compound that is suspected to be partially responsible for the health benefits of soy (52). Studies show 30%-50% of Western populations produce equol (53,54), compared to up to 80% in Japan, China, and Korea (55).

SOY ISOFLAVONES AND PROSTATE CANCER

Isoflavones in prevention and progression

Isoflavones are commonly studied in relation to prostate cancer prevention and progression, but previous interventions in cancer patients have not evaluated long-term follow-up or recurrence rates. The majority of studies found no significant decreases in PSA (56–59), though one study found a significant decrease in biopsy-detected cancer

(59). When compared to men following their usual diets, a significant decrease in PSA was seen in men who underwent comprehensive lifestyle changes consisting of a low-fat vegan diet with soy (1 serving/day of tofu plus 58 g/day of soy protein powder beverage), vitamin E, selenium, fish oil, and vitamin C supplementation accompanied by stress reduction, exercise, and weekly support groups (60), though the effects cannot be attributed to soy alone. Finally, in a study of men awaiting prostatectomy, subjects consuming soy grits (117 mg mixed isoflavones/day) had a significant percent change in total PSA compared to a control group and had a significant change in androgen index compared to men consuming soy grits plus linseed (61). These data do not strongly support the use of soy or soy isoflavones alone in prostate cancer prevention.

Isoflavones in biochemical recurrence

The few treatment options for men with rising PSA following curative treatment come with negative side effects that decrease quality of life, thus highlighting the need to find alternative ways of delaying or preventing biochemical recurrence. Previous studies have not explored the effect of isoflavone supplementation before curative treatment on rate of recurrence after treatment. Studies have used soymilk (62,63), soy beverage or soy protein isolate (64–67), or capsules/tablets in order to isolate the effects of soy isoflavones (68–70). Isoflavone content ranges from 65-900 mg/day, though amounts are omitted from two studies (63,69). Durations of interventions range from 4 weeks (66) to 12 months (62), and primary endpoints include a variety of PSA analyses, including absolute, rise, slope, percent or absolute change, PSADT, and velocity, as well as hormonal markers and overall response to soy.

Isoflavone capsules

Early studies used isoflavone capsules providing 200-900 mg/day of isoflavones for approximately 6 months. Studies reported PSA stabilization in both prostatectomy and hormone therapy patients with rising PSA (64,68), as well as a significant decrease in the rate of PSA rise in the hormone therapy patients (68). However, 35 of 52 men (67%) with rising PSA continued to biochemical progression following the 900 mg/day intervention (64). These studies suggest the ability of isoflavones to stabilize PSA and reduce rate of rise (68), but not to prevent or delay recurrence (64). Comparing these results also suggests that a higher dose does not necessarily confer greater treatment effects. Finally, both studies waited until PSA was already rising post-treatment to provide isoflavones, rather than supplementing prior to treatment as proposed here.

Soy combined with other bioactives

Several studies used supplements combined with multiple bioactives. One study used a supplement containing green tea, 100 mg isoflavones, 100 mg other phytoestrogens, and carotenoids, as well as margarine fortified with vitamin E, phytosterols, and selenium. Results showed a nonsignificant increase in PSADT after treatment, but significant decreases in free PSA, testosterone, dihydrotestosterone, and free androgen index (65). Other studies combined soy and lycopene with hopes of enhancing the effects of both. Ten weeks of supplementation with capsules containing soy isoflavones, lycopene, silymarin, and antioxidants resulted in a significant decrease in PSA slope and ²log PSA slope (69). Another study found a significant reduction in rate of PSA rise in hormone-refractory and hormone-sensitive patients after 6 months of lycopene or lycopene + isoflavone supplements; however, hormone-refractory patients in

the lycopene-only group had a significantly greater decrease in rate of PSA rise, suggesting a benefit from lycopene rather than soy (70). A similar crossover study using either lycopene or soy protein isolate with 80 mg/day of isoflavones observed PSA reduction in 34% of men at the end of 8 weeks (66). Results from these studies are confounded by the use of multiple bioactives, though a synergistic effect is probable. As in studies using isoflavone capsules, these studies waited to supplement men until PSA was already rising after treatment.

Soy foods

The most recent studies used soy beverages or commercially available soy products to provide isoflavones. Soymilk or soy beverages providing 65-141 mg/day of isoflavones (62,67) in men with biochemical recurrence have led to reductions in PSA and significant decreases in PSA slope in up to 30% of subjects. Investigators also observed a significantly lower yearly PSA increase of 20% compared to the expected value of 56% (62). In one study, men had a median PSADT that was 32% longer post-intervention, though 17% of patients had a >50% decrease in PSADT (67). Overall in this study, a decline in PSA or increase in PSADT was seen in 41% of patients. A retrospective study of 10 men consuming commercially available soy foods who had androgen deprivation-naïve or castration-resistant prostate cancer reported 50% of patients with progression, 40% of men with PSA reductions and negative PSA kinetics or PSA stabilization, and 10% with a decrease in PSA velocity and PSADT (63). The median response lasted 24 months before one subject experienced progression, which suggests response to soy can be lost. Based on these results, providing isoflavones in soy

foods does not offer any obvious benefit over capsules. Again, these studies did not supplement men before treatment.

