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Men's Eating and Living (MEAL) study (CALGB 70807 [Alliance]): recruitment feasibility and baseline demographics of a randomized trial of diet in men on active surveillance for prostate cancer

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Objective

To assess the feasibility of performing national, randomized trials of dietary interventions for localized prostate cancer.

Methods

The Men's Eating and Living (MEAL) study (CALGB 70807 [Alliance]) is a phase III clinical trial testing the efficacy of a high-vegetable diet to prevent progression in patients with prostate cancer on active surveillance (AS). Participants were randomized to a validated diet counselling intervention or to a control condition. Chi-squared and Kruskal–Wallis analyses were used to assess between-group differences at baseline.

Results

Between 2011 and 2015, 478 (103%) of a targeted 464 patients were randomized at 91 study sites. At baseline, the mean (SD) age was 64 (6) years and mean (SD) PSA concentration was 4.9 (2.1) ng/mL. Fifty-six (12%) participants were African-American, 17 (4%) were Hispanic/Latino, and 16 (3%) were Asian-American. There were no significant between-group differences for age ($P = 0.98$), race/ethnicity ($P = 0.52$), geographic region ($P = 0.60$), time since prostate cancer diagnosis ($P = 0.85$), PSA concentration ($P = 0.96$), clinical stage (T1c or T2a; $P = 0.27$), or Gleason sum (Gleason 6 or 3+4 = 7; $P = 0.76$). In a pre-planned analysis, the baseline prostate biopsy samples of the first 50 participants underwent central pathology review to confirm eligibility, with an expectation that <10% would become ineligible. One of 50 participants (2%) became ineligible.

Conclusion

The MEAL study shows the feasibility of implementing national, multi-institutional phase III clinical trials of diet for prostate cancer and of testing interventions to prevent disease progression in AS.

Keywords

diet, prevention, outcomes, active surveillance, carotenoids, #ProstateCancer, #PCSM

Introduction

Active surveillance (AS) provides a safe alternative to immediate treatment for men with low-risk and select men with low-volume, intermediate-risk prostate cancer; however, up to 40% of men on AS will undergo surgery, radiation or androgen deprivation within 5 years, most for clinical progression. A minority will opt for curative

therapy despite not meeting objective criteria for progression [1–5].

Prevention of clinical progression is a potential strategy to reduce morbidity and healthcare costs in men on AS, but although numerous studies have identified clinical and pathological variables associated with AS progression, only one has tested an intervention designed to reduce its incidence: the Reduction by Dutasteride of Clinical Progression Events in Expectant Management (REDEEM) trial [6,7]. Further clinical trials are needed to develop prevention therapies and integrate them into AS treatment paradigms.

One potential prevention therapy is diet modification. Diet may influence the risks of prostate cancer incidence, progression, metastases and death. Preliminary evidence suggests that patients with prostate cancer who increase their vegetable and decrease their fat intakes experience increased progression-free, prostate cancer-specific and overall survival [8–10]. In addition, pre-clinical and epidemiological data indicate that components of cruciferous vegetables (isothiocyanates) and tomatoes (lycopene and other carotenoids) induce apoptosis of prostate cancer cells, inhibit carcinogenesis, induce the expression of cytoprotective enzymes, promote genomic stability, and decrease the risk of lethal prostate cancer [11–15].

Using social cognitive theory, we designed and successfully pilot-tested an intervention that promotes vegetable intake in patients with prostate cancer. Among men on AS, our intervention significantly increased total daily vegetable intake and blood carotenoid levels [16,17].

The Men's Eating and Living (MEAL) study (CALGB 70807 [Alliance]) is a phase III trial testing the efficacy of this dietary intervention to prevent clinical progression in patients on AS [18]. The MEAL study is being conducted by the Alliance for Clinical Trials in Oncology (formerly the Cancer and Leukemia Group B), a National Cancer Institute (NCI)-sponsored cooperative group that conducts cancer control and treatment trials within the NCI National Clinical Trial Network (NCTN). Members of the National Clinical Trial Network, which include academic institutions, community hospitals and cancer centres across the USA, have been able to participate.

