ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

CALGB 70807

The Men's Eating and Living (MEAL) Study: A Randomized Trial of Diet to Alter Disease Progression in Prostate Cancer Patients on Active Surveillance

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CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

To submit site registration documents:	**For patient enrollments:**	**Submit study data directly to the Lead Cooperative Group**
CTSU Regulatory Office [redacted]	Please refer to the patient enrollment section for instructions on using the OPEN system.	Forms must be submitted electronically using the "Submit to CALGB" button located at the bottom of the last page of each form (see Section 6.1). Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.
The **study protocol and all related forms and documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Sites must use the current form version and adhere to the instructions and submission schedule outlined in the protocol. CTSU sites should follow procedures outlined in the protocol for Site registration, Patient Enrollment, Adverse Event Reporting, Data Submission (including ancillary studies), and Drug Procurement.		
For patient eligibility or treatment-related questions contact the Study Chair.		
For questions unrelated to patient eligibility, treatment, or data submission contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – [redacted], or [redacted] All calls and correspondence will be triaged to the appropriate CTSU representative.		
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Endorsing cooperative group:

SWOG

[redacted]

SWOG Coordinating Center

[redacted]

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Required Initial Laboratory Values

Serum PSA < 10 ng/mL

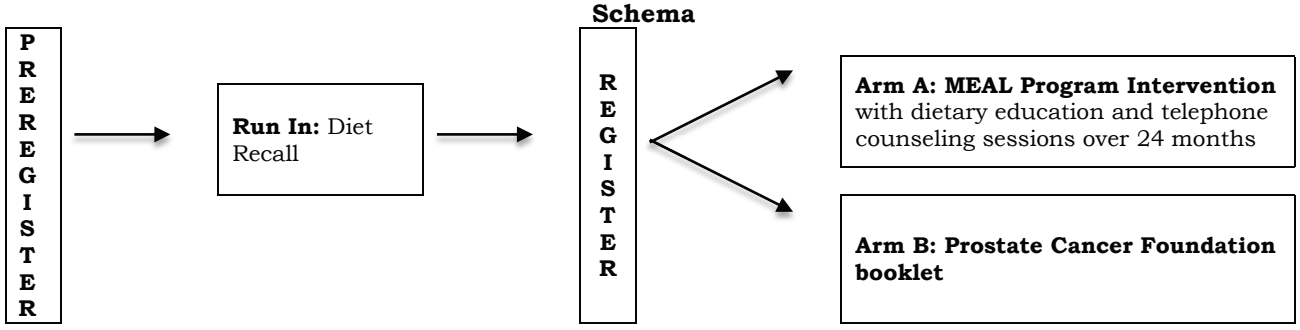
Preregistration Eligibility Criteria

Biopsy-proven adenocarcinoma of the prostate, clinical stage ≤ T2a diagnosed within 24 months prior to pre-registration (see Sec. 4.1.1)
Less than 25% of biopsy tissue cores positive for cancer.
≤ 50% of any one biopsy tissue core positive for cancer.
Patients who have prostate cancer with distant metastases are not eligible.
Patients who have had prior treatment for prostate cancer by surgery, irradiation, local ablative or androgen deprivation therapy are not eligible.
Patients with a history of non-cutaneous malignancy in the previous 5 years are not eligible.
Patients must be able to read and comprehend English language text and be able to understand spoken English over the phone.
Life expectancy of at least 3 years.
Patients may be currently taking vitamin supplements including lycopene and beta-carotene.
Patients receiving treatment with 5-alpha reductase inhibitors within 90 days prior to preregistration are not eligible (see Section 4.1.7).
Patients who are currently taking coumadin are not eligible.
Participants will be men aged 50 to 80 years.
For men ≤ 70 years, biopsy Gleason score must be ≤ 6; for men > 70 years, biopsy Gleason score must be ≤ (3 + 4) = 7.

Registration/Randomization Eligibility Criteria

Successful completion of three 24-hour dietary recalls during the run in period
Patients consuming ≥ 6 servings per day of fruits and vegetables (not including juices) are not eligible.

Schema



Stratification:

- Age: Men ≤ 70 years; Men > 70 years
- Race: Black or African American vs. Other
- Baseline Prostate Biopsy: 0-12 months prior to registration vs. >12-24 months prior to registration

MEAL Program Intervention: The counseling protocol will be divided into four phases, with the first three phases completed in 7 months. The fourth phase will continue for 17 months.

- The **first phase**, comprised of six counseling calls, will focus on education and the rapid development of self-efficacy.
- The **second phase**, comprised of four calls over a 2-month period, will focus on practical and consistent implementation of the dietary pattern.
- The **third phase**, comprised of four calls over a 4-month period, will help participants habituate to the dietary pattern by providing regular performance reviews.
- The **fourth phase**, comprised of 8 calls over a 17-month period, will be a maintenance phase.

Quality of Life Measures: Seven quality of life measures will be used: Personal Habits Questionnaire, Functional Assessment of Cancer Therapy Scale-Prostate (FACT-P); Memorial Anxiety Scale for Prostate Cancer (Max-PC); International Prostate Symptom Score (IPSS); Expanded Prostate Cancer Index Composite 26 (EPIC-26); Nutrition Self–Efficacy and MEAL Study Counseling Evaluation Form.

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1.0 INTRODUCTION

1.1 Prostate Cancer: The Concept of Overtreatment

Prostate cancer is the most commonly diagnosed non-cutaneous cancer among US men. Approximately 192,000 new cases were identified in 2009 (1). Although prostate cancer is the second leading cause of cancer death among US men, the probability of dying from prostate cancer is relatively low. The lifetime risk of prostate cancer diagnosis is 16%, but the lifetime risk of death from prostate cancer is only 3% (1). This discrepancy between prostate cancer incidence and mortality, due in large part to detection of pre-symptomatic tumors by the prostate-specific antigen (PSA) assay, is distinct among cancers. As a result of widespread PSA testing, 50% of newly diagnosed prostate cancer patients now present with localized, lower-risk disease (2).

Most patients with lower-risk prostate cancer are treated with surgery or radiation (3). Although the probability of cure with these modalities is high, both are associated with urinary, bowel, and sexual morbidities that significantly diminish quality of life (4, 5). Moreover, despite the high probability that these men will remain disease-free, whether the treatments actually reduce prostate cancer-specific or overall mortality in lower-risk patients is not known. Many men with localized, higher-risk prostate cancer have aggressive disease that warrants aggressive intervention (6); many others, with lower-risk, generally indolent prostate cancer, even younger men likely to live 15 years or more from diagnosis, derive few, if any, survival benefits from treatment (7-10).

Population studies suggest that a substantial proportion of men diagnosed with lower-risk prostate cancer in the US are over-treated (2-4). In a recent study of the US SEER registry, Miller and colleagues concluded that approximately 50% of men with lower-risk prostate cancer received unnecessarily aggressive treatment, surgery or radiation (4). The staggering scope of this public health problem that is, unnecessarily aggressive treatment of lower risk prostate cancer, treatment that diminishes quality of life for tens of thousands of US men each year, challenges us to develop innovative therapeutic and diagnostic models to refine treatment paradigms within this patient population.

1.2 Active Surveillance (AS) for Lower-Risk Prostate Cancer

The concept that substantial proportions of men diagnosed with lower-risk prostate cancer are over-treated has fostered growing interest in a management approach known as active surveillance (AS). AS entails vigilant monitoring of men with localized, lower-risk prostate cancer by serial PSA measurements, frequent digital rectal examinations, and intermittent prostate biopsies. Intervention with surgery, radiation, or other therapies is reserved until patients show evidence of disease progression (9,11-16).

Active surveillance protocols for identification of patients with lower-risk disease vary by institution, but are generally similar. Clinical criteria for enrollment in a surveillance program typically include total PSA < 10 ng/mL, tumor that is non-palpable, or palpable but small on digital rectal examination (clinical stage T1 or T2) and lower-risk tumor characteristics on prostate biopsy, namely, low-grade (Gleason sum ≤ 6) and low-volume (tumor evident only in a small number and percentage of biopsy cores) disease (9,11-16). Similarly, while there remains no clinical consensus, disease progression while on surveillance is broadly defined as a rapidly increasing PSA (manifested as decreased PSA doubling time or increased PSA velocity) or worrisome pathology on repeat biopsy (Gleason score ≥ 7 or increased tumor volume) (9,11-16).

In carefully selected men with lower-risk prostate cancer, AS is a viable and safe treatment option. Warlick and colleagues, confirming earlier results (9), observed that patients followed on AS for up to 6 years who then progressed by PSA or pathological criteria and underwent surgery were just as likely to be cured of their disease as men who underwent surgery immediately after diagnosis (14).

Approximately 30% of patients on AS will progress based on current PSA or pathological criteria and thus receive intervention with surgery or radiation, typically within 2 years of beginning surveillance (11). The Hopkins data indicate that 31% of patients progress

within 26 months (13, 15). In the Toronto cohort, 34% progressed after 64 months; however, the definition of progression for most of the follow-up period was based on a PSA DT of 2 years or pathology progression to Gleason grade 8. Klotz estimated that 20 percent of patients would progress on the basis of a PSA DT of 3 years, while 5 to 10% would progress on the basis of tumor grade progression. Moreover, up to 12% of men who do not meet objective criteria for progression will opt for intervention (11). Thus, in total, over 40% of men on AS will progress or proceed to treatment. Reducing the proportion of men who progress or choose treatment while on AS for prostate cancer represents a novel opportunity to minimize treatment-associated morbidity, improve patient quality of life, and contain health care costs.

1.3 Diet and Prostate Cancer

The existence of a distinct, relatively indolent phenotype in prostate cancer presents an important opportunity. A potential means of decreasing the number of men on AS who proceed to treatment is dietary change. There is great interest in the role of diet in the etiology and natural history of prostate cancer (17, 18). Accumulating evidence suggests that diet may alter prostate cancer initiation and progression. Macronutrients and micronutrients associated with decreased prostate cancer risk include retinoids, carotenoids (particularly lycopene), cruciferous vegetables, dietary fat, soy products, folate, retinol, vitamin D, and omega fatty acids (17-23). A range of phytochemicals in fruits and vegetables could have effects on a metabolically active organ like the prostate, and a number of plausible mechanisms have been proposed (24-39).

Experimental studies based on cell line and animal models suggest that vegetable intake may lessen the risk or retard the progress of prostate cancer. Rats fed tomato powder have decreased prostate-cancer specific mortality compared to controls (24) and, in vitro, lycopene inhibits DNA synthesis in prostate epithelial cells (25). Cell line and animal data support the anti-carcinogenic properties of isothiocyanates, which are components of cruciferous vegetables such as broccoli and cabbage. Isothiocyanates induce expression of cytoprotective phase 2 enzymes in multiple prostate tumor cell lines (26, 31) promote apoptosis of prostate cancer PC-3 cells in vitro, and inhibit growth of PC-3 xenografts in nude mice (28). In a prostatectomy model, men fed a tomato intensive diet had distinct biological changes potentially associated with suppression of prostate tumors (30).

Indirect evidence from epidemiology, ecological, case-control and cohort studies in humans suggests that altering nutritional intake may provide beneficial effects against prostate cancer (18). This evidence suggests a diet that emphasizes vegetable intake and de-emphasizes meat and fat intake may decrease the risk of prostate cancer initiation and progression. The most direct evidence for this supposition has been provided by studies of whole foods rather than micronutrients. Red meat and fat intakes tend to be associated with increased risk (particularly of aggressive cancer); cruciferous vegetables and tomatoes and tomato products tend to be most closely associated with decreased risk (20-23, 33).

Recent observational data also indicate that weight loss may alter the natural history of prostate cancer: among men in the Cancer Prevention Study II Nutrition Cohort, weight loss >11 lbs over 10 years was associated with a 40% reduction for high-grade cancer risk (34). Follow up of the Prostate Cancer Prevention Trial cohort indicated that a BMI > 30 kg/m^2 was associated with an 18% decreased risk of low-grade prostate cancer and a 29% increased risk of high-grade prostate cancer (35). Low serum cholesterol was associated in this same study with decreased risk of high grade prostate cancer (36).

To date, human experimental evidence supporting epidemiologic and pre-clinical findings, though intriguing, is limited. Isothiocyanates derived from cruciferous vegetables enter the human prostate following oral consumption and may be associated with anti-carcinogenic, phase 2 enzyme activity in prostate tissue (29, 31). In a small intervention study, patients with recurrent prostate cancer experienced decreased PSA doubling times six months after beginning treatment with diet modification and stress reduction (37). In another small clinical trial of active surveillance patients, randomization to a plant-based diet with micronutrient supplements and intensive lifestyle changes resulted in decreased

serum PSA concentrations, inhibition of prostate cancer cell growth, and progression to active treatment; (38) another non-randomized pilot study utilizing a similar intervention (plant based whole foods coupled with exercise and stress management) resulted in significant changes in prostate gene expression (39).

These studies provide preliminary clinical evidence that diet change may slow prostate cancer progression. Still, they were small studies with only short-term (~ 1 year) follow-up. Moreover, as it is impossible to isolate the effects of diet from those of exercise, stress management, and group support, these changes in PSA and cancer cell growth cannot with certainty be attributed solely to dietary change. On the other hand, the most likely factor driving these changes is diet. In addition, whether intensive lifestyle modifications such as exercise, yoga, and stress management would be practicable, sustainable behaviors in large groups of patients remain to be seen. An adequately powered trial, focusing on diet as a primary form of intervention, is needed.

We previously designed and implemented a telephone-based dietary intervention for prostate cancer patients based on well-established principles of social cognitive theory. This relatively straightforward intervention, the first to use diet change as a primary treatment for low risk prostate cancer, produced robust, beneficial diet changes (i.e. significantly increased vegetable intakes) and led to increased plasma levels of potentially anti-carcinogenic carotenoids in prostate cancer patients (40-42). We believe that the next step is to determine, in a suitable study sample, whether these diet changes, marked by increased plasma carotenoid levels, will exert a clinically relevant and sustainable effect on prostate cancer progression.

1.4 Dietary Intervention in an Active Surveillance (AS) Population

Men on AS represent a compelling population for studying diet change and prostate cancer for at least 4 reasons. First, approximately 100,000 men are diagnosed with lower-risk prostate cancer every year in the US. Some 42% of men on AS progress to treatment (30% because of disease progression, 12% because of anxiety); reducing this proportion represents a realistic and valuable therapeutic and public health goal (8, 9, 11, 13). Second, clinically localized, lower-risk cancer may potentially be more affected by dietary change than more advanced, aggressive disease. If diet is related to the risk of prostate cancer, it may well exert an impact on the earliest phases of prostate cancer; its impact may best be tested in an AS population. Third, AS patients are not receiving active therapy (i.e. radiation, surgery, or androgen) that would otherwise obscure or modify any beneficial effects of dietary change. Finally, AS patients would likely be receptive to nutritional interventions with proven benefits for cardiovascular and overall health (8, 11, 43).

Indeed, because prostate cancer diagnosis is a source of considerable anxiety and diminished quality of life for many patients diagnosed with lower-risk disease (44-46), dietary change might not only exert therapeutic biological effects on the tumor, but might also encourage men with lower-risk prostate cancer and no signs of progression to remain within an AS program. As previously noted, up to 12% of patients with no objective PSA or pathologic indications of progression nonetheless opt for treatment that may not improve their prognosis (11). Treatment preferences in this situation are generally believed to arise, to a large extent, from patient anxiety and discomfort over not receiving curative therapy. This attitude is likely fostered by the action-oriented approach that characterizes our current health care system (8). However, prostate cancer-related anxiety and its effects on treatment choice have not as yet been prospectively studied in an AS population.

Diet change presents an ideal opportunity for AS patients to alter the perception of their disease by providing an intervention on which to focus. This approach may dissuade otherwise lower-risk men from pursuing unnecessarily aggressive, morbidity-generating treatments. Such an approach would promulgate a novel therapeutic paradigm for lower-risk prostate cancer: medical management, without radical intervention, in a chronic disease state.

1.5 Quality of Life Among Prostate Cancer Patients

Cancer patients often report significant anxiety about their disease. Several investigators have documented fear of recurrence to be highly prevalent in a number of different cancer patient populations (47-50). Cancer survivors may experience lingering psychological sequelae, including fear of diagnostic tests and fear of recurrence for long periods of time after diagnosis and treatment (53).

Prostate cancer patients are not immune to worry over their disease (5, 44-46, 52, 53). However, treatment may also diminish fear of recurrence. Among prostate cancer patients undergoing definitive treatment, fear of recurrence peaked prior to treatment, then decreased within 6 months after treatment (52). A possible explanation for this finding is that patients were reassured about their prognosis after having undergone treatment. Providing prostate cancer patients the opportunity to exert control over a change in their dietary intake, a diet-based intervention may perhaps help patients overcome fear of recurrence, particularly if the intervention stabilizes PSA.

Part of the impact of a diet change program may involve social cognitive theory, which governs most current attempts to change behavior. A key element of social cognitive theory is self-efficacy. According to social cognitive theory, the interaction of the individual with the environment is influenced by his or her cognitions and beliefs about ability, expectation of behavioral outcomes, and evaluation and modification of behavior toward specific goals (54). Components of social cognitive theory include self-efficacy (confidence in ability to perform a particular behavior to accomplish a specific goal), outcome expectancies (belief that a particular behavior will result in a particular consequence), and self-regulation (adopting personal standards for behavior, appraising behavior against such standards, and creating incentives that motivate and guide behavior). Participating in diet change, as in this study, may increase patient feelings of self-efficacy, defined as their "judgments of their capabilities to organize and execute courses of action required to attain designated types of performance (55-57)." According to Bandura (56), mastery experiences are the most reliable source of efficacy information. Applied to this study, feelings of greater self-efficacy will increase patients' ability to control their diet and consequently their health. Identifying and reinforcing patients' present success is a factor that Bandura (54, 56), and Strecher and colleagues (58) suggest clinicians use to improve self-efficacy. Building a sense of self-efficacy is part of the MEAL program. Self-efficacy has been incorporated into various interventions: self-management interventions and educational programs in patients with chronic disease (61) and prostate cancer (57). Breast and colon cancer patients randomized to either an educational or nutritional intervention arm had significantly fewer depressive symptoms and better physical functioning than patients in the control group, primarily accounted for by self-efficacy (60). Cancer patients with greater self-efficacy have been found to be better adjusted and have a better overall quality of life (55, 57-59).