Limitations

None of the currently published studies evaluate the effect of soy consumption before treatment on biochemical recurrence. The wide variation in supplements used in intervention studies creates a challenge when comparing results. Routes of isoflavone delivery include soymilk, soy beverages, soy protein powder, capsules/tablets, and whole foods. Supplements also vary in isoflavone content, composition, and structure, with differing percentages of genistein, daidzein, and glycitein, as well as differences in predominant isoflavone structure (aglycone versus glucoside). Finally, several studies analyze supplements containing several bioactives, making it difficult to determine which component is responsible for treatment effects.

Nearly one third of men will experience biochemical recurrence after curative treatment for prostate cancer. Due to the high probability of developing negative side effects from salvage therapies, it is prudent to find safe, non-toxic methods of preventing or treating biochemical recurrence. Previous soy isoflavone interventions show both neutral and beneficial effects, though results are limited by small sample sizes and the use of multiple bioactives, and comparison of results is complicated by methodological differences between studies. Furthermore, previous studies have only implemented soy after biochemical recurrence has occurred, rather than prior to curative treatment.

CHAPTER III: MATERIALS AND METHODS

Study overview

Data were extended from the Role of Isoflavones in Prostate Cancer study (71) a four-week, double-blind, randomized, placebo-controlled trial conducted using 86 men with histologically confirmed prostate cancer scheduled to undergo prostatectomy. Men in the parent study were randomized to receive commercially available soy isoflavone capsules (51 mg/d aglycone units) or identical placebo capsules for up to one month prior to curative treatment.

The present study built upon this clinical trial by gathering follow-up data to compare the natural history of prostate cancer in the soy isoflavone group to the placebo group. Data were abstracted from electronic medical records (EMR) and stored using a secure online database management program. The primary aim was to compare rate and time to biochemical recurrence between soy and placebo arms, defined as PSA ≥ 0.2 ng/mL for radical prostatectomy and PSA nadir + 2 ng/mL for radiation therapy. A secondary aim compared rate and time to biochemical recurrence in subjects who underwent prostatectomy (n = 46) versus radiation therapy (including interstitial brachytherapy and external beam radiation) (n = 20) in the treatment and placebo groups.

Data collection

Study participants were men with localized prostate cancer (n = 86) recruited from the University of Kansas Hospital (KUH) Urology Clinic and the Kansas City Veterans Affairs Medical Center (VAMC) as part of the Role of Isoflavones in Prostate Cancer study (71). Men were included if they had histologically confirmed prostate cancer, were willing to avoid soy for 90 days before the study and were willing to avoid soy and other dietary or

herbal supplements during the study. Participants were excluded from analysis if they were lost to follow-up, defined as having no PSA value documented after curative treatment, if they did not receive curative treatment, or if PSA value failed to reach zero after radical prostatectomy. Participants provided informed consent for future research as part of IRB-approved protocols from each institution. Patients were excluded from the parent study if they met any of the following criteria: 1) were receiving concurrent chemotherapy, radiation, or neoadjuvant hormone therapy, 2) consumed soy foods within 90 days of enrollment, or 3) had a known history of soy allergy or intolerance. Soy intake was assessed at baseline using a validated soy foods questionnaire (72). Urine was collected at 2 weeks for analysis of isoflavones and their metabolites (O-desmethylangolensin [ODMA], daidzein, dihydrodaidzein [DHD], genistein, glycitein, and equol) and creatinine. Compliance was based on creatinine-adjusted urinary daidzein concentration due to daidzein being the primary isoflavone in the supplements. Participants in the placebo group were considered noncompliant if creatinine-adjusted daidzein was ≥ 10 nM/mL, indicating the participant was consuming soy.

Data were abstracted from EMR on the VAMC and KUMC campuses following Protocol Review and Monitoring Committee (PRMC) and Human Subjects Committee (HSC) approval. Information abstracted from the EMR was recorded and stored on KUMC's HIPAA-certified servers using Research Electronic Data Capture (REDCap), an online tool for secure database management (73). Access to the EMR was granted only to individuals directly involved with the study following the completion of KUMC and VAMC human subjects training and HIPAA certification.

Data were abstracted and verified by two researchers over a 3-week period in February 2013. Data obtained from EMR included demographic information, treatment modalities and complications, clinical and pathological staging, Gleason score, body mass index (BMI), comorbidities, PSA, PSA recurrence, time to recurrence, and death status (**Appendix A**). Age was calculated by taking the difference between date of birth and date of curative treatment. Time to recurrence was calculated using date of curative treatment and date of documented biochemical recurrence.

Statistical analysis

The data were summarized with descriptive statistics on the baseline characteristics of the subjects on study and presented as mean \pm standard deviation (**Table 1**). The data were then examined for normality using histograms and box plots (**Appendix B**). Due to the small proportion of recurrence and lack of normality, non-parametric methods were used to study the association between the biochemical recurrences with the soy intake status. Fisher Exact test was used to compare the rate of biochemical recurrences in the soy versus placebo groups and prostatectomy versus radiation therapy groups. Fisher Exact test is appropriate when the sample size is low, which calculates the exact probabilities of the occurrences of the observed frequencies, given the assumptions of independence and the size of the marginal frequencies (row and column totals of 2×2 contingency table). Mann-Whitney U test was used to compare the time to recurrence in the soy versus placebo group and also prostatectomy versus radiation therapy groups. Time to recurrence of prostate cancer was analyzed using Kaplan-Meier analysis method. The survival curves over time for the two groups were plotted and log-rank tests were used to assess the significance. Similarly, survival times

in the two groups were analyzed using Kaplan-Meier plots followed by log-rank test. Finally, logistic regression analysis using PSA recurrences (yes/no) as response was carried out adjusting for possible confounding variables age and race. SPSS® for Macintosh, Version 20, (SPSS Inc. Chicago) was used for all statistical analyses (74).