As MEAL is the first national, multicentre, randomized clinical trial measuring the impact of a dietary intervention on prostate cancer, we assessed the effectiveness of the MEAL study to enrol and randomize patients on AS.

Materials and Methods

The MEAL study protocol has been described in detail previously [18]. Briefly, MEAL is a randomized, phase III trial that uses a validated, telephone-based counselling programme to increase vegetable consumption among patients on AS

[17]. From December 2010 to September 2015, men on AS were recruited from participating urology and medical oncology clinics. Financial incentives were not used. Eligible participants were randomized 1:1 to either the telephone-based counselling intervention or a control condition, in which they received printed materials from the Prostate Cancer Foundation (PCF) recommending consumption of a healthy, vegetable-rich diet (www.pcf.org). Dynamic allocation (minimization method) was used for stratified randomization. Randomization was stratified by age (<70 years vs ≥70 years), race (African-American vs other) and time since diagnostic prostate biopsy (0–12 months prior to registration vs >12 and ≤24 months prior to registration).

Major Inclusion and Exclusion Criteria

Eligible participants were aged 50–80 years with biopsy-proven adenocarcinoma of the prostate, clinical stage T1c or T2a and a serum PSA level <10 ng/mL, diagnosed within 24 months of baseline with an extended pattern (≥10 cores) biopsy with <25% of total cores and ≤50% of any single core involving cancer. Grade criteria were Gleason 6 for men aged ≤70 years and Gleason ≤3+4 = 7 for men aged >70 years. A single pathologist performed centralized pathology review to confirm eligibility. Participants were not required to have a confirmatory biopsy prior to study entry. The initial biopsy showing diagnosis of prostate cancer was used for the purposes of determining eligibility; however, if a subsequent biopsy performed before patient enrolment showed that the patient was ineligible, he was not enrolled to the study.

Exclusion criteria included prior surgery, radiation, minimally invasive ablation, or androgen deprivation for prostate cancer and consumption of ≥6 servings per day of fruits and vegetables at baseline. Consumption of dietary supplements was permitted. Men who were taking 5-α-reductase inhibitors were eligible after discontinuation of the drug, followed by a 90-day washout period.

Each participant signed an institutional review board-approved, protocol-specific informed consent form, in accordance with federal and institutional guidelines. The study was registered at clinicaltrials.gov (NCT01238172).

Intervention

The telephone counselling protocol, performed centrally at the Moores University of California San Diego Comprehensive Cancer Center, followed a stepwise, phased approach that employed strategies adopted from social cognitive theory and motivational interviewing techniques to effect and maintain positive behaviour change [18]. After randomization, each intervention participant was assigned to a personal counsellor, who encouraged consumption of at least seven daily vegetable/fruit servings (defined as a half-cup

cut up raw or cooked vegetables, fruit or 100% vegetable juice), including at least two servings each of cruciferous vegetables and tomatoes.

The intervention was divided into four phases over a 24-month period [18]. To ensure intervention fidelity, counsellors completed an intensive 80-h training programme. A registered dietician supervised the intervention team and conducted regular performance reviews. To standardize the intervention and minimize the potential for bias, a detailed, relational database provided counsellors with a computer-assisted coaching protocol for each participant contact [18].

Primary Outcome

The primary outcome will be clinical progression, defined as PSA >10 ng/nL, PSA doubling time <3 years, or any one of the following findings on repeat prostate biopsy: >25% of cores positive for cancer; >50% of any one core positive for cancer; and Gleason sum $\geq(3+4) = 7$ for men aged <70 years or Gleason sum $\geq(4+3) = 7$ for men aged $\geq$70 years.