We expect that participating in the MEAL intervention will improve the quality of life for low risk prostate cancer patients. The literature is largely supportive, indicating that this intervention's focus on self-efficacy will add measurably to quality of life (56-63). One of the implicit messages that participants take from being in this study will be that low risk prostate cancer is a condition to monitor, but neither a death sentence nor a condition that requires radical, immediate, life-changing intervention. We will not be able to compare trial participants to non-participants. We will, however, be able to compare those randomized to the diet change to those randomized to the comparison group.

Low risk prostate cancer is a substantial public health issue that affects tens of thousands of men each year in the US. Epidemiologic, pre-clinical, and preliminary clinical studies suggest that diet is related to prostate cancer risk, so that changing to a high-vegetable diet may decrease prostate cancer progression in lower risk patients. Clearly, mature clinical data on use of diet to treat prostate cancer are lacking. We have developed a novel, practical, telephone-based intervention that has been shown to increase vegetable intake and serum carotenoid levels in men with prostate cancer. We propose to document the impact of this dietary intervention in an extended clinical trial using prostate cancer patients under AS; for such patients, the likelihood of treatment

efficacy, even after delay, is relatively high. Patient anxiety is a prominent yet understudied complaint among AS patients; diet change may decrease prostate-cancer related anxiety among these patients. Further study of diagnosis-related anxiety will yield potentially important information for improving the psychological care of prostate cancer patients.

1.6 Pilot Data Supporting Dietary Intervention: The Women's Healthy Eating and Living (WHEL) Study for Breast Cancer

A CALGB pilot study demonstrated the feasibility of implementing dietary changes among cancer patients in the Women's Healthy Eating and Living study (WHEL), a multi-center trial of diet change for breast cancer (40-42,64). Utilizing well-established behavior change techniques, this intervention achieved substantial changes in vegetable, fiber and fruit consumption, along with a substantial change in fat consumption (64).

The dietary intervention we developed employs telephone-based communication. The conceptual framework of the intervention is derived from Social Cognitive Theory (54), which emphasizes strengthening of individual self-regulatory skills, including goal-setting, self-monitoring and evaluative judgments. We utilize lay coaches to help participants frame options for decisions. The coaches focus on self-efficacy, or participant belief that they can actually succeed in behavior change (64, 65). The lay coaches also provide a supportive environment for regular discussion of triumphs and failures as participants seek to change. The lay coaches are well versed in basic nutrition, and they are supervised by experienced and knowledgeable dietitians; nonetheless, they function less as authority figures than as facilitators or guides, and as supporters, helping participants optimize their options as they proceed through change (66).

The intervention efforts are timed so that they provide the greatest support and guidance when the challenges of change, hence the threats of failure, are greatest: at the beginning (65). We have demonstrated that major changes can be implemented during the first month of the intervention (40-42, 65). The subsequent challenge is to integrate change into the participant lifestyle, then to reinforce and maintain the change. The counselors during this time watch for signs that participant self-efficacy is waning; declining self-efficacy may be an indicator that failure is increasingly likely (65). We have shown that this approach results in substantial dietary change that can be maintained for several years (67).

This telephone-based approach has been shown to result in change that can be seen in accepted biomarkers of nutritional practice (40-42). Carotenoids, which are fat-soluble pigments found almost exclusively in vegetables and fruits, accumulate in blood. The most common of these, alpha carotene, beta-carotene, lutein, lycopene and crytoxanthin, reflecting the intake of a wide range of plants, were used as general biomarkers of plant intake (65). The WHEL study intervention, on which our pilot trial was based, caused the diets and blood carotenoids of 1500 experimental subjects and 1500 control subjects to diverge substantially within a year of beginning the intervention; after that, we observed, over a period of 3 to 4 years, a slight decline in the difference between the dietary practices of experimental and control subjects (66). Nonetheless, experimental subjects in the WHEL study spent the bulk of their study participation time consuming a diet that was radically different than both their pre-enrollment diet and that of comparison subjects.

A nuance of diet change trials is that subjects are not blinded to their assignment; thus, there is always a possibility that subject behavior will be changed by subject knowledge of intervention. In particular, experimental subjects may be inclined to exaggerate their compliance with diet goals. Subjects cannot, however, readily exaggerate their blood carotenoid levels except by changing their diet. These are integrated over an extended period, and experimental subjects are unlikely to change these other than by changing their diet.

While it is certainly true that any methodology involving prospective dietary change poses challenges, the WHEL data, and the to-be discussed MEAL data, indicate that we can

profoundly change diet. In addition, these data confirm that comparison subjects will not in large part change their diets.

Although the effect of these changes on breast cancer recurrence was null for the overall study, a sub-group analysis based on hot flash status demonstrated significantly decreased risk of additional breast cancer events among women without hot flashes who had higher vegetable, fruit and fiber and lower fat intakes (70). These data tentatively support the notion that diet change may alter the natural history of breast cancer in select groups of patients.

1.7 The Men's Eating and Living (MEAL) Pilot Study

Based on the WHEL experience, we designed and implemented a pilot study of diet change in men with prostate cancer based on similar principles of behavior change: the Men's Eating and Living (MEAL) Study (40-42). This randomized, controlled clinical pilot trial of 74 men, most with clinically localized prostate cancer, utilized the same diet-change intervention outlined in this application. To increase the number of change patients for evaluation, we randomized 2 patients to intervention for every one randomized to comparison. This trial was different from the WHEL study, in that we invited the spouse or significant other of the patient, and not just the patient, to participate in the diet counseling. The study demonstrated that diet change with telephone-based counseling results in increased vegetable intake and increased plasma carotenoid concentrations among men with prostate cancer.

Dietary changes: vegetables

Consistent with counseling targets, vegetable intakes in the intervention arm increased significantly at six months, while those in the control arm remained static (Table 1). Diet was measured by a series of three 24-hour recalls collected interactively via telephone interview. In the intervention arm, mean daily intakes of total vegetables, crucifers, tomato products and other vegetables increased by 76%, 143%, 292%, and 55%, respectively. The intervention emphasized vegetable, rather than fruit intake, and white potatoes and lettuce did not count. As a result, fruit, lettuce, and potato intake declined for experimental subjects (40-42). In the control arm, there were no significant changes in mean intakes of total vegetables, crucifers, tomato products, lettuce and potatoes, or other vegetables.

Table 1. Vegetable intake* at baseline and 6 months as assessed by 24 hour dietary recall in the Men's Eating and Living (MEAL) Study

	Intervention n=45			**Control n=23**		
	Baseline	6 Months	Change	Baseline	6 Months	Change
Total vegetables	4.1	7.2	76%†‡	3.7	4.2	12%
Cruciferous vegetables	0.7	1.7	143%†‡	0.4	0.6	44%
Tomatoes	0.6	2.3	292%†‡	0.7	0.8	5%
Lettuce and potatoes	1.0	0.4	-58%†‡	0.6	0.6	-3%
Other vegetables	1.8	2.8	55%†	1.9	2.2	12%

*All intakes measured in servings per day

†Significant difference ($p<0.05$) between groups

‡Significant difference (p<0.05) within groups

Dietary changes: non-vegetables

Intakes of whole grains and beans in the intervention group increased, while fat intake decreased; mean daily intakes of whole grains and beans increased by 28% and 95%, respectively, while fat intake decreased by 12% (p<0.05). In the control arm, whole grain and fiber intakes decreased by 33% and 21%, respectively (p<0.05), and there were no significant changes in fruit, beans, fiber, or fat intakes (data not shown) (40-42).

Plasma carotenoid concentrations

Consistent with increased vegetable consumption, carotenoid concentrations increased in the intervention but not in the control group (Table 2). At baseline, plasma total carotenoid concentrations of intervention and control participants were virtually the same. At six months, however, those of intervention and control participants, respectively, rose by 26% and 3% (p=0.02). In the intervention group, α-carotene, β-carotene, lutein, and lycopene concentrations increased significantly, while those in the control group remained static (p<0.05). Cryptoxanthin levels changed in neither group. That the changes observed were qualitatively larger than those observed in such prevention interventions as the Polyp Prevention Trial (69) suggests that this test of dietary intervention might be much more sensitive and powerful than either the Polyp Prevention Trial or the Women's Health Initiative (70).

Although the MEAL study was not strictly intended for AS patients, the patients on AS (53% of the study sample) experienced dietary change and plasma carotenoid results identical to those for the entire group (42).These data support the feasibility of implementing a larger clinical trial of a telephone-based diet intervention in men with prostate cancer treated with AS.

Our data, which include blood-based biomarkers, indicate that experimental subjects changed their diets, but that comparison subjects did not. Other data, including the Polyp Prevention Trial (71) and the Women's Healthy Eating and Living study (66), confirm that comparison subjects in diet intervention trials in general do not change their diets to nearly the extent that experimental subjects do.

Table 2. Plasma carotenoid concentrations at baseline and 6 months in the Men's Eating and Living (MEAL) Study

Carotenoid (mmol/L)	**Intervention n=45**			**Control n=23**		
	Baseline	6 Months	Change	Baseline	6 Months	Change
α-Carotene	0.17	0.23	33%‡	0.16	0.17	5%
β-Carotene	0.61	0.83	36%†‡	0.63	0.66	5%
Lutein	0.44	0.53	19%†‡	0.43	0.43	0
Lycopene	0.79	1.03	30%†‡	0.86	0.87	2%
Cryptoxanthin	0.19	0.17	-11%	0.17	0.18	11%
Total Carotenoids	2.21	2.79	26%†‡	2.24	2.32	3%

†Significant difference (p<0.05) between groups

‡Significant difference (p<0.05) within groups

MEAL: Program satisfaction

The response to the intervention was almost universally positive. In a very preliminary attempt to document the extent to which the participants experienced this program positively, we administered a limited questionnaire to 33 of the participants. We asked

them to describe their satisfaction on a 5-point scale, with 1 indicating strong dissatisfaction and 5 strong satisfaction. The responses were extremely positive; 31 of 33 rated their counselor a 5 for being prompt and convenient with sessions; 30 of 33 rated the counselor a 5 for listening; 32 of 33 rated the counselor a 5 for being easy to talk to; 29 of 33 rated the counselor a 5 for knowledge; 26 of 33 gave the counselor a 5 for being helpful; 25 of 33 gave the counselor a 5 for motivating them; and 24 of 33 gave the counselor a 5 for helping them to overcome barriers.

1.8 Study Design

In summary, these promising pilot data support the feasibility of a larger clinical trial of a telephone-based dietary intervention in men with prostate cancer treated with AS. The synthesis of these two aims-optimizing management of active surveillance patients through diet-represents a novel approach to this topic with a high potential for providing near-term patient benefits that would serve both the prostate cancer population and the broader public health. An adequately powered trial, focusing on diet as a primary form of intervention is needed.

CALGB 70807 is a randomized, phase III clinical trial designed to test this practical, diet-based intervention for prostate cancer in a broader clinical setting. Patients on AS will be randomized either to an intervention of centralized, telephone-based dietary counseling and structured dietary education or to a comparison control condition in which they receive the Prostate Cancer Foundation booklet entitled "Nutrition, Exercise and Prostate Cancer." Study endpoints will include disease progression, incidence of treatment, and health-related quality of life.

1.9 Inclusion of Women and Minorities

Because prostate cancer occurs primarily in men above the age of 50, recruitment of participants for this study will focus upon men aged 50 years and older. Since women and children are not subject to prostate cancer, they will be excluded from this study. Efforts will be made to enroll individuals of all races and ethnic backgrounds, with the added goal of recruiting relatively high numbers of individuals of Hispanic origin and of African-American origin. The increased risk of prostate cancer and especially of lethal prostate cancer among African Americans makes it imperative that we secure adequate representation of African Americans in this study.

CALGB has a long history of effort to ensure adequate representation of minorities in all clinical trials, including prevention trials. The recent experience of the Selenium and Vitamin E Cancer Prevention Trial (SELECT) (80) is instructive: 29% of the CALGB participants were African Americans. In our MEAL pilot study, 12% of participants were non-white. Our goal with the full MEAL trial is for 29% of participants to be members of racial minorities, especially African Americans.

Racial Categories	DOMESTIC PLANNED ENROLLMENT REPORT				
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native	0	3	0	0	3
Asian	0	9	0	0	9
Native Hawaiian or Other Pacific Islander	0	1	0	0	1
Black or African American	0	53	0	1	54
White	0	381	0	16	397
More Than One Race	0	0	0	00	0

Total	0	447	0	17	464

2.0 OBJECTIVES

2.1 Primary Objective

To determine if a telephone-based dietary intervention compared to no intervention will decrease clinical progression in AS patients.

2.2 Secondary Objectives

2.2.1 To compare the incidence of active treatment (surgery, irradiation, local ablation, or androgen deprivation) in AS patients receiving dietary intervention compared to no intervention.

2.2.2 To compare prostate cancer-related anxiety in AS patients receiving dietary intervention compared to no intervention.

2.2.3 To compare health-related quality of life in AS patients receiving dietary intervention compared to no intervention.

[See Section 10.0 for correlative science objectives.]

3.0 ON STUDY GUIDELINES

The following guidelines are to assist physicians in selecting patients for whom protocol therapy is safe and appropriate. Physicians should recognize that the following might increase the risk to the patient entering this protocol:

- Patients with medical conditions which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient should not be enrolled. Such conditions may include uncontrolled chronic diseases (including uncontrolled diabetes mellitus, cardiac disease, ulcerative colitis, and Crohn's disease); or psychiatric illness/social situations that would limit compliance with study requirements and/or prevent the patient from giving informed consent.
- Intolerance of cruciferous vegetables.
- Unwillingness to adopt a vegetable-intense diet.

4.0 ELIGIBILITY CRITERIA

4.1 Preregistration Eligibility

4.1.1 Histologic Documentation: The initial biopsy showing diagnosis of prostate cancer should be used for the purposes of determining eligibility. However, if a subsequent biopsy performed before patient enrollment shows that the patient is ineligible, he may not be enrolled to the study. Eligible patients must meet all of the following criteria:

- Biopsy-proven (consisting of ≥ 10 tissue cores) adenocarcinoma of the prostate diagnosed within 24 months prior to pre-registration.
- < 25% of biopsy tissue cores positive for cancer.
- ≤ 50% of any one biopsy tissue core positive for cancer.
- Clinical stage ≤ T2a.
- Patients who have prostate cancer with distant metastases are not eligible.

NOTE: If a patient undergoes a transurethral resection of the prostate (TURP) for benign prostatic hyperplasia (BPH), and prostate cancer is diagnosed incidentally from the TURP specimen, eligibility for CALGB 70807 cannot be determined from the TURP specimen. However, if the patient subsequently undergoes a minimum 10-core prostate biopsy within 2 years of prostate cancer diagnosis from the TURP, and

prostate cancer is detected in the biopsy specimen and meets the requirements above, the patient is eligible for this study. If prostate cancer is not detected in the biopsy specimen, the patient is not eligible.

4.1.2 Prior Treatment: Patients who have had prior treatment for prostate cancer by surgery, irradiation, local ablative (i.e. cryosurgery or high-intensity focused ultrasound) or androgen deprivation therapy are not eligible.

4.1.3 Patients who have had a history of non-cutaneous malignancy (other than non-melanoma skin cancer) in the previous 5 years are not eligible.

4.1.4 Language: Patients must be able to read and comprehend English language text and be able to understand spoken English over the phone.

4.1.5 Life expectancy of at least 3 years.

4.1.6 Patients who are currently taking vitamin supplements including lycopene and beta-carotene are eligible.

4.1.7 Patients receiving treatment with 5-alpha reductase inhibitors (e.g., finasteride, dutasteride) within 90 days prior to preregistration are not eligible. Treatment with these agents during the protocol intervention is not permitted.

4.1.8 Patients who are currently taking coumadin are not eligible.

4.1.9 Participants will be men aged 50 to 80 years.

4.1.10 For men ≤ 70 years, biopsy Gleason score ≤ 6; for men > 70 years, biopsy Gleason score ≤ (3 + 4) = 7.

4.1.11 Required Initial Laboratory Values:

- Serum PSA < 10 ng/mL

NOTE: Baseline PSA for determination of eligibility must be measured after discontinuation of any 5-alpha reductase inhibitors.

4.2 Registration Eligibility

4.2.1 Successful completion of three 24-hour dietary recalls during the run-in period.

4.2.2 Patients consuming ≥ 6 servings per day of fruits and vegetables (not including juices), as determined by the run-in dietary recalls are <u>not</u> eligible.

5.0 REGISTRATION

Informed Consent: The patient must be aware of the neoplastic nature of his disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the study, alternatives, potential benefits, side effects, risks and discomforts.

Protected Health Information: In order to contact patients by telephone and by mail, it will be necessary to collect those participants' names, addresses, and telephone numbers. This information will be sent to the University of California, San Diego Moores Cancer Center and will be destroyed upon completion of the study.

5.1 CTSU registration requirements

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Prior to the recruitment of a patient for this study, investigators must be registered members of a Cooperative Group. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management

Branch, CTEP, DCTD, NCI. These forms are available on the CTSU Web site (enter credentials at https://www.ctsu.org; then click on the Register tab) or by calling the PMB at [redacted] Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site by entering credentials at https://www.ctsu.org.

Requirements for CALGB 70807 site registration:

- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet

5.2 Patient Pre-registration

Pre-registration must occur prior to providing patients with access to the online patient data entry site, login information or training. Pre-registration to the optional companion studies will be performed at the time pre-registration occurs to the intervention study.