CHAPTER IV: RESULTS

Eight patients were lost to follow-up, 3 patients remained under active surveillance or watchful waiting, 8 patients had a post-prostatectomy PSA that failed to reach zero, and 1 patient was noncompliant, leaving 66 patients for the final analysis (**Appendix C**). Baseline characteristics for the 66 participants are displayed in **Table 1**. Data on equol production were known for 35 men in the soy group out of the original 86 men. Out of these 35 patients, 10 (29%) were equol producers. In the 66 men included in the analysis, 5 out of 25 (20%) were equol producers.

Table 1. Baseline Characteristics		
Characteristic	Soy	Placebo
Participants, no.	32	34
Mean age, y	64 ± 7	63 ± 7
Mean baseline PSA, ng/mL	8.76 ± 4.66	8.45 ± 4.74
Gleason score, no.	6.8 ± 0.8	6.6 ± 0.7
Body weight, lb	202 ± 37	208 ± 37
Height, in.	70.2 ± 3	69.3 ± 3
BMI, kg/m ²	29 ± 5	30.5 ± 5

Date represent Mean ± Standard Deviation. Means were compared using Mann-Whitney U test. No significant differences were found between soy and placebo groups. $p < 0.05$ was considered statistically significant. PSA = prostate-specific antigen; BMI = body mass index.

Rate of recurrence

Biochemical recurrence occurred in 6 patients (9%), including 3 in the soy group (9.3%) and 3 in the placebo group (8.8%). Characteristics of the six patients with biochemical recurrence are outlined in Table 2 (**Appendix D**). Rate of recurrence was not significantly different between soy and placebo groups ($p = 0.63$), nor did it differ between curative treatment types (RP: $n = 5$ [11%], RT: $n = 1$ [5%]) ($p = 0.41$). Finally, logistic regression analysis did not find an association between biochemical recurrence and soy/placebo or curative treatment types.

Time to recurrence

Mean time to recurrence overall was 33 ± 22 months. Time to recurrence in the soy group was 27 ± 26 months, and in the placebo group was 40 ± 20 months ($p = 0.53$). Mean time to recurrence in men that underwent radical prostatectomy was 29 ± 22 months, compared to 54 months in the one patient with recurrence that received radiation therapy ($p = 0.36$). Median time to recurrence overall was 34 months, with a median of 20 months in the soy group, 48 months in the placebo group, and 20 months in the prostatectomy group. Individual times to recurrence are displayed in **Appendix D**.

Mean follow-up time, defined as time to last PSA (SD), was 50 ± 19 months. Biochemical recurrence was reported in 3 patients in each group. No significant differences were found between times to recurrence in the soy versus placebo groups (Log-rank $p = 0.93$) or curative treatment groups (Log-rank $p = 0.29$) (**Appendix E**).

Three patients in the soy group (9.3%) and 2 patients in the placebo group (5.9%) were deceased at the time chart reviews were completed. There was no significant difference in survival time between soy and placebo groups (Log-rank $p = 0.62$) or curative treatment groups (Log-rank $p = 0.47$) (**Appendix E**).

CHAPTER V: DISCUSSION

Implications

Results of this study showed a 9% rate of biochemical recurrence overall, 9.3% in the soy group, and 8.8% in the placebo group. Previous data has found the natural history of prostate cancer leads to recurrence in 20-40% of men (14). Since the number of people who recurred was equal in the soy and placebo groups, it is unlikely this low rate of recurrence was due to soy isoflavone supplementation prior to curative treatment. Possible explanations for this low rate of recurrence include improved surgical techniques and short follow-up duration (range 4-7 years) that did not capture all those who may recur.

Mean time to recurrence in this study was 33 ± 22 months overall, 27 ± 26 months in the soy group, 40 ± 20 months in the placebo group, and 29 ± 22 months for prostatectomy patients. When comparing only the five patients who had radical prostatectomy, the mean time to recurrence is slightly less than previous reports of 34 months (29). The only patient with recurrence who underwent radiation therapy recurred at 54 months, which is greater than previous data that shows mean time to recurrence after radiation of 38 months (29).

The overall median time to recurrence of 34 months, as well as a median of 20 months in the prostatectomy group, in the present study are consistent with previous reports of 19-41 months for all treatments and 19-40 for prostatectomy alone (13,14,22,34). Time to recurrence in the placebo group could be skewed by the patient who underwent radiation therapy, as longer time to recurrence is usually seen after

radiation due to the definition of recurrence, which requires an increase of 2 ng/mL from PSA nadir.

Limitations

Despite the strong design of the parent study, the present study had several limitations. First, duration of isoflavone intervention was short, ranging from 2-4 weeks. The soy isoflavone supplement used contained primarily daidzein instead of genistein, which makes it difficult to compare to other studies. Abstracting data from EMR introduces further limitations due to unavailable, missing, or incomplete information. Diet and physical activity were not monitored after curative treatment, nor is it known whether participants continued taking soy isoflavones after the study concluded. Based on previous data, the expected rate of recurrence was 20-40%, or 17-34 of the original 86 participants. After exclusions, and with the relatively small recurrence rate in the current study, the study was not sufficiently powered to detect significance. Finally, mean follow-up time was 50 months, or approximately 4 years. Due to the greater time to recurrence in radiation versus prostatectomy patients in previous literature, the length of time to follow-up may not have been adequate to capture recurrence in this population.