Secondary Outcomes

Secondary outcomes will include incidence of prostate cancer treatment in men who did not meet progression criteria, prostate-cancer specific anxiety as measured by the Memorial Anxiety Scale for Prostate Cancer, urinary symptoms as measured by the IPSS, and quality of life as measured by the Functional Assessment of Cancer Therapy Scale-Prostate (FACT-P) and Expanded Prostate Cancer Index Composite 26 (EPIC-26) [18].

Outcome Evaluation

The duration of follow-up for the MEAL study is 24 months. PSA is evaluated every 3 months, starting from baseline. Beginning 6 months after baseline, PSA doubling time is calculated at the Alliance Statistics and Data Center as $\log_2$ divided by the slope (the least squares estimator) of log (PSA) observations over time using the latest three PSA measurements.

Participants who do not receive definitive treatment with surgery or radiation undergo an end-of-study biopsy 24 months after baseline. Additional for-cause biopsies are performed as clinically indicated at the discretion of the treating physician. An independent team of telephone assessors evaluates the diets of participants at baseline, 12 and 24 months by telephone interview using the Nutrition Data Systems for Research (current version 2010, University of Minnesota Nutrition Coordinating Center, University of Minnesota, Minneapolis, MN, USA) software and nutrient database.

Fasting blood samples are collected at baseline, 12 and 24 months, and analysed for plasma carotenoids (total

carotenoids, α-carotene, β-carotene, lutein, lycopene and cryptoxanthin) using high-performance liquid chromatography methodology [16].

Statistics

Patients were randomized 1:1 to receive the dietary intervention (experimental arm) or dietary information (control arm). The log-rank test, with a two-sided $\alpha = 5\%$ and a sample size of 418, has 80% power to detect a difference in progression rate of 20% in the control vs 10% in the experimental arm during the 24-month follow-up period.

Under the exponential distribution assumption for the time to progression, the 2-year progression rate of 20% vs 10% corresponds to a hazard ratio of 2.1. Assuming a 10% dropout rate, targeted enrolment was 464 patients. We based the expected 10% dropout rate on our pilot study, in which the observed dropout rate was 2%; we conservatively assigned an expected fivefold increase in the dropout rate compared with the pilot study [17]. Randomization was stratified by age (≤70 years vs >70 years), race (African-American vs other) and time since original diagnostic prostate biopsy (≤12 months prior to registration vs >12–24 months prior to registration).

We are comparing time to clinical progression in the two arms using the log-rank test for univariate analysis and Cox's proportional hazards regression for multivariate analysis, adjusting for stratification and other prognostic factors, comparing the probability to proceed to treatment within 2 years using the chi-squared test, and estimating the time trajectory of quality of life using the generalized estimating equation method [18,19].

We are comparing the changes from baseline in mean daily intakes of total vegetables, crucifers, tomato products, beans/legumes and fat between the two study arms with two-sample t-tests at 12 and 24 months and the changes in plasma carotenoid concentrations from baseline between the two arms using a two-sample t-test.

This phase III trial was monitored at least twice annually by the Alliance Data and Safety Monitoring Committee, a standing committee composed of individuals from within and outside the Alliance. Data quality was ensured by review of data by the Alliance Statistics and Data Center and by the study chairperson according to Alliance policies. Statistical analyses were conducted by the Alliance Statistics and Data Center.

Results
Randomization

During enrolment, 478 of the targeted 464 participants (103%) were randomized from 91 sites. Of these, 237 were randomized to the telephone intervention arm and 241 were

Fig. 1 Screening and randomization of patients enrolled in the Men's Eating and Living (MEAL) study (CALGB 70807 [Alliance]). PCF, Prostate Cancer Foundation.
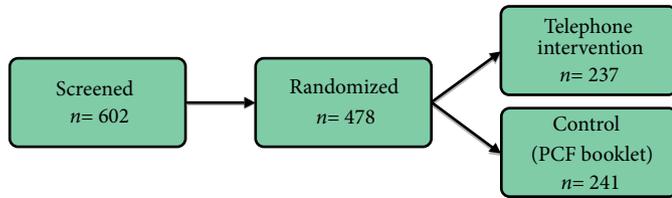
randomized to the control arm of PCF-printed materials. The screen failure rate was 21% (Fig. 1).