All site staff (Lead Group and CTSU Sites) will use OPEN to enroll patients to this study. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org.

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the OPEN Enrollment forms provided on the group or CTSU web site as a tool to verify eligibility.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Access requirements for OPEN:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user id and password) used for the CTSU members' web site.
- To perform registrations, the site user must have been assigned the 'Registrar' role on the relevant Group or CTSU roster.
- To perform registrations on protocols for which you are a member of the Lead Group, you must have an equivalent 'Registrar' role on the Lead Group roster. Role assignments are handled through the Groups in which you are a member
- To perform registrations to trials accessed via the CTSU mechanism (i.e., non-Lead Group registrations) you must have the role of Registrar on the CTSU roster. Site and/or Data Administrators can manage CTSU roster roles via the new Site Roles maintenance feature under RSS on the CTSU members' web site. This will allow them to assign staff the "Registrar" role.

The OPEN system will provide the site with a printable confirmation of pre-registration. Please print this confirmation for your records.

Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at [redacted]

Within 24 hours of receiving the Confirmation of Preregistration, fax the C-2010, MEAL Participant Contact Information Form to Nutrition Shared Resource at UCSD at [redacted] and notify [redacted] via email at [redacted].

5.3 Preregistration to companion study 151105

There is one substudy within CALGB 70807. This substudy must be offered to all patients enrolled on CALGB 70807 (although patients may opt not to participate). The substudy included within CALGB 70807 is CALGB 151105, "Carotenoid and polymorphism analysis of patients enrolled to CALGB 70807." This study does not require separate IRB approval.

If a patient answers "yes" to "I agree that my specimens may be used for the research described above," (Question #1) in the Model Consent, he has consented to participate in the correlative science studies described in Sections 10.2, 10.3, and 10.4. The patient should be pre-registered to CALGB 151105 at the same time that he is pre-registered to CALGB 70807 and in addition to collecting the required plasma for carotenoid and cholesterol testing; whole blood, serum, and unstained slides should be collected per Section 6.2. Whole blood samples should be submitted at the time of pre-registration.

5.4 Run-In

Within one week of receiving the C-2010, MEAL Participant Contact Information Form from sites, patients will be called by the nutrition unit at UCSD on randomly selected days to complete three 24-hour dietary recalls. The series of dietary recalls will be completed within 2-3 weeks. Participants will have two chances to successfully complete the run-in.

5.5 Patient Registration/Randomization

Upon completion of the run-in, UCSD staff will notify the site and the study Data Coordinator about patient eligibility. Eligible patients who completed the run-in and consumed fewer than 6 servings of fruit and vegetables per day will then be registered and randomized by the site. Patients who are determined to be ineligible for the study should be notified by participating institution staff.

Registration procedures:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user id and password) used for the CTSU members' web site.
- To perform registrations, the site user must have been assigned the 'Registrar' role on the relevant Group or CTSU roster.

The OPEN system will provide the site with a printable confirmation of registration. Please print this confirmation for your records.

Once the randomization is complete, patients will be contacted by UCSD staff for their initial orientation telephone call. Patients will also receive an enrollment packet, provided by UCSD, which will contain the informational materials described in Section 8.3.

5.6 Registration to companion study 151105

If a patient answered "yes" to "I agree that my specimens may be used for the research studies described above." (Question #1) in the Model Consent, the patient should have been pre-registered to CALGB 151105 at the same time that he was pre-registered to 70807. At this time, patients who were pre-registered to 151105 should be registered to the study and samples submitted per Section 6.2.

5.7 Stratification Factors

1. Age
   - a) Men ≤ 70 years
   - b) Men > 70 years
2. Race
   - a) Black or African American
   - b) Other
3. Baseline Prostate Biopsy
   - a) 0-12 months prior to pre-registration
   - b) > 12-24 months prior to pre-registration

6.0 DATA SUBMISSION AND SAMPLE SUBMISSION

6.1 Data Submission

Forms should be submitted to the Alliance Statistics and Data Center (SDC) in compliance with the Data Submission Schedule below.

Forms must be submitted electronically using the "Submit to CALGB" button located at the bottom of the last page of each form. Any required forms, supporting documentation or amended forms that cannot be submitted electronically should be mailed directly to the Alliance Data Center for scanning and quality review at the address below:

Alliance Data Center

[redacted]

For the most up-to-date forms, please visit the Alliance or CTSU web site.

Data Submission Schedule:

Form		Submission Schedule
	Pre-Registration	
	Pre-Registration Worksheet	Submit at pre-registration
C-2010	MEAL Participant Contact Information Form	Submit to UCSD staff (See Sec. 5.2)
	Registration	
	Registration Worksheet	Submit within 2 weeks of registration
C-2012	CALGB 70807 On Study Form	
C-2002	CALGB 70807 Personal Habits Questionnaire	**To be administered to patients at the pre-registration visit** and submitted to the Alliance Statistics and Data Center within 2 weeks of registration.
C-2003	CALGB 70807 MAX-PC Form	
C-2004	CALGB 70807 Nutritional Self Efficacy Form	
C-2005	CALGB 70807 IPSS Form	
C-2023	CALGB 70807 EPIC-26 Form	
C-2007	CALGB 70807 FACT-P Form	
	During Intervention	
C-2013	CALGB 70807 Follow Up Form	Submit at 3, 6, 9, 12, 15, 18, 21, 24 months
C-2081	CALGB 70807 PSA Doubling Time Form	Submit at 6 months
C-2003	CALGB 70807 MAX-PC Form	Submit at 6, 12, 18 and 24 months
C-2005	CALGB 70807 I-PSS Form	
C-2023	CALGB 70807 EPIC-26 Form	
C-2007	CALGB 70807 FACT-P Form	
C-2004	CALGB 70807 Nutritional Self Efficacy Form	**Arm A patients only:** Submit at 6, 12, 18 and 24 months
C-2008	CALGB 70807 MEAL Study Counseling Evaluation Form	**Arm A patients only:** Submit at 12 and 24 months
	Post Intervention Follow-Up	
C-2013	CALGB 70807 Follow Up Form	Submit every 3 months until 2 years from date of registration (see Section 8.7)
	Other	
C-260	CALGB Remarks Addenda	Submit as needed

If a study participant chooses to withdraw from the study, submit the C-260 CALGB Remarks Addenda to the Alliance Data Center and copy by fax [redacted]

6.2 Sample Collection and Submission

Histopathology review will be conducted using specimens from prostate biopsies. **The submission of these samples for histopathology review is required for all patients registered to this study.**

In addition, submission of plasma samples for carotenoid and cholesterol analyses is required for all patients registered to this study. Rationale and methods for the scientific components of these studies are described in Section 10.1.

Finally, all participating institutions must ask patients for their consent for the use of serum, whole blood, and unstained slides for the additional carotenoid and polymorphism analyses described in Sections 10.2, 10.3, and 10.4 (sub-study CALGB 151105).

Submit slides and blood samples as described below.

	Pre-registration*	**12 months****	**24 months****	**Ship to:**
	Required for all patients registered to 70807			
H&E slides	X		X	OSU
Plasma (Green top)	1 x 10 mL	1 x 10 mL	1 x 10 mL	OSU
	Required for patients registered to 70807 and substudy 151105			
Serum (Red top)	1 x 10 mL	1 x 10 mL	1 x 10 mL	OSU
Whole blood (Lavender top)	1 x 10 mL			OSU
Unstained slides	X			OSU

- Pre-registration samples should be submitted within two weeks after the patient has been registered and randomized to the study; except whole blood samples, which should be submitted on the same day as collection. If the patient does not complete the run-in, or is not registered/randomized to the study for any other reason, samples collected at pre-registration should be destroyed per institutional practice. The whole blood sample submitted at pre-registration will be destroyed by staff at the Alliance Biorepository at OSU.

** Blood samples should be collected and submitted regardless of whether the patient has progressed or elected to receive therapy. H & E slides at the 24-month time point are not required for patients who have started definitive treatment (e.g., prostatectomy or radiation therapy).

USE OF THE ALLIANCE BIOSPECIMEN MANAGEMENT SYSTEM (BioMS) IS MANDATORY AND ALL SPECIMENS MUST BE LOGGED AND SHIPPED VIA THIS SYSTEM.

BioMS is a web-based system for logging and tracking all biospecimens collected on Alliance trials. Authorized individuals may access BioMS at the following URL: http://bioms.allianceforclinicaltrialsinoncology.org using most standard web browsers (Safari, Firefox, Internet Explorer). For information on using the BioMS system, please refer to the 'Help' links on the BioMS web page to access the on-line user manual, FAQs, and training videos. To report technical problems, such as login issues or application errors, please contact: [redacted]. For assistance in using the application or questions or problems related to specific specimen logging, please contact: [redacted]

After logging collected specimens in BioMS, the system will create a shipping manifest. This shipping manifest must be printed and placed in the shipment container with the specimens.

All submitted specimens must be labeled with the protocol number (70807), patient study ID number, patient's initials and date and type of specimen collected (e.g., serum, whole blood). A copy of the Shipment Packing Slip produced by BioMS must be printed and placed in the shipment with the specimens.

Instructions for the collection of samples are included below. Please be sure to use a method of shipping that is secure and traceable. Extreme heat precautions should be taken when necessary.

Shipment on Monday through Friday by overnight service to assure receipt is encouraged. If shipping on Friday, FedEx or UPS must be used and the air bill must be marked "For Saturday delivery." Do not ship specimens on Saturdays.

All specimens should be sent to the following address:

Alliance Biorepository at Ohio State University
The Ohio State University
Innovation Centre
[redacted]

6.2.1 Submission of H&E stained prostate biopsy slides (required for all patients)

Pathology specimens will be collected with a minimum of 10 tissue cores obtained utilizing a standard, extended biopsy pattern for confirmation of prostate pathology. Prostate biopsy slides will be submitted at baseline and 24 months.

Additional biopsies: If, at the discretion of the treating physician, a patient undergoes additional prostate biopsies at a time other than 24 months, the prostate biopsy slides from these additional prostate biopsies should be submitted as well.

Representative stained hematoxylin and eosin (H&E) diagnostic slides from each biopsy site/container are to be submitted to the Alliance Biorepository at Ohio State University for review. The pre-registration sample should be from the initial biopsy showing diagnosis of cancer. Submission of paraffin embedded tissue blocks is not required. Submission of the local pathology report is required. The local pathology report should contain the number of cores obtained for each biopsy to allow central verification that ≥ 10 cores were obtained for each biopsy.

Biopsy slides will be reviewed by [redacted]. The Alliance Biorepository at Ohio State University will scan the slides and upload the images to a website and [redacted] will review the scanned images. She will forward her evaluation to the Alliance Statistics and Data Center.

If H&E stained slides are not available for submission, digital images may be submitted. Please contact [redacted] for further instructions.

6.2.2 Plasma samples (required for all patients)

Throughout all stages of blood processing, shipping, and handling, it is very important to prevent prolonged exposure of samples and separated blood components to light. Work quickly and efficiently. When samples and sample components must be set aside, cover them or put them away from light.

First prepare the vacutainer tubes for protection from light by wrapping aluminum foil around the tube prior to filling it or putting it in a red or amber colored specimen bag.

Draw 10 mL of whole blood in a green top (heparin coagulant) tube and gently invert it once or twice to mix the additive with the blood. Immediately replace the tube into the previously prepared aluminum foil slip or place it into the red or amber colored specimen bag.

Samples should be processed within 30 minutes of collection. If this is not possible, the tube(s) should be refrigerated until centrifugation. Before centrifugation, make sure the brake is off, the speed is set between 2,800 – 3,000 rpm, the temperature is 4° to 8° C and the centrifugation time is set at 10 minutes.

After centrifuging for 10 minutes, allow the centrifuge to come to a complete stop before opening the cover. Do not use the brake as it may cause the red blood cells to become re-suspended in the plasma. Any tube containing red blood cells in the plasma should be re-centrifuged. Immediately return the tubes to the light protection device (aluminum foil pouch or red or amber bag).

The plasma should be aliquotted into cryovials* within 15 minutes after centrifuging. All plasma samples will be pipetted as 0.8 mL amounts into the cryogenic storage vials. Place the samples in the -70°C freezer as soon as possible after aliquotting. Samples must be frozen at least 2 hours before packing them for shipment. If a -70° C freezer is not available, the cryovials can be stored in a -20°C freezer immediately after aliquotting, and then transferred to a -70° C freezer as soon as possible, but for no longer than 2 days (over the weekend). Placing the samples on wet ice or dry ice does not sufficiently preserve the sample; at least a -20° C freezer is required. Samples may NOT be thawed after freezing. See Section 6.2.4 for packing and shipping instructions.

* Cryovial Choices: Some examples of acceptable 2.0 ml cryovials are: Nalgene (Cat #5012-0020), Fisher (Cat #05-669-57), Corning (Cat #430488), VWR (Cat #16001-102).

6.2.3 Serum samples (required for patients enrolled to substudy 151105)

Throughout all stages of blood processing, shipping, and handling, it is very important to prevent prolonged exposure of samples and separated blood components to light. Work quickly and efficiently. When samples and sample components must be set aside, cover them or put them away from light.

First prepare the vacutainer tubes for protection from light by wrapping aluminum foil around the tube prior to filling it or putting it in a red or amber colored specimen bag.

Draw 10 mL of whole blood in a red top tube and gently invert 5 times to mix clot activator with blood. Let blood clot for 30 minutes. Observe a dense clot. Immediately replace the tube into the previously prepared aluminum foil slip or place it into the red or amber colored specimen bag.

Samples should be processed within 30 minutes of collection. If this is not possible, the tube(s) should be refrigerated until centrifugation. Before centrifugation, make sure the brake is off, the speed is set between 2,800 – 3,000 rpm, the temperature is 4° to 8° C and the centrifugation time is set at 10 minutes.

Before you start the centrifugation, make sure the brake is off, the speed is set between 2,800 - 3,000 rpm, the temperature is 4-degrees C to 8-degrees C and the centrifugation time is set at 10 minutes.

After centrifuging for 10 minutes, allow the centrifuge to come to a complete stop before opening the cover. Do not use the brake as it may cause the red blood cells to become re-suspended in the serum. Any tube containing red blood cells in the serum should be re-centrifuged. Immediately return the tubes to the light protection device (aluminum foil pouch or red or amber bag).

The serum should be aliquotted into cryovials* within 15 minutes after centrifuging. All serum samples will be pipetted as 0.8 mL amounts into the cryogenic storage vials. Place the samples in the -70°C freezer as soon as possible after aliquotting. Samples must be frozen at least 2 hours before packing them for shipment. If a -70° C freezer is not available, the cryovials can be stored in a -20°C freezer immediately after aliquotting, and then transferred to a -70°C freezer as soon as possible, but for no longer than 2 days (over the weekend). Placing the samples on wet ice or dry ice does not sufficiently preserve the sample; at least a -20°C freezer is required. Samples may NOT be thawed after freezing. See Section 6.2.4 for packing and shipping instructions.

* Cryovial Choices: Some examples of acceptable 2.0 ml cryovials are: Nalgene (Cat #5012-0020), Fisher (Cat #05-669-57), Corning (Cat #430488), VWR (Cat #16001-102).

6.2.4 Packing and shipping instructions for plasma and serum samples

(1) Place dry ice nuggets on the bottom of the insulated shipping container.

(2) Place each freezer box in a sealed plastic bag. Remove as much air as possible from the bag before sealing.

(3) Place the sealed bags in the insulated shipping container on top of the dry ice.

(4) Layer additional* dry ice on top of and around the plastic bags. Place any remaining freezer boxes in sealed plastic bags on top of the dry ice.

* Overnight deliveries should contain about 10-12 pounds of dry ice. This will allow the package to remain frozen for 48 hours in case the shipment is delayed.

(5) Seal the shipping fiberboard box tightly and tape all seams with waterproof tape. To delay thawing, place the box in the -70° C freezer to await pickup. This step need not be done if the box is packed within 2-3 hours of pickup.

Ship specimens to:

Alliance Biorepository at Ohio State University
The Ohio State University
Innovation Centre
[redacted]

Shipment on Monday through Friday by overnight service to assure receipt is encouraged. If shipping on Friday, FedEx or UPS must be used and the air bill must be marked "For Saturday delivery." Do not ship specimens on Saturdays.

6.2.5 Whole blood (required for patients enrolled to substudy 151105)

Draw 10 mL whole blood in a lavender top (EDTA coagulant) tube and keep refrigerated until shipped overnight to the Alliance Biorepository at Ohio State University. Label the tube with the patient's initials, patient study ID number, study number (CALGB 70807), and date of collection. The sample should be shipped the same day on a cold pack by overnight mail to:

Alliance Biorepository at Ohio State University
The Ohio State University
Innovation Centre
[redacted]

Shipment on Monday through Friday by overnight service to assure receipt is encouraged. If shipping on Friday, FedEx or UPS must be used and the air bill must be marked "For Saturday delivery." Do not ship specimens on Saturdays.

6.2.6 Submission of unstained diagnostic prostate biopsy slides (required for patients enrolled to substudy 151105)

Submit ten, or as many slides as contain cancer, 5 μm unstained sections on charged glass slides from the formalin-fixed, paraffin-embedded, diagnostic prostate biopsy blocks to the Alliance Biorepository at The Ohio State University (see Section 6.2). Label the slides with patient study ID number, accession number, and order of sections.

7.0 REQUIRED DATA

Guidelines for Pre-Study Testing

To be completed within 3 months before preregistration

- Baseline PSA, history and physical, DRE

To be completed within 24 months before preregistration

- Prostate Biopsy

	Preregis-tration	Run-in	Month*							
			3	6	9	12	15	18	21	24
Test and Observations										
History and Physical	X			X		X		X		X
Height†	X									
Weight†	X			X		X		X		X
DRE	X					PRN				PRN
Diet Recall		A				A				A
Labs and Staging										
PSA	X		X	X	X	X	X	X	X	X
QOL Instruments										
Personal Habits Questionnaire	B									
MAX-PC	B			X		X		X		X
Nutritional Self-Efficacy	B			D		D		D		D
I-PSS	B			X		X		X		X
EPIC-26	B			X		X		X		X
FACT-P	B			X		X		X		X
MEAL Counseling Evaluation						D				D
Sample Submission										
Plasma for Carotenoid Analysis	C					X				X
H & E biopsy slides‡	C									X(1)
Correlative Study										
Serum Whole Blood Unstained Slides‡	*See Section 6.2.*									

A To be conducted by UCSD staff.