Future Research

Though this study failed to find significant results, it offers insight into how future studies can be improved. Learning from the limitations of this study, future studies should recruit larger sample sizes so the expected rate of recurrence includes enough participants to detect significance. The duration of isoflavone intervention should be varied to determine if longer interventions affect recurrence. Additionally, using a soy supplement with a greater percentage of genistein, the primary soy isoflavone used in

previous studies, may yield different results. Most importantly, this study can be analyzed with ancillary studies examining the effect of soy isoflavones on gene transcription to link clinical outcomes of the present to study to genetic markers. Comparing gene transcription in normal versus tumor tissue in soy and placebo groups will provide insight into individual responses to soy isoflavone supplementation and may help direct future research.

Conclusion

This is the first study to examine the effect of soy isoflavones prior to curative treatment on the natural history of prostate cancer. Short-term isoflavone supplementation prior to curative treatment was not found to prevent or delay biochemical recurrence in 66 men with localized prostate cancer, though time to recurrence in one patient from the placebo group who had radiation therapy was longer than times reported in previous literature, and no radiation patients in the soy group recurred at the time of data collection. Lack of significant results are likely due to the unusually low rate of recurrence in this study. Future research should link the clinical outcomes of this study to gene transcription to determine if soy isoflavones regulate cell signaling in prostate tissues.

CHAPTER VI: REFERENCES

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Appendix A. REDCap Data Collection Form

Demographics

Patient Demographics

Study ID	_____
Medical Record #	_____
First Name	_____
Last Name	_____
Date of Enrollment	_____ (Date of Initiation of Soy Treatment)
Date of Curative Treatment	_____ (YYYY-MM-DD)
Date of Birth	_____ (YYYY-MM-DD)
Race	<input type="checkbox"/> White <input type="checkbox"/> Black <input type="checkbox"/> Asian <input type="checkbox"/> Other
Ethnicity	<input type="checkbox"/> Hispanic or Latino <input type="checkbox"/> Non-hispanic or latino
Age	_____
Soy vs. Placebo	<input type="checkbox"/> Soy <input type="checkbox"/> Placebo (Soy vs. placebo)
Lost to follow up	<input type="checkbox"/> Yes <input type="checkbox"/> No

Pre Op

Pre-Operative Data

PSA at Presentation _____

Salvage Case After PreOp Radiation

- Yes
- No
- DNA

Pre-Op Hormones:

- Yes
- No
- unknown
(Examples: Lupron(leuprolide), Zoladex (goserelin), Trelstar (triptorelin) Vantas (histrelin) or Frimagon (degarelix))

Pre-Op 5-ARI use : Avodart/Proscar

- Yes
- No
- DNA
(Finasteride or Dutasteride)

Pre-Op Antibiotics

- Yes
- No
(Antibiotic use within 6 weeks of treatment)

Pre-Op Antibiotics

(Comments about type, time, duration, etc.)

T Clinical Stage 2010

- TX
- TO
- T1A
- T1B
- T1C
- T2A
- T2B
- T2C
- T3A
- T3B
- T4
- DNA

N Clinical Stage 2010

- NX
- N0
- N1
- DNA

M Clinical Stage 2010

- MX
- M0
- M1
- M1A
- M1B
- M1C
- DNA

Gleasons Primary @ BX

- 1
- 2
- 3
- 4
- 5
- DNA

Gleasons Secondary @ BX

- 1
- 2
- 3
- 4
- 5
- DNA

Gleasons Sum @ BX

D'Amico Risk Classification

- Very Low Risk
 - Low Risk
 - Intermediate Risk
 - High Risk
- (Low - GS 6 or less, PSA 10 or less, T2a or less
Intermediate: G1 7, PSA 10-20, T2a-T2b, High
Risk: G1 8-10, PSA >20, T2c>)

Other Text

Pre-Op Comments

Height (inches)

Screening weight (lbs)

Screening BMI

(BMI at initial evaluation)

Pre-Treatment Weight (lbs)

Pre-Treatment BMI

(BMI at time of curative treatment)

Comorbidities at time of surgery

- Hypertension
- Dyslipidemia
- Diabetes I/II
- Cardiovascular Disease
- Peripheral Vascular Disease
- Cerebrovascular Disease
- Congestive Heart Failure
- Pulmonary disease (asthma, COPD, reactive airway disease, obstructive sleep apnea)
- Other
- None

Other Comorbidities

(If not listed above)

Charlson Comorbidity Index

Comorbidity (Choose all that are present)brbrAssigned weights for each condition the patient has ()

- Myocardial infarct (+1)
- Congestive heart failure (+1)
- Peripheral vascular disease (+1)
- Cerebrovascular disease (except hemiplegia) (+1)
- Dementia (+1)
- Chronic pulmonary disease (+1)
- Connective tissue disease (+1)
- Ulcer disease (+1)
- Mild liver disease (+1)
- Diabetes (without complications) (+1)
- Diabetes with end organ damage (+2)
- Hemiplegia (+2)
- Moderate or severe renal disease (+2)
- Solid tumor (non metastatic) (+2)
- Leukemia (+2)
- Lymphoma, Multiple myeloma (+2)
- Moderate or severe liver disease (+3)
- Metastatic solid tumor (+6)
- AIDS (+6)