Baseline Characteristics

The mean (SD) age of the participants was 63.5 (6.4) years and the mean (SD) PSA concentration was 4.9 (2.1) ng/mL. Fifty-six (12%) participants were African-American, 17 (4%) were Hispanic or Latino, and 16 (3%) were Asian-American (Table 1). There were no significant differences between groups with respect to age ($P = 0.98$), race/ethnicity ($P = 0.52$), geographic region ($P = 0.60$), time since prostate cancer diagnosis ($P = 0.85$), PSA ($P = 0.96$), clinical stage ($P = 0.27$), or Gleason sum ($P = 0.76$; Table 1).

Pathology Central Review

In a pre-planned analysis, the baseline prostate tissue samples of the first 50 participants underwent central pathology review to confirm eligibility. The expectation was that <10% of the participants would become ineligible after central review, and only one of 50 participants (2%) became ineligible.

Discussion

The MEAL study is the first phase III clinical trial of a dietary intervention for prostate cancer. These initial results

Table 1 Baseline characteristics of men enrolled in the Men's Eating and Living (MEAL) Study (CALGB 70807 [Alliance]).

	MEAL intervention (N = 237)	PCF booklet (N = 241)	Total (N = 478)	P
Age, years				
N	237	241	478	0.978[†]
Mean (SD)	63.6 (6.4)	63.5 (6.5)	63.5 (6.4)	
Median	64.0	64.0	64.0	
Q1, Q3	59.0, 67.0	59.0, 68.0	59.0, 68.0	
Range	(50.0–80.0)	(47.0–77.0)	(47.0–80.0)	
Race/ethnicity, n (%)				
Unknown	1 (0.4)	1 (0.4)	2 (0.4)	0.523[†]
Non-Hispanic white	193 (50.8)	187 (49.2)	380 (78.0)	
Black or African-American	25 (10.5)	31 (12.9)	56 (11.7)	
Hispanic or Latino	10 (4.2)	7 (2.9)	17 (3.6)	
Asian	6 (2.5)	10 (4.1)	16 (3.3)	
Native Hawaiian or Pacific Islander	0 (0.0)	1 (0.4)	1 (0.2)	
American-Indian or Alaska Native	1 (0.4)	0 (0.0)	1 (0.2)	
Not reported	1 (0.4)	2 (0.8)	3 (0.6)	
More than one race	0 (0.0)	2 (0.8)	2 (0.4)	
Region, n (%)				
Midwest	42 (17.7)	54 (22.4)	96 (20.1)	0.601*
North East	61 (25.7)	56 (23.2)	117 (24.5)	
South	43 (18.1)	45 (18.7)	88 (18.4)	
West	91 (38.4)	86 (35.7)	177 (37.0)	
Time since cancer diagnosis, n (%)				
≤12 months	203 (98.7)	205 (98.3)	408 (85.4)	0.855*
>12 and ≤24 months	34 (14.3)	36 (14.9)	70 (14.6)	
PSA, ng/mL				
N	235	238	473	0.959[†]
Mean (SD)	4.9 (2.1)	4.9 (2.2)	4.9 (2.1)	
Median	4.8	4.7	4.7	
Q1, Q3	3.6, 6.1	3.4, 6.0	3.5, 6.0	
Range	(0.0–13.5)	(0.8–11.0)	(0.0–13.5)	
Pending verification[‡]			5	
Clinical T stage, n (%)				
1c	194 (81.8)	196 (81.3)	390 (81.6)	0.271*
T2a	23 (9.7)	32 (13.3)	55 (11.5)	
Pending verification[‡]	20 (8.5)	13 (5.4)	33 (6.9)	
Gleason sum, n (%)				
6	225 (94.9)	228 (94.6)	453 (94.8)	0.756*
3+4 = 7	4 (1.7)	5 (2.1)	9 (1.9)	
Pending verification[‡]	8 (3.4)	8 (3.3)	16 (3.3)	

*PCF, Prostate Cancer Foundation; *Chi-squared test. [†]Kruskal–Wallis test. [‡]By the Alliance for Clinical Trials in Oncology central review office.*

show that implementation of a large-scale clinical trial of diet for prostate cancer—with appropriately balanced study arms, a racially diverse patient sample, and broad national representation from both academic and community facilities —is feasible. These results also confirm the viability of performing large randomized trials of interventions to prevent clinical progression in patients on AS.