B To be administered to all patients at the pre-registration visit and submitted after the patient is registered to the study.

C To be collected for all patients at the pre-registration visit and submitted after the patient is registered to the study.

D To be administered to patients randomized to Arm A only.

* Clinic visits may be done within +/- 2 weeks of the scheduled 3-, 6-, 9-, etc. month visit. These visits are to be scheduled from the date of randomization.

† Refer to Section 8.1 for height and weight measurement instructions.

‡ Slides should be from the initial biopsy showing diagnosis of cancer.

1 24-month biopsy is not required for patients who have started definitive treatment (e.g., prostatectomy or radiation therapy).

8.0 INTERVENTION

The principal strategy to promote dietary change in the intervention arm will be a telephone counseling protocol with individualized, one-on-one assistance tailored to each participant. The intervention will last 24 months. Intervention participants will engage in a series of telephone-based diet counseling sessions throughout the study. The first phase of sessions will guide initial diet-change attempts, the second will help participants complete their diet changes, and the third and fourth phases will enable participants to maintain and monitor their diet changes. This highly structured, computer-assisted telephone counseling protocol will facilitate standardization of the intervention.

8.1 Preregistration

8.1.1 Contact information and QOL assessments: At preregistration participants will complete the C-2010, MEAL Participant Contact Information Form. This form is to be faxed by institutional staff to UCSD within 24 hours of preregistration.

All patients will be asked to complete the QOL instruments listed in Section 7.0. These forms should be submitted to the Alliance Statistics and Data Center after the run-in period and within 2 weeks of registration.

8.1.2 Blood sample collection: In addition, all patients will be asked to provide a 6-hour fasting blood sample for carotenoid and cholesterol analysis. This sample should not be submitted until within 2 weeks after registration.

8.1.3 Clinical assessments

Urologic assessment: At initial assessment, participants will be evaluated in a urology clinic as per typical AS protocols and current standard of care (2-4, 11, 13). Urological evaluations will be conducted by the GU Investigator or appropriate designee at each site. The baseline visit will include a DRE to confirm clinical stage. DRE will entail palpation of the posterior and posterolateral aspects of the entire prostate in the standard fashion.

Height and weight must be obtained during preregistration. Below are recommended guidelines to obtain these measurements in an accurate manner.

Height: Measure the participant's height without shoes, using a stadiometer. Ask participant to stand up with heels together and weight equally distributed. Ideally, participants heels, buttocks, shoulders, and head should all touch the vertical board; however, in some cases this may not be possible. In this event, take the measurement with buttocks and heels touching the vertical board, or with head and buttocks touching the vertical board. Ask the participant to breath in deeply at which juncture the movable headboard should be placed on the head with only enough pressure to slightly compress the hair. Record height to the nearest 0.25 inch, rounding down.

Weight: Weigh each participant on a medical balance or electronic scale in light clothing without shoes. Each participant should be weighed on the same scale throughout the study. Place the scale on a level uncarpeted floor surface. Before each weighing, check the scale to confirm that it reads zero in the absence of a load, and if necessary adjust it to read zero. If the participant's feet are bare, one may place a disposable paper towel on the scale platform. Ask the participant to stand still on the scale platform, arms down at their sides, and feet centered on the platform with weight evenly distributed. Record weight to the nearest pound.

8.2 Run-In

Eligible patients will be contacted by UCSD staff within a week to schedule a series of three 24-hour dietary recalls which will be completed within 3 weeks.

8.3 Registration/Randomization

Upon completion of the run-in, UCSD staff will notify the site and the study Data Coordinator about patient eligibility. Eligible patients who successfully completed the

run-in and consumed fewer than 6 servings of fruits and vegetables (not including juices) per day will then be randomized.

After randomization, all patients will participate in a 5-10 minute telephone orientation conducted by staff from the Moores UCSD Cancer Center explaining the randomization results and the next study-related events. The orientation call for intervention participants randomized to Arm A will briefly explain the counseling program, the dietary targets, and the scientific rationale supporting these targets. The UCSD study staff will mail all participants (Arm A and Arm B) a copy of the Prostate Cancer Foundation Booklet entitled "Nutrition, Exercise and Prostate Cancer." In addition, participants randomized to the counseling intervention (Arm A) will also be mailed a copy of the study-specific "Lifestyle Intervention Manual" which will be referred to during every counseling call. The manual outlines the dietary targets, offers supporting information on strategies to achieve these targets, supplies reference tools to help participants accurately estimate servings of target foods, and offers recipes and articles about diet and prostate cancer.

All counseling will be performed by telephone from the Moores UCSD Cancer Center using a counseling program and infrastructure of personnel developed during the WHEL (68) and MEAL (40, 42) studies. The protocol will follow a step-wise, phased approach employing strategies adopted from social cognitive theory. Motivational interviewing techniques will be utilized to help patients maintain responsibility for their own behavior change.

Each participant in Arm A will be assigned to a personal counselor/coach; if the participant has a spouse or significant other, the counselor/coach will also seek to enlist his or her cooperation and support. Counselors will work morning, afternoon, or evening shifts, and every effort will be made to assign participants to a counselor working when they prefer to receive calls. Call length will range from 20-40 minutes. Calls will be more frequent and of longer duration during the early phases of counseling.

Educational materials will be sent to patients on a schedule that supports the behavioral intervention goals.

The Lifestyle Intervention Manual that patients enrolled to Arm A receive will include background material on dietary targets, as well as monitoring forms that patients can use to monitor their dietary change.

Newsletters: In order to maintain participant morale, UCSD staff will develop eight newsletters for participants on both arms of the study. Each newsletter will be four pages and will contain information about diet and healthy lifestyle, as well as diet and cancer. Recipes will also be included in these newsletters. The content of the first three pages of the newsletters will be nearly identical. The fourth page of the newsletters, which will provide recipes to participants, will vary by group.

These newsletters will be distributed to participants by participating sites every three months (quarterly). Electronic versions of the newsletters will be made available on the Alliance and the CTSU Web sites. Institutions must receive IRB approval of these newsletters prior to their distribution to patients. Care should be taken to ensure that patients receive the newsletter tailored to the arm to which they are randomized.

Each participant will receive a total of 8 newsletters, beginning with the newsletter scheduled for distribution during the quarter in which they were randomized. For example, patients randomized during the first quarter of 2012 should receive the newsletter entitled "Comfort Foods" as their first newsletter while on study. The planned distribution schedule is as follows:

Number	Topic	Distributed to study participants
1	Portion Control	July-Sept. 2011
2	Quick & Easy	Oct.-Dec. 2011
3	Comfort Foods	Jan.-Mar. 2012
4	Social Support	Apr.-June 2012
5	Breakfast	July-Sept. 2012
6	Meal and Energy Bars	Oct.-Dec. 2012
7	Solo Suppers	Jan.-Mar. 2013
8	Cheap Eats	Apr.-June 2013

Number	Topic	Distributed to study participants
1	Portion Control	July-Sept. 2013
2	Quick & Easy	Oct.-Dec. 2013
3	Comfort Foods	Jan.-Mar. 2014
4	Social Support	Apr.-June 2014
5	Breakfast	July-Sept. 2014
6	Meal and Energy Bars	Oct.-Dec. 2014
7	Solo Suppers	Jan.-Mar. 2015
8	Cheap Eats	Apr.-June 2015

8.4 Clinic Visits

PSA Measures (Every 3 Months)

Serum PSA levels will be measured at baseline and at every 3 months thereafter. PSADT will be calculated as log2 divided by the slope (the least squares estimator) of log (PSA) observations over time using the last three PSA measurements (44, 83, 100). An example of a PSADT calculator can be found at www.ASURE.ca.

History & Physical (Every 6 Months)

Participants will be evaluated in a urology clinic at initial assessment and every 6 months thereafter as per typical AS protocols and current standard of care (2-4, 11, 13). Patients must be weighed and their height measured according to the instructions in Section 8.1. Urological evaluations will be conducted by the GU Investigator or appropriate designee (e.g., medical oncologist, PA, NP) at each site. The baseline visit will include a DRE to confirm clinical stage. Since PSA and biopsy changes are much more sensitive for detecting clinical progression than changes in prostate examination among patients on AS (11), subsequent DRE will be performed at the discretion of the individual urologist. These results will not be used to define progression.

Prostate Biopsy (24 Months)

Prostate biopsy will be performed by the treating urologist at 24 months with a minimum of 10 tissue cores obtained utilizing a standard, extended biopsy pattern. This practice is consistent with current standard of care in the urological community. The urologist or the participant will have the right to secure a biopsy earlier than 24 months. Although DRE is commonly used in oncologic practice, it is not highly quantifiable for men with the very small, often non-palpable tumors of our study participants.

Blood Sample Submission (12, 24 Months)

Six-hour fasting blood samples will be collected at preregistration, 12 and 24 months and will be submitted to the Alliance Biorepository at Ohio State University (see Section 6.2.1) and analyzed for carotenoid and cholesterol concentrations.

Quality of Life Instruments (Every 6 Months)

Seven quality of life measures will be used: Personal Habits Questionnaire will be completed at pre-registration only, the Functional Assessment of Cancer Therapy Scale-Prostate (FACT-P); Memorial Anxiety Scale for Prostate Cancer (Max-PC); International Prostate Symptom Score (IPSS); Expanded Prostate Cancer Index Composite 26 (EPIC-26); and the Nutrition Self–Efficacy will be completed at preregistration and every 6 months. Finally, the MEAL Study Counseling Evaluation Form will be completed at 12 and 24 months (see Section 9.0).

8.5 Dietary Recall

Diets will be evaluated at baseline and at 12 and 24 months by a series of three separate 24-hour dietary recalls collected interactively via telephone interview conducted by the Moores Cancer staff. These telephone interviews will last approximately 20 minutes. Patient recalls will be performed on three randomly selected days over a three-week period and include two weekdays (Monday through Thursday) and one weekend (Friday through Sunday). Data will be catalogued and analyzed utilizing Minnesota Nutrition Data System (NDS) software (Nutrition Coordinating Center, University of Minnesota).

8.6 Telephone Counseling Intervention (Arm A Only)

The counseling intervention will be divided into four phases, with the first three phases completed in 7 months. The fourth phase will continue for 17 months. Each counseling call will take an average of 30 minutes.

Phase I: The first phase, composed of six counseling calls, will focus on education and the rapid development of self-efficacy skills. During this phase, frequent counseling sessions (every 3-4 days) will focus on short-term goals, emphasizing to participants and partners that the study dietary pattern can be compatible with their lifestyle. The counselor will monitor self-reported dietary intake interactively using dietary analysis software (The Food Processor for Windows, Version 7.8, ESHA Research, Salem, OR) to help the participant evaluate his performance and encourage him to concentrate on the positive aspects of his achievements before setting new sub-goals. Throughout this phase (and all other phases), counselors will encourage participants to report any difficulties in adopting the dietary pattern, and dietary targets will be adjusted accordingly to maximize chances of success.

Phase 2: The second phase, composed of four calls over a 2-month period, will focus on practical and consistent implementation of the dietary pattern. Counselors will help participants make structural changes to their food environments, such as altering the type of food available in the house, modifying recipes and patterns of food preparation, and focusing on portion sizes. Participants will learn to monitor their performance regularly, as counselors encourage goal setting and review.

Phase 3: The third phase, composed of four calls over a 4-month period, will help participants habituate to the dietary pattern by providing regular performance reviews. Studies of behavior change demonstrate that a declining sense of self-efficacy is associated with vulnerability to relapse. During this phase, social guidance and assistance in evaluating performance will be used to maintain interest in behavior maintenance, even as the level of necessary social guidance declines.

Phase 4: The counselors will regularly check on progress (8 calls over a 17-month period), providing positive feedback on achievements in maintaining the study targets while monitoring for warning signs of declining interest or self-efficacy. Ensuring participants that they can maintain the change they have implemented will still be critical. Intervention contacts will take place once every other month by those in Arm A only.

Dietary Targets: Participants in the intervention arm will be encouraged to achieve a challenging but attainable dietary pattern: 7 servings per day of vegetables (2 cruciferous, 2 tomato products, 3 other vegetables), 2 servings per day of whole grains, 1 serving per day of beans or other legumes, and 2 servings per day of fruit. Vegetable juice will be promoted as a means of increasing vegetable nutrients without the potential gastrointestinal problems of very high fiber intake. As vegetable intake appears most strongly associated with protection, the intervention will emphasize vegetable intake.

To maximize intake of the most bioactive nutrients and phytochemicals, intervention participants will be instructed to omit fruit juice, iceberg lettuce, and white potatoes from their calculations of plant vegetable and fruit servings. Counselor/coaches will emphasize colorful vegetables along with strong-flavored produce (cruciferous vegetables, onions, garlic), since strong flavor is an indicator (albeit crude) of phytochemical concentration. Within the context of these overall dietary targets, participants will be guided to obtain an adequate intake of all essential nutrients.

8.6.1 Quality control

Quality control will be enhanced by providing the telephone counseling from a centralized location at the Moores UCSD Cancer Center, thus enabling weekly case management meetings and flexibility in scheduling. Dietary counselors will be hired based on their demonstrated communication skills, telephone manner, knowledge of food and nutrition, and their enthusiasm for achieving the study dietary targets. Counselors will complete an intensive 80-hour training program addressing the rationale for the study, protocols for conducting 24-hour dietary recalls, the principles and practice of motivational interviewing and review of a random selection of recorded calls.

All counselors will practice extensive role-playing before conducting their first coaching session. This training will be overseen by the UCSD behavior change study team; the team has been involved in a multitude of behavior change studies.

We have developed a detailed, relational database that provides counselors with a computer-assisted coaching protocol for their participant contacts. All contacts will be recorded in the database, and the database will generate the call schedule for each counselor each day. Calls will then follow a script that includes suggested question phrasing and responses to key questions inserted into the database in real time; these standardize intervention delivery. Automatic range checks will ensure quality in the dataset. At the completion of each call, the counselor will be prompted for detailed comments that can be used in the next contact. These comments will be reviewed by the supervisor as a component of performance review. Each counselor's performance will be compared to that of his or her peers, in terms of achieving dietary change toward study goals and in keeping the database complete.

The database will provide weekly management reports to focus on key aspects of study progress, including delinquent data collection. The database will help us monitor regularly scheduled study operations, to comply with aspects of the protocol. For example, study reports will be generated, as needed, to identify intervention participants who have not been contacted as scheduled in the protocol. The reports will be provided to the counselors to help keep them on schedule, and to ensure that participants with lagging performance or possibly lagging interest do not drop out of the study.

To maximize effectiveness of the intervention, we will seek participant permission, in advance, to monitor calls. We will then monitor 10% of calls. The calls will be audio-taped and reviewed by peers and by supervisors to ensure that the intervention is standardized across participants. Throughout the study period, weekly case-management sessions will be conducted; supervisors, study investigators and counselors will use these to resolve challenging issues that have emerged.

A registered dietitian will supervise the telephone counseling intervention team. Counselors will also attend monthly 2-hour meetings, which will include updates on

study progress and in-service training on nutrition and behavior change counseling. On a quarterly basis, counselors will be provided with an assessment of their caseload's adherence to the dietary targets as a means of maintaining or improving performance. Together, these procedures, have contributed to the success of the WHEL (68) and MEAL (40-42) interventions.

8.7 Completion of Intervention

All patients are expected to participate in the diet intervention for 24 months.

8.7.1 Off Treatment Criteria

Off-Treatment criteria will include the following: 1) physician determination that continuation of the diet is medically contraindicated, 2) participant decision to withdraw from the dietary intervention, or 3) participant death. If a study participant chooses to withdraw from the study, submit the C-260 CALGB Remarks Addenda to the Alliance Data Center and copy by fax [redacted]

8.7.2 Clinical Criteria for Progression and Active Treatment

The primary outcome of interest in this prevention trial is disease progression defined by (a) PSA doubling time (PSADT) less than 3 years, (b) PSA above 10 at any time, or (c) Gleason score on repeat biopsy ≥ 7 for men younger than 70 years and ≥ 4+3 = 7 for men 70 years or older. These criteria are drawn from one of the largest active surveillance studies to date, the Toronto cohort (12).

Participants who do not meet PSA or biopsy criteria for progression are strongly encouraged to remain on AS while in the study and not undergo treatment with surgery, radiation, local ablation, or androgen deprivation. These criteria reflect the current standard of care (11,12) and are as follows:

a) PSA doubling time (PSADT) < 3 years

b) PSA ≥ 10 ng/mL

If the treating physician suspects that a single measurement of PSA ≥ 10 ng/mL represents a spurious rise unrelated to cancer progression (e.g., clinical prostatitis, asymptomatic prostatitis in association with a viral syndrome, or instrumentation of the urinary/gastrointestinal tracts), a repeat PSA may be drawn up to 2 weeks later. If the repeat PSA value is less than 10 ng/mL, then that repeat PSA value shall be recorded for that visit. If the repeat PSA value ≥ 10 ng/mL, the first PSA value should be recorded for that visit.

c) Repeat biopsy

- ≥ 25% of biopsy tissue cores positive for cancer
- > 50% of any one biopsy tissue core positive for cancer
- Men < 70 years at baseline: Gleason sum ≥ 7
- Men ≥ 70 years at baseline: Gleason sum ≥ 4+3 = 7

It is recognized that some participants will elect to pursue treatment during the study despite not meeting these criteria for progression. These participants will be censored at the time they begin treatment.

8.7.3 Continuation of the Dietary Intervention

Patients should continue intervention and follow-up for the two-year duration of the study regardless of progression or electing to receive therapy.