Age

- 50 - 59 (+1)
- 60 - 69 (+2)
- 70 - 79 (+3)
- 80 - 89 (+4)
- 90 - 99 (+5)

Comments:

Total points:

Treatment Modality

Treatment

- Radical Prostatectomy
- External Beam Radiation
- Interstitial Brachytherapy
- Active Surveillance/Watchful Waiting
- Other
(If Radical Prostatectomy Selected Proceed to
Surgical Data Collection Form)

Other Treatment

Surgical Approach

- Robotic/Laparoscopic
- Retropubic
- Perineal
- Lap converted to open
- unknown

Concurrent Androgen Deprivation Therapy?

- Yes
- No

Length of hormonal therapy (months)

- 3-6
- 7-12
- 13-24
- >24

Date of ADT

(Date of first dose ADT)

Last known dose of ADT

(Last dose ADT administered)

Date of Radiation Therapy Start

Date Radiation Therapy Complete

PSA nadir

(Lowest PSA after treatment)

Date of PSA Nadir

Post Op

Minor Complications

Minor Complications

- Yes
- No
- DNA

Check all that apply

- DVT
- Urine Leak
- Pneumonia
- Ileus
- Other

Other Minor Complication(s):

Major Complications

Major Complications

- Yes
- No
- DNA

Check all that apply

- MI
- PE
- CVA
- Return to OR
- Death
- Other

Other Major Complication(s):

Post-Op Dietary Supplements

(List any dietary supplements taken post-op)

Post-Op Comments

Path

Pathology - Please note only those whom had surgery will have information for below.

Gleasons Primary PostOp 1
 2
 3
 4
 5
 DNA

Gleasons Secondary PostOp 1
 2
 3
 4
 5
 DNA

Gleason Tertiary PostOp 1
 2
 3
 4
 5
 DNA

Gleasons Sum PostOp _____

Margin Status negative
 positive
 DNA

Pathological Tumor Stage 2010 TX
 T0
 T2A
 T2B
 T2C
 T3A
 T3B
 T4
 DNA

AJCC Stage 2010 I
 IIA
 IIB
 III
 IV
 DNA

Seminal vesicle invasion Yes
 No
 DNA

Nodal Involvement

Pathological Nodal Stage 2010

- Nx
- N0
- N1
- N2
- N3

If positive lymph nodes, assess whether patient started on hormonal therapy.

If gleason score >7, positive margins, OR T3 disease or greater, assess whether patient given adjuvant radiation.

Distant Metastasis

- PCS
- pM0
- pM1
- pM1A
- pM1B
- pM1C

Bladder Neck Invasion

- Microscopic
- Gross
- None
- DNA

Extracapsular extension

- Yes
- No
- DNA

Path Comments

Follow Up

Look at PSA labs and evaluate profile. PSA after surgery should be

Last Follow up	_____
	(Date of last encounter)
PSA at last follow up	_____
Date of Last PSA	_____
	(if other than date of last follow up)
Biochemical Recurrence	<input type="checkbox"/> Yes <input type="checkbox"/> No (For radiation, biochemical recurrence is nadir +2. For surgery PSA >0.2)
Date of documented biochemical recurrence	_____
Time to Recurrence (months)	_____
Time to Last PSA (months)	_____
	(Months from curative treatment to last PSA)
Adjuvant Treatment Administered?	<input type="checkbox"/> Yes <input type="checkbox"/> No (This would be any treatment given after curative treatment PRIOR to PSA recurrence)
Adjuvant Treatment Type	<input type="checkbox"/> Radiation <input type="checkbox"/> Androgen Deprivation Therapy <input type="checkbox"/> Other
Date of Start of Adjuvant Treatment	_____
Salvage Treatment	<input type="checkbox"/> Yes <input type="checkbox"/> No (Any treatment (hormones, surgery, radiation) given AFTER PSA recurrence)
Salvage Treatment(s)	<input type="checkbox"/> Radiation <input type="checkbox"/> Surgery <input type="checkbox"/> Hormonal ablation <input type="checkbox"/> other
Other Comorbidities	_____
	(If not listed above)
Alive?	<input type="checkbox"/> Yes <input type="checkbox"/> No
Did patient die from prostate cancer?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown
Cause of death	_____
	(if not from prostate cancer)
Date of Death	_____
Age at Death	_____

Time to Death (months)

(Time from curative treatment to death)