Accrual for MEAL exceeded targets. The low screen failure rate (21%) suggests robust generalizability. Study groups were similar with respect to age, race/ethnicity, geographic region, PSA, clinical stage and Gleason sum. Over 21% of participants in the MEAL study represent racial/ethnic minorities, slightly fewer than the enrolment goal of 29%. Nevertheless, a large proportion—12%—is African-American (Table 1). Clinical progression data for African Americans on AS have been inconsistent: some studies have suggested an elevated progression risk, while others have not [20,21]. The final results of MEAL, projected to be available in 2018, should thus substantially inform care of African-American men on AS.

Previous studies have observed beneficial prostate cancer-specific effects of vegetable-intense diets in patients on AS. In a cohort study of 93 patients on AS, adoption of lifestyle changes—including a low-fat, plant-based diet—was associated with diminished serum PSA concentrations and decreased rates of progression to curative treatment for up to 2 years [9,22]. Gene expression profiling of prostate biopsies in a subset of these men ($n = 30$) identified significant post-lifestyle intervention changes in cellular processes related to carcinogenesis [9], and analyses of peripheral blood mononuclear cells showed significantly increased telomerase activity and longer telomeres [23], indicating that nutritional and other lifestyle changes may potentially promote chromosome stability.

In contrast to previous diet interventions, which required intensive in-person counselling sessions [22], the MEAL intervention produces robust diet changes through a centralized phone-based counselling system [16–18]. Compared with in-person counselling, a telephone-based system for dietary intervention is advantageous for several reasons. First, for patients, it minimizes economic burden and removes practical barriers to care. Second, it promotes intervention fidelity through standardized treatment protocols. Finally, it provides substantial economies of scale and efficient delivery of care to relatively large patient populations.

Our results validate the feasibility of implementing trials to prevent clinical progression in patients on AS. The overwhelming majority of AS studies have focused on quantifying risks of clinical progression rather than identifying and testing therapies to prevent it [1–5]. The MEAL trial is the first phase III prevention study undertaken in patients on AS since the REDEEM trial. REDEEM assessed the efficacy of dutasteride to prevent progression—defined as Gleason sum ≥7 on follow-up biopsy or incident curative therapy—in 340 patients on AS over 3 years. Compared with placebo, dutasteride significantly reduced progression incidence by 38% [6].

Men with low-risk prostate cancer are entering AS with increasing frequency [24,25]. Reductions in the number of men on AS who undergo surgery or radiation would minimize treatment-associated morbidity, improve patient quality of life, and contain healthcare costs; however, interventions to prevent progression, such as dutasteride, remain underused and understudied; consequently, even as the prevalence of men on AS increases, the incidence of AS progression has not changed appreciably over the past decade. Nevertheless, at least one additional prevention trial is currently enrolling: a randomized phase II study of a prostate cancer vaccine, PROSTVAC® (PSA-TRICOM), in 150 men on AS (clinicaltrials.gov). Further AS prevention trials, based on the successful MEAL and REDEEM models, could substantively inform care of the AS population.

In conclusion, the MEAL study shows the feasibility of implementing randomized trials of diet for prostate cancer and of testing interventions to prevent clinical progression in men on AS.

Acknowledgments

Conflicts of Interest

None declared.

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Abbreviations: AS, active surveillance; MEAL study, Men's Eating and Living study; NCI, National Cancer Institute; NCTN, NCI National Clinical Trial Network; PCF, Prostate Cancer Foundation.