9.0 OUTCOMES ASSESSMENT/QUALITY OF LIFE MEASURES

Seven quality of life measures will be used: Personal Habits Questionnaire, Functional Assessment of Cancer Therapy Scale-Prostate (FACT-P); Memorial Anxiety Scale for Prostate Cancer (Max-PC); International Prostate Symptom Score (IPSS); Expanded Prostate Cancer Index Composite 26 (EPIC-26); Nutrition Self –Efficacy and Satisfaction with the MEAL Program.

9.1 Personal Habits Questionnaire

The personal habits questionnaire, used in the Women's Health Initiative (WHEL) study (66), consists of 8 sets of questions that address a number of generic health behavior questions: cigarette smoking; alcohol consumption; weight change during adult life; adherence to any kind of special diet (e.g. low-calorie, low-fat, low-cholesterol, low salt, high-fiber); recreational physical activity, including mild, moderate and strenuous activity; and physical activity at various ages. These questions, which will be used mainly to make sure randomization produced comparable groups, are as appropriate for men as for women.

9.2 Functional Assessment of Cancer Therapy Scale-Prostate [FACT-P]

The FACT-P [version 4.0], developed by Cella and colleagues (44, 51) is a prostate cancer specific quality of life questionnaire which includes a 27 item 'core' quality of life measure [FACT-G] grouped into four subscales: physical well-being, social/family well-being, emotional well-being, and functional well-being. There are an additional 12 items specific to prostate cancer, 10 of which are prostate cancer-specific physical problems. Almost all FACT-P subscale items are rated on a 5 item Likert scale, from 0, 'not at all' to 4, 'very much'. The FACT-G has been tested on 630 patients with mixed cancer diagnoses. The internal consistency of the subscales ranges from .65-.82, with excellent internal consistency of the total score: an alpha coefficient of .89. Test-retest reliability is excellent within a 7 day period, with correlations ranging from .82-.92. Convergent validity has been demonstrated, with the FACT correlating significantly with other quality of life measures (FLIC, r=.79), and related constructs of psychological distress (e.g. Brief POMS, r=-.68) and the ECOG performance rating (r=-.52). The FACT-G has been able to distinguish between patients with metastatic and non-metastatic disease. Internal consistency of the Prostate-Specific Concerns subscale was of moderate strength (alpha coefficients ranging from .65-.69] when tested with 130 prostate cancer patients (44). Evidence of convergent validity of the Prostate-Specific Concerns subscale was provided by its significant negative correlations with depression (Inventory to Diagnose Depression, r= -.34, p< .001), and anxiety (Spielberger Trait Anxiety Scale, r= -.33, p< .001). Further, significantly greater Prostate-Specific Concerns scores were found for those with more advanced disease than those with earlier stage disease. Sensitivity to change over time was also demonstrated by significantly greater worsening of Physical and Functional Well-being, and Prostate-Specific Concerns subscale scores over a two month period for those with worsening Performance Status (44).

9.3 Memorial Anxiety Scale for Prostate Cancer [MAX-PC]

The Memorial Anxiety Scale for Prostate Cancer [MAX-PC] is a prostate cancer-specific measure to assess patient anxiety due to prostate cancer, PSA tests and fears of recurrence (45, 46). It consists of 18 items: 11 items that parallel items from the Impact of Event Scale, including avoidant and intrusive thoughts about prostate cancer (48); 3 items specific to PSA tests, and 4 items concerning fear of recurrence. The items are grouped into three subscales: Prostate Cancer Anxiety (PCA), PSA Anxiety, and Fear of Recurrence. Fourteen items are rated on a four point Likert scale ranging from 'not at all' to 'often' and 4 items are rated on a Likert scale ranging from 'strongly agree' to 'strongly disagree'. Internal consistency for the total score is excellent (alpha coefficient = .89). The PCA and Fear of Recurrence also demonstrated strong internal consistency (PCA alpha coefficient = .90; Fear = .85) (45). Test-retest reliability is excellent for the total score and three subscales (.74 - .89). The three factor model was confirmed in a second study of the MAX-PC (46). Total scores correlated significantly with other measures of distress, including the HADS (r=.52, p< .0001) and the Distress Thermometer (r =.45, p< .0001). Significant correlations were also found between changes in the MAX-PC score with changes in the HADS total score (r=.30, p< .0001). Further, there was a significant difference among four PSA change groups (i.e. steady, rising, falling and unstable) for the MAX-PC (p = .003), PCA (p = .045), and the Fear of Recurrence subscale (p= .0001).

Anxiety reduction is a legitimate and robust outcome variable and a potential benefit of the counseling intervention. Moreover, it is likely that the distribution of printed dietary guidelines and intermittent phone calls to monitor diet intake, would potentially diminish anxiety in the control group because it involves more attention than active surveillance patients normally receive as part of clinical care (72).

9.4 International Prostate Symptom Score (IPSS)

This is an 8-item scale, widely used in clinical practice, which measures lower urinary tract symptoms. It includes questions encompassing incomplete bladder emptying, frequent urination, urgency, nocturia, intermittency, weak stream, straining, and quality of life related to urinary symptoms (73).

There are robust data to suggest that prostate cancer patients on active surveillance experience significantly decreased urinary health relative to men without prostate cancer. In a cohort analysis of 6,000 community dwelling older men, we observed that compared to men without prostate cancer, men with prostate cancer on active surveillance (i.e. those who had not undergone treatment) reported a significantly diminished quality of life due to urinary symptoms (74). In addition, several published studies have noted that high vegetable diets and higher serum carotenoid concentration are associated with decreased urinary symptoms (75-77).

9.5 Expanded Prostate Cancer Composite Index 26 (EPIC-26)

This instrument is an abbreviated version of the Expanded Prostate Cancer Composite Index (EPIC). It contains 26 questions focusing on 5 distinct health-related quality of life domains relevant to prostate cancer: urinary incontinence, urinary irritation/obstruction, bowel, sexual and vitality/hormonal. Each domain has function and other subdomains. All of the domains for EPIC-26 are reported using a 0-100 score, with higher scores representing favorable health related quality of life. The EPIC-26 demonstrates robust consistency and validity for measuring these important outcomes related to prostate cancer survivorship (78).

9.6 Nutrition Self-Efficacy Scale

The Nutrition Self-Efficacy scale assesses the degree to which individuals are confident that that they can control their nutrition (79). The scale assesses perceived self-efficacy, the confidence in one's ability to meet one's goals, and coping self-efficacy, defined as optimistic beliefs about one's capability to deal with barriers that arise in plans. The scale consists of 5 items rated on a 5 point Likert scale, ranging from 'very confident' to 'not confident at all'. Internal consistency was excellent (alpha coefficient = .87, n= 1,722). Evidence of validity was provided by the Nutritional Efficacy Scale correlating significantly with nutritional behavior ($r = .34$, $p < .01$) (80). Because quality of life or anxiety has not been formally evaluated in an AS population or in the setting of a randomized clinical trial among AS patients, a battery of scores will be assessed as exploratory variables, with scores at each time point and changes in scores over time assessed between the intervention and control groups using student's t-test and linear regression modeling.

9.7 Satisfaction with the MEAL Program

At 12 and 24 months, those in the MEAL arm of the study will be asked to complete a series of questions about their satisfaction with the MEAL program (C-2008, CALGB 70807 MEAL Study Counseling Evaluation Form). All but one question has been used in WHEL, (Women's Healthy Eating and Living, the prior diet study on which this study is based). The MEAL Satisfaction Questionnaire, developed by Pierce and colleagues, includes 26 items with all items rated on Likert scales, with response categories varying by the type of question. The following areas of satisfaction are assessed: satisfaction with the nutritional plan, counseling calls, the counselor, the time and frequency of the calls, expectations that the diet will help to prevent recurrence and improve their overall health, barriers in attaining the dietary goals, and the difficulty encountered in changing and maintaining their diet. Internal consistency meets acceptable standards for the satisfaction with their food intake for the different types of food (5 questions, alpha coefficient = .71), satisfaction with the counselor (9 items, alpha coefficient = .87), and near an acceptable standard for the 2 items assessing how enjoyable and important the counseling calls have been (alpha coefficient = .69).

10.0 CORRELATIVE STUDIES

10.1 Plasma carotenoid and cholesterol analysis

10.1.1 Background

Carotenoids are organic, plant-based pigments. One of the most common carotenoids is lycopene. Lycopene is an antioxidant and free radical scavenger commonly found in tomatoes. Increased lycopene and tomato intake have been associated with decreased prostate cancer risk. An analysis of the Health Professionals Cohort observed a 21% lower prostate cancer incidence among those with the highest compared to the lowest lycopene intakes. Moreover, those with the highest frequencies of tomato and tomato-based product intake had up to a 35% risk reduction compared to those with the lowest intake (20). In a meta-analysis of 21 published studies, Etminan and colleagues observed that participants with the highest intake (fifth quintile of intake) of raw tomatoes [Relative Risk (RR) 0.89, 95% CI 0.8 to 1.0] or cooked tomatoes (RR 0.81, 95% CI 0.71 to 0.92) had a modest reduction in prostate cancer risk (10). These investigators also noted that while lycopene consumption was not associated with prostate cancer risk (RR 0.99, 95% CI 0.93-1.06), higher serum lycopene concentrations were associated with decreased risk (RR 0.85, 95% CI 0.75-0.97) (81).

Interest in the potential therapeutic benefits of lycopene and/or tomatoes has led to a small number of clinical trials that have produced promising, yet preliminary, results. Stacewicz-Sapuntzakis and Bowen placed 32 patients with prostate cancer on tomato paste-rich diet, 3 weeks before their scheduled prostatectomy. The patients consumed 26.8 mg of lycopene per day, compared with their usual mean intake of 5 mg/day. These investigators noted significant reductions in serum PSA concentrations and increases in apoptotic index in the intervention group compared with the controls (82). Similarly, Kucuk and colleagues randomized 26 patients with newly diagnosed prostate cancer to receive tomato oleoresin extract containing 30 mg of lycopene or no supplementation for 3 weeks before radical prostatectomy. When compared with the intervention group was found to have smaller tumors, less involvement of surgical margins, and less diffuse involvement of the prostate by high-grade prostatic intraepithelial neoplasia (83). Chen and colleagues observed in a radical prostatectomy model that men who consumed large amounts of tomato products prior to surgery had less oxidative damage in the prostate (30), while Barber and colleagues noted decreased PSA velocities in men with prostate cancer treated with lycopene supplementation (25).

While these data are compelling, associations of carotenoids with prostate cancer remain unclear. In the MEAL pilot study, there was no significant association of plasma lycopene or other carotenoids with plasma PSA over a 6-month period for AS patients or patients with PSA-only recurrence following surgery or radiation (40-42).

10.1.2 Objectives

10.1.2.1 To compare plasma carotenoid concentrations in AS patients receiving dietary intervention compared to no intervention.

10.1.2.2 To correlate plasma carotenoid concentrations with PSADT in AS patients.

10.1.2.3 To correlate plasma carotenoid concentrations with time to pathological progression in AS patients.

10.1.3 Methods

Carotenoids: The blood nutrient analysis will take place at UCSD under the direction of [redacted] The carotenoid analysis will be done at UCSD. Plasma carotenoids will be separated and quantified using the HPLC methodology that we have used previously (40, 67, 68), with modifications to reduce oxidative loss and improve recovery of compounds during analysis. Standard reference materials from the manufacturer will be used to validate analytical precision of these procedures. At UCSD, samples will be stored at all times at -70º C or lower temperatures in freezers equipped with temperature alarms in the Moores UCSD Cancer Center that are under the direct supervision of [redacted].

Cholesterol is analyzed using the KODAK EKTACHEM DT SLIDE. The slide is a multilayered film in a plastic support. It contains all the reagents necessary to determine cholesterol level in serum or plasma. A 10 uL drop of specimen is deposited on the slide. The sample spreads evenly and diffuses into the reagent layers. Cholesterol in the sample undergoes a series of reactions in the slide to produce a colored compound. The intensity of the color ids proportional to the amount of cholesterol in the sample and is measured by the KODAK EKTACHEM DT60 analyzer.

Principles of the procedure: The spreading layer distributes the sample evenly on the slide and causes the cholesterol to dissociate from lipoprotein carriers. Cholesterol esters are hydrolyzed to free cholesterol which then undergoes a series of reactions beginning with oxidation by the specific enzyme, cholesterol oxidase. In the final reaction, a colored dye is produced. By measuring the amount of light reflected from the dyed layer after a fixed incubation period, the DT60 Analyzer can calculate the amount of cholesterol present in the sample.

10.2 Serum carotenoid analyses (Substudy 151105)

Carotenoid analysis can be evaluated on plasma or serum. Therefore, in addition to the plasma sample, we will be collecting and banking serum for evaluation of carotenoids, if needed, as well as for the evaluation of other circulating markers of interest.

10.3 Polymorphism Analysis (Substudy 151105)

10.3.1 Background

Multiple genetic variants have been identified which are linked to increase risk of developing prostate carcinoma (84-89). There is increasing evidence that genetic factors could not only predispose men to prostate cancer in general but specifically for aggressive disease. For example CASP8 and MDM2 contain variants associated with risk of aggressive prostate carcinoma (90, 91). Cheng et al (92) and Beebe-Dimmer et al (93) demonstrated that at least some 8q24 variants are associated with risk of advanced disease. Duggan et al identified rs1571801, located in the DAB2IP gene, as a candidate which was associated with aggressive PCa in both European-Americans (p=0.004) and African-Americans (p=0.02) (94). Mononen et al found that 5' untranslated variant in CYP17A1 was associated with an increased risk of high grade PCa (95).

Identification of a population of patients at risk for aggressive disease is only useful if the disease can be prevented or treated effectively. Dietary manipulation holds promise as a way of preventing or ameliorating the risk of developing prosate carcinoma. There is a growing body of evidence that dietary factors may modify genetic risk. Several genes, such as *MnSOD, XRCC1*, and *GST*, may modify the association of specific nutrients and foods with prostate cancer risk and groups have called for further research to confirm these initial observations (96). For example, evidence from the Physicians Health Study suggests that manganese superoxide dismutase (*MnSOD*) polymorphism V16A may interact with selenium levels to modify risk of clinically aggressive PCa (97). *MnSOD* genotype were not associated with increased risk of disease. However, when they stratified the cases by prediagnostic

selenium levels they found that the cohort with the highest selenium levels and AA genotype were protected against prostate cancer in general and clinically aggressive prostate cancer specifically. Another example of genotype environment interaction is vitamin D and Vitamin D Receptor polymorphisms. A study from the Physicians Health Study demonstrated that while the Vitamin D Receptor polymorphism *Bsm*I or *Fok*I were not associated with prostate carcinoma, men with *Fok*I *ff* genotype and low vitamin D levels had the highest risk of developing PCa in general and aggressive disease specifically (98). Given that vitamin D oral formulations have been explored as a treatment option for PCa (99), identification of an interaction between genotype and environment could have potential clinical application.

The MEAL study offers the ideal population to study the interaction between genetic risk and diet. First and foremost, if genetic risk is associated with aggressive disease, then patients with the high risk genetic background should be more likely to progress. What is unique about the MEAL study is to determine if dietary modification alters that genetic risk. If it does then genetically high risk patients could modify their diet at the time of diagnosis or possibly sooner. Alternatively, if diet does not modify risk of progression then more aggressive management could be instituted.

10.3.2 Objectives

10.3.2.1 To compare MnSOD, XRCC1, and GST gene polymorphisms to PSADT in AS patients receiving dietary intervention versus no intervention.

10.3.2.2 To compare MnSOD, XRCC1, and GST gene polymorphisms to time to pathological progression in AS patients receiving dietary intervention versus no intervention.

10.3.3 Methods

Whole blood samples are being collected at baseline for DNA isolation and evaluation of genetic polymorphisms that affect antioxidant metabolism such as MnSOD. In addition, there is evidence of other interactions between antioxidant systems and dietary practice. Some of these could have an impact on the prostate such as catechol-o-methyl transferase and glutathione peroxidase.

10.4 Analysis of diagnostic prostate biopsy sections (Substudy 151105)

10.4.1 Background

A great deal of information is contained in the prostate tissue in the diagnostic biopsy: the Gleason score, which indicates the aggressiveness of the cancer, and the size and location of the cancer. Higher Gleason score and larger tumor are associated with disease progression. The biopsy tissue can be used to describe the rates at which prostate cells are proliferating and at which prostate cells are undergoing apoptosis. Together, these factors provide an indicator of overall tumor growth index, which is associated with disease progression. The biopsy also can be used to describe the degree to which androgen-signaling proteins, including the androgen receptor, and androgen metabolism enzymes, including 5-alpha reductase 1, 2, and 3, are expressed. Androgen-signaling proteins have been linked to prostate cancer risk and to treatment outcome, with androgen signaling generally associated with the presence or development of more aggressive disease (108-110). Recent advances make possible the detection of small noncoding segments of RNA, known as microRNA, which can be extracted from serum and from tissue fragments. MicroRNAs 141 and 375, which have received a great deal of attention as likely predictors of prostate cancer treatment outcome, will be examined in this study (111, 112). These two microRNAs have been associated with more aggressive disease and with tumor progression.

Taking these key indicators into account in analyses may enable better description of the likelihood that the prostate will respond to dietary change. Although randomized assignment should greatly lessen the likelihood of confounding of outcome by such

baseline characteristics as tumor growth, proteins predictive of outcome, or microRNA; taking these characteristics into account may increase the power of these analyses. In addition, it is possible that these factors may interact with treatment assignment to affect cancer progression.

10.4.2 Objectives

10.4.2.1 To compare proliferation, apoptosis and the tumor growth index to dietary intervention assignment as predictors of cancer progression in AS patients.

10.4.2.2 To compare proliferation, apoptosis and tumor growth index to outcome predictors among AS patients randomized to dietary intervention as opposed to those assigned to the comparison group.