Disease status at death

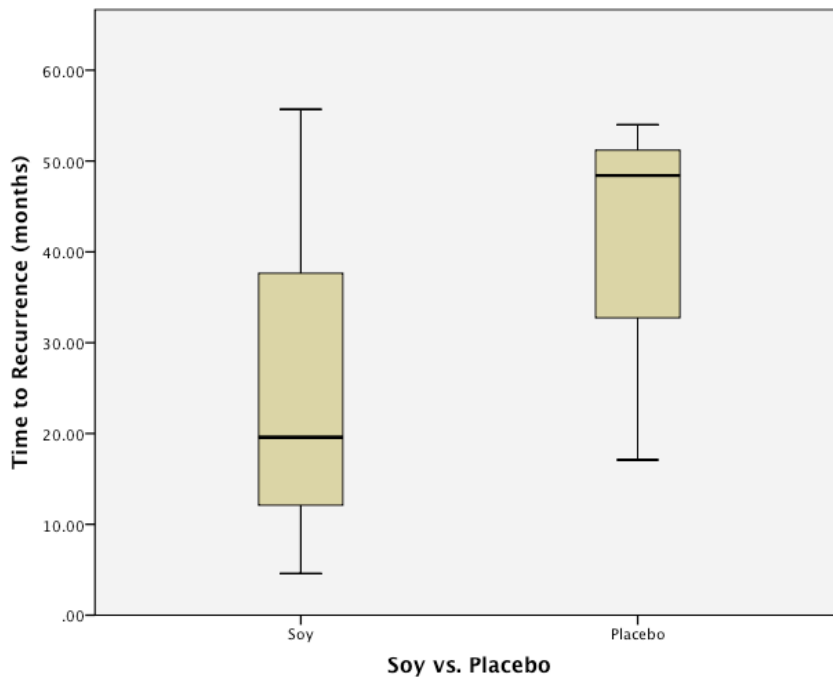
- No evidence of biochemical recurrence
- No evidence of metastatic disease
- Biochemical recurrence but no measurable disease
- Biochemical recurrence and measurable disease
- other

Urinary Isoflavone Concentration

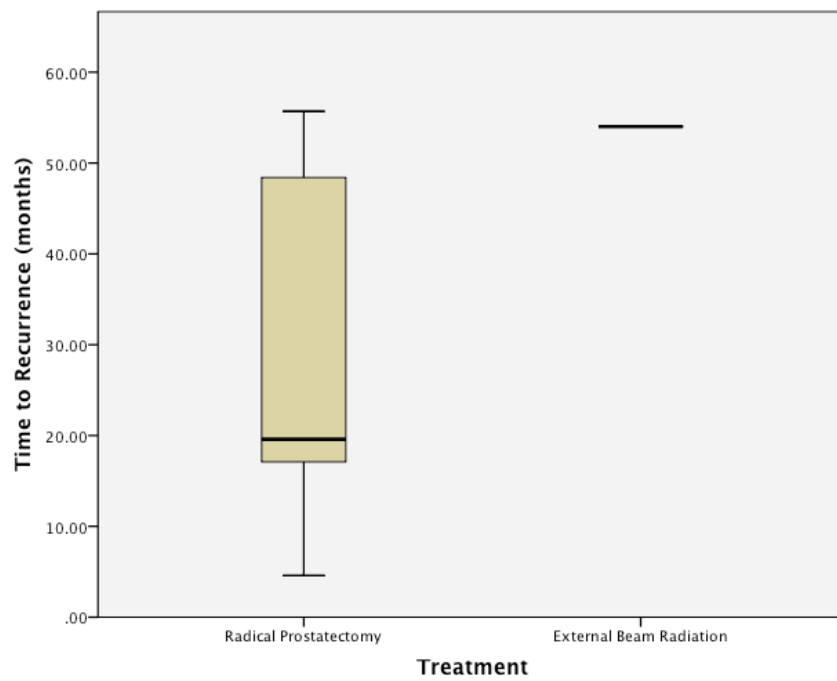
Urinary Creatinine Concentration	_____
ODMA	_____
ODMA Creatinine Adjusted	_____
Equol Producer	<input type="checkbox"/> Yes <input type="checkbox"/> No
Equol Concentration	_____
Equol Creatinine Adjusted	_____
Log 10 Equol	_____
DHD	_____
DHD Creatinine Adjusted	_____
Daidzein	_____
Daidzein Creatinine Adjusted	_____
Genistein	_____
Genistein Creatinine Adjusted	_____
Glycitein	_____
Glycitein Creatinine Adjusted	_____
Compliant to intervention	<input type="checkbox"/> Yes <input type="checkbox"/> No
Compliance Comments	_____