10.4.2.3 To compare protein levels of the androgen receptor and 5-alpha reductase 1, 2, and 3 to dietary intervention assignment as predictors of cancer progression in AS patients.

10.4.2.4 To compare protein levels of the androgen receptor and 5-alpha reductase 1, 2, and 3 as outcome predictors among AS patients randomized to dietary intervention as opposed to those assigned to the comparison group.

10.4.2.5 To compare expression of microRNAs 141 and 375 to dietary intervention assignment as predictors of cancer progression in AS patients.

10.4.2.6 To compare expression of microRNAs 141 and 375 as outcome predictors among AS patients randomized to dietary intervention as opposed to those assigned to the comparison group.

10.4.3 Methods

Institutions will be asked to provide 10 x 5 um unstained sections that show cancer on charged glass slides from the formalin-fixed, paraffin-embedded, diagnostic prostate biopsy blocks to the Alliance Biorepository at The Ohio State University (see Section 6.2). Only one core should be placed on each slide. Label the slides with CALGB 70807 patient ID number, accession number, and order of sections.

The immunohistochemistry will be performed at Roswell Park Cancer Institute, under the direction of [redacted]. Commercially available antibodies will be used to immunostain the slides for the following: Ki-67 (proliferation), cleaved caspase 3 (apoptosis), androgen receptor, and 5-alpha reductases 1, 2, and 3. A panel of microRNAs will be extracted from the serum collected as part of sub-study CALGB 151105 (see Section 6.2.3). microRNA 141 and 375 expression will be assayed by procedures developed by Exiqon Laboratories (Blondal et al, 2013).

10.4.4 Statistical considerations

The baseline biomarkers will be associated with progression-free survival (PFS), time to progression as defined for the main study or death. Specific statistical analysis plans are as follows for each study objective. About 80% of the patients in the main study will participate in this correlative study. With n= 334 (=418x0.8) patients, a Cox regression model to regress PFS on a continuous biomarker will have 95% of power to detect a log-hazard ratio (or, regression coefficient of the Cox proportional hazards model) of 0.4 between two patient groups whose biomarker values are 1 standard deviation away with a two-sided alpha level of 5%. This power calculation is based on 85% of 2-year PFS for the whole population, the accrual and follow-up periods assumed for the main study and the assumption that each marker is normally distributed (possibly after a transformation).

10.4.4.1 To compare proliferation, apoptosis and the tumor growth index to dietary intervention assignment as predictors of cancer progression in AS patients

PFS will be regressed on each biomarker of proliferation (KI-67), apoptosis (cleaved caspase 3) and tumor growth rate (a composite of proliferation and apoptosis) using a Cox regression model. In order to see which biomarkers are independently prognostic, we will also perform a Cox regression to regress PFS on all three of the biomarkers. We will repeat these regression analyses adjusting for treatment allocation to investigate if the effect of these biomarkers is confounded with treatment allocation.

10.4.4.2 To compare proliferation, apoptosis and tumor growth index to outcome predictors among AS patients randomized to dietary intervention as opposed to those assigned to the comparison group

The analyses adjusting for treatment allocation as described in in Section 10.4.4.1 will be repeated by adding the interaction term between each marker and treatment allocation to the regression models to see if the effect of each biomarker is different between the two treatment arms. If any of these interaction terms are significant, then we will also fit a regression model within each arm to develop a prediction model based on the biomarkers for each treatment arm.

10.4.4.3 To compare protein levels of the androgen receptor and 5-alpha reductase 1, 2, and 3 to dietary intervention assignment as predictors of cancer progression in AS patients

PFS will be regressed on each biomarker of androgen receptor, 5 alpha reductase 1, 5 alpha reductase 2, and 5 alpha reductase 3 using a Cox regression model. In order to see which of these protein level biomarkers are independently prognostic, we will also perform a Cox regression to regress PFS on all four of these biomarkers. We will repeat these regression analyses adjusting for treatment allocation to investigate if the effect of the biomarkers is confounded with treatment allocation.

10.4.4.4 To compare protein levels of the androgen receptor and 5-alpha reductase 1, 2, and 3 as outcome predictors among AS patients randomized to dietary intervention as opposed to those assigned to the comparison group

The analyses adjusting for treatment allocation as described in in Section 10.4.4.3 will be repeated by adding the interaction term between each marker and treatment allocation to the regression models to see if the effect of each biomarker is different between the two treatment arms. If any interaction terms are significant, then we will fit a regression model within each arm to develop a prediction model based on the biomarkers for each treatment arm.

10.4.4.5 To compare expression of microRNAs 141 and 375 to dietary intervention assignment as predictors of cancer progression in AS patients

PFS will be regressed on each biomarker of microRNAs 141 and 375 using a Cox regression model. In order to see which of these microRNAs are independently prognostic, we will also perform a Cox regression to regress PFS on both of the microRNAs. We will repeat these regression analyses adjusting for treatment allocation to investigate if the effect of these biomarkers is confounded with treatment allocation.

The microRNA package we are going to use will examine many more (~200) microRNA biomarkers. We will develop a prediction model for PFS using all the examined microRNA biomarkers as candidate predictors using the gradient lasso procedure,113 and compare the prediction power of this model with that based on microRNAs 141 and 375. A Cox regression will be conducted including the risk score fitted using the gradient lasso method and treatment allocation.

10.4.4.6 To compare expression of microRNAs 141 and 375 as outcome predictors among AS patients randomized to dietary intervention as opposed to those assigned to the comparison group

The analyses adjusting for treatment allocation as described in Section 10.4.4.5 will be repeated by adding the interaction term between each biomarker and treatment allocation to the regression models to see if the effect of each biomarker is different

between the two treatment arms. If any interaction terms are significant, then we will fit a regression model within each arm to develop a prediction model based on the biomarkers for each treatment arm.

In order to investigate the prediction power of the fitted model using the gradient lasso in Section 10.4.4.5, a Cox regression will be conducted including the risk score fitted using the gradient lasso method, treatment allocation and their interaction term.

11.0 STATISTICAL CONSIDERATIONS

11.1 Randomization

Patients will be randomized with equal probability to receive the dietary intervention (experimental arm) or dietary information (control arm). A total of 464 patients will be enrolled to this trial, 232 patients per arm. The study will take a total of 5 years: about 3 years of accrual with an expected accrual rate of 15 patients per month, and 2 years of follow-up for each patient.

Stratification factors: Randomization will be stratified by age (≤ 70 years vs. > 70 years), race (African American vs. Other) and baseline prostate biopsy (0-12 months prior to registration vs. >12-24 months prior to registration).

11.2 Design

Each patient will be followed for 24 months, and PSA will be evaluated every 3 months starting from baseline. Prostate biopsies are taken at baseline and 24 months.

The primary outcome of interest in this prevention trial is disease progression defined by (a) PSA doubling time (PSADT) < 3 years, (b) PSA ≥ 10 at any time, or (c) Gleason sum on repeat biopsy ≥ 7 for men younger than 70 years and ≥ 4+3 = 7 for men 70 years or older. These criteria are drawn from one of the largest active surveillance studies to date, the Toronto cohort (12). Data from this cohort indicate that approximately 20% of patients on active surveillance will progress by these criteria: 14% by PSA doubling time and 8%-10% by Gleason score.

Thus, using the log-rank test with a two-sided α = 5%, a sample size of 418 will provide 80% power to detect a difference in progression rate (PGR) of 20% in the control and 10% in the experimental arm during 24 months of follow-up. Under the exponential distributions for the time to progression, the 2-year PGR of 20% vs. 10% corresponds to a hazard ratio (HR) of 2.118. Assuming 10% of dropout rate (including patients who are treated before progression), a total of 464 patients will be enrolled to this trial.

Centralized pathology review will be conducted on the tissue specimens of the first 50 patients. From an analysis of grading by community vs. Johns Hopkins pathologists, Gleason grading of adenocarcinoma in prostate needle biopsy tissue (106), Gleason score was changed from 3+4 by community review to 4+3 by Johns Hopkins review for about 14% of men and from 6 or below to 7 or above for about 8% of men. Assuming about 30% of men in this study will be >70 years old and these two types of changes occur uniformly over the whole range of age, we believe that no more than 10% of men will become ineligible for the study by the centralized pathology review. We will consider increasing the sample size by a maximum of 10% depending on the proportion of men who become ineligible by central pathology review.

11.3 Analysis

The proportion of men who become ineligible by central pathology review will be estimated for each arm. The primary analysis will be done using data from eligible subjects, especially using Gleason scores from central review. However, all statistical analyses will be conducted for the data sets from eligible patients only, as well as all patients randomized in the sensitivity analysis.

Progression: PSADT will be calculated as log2 divided by the slope (the least squares estimator) of log (PSA) observations over time using all available PSA measurements, starting from the time point at which we have three PSA measurements (i.e. the first

PSADT of a patient is calculated at month 6 using the PSA measurements collected at months 0, 3 and 6 if there are no missing PSA measurements." In order to avoid any miscalculation, the PSADT will be calculated at the Alliance Statistics and Data Center, not by each individual site.

Time to progression data will be analyzed using the log-rank test for univariable analysis and the Cox's proportional hazards regression for multivariable analysis adjusting for the stratification factors and other prognostic factors. For the patients who proceed to treatment with surgery, radiation, local ablative therapy or hormonal therapy before progression within the 2-year follow-up period, the progression time will be censored at the time of withdrawal for treatment.

A recent study in a similar cohort of men undergoing active surveillance (102) reported that PSA kinetics was not closely associated with progression on subsequent surveillance biopsies. In order to address this issue, as a secondary analysis, we will also compare time to progression defined only by Gleason sum on repeat biopsy ≥ 7 for men younger than 70 years and ≥ 4+3 = 7 for men 70 years or older. Because of decreased number of events, the log-rank test using this definition of time to progression may not have enough power. For example, if the 2-year PGR for the control arm is only 10% by this new definition, then the log-rank test will have only 50% of power with 418 eligible patients with events or full 2 years of follow-up.

Time to Treatment: Probability to proceed to treatment within 2 years (binary observation) and time to treatment (censored time to an event observation) will be analyzed using the chi-squared test and the log-rank test, respectively. We expect that the control arm will have more patients receiving treatment and shorter time to treatment than the experimental arm because of anxiety.

QOL: Quality of life (anxiety and depression, prostate cancer symptom checklist) will be compared between the two arms. The time trajectory of QOL will be estimated using the generalized estimating equation method based on working independent correlation structure (103) and the slope of the time trajectory will be compared between the two arms (104). We will consider taking a log-transformation of QOL observations if it improves the linearity of the time trajectory of QOL. The significance of the two arm comparisons will be adjusted for multiple testing among different QOL subscales using the methodology of Bang, Jung and George (105).

Dietary Recall: Diets will be evaluated at baseline and at 12 and 24 months by a series of three separate 24-hour dietary recalls collected interactively via telephone interview. The increase (from baseline) in mean daily intakes of total vegetables, crucifers, tomato products, beans/legumes and fat will be compared between arms using a two-sample t-test at 12 and 24 months. We may consider transforming (e.g. using logarithm) the data to improve normality of the distributions and variance stabilization. Data will be catalogued and analyzed utilizing Minnesota Nutrition Data System (NDS) software (Nutrition Coordinating Center, University of Minnesota).

Plasma carotenoid analyses:

(1) Plasma carotenoid concentrations (PCC) will be compared between the two arms using a two-sample t-test. A log-transformation of the PCC observations may be considered in order to improve the normality of the distributions and variance stabilization.

(2) PCC will be correlated with PSADT for the patients. Descriptive analysis using scatter plots and regression analysis will be conducted. Intervention and known predictors including the stratification factors will be adjusted in multivariable analysis.

(3) Time to pathological progression (i.e., Gleason sum on repeat biopsy ≥ 7 for men younger than 70 years and ≥ 4+3 = 7 for men 70 years or older) will be regressed on PCC in AS patients using Cox's regression method. Intervention and known predictors including the stratification factors will be adjusted in multivariable analysis.

11.4 Interim Analysis

11.4.1 Primary Endpoint

At each interim analysis, superiority and futility tests on PFS will be conducted as follows.

Superiority: A superiority test is to test if the experimental arm has a longer PFS than the control arm. The first interim analysis for superiority will be conducted when 80 patients progress or complete the 2 years of follow-up. With 6 months of run-in period and a monthly accrual of 15 patients, this will occur at approximately 33 months. After this time, interim analyses will be conducted every six months corresponding with scheduled meetings of the Alliance Data and Safety Monitoring Board (DSMB). The final analysis will be conducted 2 years after the completion of accrual. With the expected study plan, there should be about 4 or 5 interim analyses before the final analysis. The superiority testing during the interim analyses will be using one-sided alpha=0.0025. (A one-sided p-value smaller than 0.5 and a test statistic larger than 0 imply the superiority of the experimental arm.) The final analysis will be using one-sided alpha=0.025. Due to the relatively small number of interim analyses and the small alpha spending at each interim analysis, the overall type I error rate will not be much larger than the nominal one-sided alpha=0.025 (107).

Futility: Futility testing will be conducted at the time of each interim analysis scheduled for a superiority test. We will consider stopping the study early due to futility if the 1-sided p-value is larger than or equal to 0.5 (or the standardized log-rank test statistic is smaller than 0) at any interim analysis.

11.4.2 Progression Rate

The power of the log-rank test depends on the PGR in the two arms. An interim analysis will be conducted when 400 patients are enrolled on the study to check if the specified 20% of 2-year PGR is accurate or not. At the interim analysis, the 2-year PGR of the control arm will be estimated. If the estimate is smaller than 20%, we will recalculate the sample size using the estimated 2-year PGR for the control arm, HR=0.472, two sided alpha=0.05 and a power of 80% and consider increasing the sample size by a maximum of 20% of the current sample size. For example, if the estimated 2-year PGR for the control arm is 18%, then we need 466 eligible patients (about 11% increase from 418 eligible patients). In case the observed progression rate is so low that a maximum of 20% increase in sample size does not guarantee a reasonable power for the primary endpoint, we will consider suspending the study for revision.

11.4.3 Accrual Monitoring

The accrual rate will be monitored by DSMB complying with CTEP's Early Stopping Guidelines for Slow Accruing Trials.

11.5 Statistical analyses for substudy 151105

For Objective 10.3.2.1, the expression level of MnSOD, XRCC1 and GST will be correlated with PSADT within each arm. The expression level of these genes may be highly correlated with PSADT in the control arm. However, if dietary modification alters the genetic risk, the association may be insignificant or less significant in the experimental arm.

For Objective 10.3.2.2, the expression level of MnSOD, XRCC1 and GST will be correlated with time to pathological progression using Cox regression method within each arm. The expression level of these genes may be highly correlated with time to pathological progression in the control arm. However, if dietary modification alters the genetic risk, the association may be insignificant or less significant in the experimental arm.

12.0 REFERENCES

1. Society AC. Cancer Facts and Figures 2009. 2009 cited; Available from: http://cancer.org.
2. Cooperberg MR, Lubeck DP, Meng MV, Mehta SS, Carroll PR. The changing face of low-risk prostate cancer: Trends in clinical presentation and primary management. J Clin Oncol. 2004; 22(11):2141-2149.
3. Miller DC, Gruber SB, Hollenbeck BK, Montie JE, Wei JT. Incidence of inital local therapy among men with lower-risk prostate cancer in the united states. JNCI. 2006; 98(16):1134-1141.
4. Miller DC, Sanda MG, Dunn RL, et al. Long-term outcomes among localized prostate cancer survivors: Health-related quality-of-life changes after radical prostatectomy, external radiation, and brachytherapy. JCO. 2005; 23(12):2772-2780.
5. Potosky AL, Davis WW, Hoffman RM, et al. Five-year outcomes after prostatectomy or radiotherapy for prostate cancer; the prostate cancer outcomes study. JNCI. 2004; 96(18):1358-1367.
6. Etzioni R, Penson DF, Legler JM, et al. Overdiagnosis due to prostate-specific antigen screening: Lessons from U.S. prostate cancer incidence trends. JNCI. 2002; 94(13):981-990.
7. Welch HG, Schwartz LM, Woloshin S. Prostate-specific antigen levels in the united states: Implications of various definitions for abnormal. JNCI. 2005; 97(15):1132-1137.
8. Carroll PR. Early stage prostate cancer--do we have a problem with over-detection, overtreatment or both? J Urol. 2005; 173(4):1061-1062.
9. Carter HB, Walsh PC, Landis P, Epstein JI. Expectant management of nonpalpable prostate cancer with curative intent: Preliminary results. J Urol. 2002; 167(March):1231-1234.
10. Albertsen PC, Hanley JA, Fine J. 20-year outcomes following conservative management of clinically localized prostate cancer. J Am Med Assoc. 2005; 293(17):2095-2101.
11. Klotz L. Active surveillance for prostate cancer: For whom? JCO. 2005; 23(32):8165-8169.
12. Klotz L, Zhang L, Adam L, Nam R, Mamedov A, Loblaw A. Clinical results of long-term follow-up of a large, active surveillance cohort with localized prostate cancer. JCO 2010; 28(1):126-131.
13. Khan MA, Carter HB, Epstein JI, et al. Cancer prostate specific antigen dervatives and pathological parameters predict significant change in expectant management criteria for prostate cancer? J Urol. 2003; 170(6):2274-2278.
14. Warlick C, Trock BJ, Landis P, Epstein JI, Carter HB. Delayed versus immediate surgical intervention and prostate cancer outcome. J Natl Cancer Inst. 2006; 98(5):355-357.
15. Carter HB, Kettermann A, Warlick C, et al. Expectant management of prostate cancer with curative intent: An update of the Johns Hopkins experience. J Urol. 2007; 178(6):2359-2365.
16. Kahn MA, Partin AW. Expectant management: An option for localized prostate cancer. Prostate Cancer and Prostatic Diseases. 2005; 8:311-315.
17. Sonn GA, Aronson WJ, Litwin MS. Impact of diet on prostate cancer: A review. Prostate Cancer and Prostatic Dis. 2005; 8(4):304-310.
18. Chan JM, Giovannucci EL. Vegetables, fruits, associated micronutrients, and risk of prostate cancer. Epidemiol Rev. 2001; 23(1):82-86.