Appendix B. Boxplots

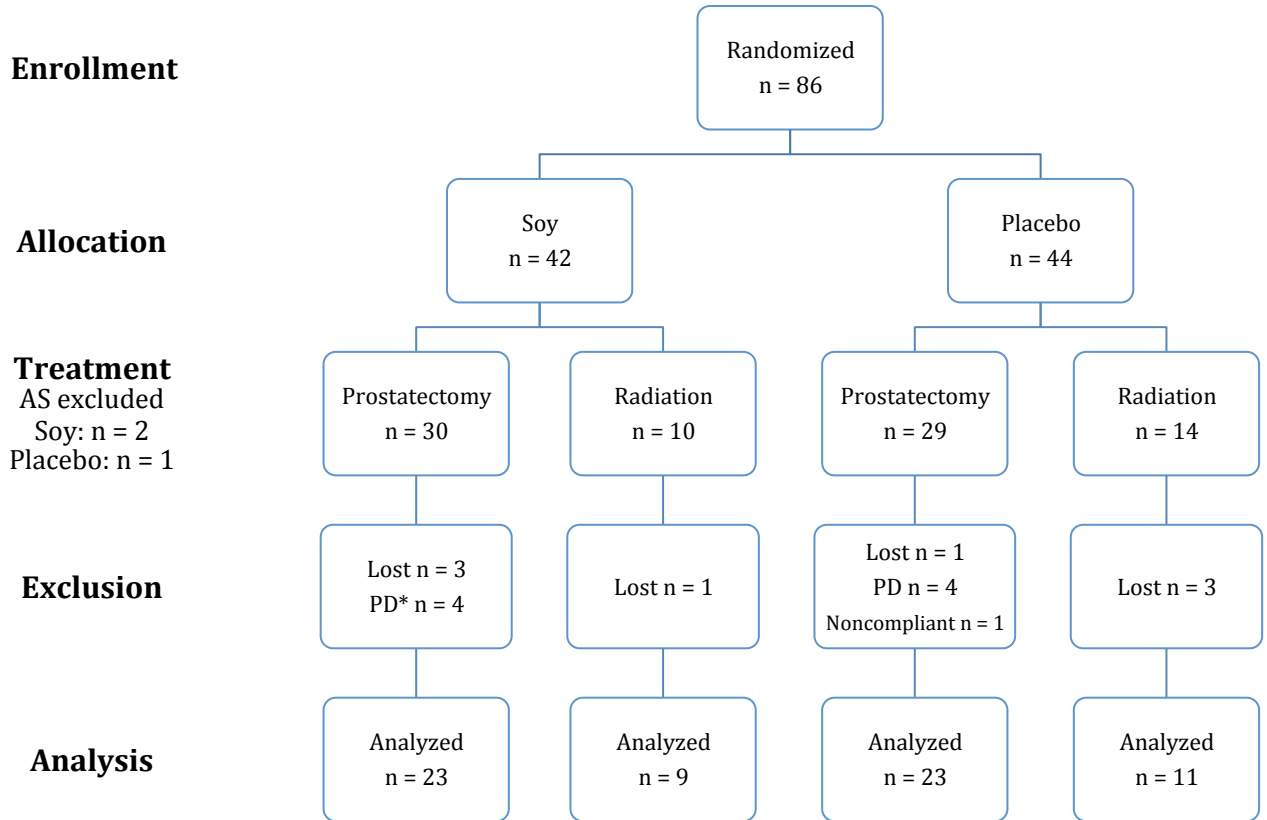
Time to Recurrence in Soy vs. Placebo Groups



Time to Recurrence in Prostatectomy vs. Radiation



Appendix C: CONSORT Diagram



Appendix D. Baseline Characteristics of Patients with Biochemical Recurrence

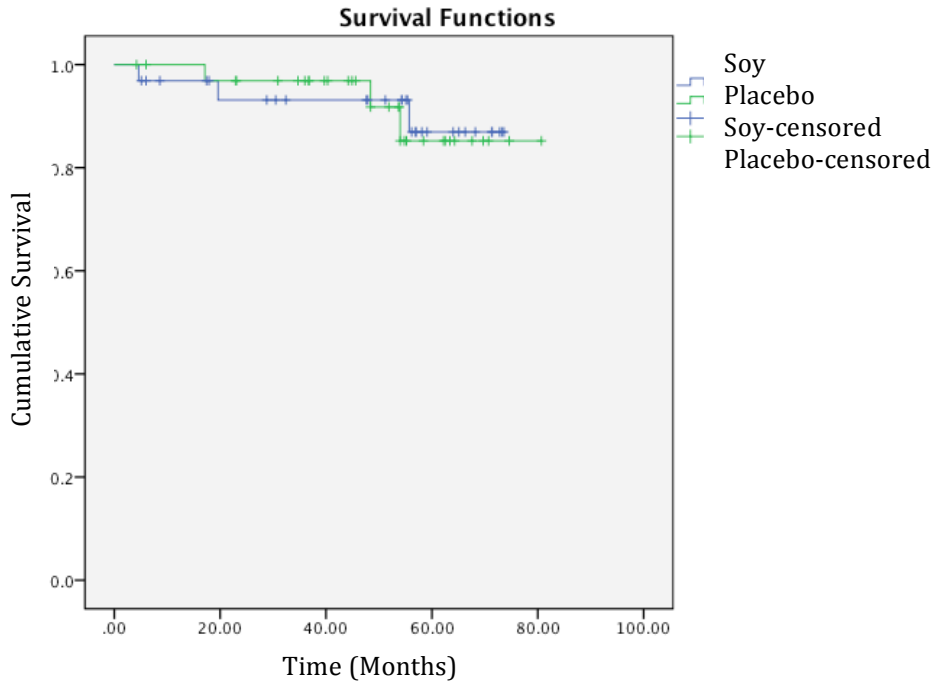
Table 2. Baseline Characteristics of Patients with Biochemical Recurrence

Study ID	Soy vs. Placebo	Treatment	Age (yrs)	Race/Ethnicity	Height (in)	Weight (lb)	BMI (kg/m ²)	PSA (ng/dL)	Gleason Score	Path Stage	Margin Status	Compliant	Equol Producer	Alive
09	Soy	RP	64	White/Non	68.5	179	26.8	9.88	7	T3B	Positive	Yes	Unknown	Yes
33	Placebo	RP	55	White/Non	71	198	27.6	10.9	6	T2C	Positive	Yes	N/A	Yes
45	Placebo	RT	65	White/Non	71	202	28.2	9.86	7	N/A	N/A	Yes	N/A	Yes
49	Soy	RP	53	White/Non	71	190.5	26.6	12.4	6	T2A	Positive	Yes	No	Yes
62	Placebo	RP	63	Black/Non	72.25	238	32.1	4.62	9	T3B	Negative	Yes	N/A	Yes
64	Soy	RP	55	White/Non	72.5	240	32.1	17	7	T2C	Positive	Yes	No	Yes