19. Stevens V, Rodriguez C, Pavluck A, McCullough ML, Thun MJ, Calle EE. Folate nutrition and prostate cancer incidence in a large cohort of US men. Am J Epidemiol. 2006; 163(11):989-996.

20. Giovannucci E, Ascherio A, Rimm EB, Stampfer MJ, Colditz GA, Willett WC. Intake of carotenoids and retinol in relation to risk of prostate cancer. J Natl Cancer. Inst. 1995; 87(23):1767-1776.

21. Cohen JH, Kristal AR, Stanford JL. Fruit and vegetable intakes and prostate cancer risk. J Natl Cancer Inst. 2000; 92(1):61-68.

22. Kristal AR, Stanford JL. Cruciferous vegetables and prostate cancer risk: Confounding by PSA screening. Cancer Epidemiology Biomarkers & Prevention. 2004; 13(7):1265.

23. Kristal AR, Lampe JW. Brassica vegetables and prostate cancer risk: A review of the epidemiological evidence. Nutrician and Cancer. 2002; 42(1):1-9.

24. Boileau TWM, Liao Z, Kim S, Lemeshow S, Erdman JW, Clinton SK. Prostate carcinogenesis in N-methyl-N-nitrosourea (NMU)-testosterone-treated rats fed tomato powder, lycopene, or energy-restricted diets. JNCI. 2003; 95(21):1578-1586.

25. Barber NJ, Zhang X, Zhu G, et al. Lycopene inhibits DNA synthesis in primary prostate epithelial cells in vitro and its administration is associated with a reduced prostate-specific antigen velocity in a phase II clinical study. Prostate Cancer and Prostatic Dis. 2006; 9(4):407-413.

26. Brooks JD, Paton V. Potent induction of carcinogen defence enzymes with sulforaphane, a putative prostate cancer chemopreventive agent. prostate cancer and prostatic dis. 1999; 2(S3):S8.

27. Brooks JD, Paton VG, Vidanes G. Potent induction of phase II enzymes in human prostate cells by sulforaphane. Cancer Epidemiology Biomarkers & Prevention. 2001; 10(September):949-954.

28. Singh AV, Xiao D, Lew KL, Dhir R, Singh SV. Sulforaphane induces caspase-mediated apoptosis in cultured PC-3 human prostate cancer cells and retards growth of PC-3 xenografts in vivo. Carcinogenesis. 2004; 25(1):83-90.

29. Caruso AJ, Yegnasubramanian S, Lin X, Kesler TW, Nelson WG. Hot water extracts from broccoli sprouts trigger induction of carcinogen-detoxification enzymes in prostate tissues. Proceedings of the American Association for Cancer Research 95th Annual Meeting, 2004.

30. Chen L, Stacewicz-Sapuntzakis M, Duncan C, et al. Oxidative DNA damage in prostate cancer patients consuming tomato sauce-based entrees as a whole-food intervention. J Natl Cancer Inst. 2001; 93(24):1872-1879.

31. Brooks JD, Paton VG, Vidanes G. Potent induction of phase II enzymes in human prostate cells by sulforaphane. CEBP. 2001;10(9):949-954.

32. Giovannucci E, Rimm EB, Colditz GA, et al. A prospective study of dietary fat and risk of prostate cancer. J Natl Cancer. Inst. 1993;85(19):1571-1579.

33. Sinha R, Park Y, Graubard Bl, et al. Meat and meat-related compounds and risk of prostate cancer in a large prospective cohort study in the united states. AJE. 2009;170(9):1165-1177.

34. Rodriguez C, Freedland SJ, Deka A, et al. Body mass index, weight change, and risk of prostate cancer in the cancer prevention study II nutrition cohort. Cancer Epidemiology Biomarkers & Prevention. 2007;16(1):63-69.

35. Gong Z, Neuhouser ML, Goodman PJ, et al. Obesity, diabetes, and risk of prostate cancer: Results from the prostate cancer prevention trial. Cancer Epidemiology Biomarkers & Prevention. 2006;15(10):1977-1983.

36. Platz EA, Till C, Goodman PJ, et al. Men with low serum cholesterol have a lower risk of high-grade prostate cancer in the placebo arm of the prostate cancer prevention trial. CEBP. 2009; 18(11):2807-2813.

37. Saxe GA, Major JM, Nguyen JY, Freeman KM, Downs TM, Salem CE. Potential attenuation of disease progression in recurrent prostate cancer with plan-based diet and stress reduction. Integ Cancer Ther. 2006;5(3):206-213.

38. Ornish D, Weidner G, Fair WR, et al. Intensive lifestyle changes may affect the progression of prostate cancer. J Urol. 2005;174(September):1065-1070.

39. Ornish D, Magbanua MJM, Weidner G, et al. Changes in prostate gene expression in men undergoing an intensive nutrition and lifestyle intervention. PNAS. 2008;105(24):8369-8374.

40. Parsons JK, Newman VA, Mohler JL, Pierce JP, Paskett E, Marshall J. The men's eating and living (MEAL) study: A cancer and leukemia group B pilot trial of dietary intervention for the treatment of prostate cancer. Urology. 2008;72(3):633-637.

41. Parsons JK, Newman VA, Mohler JL, Pierce JP, Flatt S, Marshall J. Dietary modification in patients with prostate cancer on active surveillance: A randomized multicentre feasibility study. British Journal of Urology International. 2008; 101(10):1227-1231.

42. Parsons JK, Newman VA, Mohler J, et al. Dietary intervention after definitive therapy are localized prostate cancer: Results from a pilot study. Can J Urol. 2009; 16(3):4648-4654.

43. Wilkinson S, Gomella LG, Smith JA, et al. Attitudes and use of complementary medicine in men with prostate cancer. J Urol. 2002; 168(6):2505-2509.

44. Esper P, Mo F, Chodak G, Sinner M, Cella D, Pienta KJ. Measuring quality of life in men with prostate cancer using the functional assessment of cancer therapy-prostate instrument. Urology. 1997; 50:920-928.

45. Roth AJ, Rosenfeld B, Kornblith AB, et al. The memorial anxiety scale for prostate cancer validation of a new scale to measure anxiety in men with prostate cancer. Cancer. 2003; 97(11):2910-2918.

46. Roth AJ, Nelson CJ, Rosenfeld B, et al. Assessing anxiety in men with prostate cancer: Further data on the reliability and validity of the memorial anxiety scale for prostate cancer. Psychosomatics. 2006; 47:340-347.

47 Figueiredo MI, Fries E, Ingram KM. The role of disclosure patterns and unsupportive social interaction in the well-being of breast cancer patients. Psycho-Oncology. 2004; 13:96-105.

48. Humphris GM, Rogers S, McNally D, Lee-Jones C, Brown J, Vaughan D. Fear of recurrence and possible cases of anxiety and depression in orofacial cancer patients. International Journal of Oral Maxillofacial Surgery. 2003;32:486-491.

49. Meyer L, Apegren L. Long-term psychological sequelae of mastectomy and breast conserving treatment for breast cancer. Acta Oncology. 1989;28:13-18.

50. Wenzel LB, Donnelly JP, Fowler JM, et al. Resilience, reflection and residual stress in ovarian cancer survivorship: A gynecologic oncology group study. Psycho-Oncology. 2002;11:142-153.

51. Cella DF, Tulsky DS, Gray G, et al. The functional assessment of cancer therapy scale: Development and validation of the general measure. JCO. 1993;11:570-579.

52. Mehta SS, Lubeck DH, Pasta DJ, Litwin MS. Fear of cancer recurrence in patients undergoing definitive treatment for prostat cancer: Results from Capsure. J Urol. 2003; 170:1931-1933.

53. Korfage IJ, Essink-Bot ML, Janssens AC, Schroder FH, DeKoning HJ. Anxiety and depression after prostate cancer diagnosis and treatment: 5-year follow-up. Br J Cancer Canc. 2006;94(8):1093-1098.

54. Bandura A. Social foundations of thought and action: A social cognitive theory. Englewood Cliffs, NJ: Prentice-Hall, 1986.

55. Marks R, Allegrante JP, Lorig K. A review and synthesis of research evidence for self-efficacy-enhancing interventions for reducing chronic disability: Implications for health education practice (part 1). Health Promotion Practice. 2005;6:37-43.

56. Bandura A. Self-efficacy: Toward a unifying theory of behavioral change. Psychological Review. 1977;84:191-215.

57. Helgeson VS, Lepore SJ, Eton DT. Moderators of the benefits of psychoeducational interventions for men with prostate cancer. Health Psychology.2006;25:348-354.

58. Strecher VJ, McEvoy DeVellis B, Becker MH, Rosenstock IM. The role of self-efficacy in achieving health behavior change. Health Education & Behavior. 1986;13(1):73-92.

59. Lorig KR, Sobel DS, Ritter PL, Laurent D, Hobbs M. Effect of a self-management program on patients with chronic disease. Effective Clinical Practice. 2001;39:1217-1223.

60. Lee V, Robin Cohen S, Laizner AM, Gagnon AJ. Meaning-making intervention during breast or colorectal cancer treatment improves self-esteem, optimism and self-efficacy. Social Science and Medicine. 2006;62:3133-3145.

61. Boehm S, Coleman-Burns P, Schlenk EA, Funnell MM, Parzuchowski J, Powell IJ. Prostate cancer in African-American men: Increasing knowledge and self-efficacy. Journal of Community Health Nursing. 1995; 12:161-169.

62. Merluzzi TV, Martinez Sanchez M. Assessment of self-efficacy and coping with cancer: Development and validation of the cancer behavior inventory. Health Psychology. 1997;16:163-170.

63. Campbell LC, Keefe FJ, McKee DC, et al. Prostate cancer in African-Americans: Relationship of patient and partner self-efficacy to quality of life. Journal of Pain and Symptom Management. 2004;18:433-444.

64. Pierce JP, Faerber S, Wright FA, et al. Feasibility of a randomized trial of a high-vegetable diet to prevent breast cancer recurrence. Nutr Cancer. 1997; 28(3):282-288.

65. Newman VA, Thomson CA, Rock CL, et al. Achieving substantial changes in eating behavior among women previously treated for breast cancer-an overview of the intervention. J Amer Diet Assoc. 2005;105(3):382-391.

66. Pierce JP, Natarajan L, Caan BJ, et al. Influence of a diet very high in vegetables, fruit, and fiber and low in fat on prognosis following treatment for breast cancer. The women's health eating and living (WHEL) randomized trial. JAMA. 2007;298(3):289-298.

67. Pierce JP, Newman VA, Flatt SW, et al. Telephone counseling intervention significantly increases intakes of micronutrient and phytochemical-rich vegetables, fruit, and fiber in breast cancer survivors. J Nutr. 2004;134:452-458.

68. Gold EB, Pierce JP, Natarajan L, et al. Dietary pattern influences breast cancer prognosis in women without hot flashes: The women's health eating and living trial. Journal of Clinical Oncology. 2009;27(3):352-259.

69. Lanza E, Schatzkin A, Daston C, et al. Implementation of a 4-y, high-fiber, high-fruit – and vegetables, low-fat dietary intervention: Results of dietary changes in the polyp prevention trial. Am J Clin Nutr. 2001;74(3):387-401.

70. Prentice RL, Caan B, Chlebowski RT, et al. Low-fat dietary pattern and risk of invasive breast cancer the women's health initiative randomized controlled dietary modification trial. J Am Med Assoc. 2006;295(6):629-642.

71. Schatzkin A, Lanza E, Corle D, et al. Lack of effect of a low-fat, high-fiber diet on the recurrence of colorectal adenomas: The polyp prevention trial study group. N Engl J Med. 2000;342(16):1149-1155.

72. Bailey DE, Mishel MH, Belyea M, Stewart JL, Mohler J. Uncertainty intervention for watchful waiting in prostate cancer. Cancer Nurs. 2004;27(5):339-346.

73. Barry MJ, Fowler FJ, O'Leary MP, et al. The American Urological Association symptom index for benign prostatic hyperplasia. J Urol. 1992;148(5):1549-1557.

74. Parsons JK, Wang PY, Bauer DC, Barrett-Connor E, Marshall LM. Prostate cancer and lower urinary tract symptoms in community dwelling older men. Presented at the Annual Meeting of the American Urological Association; May 2010; San Francisco, CA. [abstract 494]. J Urol. 2010 (Vol. 183, Issue 4, Supplement, Page e195).

75. Kristal AR, Arnold KB, Schenk JM, et al. Dietary patterns, supplement use, and the risk of symptomatic benign prostatic hyperplasia: results from the prostate cancer prevention trial. Am J Epidemiol. 2008;167(8):925-934.

76. Parsons JK. Modifiable risk factors for benign prostatic hyperplasia and lower urinary tract symptoms: new approaches to old problems. J Urol. 2007;178:395-401.

77. Rohrmann S, Smit E, Giovannucci E, Platz EA. Association between serum concentrations of micronutrients and lower urinary tract symptoms in older men in the Third National Health and Nutrition Examination Survey. Urology. 2004;64(3):504-509.

78. Szymanski KM, Wei JT, Dunn RL, Sanda MG. Abbreviated version of the Expanded Prostate Cancer Index Composite instrument for measuring health-related quality of life among prostate cancer survivors. Urology, in press.

79. Schwarzer R, Renner B. Social-cognitive predictors of health behavior: Action self-efficacy and coping self-efficacy. Health Psychol. 2000;19:487-495.

80. Lippman SM, Klein EA, Goodman PJ, et al. Effect of selenium and vitamin E on risk of prostate cancer and other cancers the selenium and vitamin E cancer prevention trial (SELECT). Journal of the American Medical Association. 2009;301(1):E1-E13.

81. Etminan M, Takkouche B, Caamano-Isorna F. The role of tomato products and lycopene in the prevention of prostate cancer: a meta-analysis of observational studies. Cancer Epidemiol Biomarkers Prev. 2004 Mar; 13(3):340-5.

82. Stacewicz-Sapuntzakis M, Bowen PE. Role of lycopene and tomato products in prostate health. Biochem Biophys Acta. 2005 May 30;1740(2):202-5.

83. Kucuk O, Sarkar FH, Djuric Z, Sakr W, Pollak MN, Khachik F, et al. Effects of lycopene supplementation in patients with localized prostate cancer. Exp Biol Med (Maywood). 2002 Nov;227(10):881-5.

84. Eeles, R. A., Kote-Jarai, Z., Giles, G. G. et al.: Multiple newly identified loci associated with prostate cancer susceptibility. Nat Genet, 2008.

85. Gudmundsson, J., Sulem, P., Rafnar, T. et al.: Common sequence variants on 2p15 and Xp11.22 confer susceptibility to prostate cancer. Nat Genet, 2008.

86. Thomas, G., Jacobs, K. B., Yeager, M. et al.: Multiple loci identified in a genome-wide association study of prostate cancer. Nat Genet, 2008.

87. Amundadottir, L. T., Sulem, P., Gudmundsson, J. et al.: A common variant associated with prostate cancer in European and African populations. Nat Genet, 38: 652, 2006.

88. Yeager, M., Orr, N., Hayes, R. B. et al.: Genome-wide association study of prostate cancer identifies a second risk locus at 8q24. Nat Genet, 39: 645, 2007.

89. Gudmundsson, J., Sulem, P., Manolescu, A. et al.: Genome-wide association study identifies a second prostate cancer susceptibility variant at 8q24. Nat Genet, 39: 631, 2007.

90. Kibel, A. S., Jin, C. H., Klim, A. et al.: Association between polymorphisms in cell cycle genes and advanced prostate carcinoma. Prostate, 68: 1179, 2008.

91. Lubahn, J., Berndt, S. I., Jin, C. H. et al.: Association of CASP8 D302H polymorphism with reduced risk of aggressive prostate carcinoma. Prostate, 70: 646, 2010.

92. Cheng, I., Plummer, S. J., Jorgenson, E. et al.: 8q24 and prostate cancer: association with advanced disease and meta-analysis. Eur J Hum Genet, 16: 496, 2008.

93. Beebe-Dimmer, J. L., Levin, A. M., Ray, A. M. et al.: Chromosome 8q24 markers: risk of early-onset and familial prostate cancer. Int J Cancer, 122: 2876, 2008.

94. Duggan, D., Zheng, S. L., Knowlton, M. et al.: Two genome-wide association studies of aggressive prostate cancer implicate putative prostate tumor suppressor gene DAB2IP. J Natl Cancer Inst, 99: 1836, 2007.

95. Mononen, N., Seppala, E. H., Duggal, P. et al.: Profiling genetic variation along the androgen biosynthesis and metabolism pathways implicates several single nucleotide polymorphisms and their combinations as prostate cancer risk factors. Cancer Res, 66: 743, 2006.

96. Chan, J. M., Gann, P. H., Giovannucci, E. L.: Role of diet in prostate cancer development and progression. J Clin Oncol, 23: 8152, 2005.

97. Li, H., Kantoff, P. W., Giovannucci, E. et al.: Manganese superoxide dismutase polymorphism, prediagnostic antioxidant status, and risk of clinical significant prostate cancer. Cancer Research, 65: 2498, 2005.

98. Li, H., Stampfer, M. J., Hollis, J. B. et al.: A prospective study of plasma vitamin D metabolites, vitamin D receptor polymorphisms, and prostate cancer. PLoS Med, 4: e103, 2007.

99. Beer, T. M., Ryan, C. W., Venner, P. M. et al.: Double-blinded randomized study of high-dose calcitriol plus docetaxel compared with placebo plus docetaxel in androgen-independent prostate cancer: a report from the ASCENT Investigators. J Clin Oncol, 25: 669, 2007.

100. Raaijmakers R, Wildhagen M, Ito K, et al. Prostate-specific antigen change in the European randomized study of screening for prostate cancer, section rotterdam. Urology. 2004;63(2):316-320.