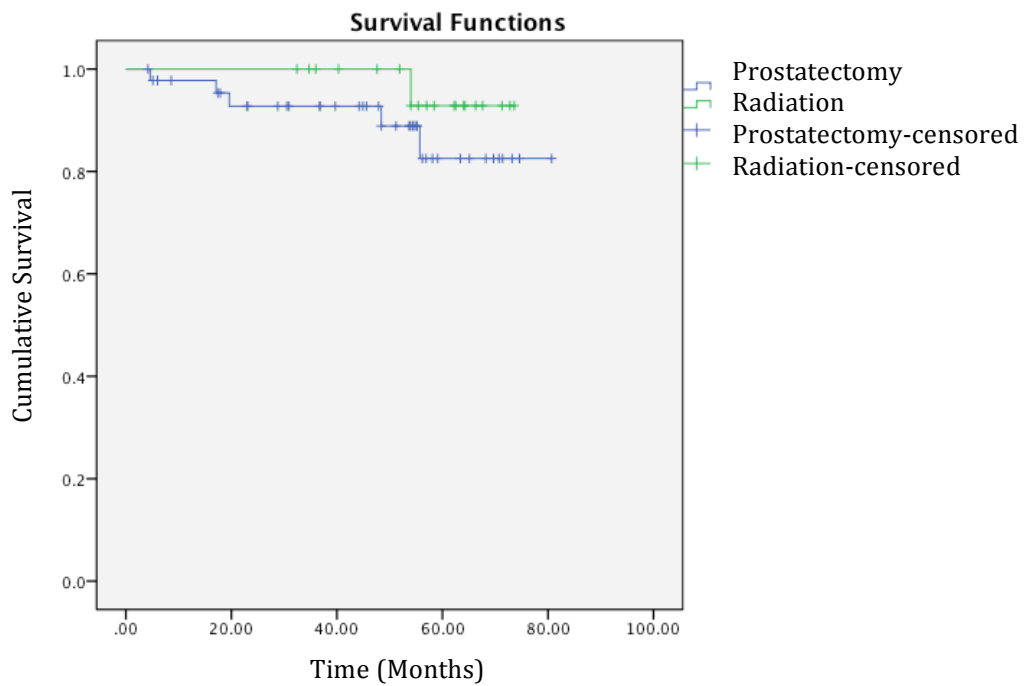
RP = radical prostatectomy; RT = radiation therapy
 Pathological staging and margin status unavailable for patients who underwent radiation therapy
 Equol production measured in soy group only; defined as equol:daidzein ratio > 0.018

Appendix E. Kaplan-Meier Plots

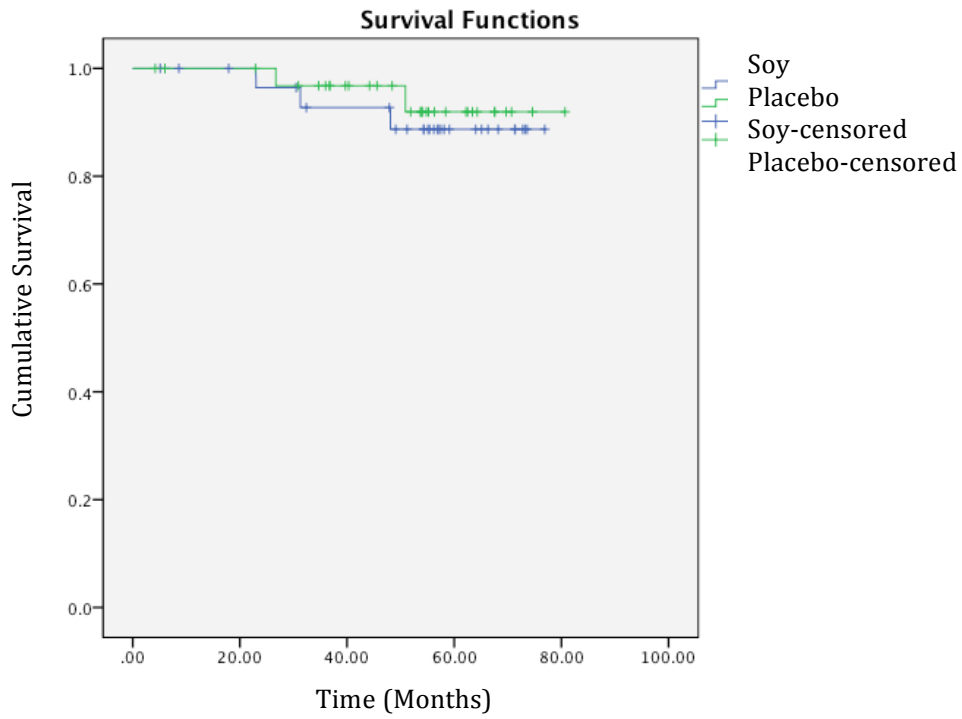
Time to Biochemical Recurrence by Soy vs. Placebo



Time to Biochemical Recurrence by Curative Treatment



Survival Time by Soy vs. Placebo



Survival Time by Curative Treatment