101. Daskivich TJ, Regan MM, Oh WK. Prostate specific antigen doubling time calculation: Not as easy as 1, 2, 4. J Urol. 2006;176:1927-1937.

102. Ross AE, Loeb S, Landis AW, et al. Prostate-specific antigen kinetics during follow-up are an unreliable trigger for intervention in a prostate cancer surveillance program. J Clin Oncol. 2010; 28:2810-2816.

103. Liang KY, Zeger S. Longitudinal data analysis using generalized linear models. Biometrika. 1986;73:13-22.

104. Jung SH, Ahn C. Sample size estimation for GEE method for comparing slopes in repeated measurements data. Statistics in Medicine. 2003;22:1305-1315.

105. Bang HJ, Jung SH, George SL. A simulation-based multiple testing procedure and sample size calculation. J Biopharmaceutical Stats. 2005;15:957-967.

106. Fine SW, Epstein JI. (2008). A Contemporary Study Correlating Prostate Needle Biopsy and Radical Prostatectomy Gleason Score. 179(4):1335-1339.

107. Freidlin B, Korn EL, George SL. Data Monitoring Committees and Interim Monitoring Guidelines. Controlled Clinical Trials. 20:395-407.

108. Wu Y, Godoy A, Azzouni F et al. Prostate cancer cells differ in testosterone accumulation, dihydrotestosterone conversion, and androgen receptor signaling response to steroid 5-alpha reductase inhibitors. The Prostate 73: 1470-1482, 2013.

109. Andriole G, Bostwick D, Brawley O et al. Effect of Dutasteride on the Risk of Prostate Cancer. NEJM 362: 1192-1202, 2010.

110. Mohler, James L. Concept and Viability of Androgen Annihilation for Advanced prostate Cancer. Cancer (In Press)

111. Selth LA, Townley S, Gillis JL et al. Discovery of circulating microRNAs associated with human prostate cancer using a mouse model of disease. International Journal of Cancer 131: 652-61, 2011.

112. Selth LA, Tilley WD, Butler LM. Circulating microRNAs: Macro-utility as markers of prostate cancer? Endocrine-related cancer 19: R99-R113, 2012.

113 Sohn I, Kim J, Jung SH, Park C. Gradient lasso for Cox proportional hazards model, Bioinformatics, 2009; 25: 1775-1781.

13.0 MODEL CONSENT FORM

The Men's Eating and Living (MEAL) Study: A Randomized Trial of Diet to Alter Disease Progression in Prostate Cancer Patients on Active Surveillance

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only patients who choose to take part. Please take your time to make your decision. Discuss it with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

[Attach NCI booklet "Taking Part in Clinical Trials: What Cancer Patients Need to Know"]

You are being asked to take part in this study because you have been diagnosed with prostate cancer and are receiving regular follow-up care with your primary physician.

Why is this study being done?

You are being asked to take part in a research study of men who are undergoing active surveillance for their prostate cancer. The purpose of the study is to find out more about how diet may prevent prostate cancer from getting worse.

How many people will take part in this study?

About 464 men will participate in this study.

What will happen if I take part in this research study?

Before you begin the study . . .

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- A complete history and physical exam including a digital rectal exam
- A PSA test

After you are enrolled in the study, you will be asked to provide about 2 teaspoons of blood for research. Study researchers will analyze the blood to determine carotenoid and cholesterol levels. Carotenoid refers to the red to yellow pigments responsible for the color of many plant organs or fruits, such as tomatoes or carrots. Cholesterol is a fat-like substance that is made by the body and is found naturally in animal foods such as meat, fish, poultry, eggs, and dairy products. The blood samples will be used to see if changes in your diet have affected carotenoid and cholesterol levels in your blood. Your carotenoid, and cholesterol levels as measured in this study will not be reported to you or your doctor.

Also, you will be asked to complete questionnaires about your current health, your food preparation and eating habits, your usual food intake over the past year, your quality of life, function and anxiety.

Run-in: During a two-week period after enrollment (called "Run-in"), study researchers from the University of California at San Diego (UCSD) will call you on three different days over the telephone and ask you questions about your medical history and diet. During these interviews, called "24-hour dietary recalls," you will be asked to recall everything you ate and drank during the previous 24 hours. You may skip any question that makes you uncomfortable. These telephone interviews will take approximately 20 minutes.

During the study . . .

If you are able to complete the three 24-hour dietary recall interviews and you choose to participate in the study, you will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. A computer program will place you in one of the study groups. Neither you nor your doctor can choose the group you will be in. You will have an equal chance of being placed in either group.

Group 1

If you are in Group 1 (often called "Arm A") you will be assigned to a program providing you with telephone counseling to help change your diet. You will be asked to change your diet to increase the amounts of fiber-rich plant foods (vegetables, fruit, whole grains, and beans) that you eat. You will receive assistance from diet counselors at UCSD to help you achieve the dietary goals. These counseling calls will take an average of 30 minutes and will occur twice weekly for the first two weeks, and gradually decrease in frequency (weekly, bi-monthly, monthly). The counseling calls may be monitored and audio-taped for quality assurance purposes. After the first six months, your telephone counselor will call you periodically throughout the remainder of the study to check on how you are maintaining the study diet. You will receive a total of 22 calls over the 24-month period. A diet intervention manual, a booklet, and regularly scheduled newsletters will also be provided to you.

Group 2

If you are in Group 2 (often called "Arm B") you will be assigned to a program providing you with information about diet and cancer. You will receive an initial orientation telephone call that will take about 5 to 10 minutes as well as a booklet containing information about nutrition, exercise and prostate cancer. Regularly scheduled newsletters will also be provided to you.

Tests and Procedures

Participants in groups 1 and 2 will complete the tests and procedures listed below. They are part of regular cancer care.

- A PSA test every 3 months
- A complete history and physical exam every 6 months
- A digital rectal examination every 12 months at the urologists discretion
- A prostate biopsy after you have completed the study (after 24 months)

You will also be asked to do the following while you are on the study:

- Every 6 months you will be asked to complete questionnaires about your current health, your food preparation and eating habits, your usual food intake over the past year, your quality of life, function and anxiety.
- Participate in 24-hour dietary recall interviews 12 and 24 months after you start the study. There will be three interviews at each of these times. Each set of these recalls will happen on 3 separate days during a scheduled 3-week period. You may skip any question that makes you uncomfortable.
- Provide about 2 teaspoons of blood 12 and 24 months after you start the study. These blood draws will normally be scheduled early in the morning and you must agree to eat and drink nothing but water and your normal medications for 6 hours prior to the blood collection.

	Month							
	3	**6**	**9**	**12**	**15**	**18**	**21**	**24**
PSA test	X	X	X	X	X	X	X	X
Clinic Visit*		X		X		X		X
Diet Recall				X				X
Questionnaires		X		X		X		X
Blood for carotenoid and cholesterol levels				X				X
Prostate Biopsy								X
Telephone Counseling	For patients in Group 1 only: 22 telephone calls over 2 years							

- Includes history and physical, height, weight, and a digital rectal examination every 12 months at the urologists discretion.

When I am finished . . .

After you have completed the study, you will continue with your usual cancer care.

How long will I be in the study?

You will be in the study for 2 years.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor or nurse if you are thinking about stopping or decide to stop.

It is important to tell your study doctor if you are thinking about stopping so you can discuss what follow up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

What side effects or risks can I expect from being in the study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. You should talk to your study doctor about any side effects that you have while taking part in the study.

Possible risks from changing your diet

- Your skin, especially on the palms of your hands and the soles of your feet, may become yellow because of a diet high in carotenoids.
- You may become bloated or have a lot of gas for a short period because you may be eating more vegetables and dietary fiber than usual. You may get diarrhea or become constipated at first, but only until your body can adjust to your new diet.

Other risks

- There may be a small risk in the process of drawing blood. You may faint or become dizzy. You may feel a little pain or discomfort as the needle goes through the skin. Some bleeding or bruising may occur at the site where blood is drawn. Pressing hard on the spot for 1 or 2 minutes after the needle is removed will help to prevent this. Very rarely, your arm may swell or become infected.

Are there benefits to taking part in the study?

There will be no direct benefits to you other than those associated with changing your diet. The investigators may learn more about how diet plays a role in changing the way prostate cancer can spread in the body. This information could help future prostate cancer patients.

It is important to remember that while there may be benefits, you should continue to be followed by your doctor for your prostate cancer.

What other choices do I have if I do not take part in this study?

You may choose not to take part in this study. If you do not take part in the study, you should discuss with your doctor the appropriate treatment or surveillance plan for your prostate cancer. Those who choose not to participate in this study will continue under the care of their doctors for prostate cancer. You may also choose to take part in another research study.

Talk to your doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

In order for the diet counselors at the University of California at San Diego to contact you, it will be necessary for you to fill out a contact information form that will include your name, address, telephone number, and other personal information. Your contact information will be kept only for the duration of the study.

Organizations that may look at and/or copy your medical record for research, quality assurance, and data analysis include:

- Alliance for Clinical Trials in Oncology (Alliance)
- National Cancer Institute
- The Cancer Trials Support Unit (CTSU), a service sponsored by the National Cancer Institute (NCI) to provide greater access to cancer trials, may also view your records if you are participating in this trial through one of their institutions.

The Alliance has received a Certificate of Confidentiality from the federal government, which will help us to protect your privacy. The Certificate protects against the involuntary release of information about you collected during the course of the study. The researchers involved in this project may not be forced to identify you in any legal proceedings (criminal, civil, administrative, or legislative) at the federal, state or local level. However, some information may be required by the Federal Food, Drug, and Cosmetic Act, the U.S. Department of Health and Human Services, or for purposes of program review or audit. Also, you may choose to voluntarily disclose the protected information under certain circumstances. For example, if you or your guardian requests the release of information about you in writing (through, for example, a written request to release medical records to an insurance company), the Certificate does not protect against that voluntary disclosure.

What are the costs of taking part in this study?

You and/or your health plan/insurance company will be responsible for the charges related to your cancer care. All study measurements and materials directly related to the research will be provided to you free of charge.

You will be responsible for the cost of the food specified by the study.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinical trials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor _____ if you feel that you have been injured because you took part in this study. You can tell the doctor in person or call him at _____.

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from your institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

A Data and Safety Monitoring Board will be regularly meeting to monitor safety and other data related to this study. The Board members may receive confidential patient information, but they will not receive your name or other information that would allow them to identify you by name.

It may be necessary to contact you at a future date regarding new information about the intervention you have received. For this reason, we ask that you notify the institution where you participated in the study of any changes in address. If you move, please provide your new address to:

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ at _____.

For questions about your rights while taking part in this study, call the _____ Institutional Review Board (a group of people who review the research to protect your rights) at _____.

RELATED STUDIES

Please note: The following section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be a part of the main study even if you say "no" to taking part in any of these additional studies.

The results of these research studies will not be provided to you or your doctor, nor will the results have any effect on your treatment. It is unlikely that what we learn from these studies will have a direct benefit to you. However, the information learned from these studies may benefit other patients in the future.

The results from these studies may be published, but individual patients will not be identified in these publications.

There will be no charge to you for participating in these research studies. Your sample and information will only be used for research and will not be sold. The research done with your sample may help to develop new products in the future.

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone inappropriate is very small.

In the future, people who do research may need to know more about your health. While the Alliance for Clinical Trials in Oncology may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

If you decide now to participate and then change your mind at any time about participating in these studies for any reason, you should contact your institution and let them know that you do not want the researchers to use your sample. The sample will then no longer be used for research. It will either be destroyed or returned to your institution for storage. The sample will also be returned to your institution upon request if needed for any other medical or legal reasons.

You can say "yes" or "no" to the following study. No matter what you decide to do, it will not affect your care.

Studies on blood and tissue (includes genetic studies):

Blood: Study researchers would like to collect additional samples of your blood. The researchers would like to conduct other studies on carotenoid and cholesterol levels in your blood. Also, they would like to investigate whether substances in your blood (sometimes called tumor markers) are related to the way that your body responds or doesn't respond to changes in your diet.

In addition to the studies on carotenoid and cholesterol levels, researchers wish to determine whether there is a relationship between genes and the severity of your disease. In order to study genes, the DNA must be removed from your blood sample. DNA is the substance that makes up your genes. Genes are the units of inheritance that are passed down from generation to generation. They are responsible for eye color, hair color, blood type, and hundreds of other traits.

If you agree to these additional studies, about 4 teaspoons of additional blood would be collected at the beginning of the study and then about 2 teaspoons of blood would be collected 12 and 24 months after you start the study.

Tissue: A section of the material from the prostate biopsy that was used to diagnose your prostate cancer was reviewed by the study pathologist to confirm that you had cancer. Study researchers would also like to test additional sections of this tissue from this prostate biopsy to look at tissue tumor markers. Investigators want to look at how the tumor is growing, if some hormones were present, and to examine genetic activity in your biopsy tissue. No extra prostate biopsies would be needed for these extra tissue studies. Tissue would be used from your prostate biopsies already done as part of the main study.

About genetic studies:

New scientific tools will now allow researchers to look at your whole DNA, not just one part or one gene. This kind of research can provide information to researchers about the development of cancer and response to treatment. It can also provide information about a variety of other conditions and diseases, including heart disease, diabetes and Alzheimer's disease.

Because the information gained in these genetic studies can be very useful to the research community, the National Institutes of Health (NIH) has requested that these data be placed in a central database housed at the NIH. The goal is to speed up the process for discovery of new treatments, prevention and diagnosis of disease. Researchers must get approval from the NIH before they can access the research results and health-related information from your specimen. All information will be coded with a unique number. Researchers will not have access to your identity; they will only see coded information.

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone is very small. Below are some of the steps we have taken to protect your privacy and confidentiality:

- Blood and tissue samples will be stored at an Alliance laboratory. The Alliance Statistics and Data Center will perform all analyses of data and store all study results. Your blood and tissue samples will not be stored with your name on them. Instead, they will be labeled with a special Alliance identification number. The only location where your name and special identification number will be stored together is at the Alliance Statistics and Data Center. The greatest effort will be made to see that all personal information that can identify you is kept under conditions that protect your privacy.
- Information about your participation in this study and results of any tests performed on your samples will be kept only at the Alliance Statistics and Data Center. This information will not be made available to your doctors or to individual researchers at the Alliance. Test results from this study will not be put in your medical records. All study information, including test results, is stored under conditions that limit access in order to protect the privacy of the people participating in the study.
- The Alliance has received a Certificate of Confidentiality from the federal government, which will help us to protect your privacy. More information about the Certificate can be found in the paragraph "Will my medical information be kept private?"
- A federal law (Genetic Information Non-Discrimination Act, GINA) will help lower the risk from health insurance or employment discrimination on the basis of genetic information. The federal law does not include other types of misuse by life insurance, long-term care or disability insurance. If you want to learn more about the GINA Law, which went into effect in 2009, you can find information about it on the internet or ask the study staff. In addition to the federal law, some states have laws that also help protect against genetic discrimination.

While we believe that the risks to you and your family are very low, we cannot tell you exactly what all of the risks are from taking part in genetic research studies. Your privacy and confidentiality will be protected to the fullest extent possible.

You have the right to participate in this study without participating in the proposed research studies on your blood samples. Please read the sentence below and think about your choice. After reading the sentence, please mark your choice and provide the current date. **No matter what you decide to do, it will not affect your care.**

1) I agree that my specimens may be used for the research described above.

_____ Yes _____ No Initials _____

Storage of your specimens:
The researchers would also like to store any blood that is not used up by the related studies described above. These samples may be stored indefinitely. You can still take part in the treatment study, and the research study described above without giving your consent for your samples to be stored.

It is not possible for you or the Alliance to know what studies of cancer may be appropriate in the future. We ask that you give permission in advance for other studies to be performed using the blood without being re-contacted to give permission for each test.

2) My specimens may be kept for future unknown use in research to learn about, prevent, treat, or cure cancer.

_____ Yes _____ No Participant _____ Date _____

3) My specimens may be kept for research about other health problems (for example: causes of diabetes, Alzheimer's disease and heart disease.

_____ Yes _____ No Participant _____ Date _____

4) My doctor or someone from CALGB/Alliance may contact me in the future to ask me to take part in more research.

_____ Yes _____ No Participant _____ Date _____

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:
1-800-4-CANCER (1-800-422-6237)

You may also visit the NCI web site at http://cancer.gov/
- For NCI's clinical trials information, go to: http://cancer.gov/clinical trials/
- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of _____ [insert total of number of pages] pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in the study.

Participant_____ Date_____

Participant Name (please print) _____

14.0 MODEL CONSENT FORM: ADDENDUM FOR PATIENTS WHO CONSENTED TO PARTICIPATE IN THE EMBEDDED COMPANION STUDY TO 70807 PRIOR TO THE APPROVAL OF UPDATE 8

The Men's Eating and Living (MEAL) Study: A Randomized Trial of Diet to Alter Disease Progression in Prostate Cancer Patients on Active Surveillance

You are either currently participating in, or have previously participated in the research study called CALGB 70807. You are being contacted again because you agreed to participate in the related studies and provide blood samples for research.

Additional related studies

At the time that you enrolled to CALGB 70807, a section of the material from the prostate biopsy that was used to diagnose your prostate cancer was reviewed by the study pathologist to confirm that you had cancer. Study researchers would now like to test additional sections of this tissue from that prostate biopsy to look at tissue tumor markers. Investigators want to look at how the tumor is growing, if some hormones were present, and to examine genetic activity in your biopsy tissue. No extra prostate biopsies would be needed for these extra tissue studies. If you agree to these additional related studies, tissue from your previous prostate biopsy would be sent to the Alliance Biobank for this research.

The risks and protections regarding the additional studies on the blood samples that were described to you in the consent form you previously signed will apply to this additional study on your tissue sample. You have the right to refuse that your tissue be used for this additional study, and your decision will not affect whether you may continue with the main CALGB 70807 diet study.

Signature

I have been given a copy of all _____ *[insert total of number of pages]* pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant _____

Date _____