Consumption of a cranberry juice beverage lowered the number of clinical urinary tract infection episodes in women with a recent history of urinary tract infection[1]

Kevin C Maki,[2,3] Kerrie L Kaspar,[4] Christina Khoo,[4] Linda H Derrig,[2] Arianne L Schild,[2] and Kalpana Gupta[5,6]*

[2]Biofortis Clinical Research, Addison, IL; [3]MB Clinical Research, Glen Ellyn, IL; [4]Ocean Spray Cranberries, Lakeville-Middleboro, MA; [5]Department of Medicine, Boston University School of Medicine, Boston, MA; and [6]VA Boston Healthcare System, Boston, MA

ABSTRACT

Background: Urinary tract infections (UTIs) are among the most common bacterial infections and are often treated with antibiotics. Concerns about multidrug-resistant uropathogens have pointed to the need for safe and effective UTI-prevention strategies such as cranberry consumption.

Objective: We assessed the effects of the consumption of a cranberry beverage on episodes of clinical UTIs.

Design: In this randomized, double-blind, placebo-controlled, multicenter clinical trial, women with a history of a recent UTI were assigned to consume one 240-mL serving of cranberry beverage/d (n = 185) or a placebo (n = 188) beverage for 24 wk. The primary outcome was the clinical UTI incidence density, which was defined as the total number of clinical UTI events (including multiple events per subject when applicable) per unit of observation time.

Results: The dates of the random assignment of the first subject and the last subject's final visit were February 2013 and March 2015, respectively. The mean age was 40.9 y, and characteristics were similar in both groups. Compliance with study product consumption was 98%, and 86% of subjects completed the treatment period in both groups. There were 39 investigator-diagnosed episodes of clinical UTI in the cranberry group compared with 67 episodes in the placebo group (antibiotic use–adjusted incidence rate ratio: 0.61; 95% CI: 0.41, 0.91; P = 0.016). Clinical UTI with pyuria was also significantly reduced (incidence rate ratio: 0.63; 95% CI: 0.40, 0.97; P = 0.037). One clinical UTI event was prevented for every 3.2 woman-years (95% CI: 2.0, 13.1 woman-years) of the cranberry intervention. The time to UTI with culture positivity did not differ significantly between groups (HR: 0.97; 95% CI: 0.56, 1.67; P = 0.914).

Conclusion: The consumption of a cranberry juice beverage lowered the number of clinical UTI episodes in women with a recent history of UTI. This study was registered at clinicaltrials.gov as NCT01776021. *Am J Clin Nutr* 2016;103:1434–42.

Keywords: antibiotics, bacteria, cranberry, inflammation, proanthocyanidin, urinary tract infection, women

INTRODUCTION

A urinary tract infection (UTI) is common and increasingly difficult to treat because of the rising rates of antibiotic resistance (1, 2). Approximately 60% of women will experience ≥1 UTI in their lifetimes, and UTIs are responsible for ∼10.5 million physician office and emergency department visits annually in the United States (3, 4). The costs attributable to UTIs include those for antibiotic therapy, visits to health care providers, laboratory testing, and lost productivity (1). It has been estimated that 25–35% of women diagnosed with a UTI will suffer a recurrence within 6 mo (1, 5). The prevention of a UTI is most effectively achieved with antibiotic prophylaxis (6), although it has been recommended that, in women with recurrent cystitis, prophylactic antimicrobial therapy should be used only when nonantimicrobial therapy is not effective (7, 8). Increasing rates of antibiotic resistance (9–12) and other adverse effects from antibiotic exposure make this approach important to consider.

Cranberry consumption has been evaluated as a strategy for reducing clinical UTI recurrence in women with a recent history of a UTI (5, 13). Results from randomized clinical trials have been generally suggestive of a benefit but have often lacked sufficient statistical power to provide definitive results (14). The current study was conducted to compare the effects of the consumption of a cranberry beverage with that of a placebo beverage on the clinical (symptomatic) UTI incidence density in healthy women with a recent history of a UTI.

METHODS

Study design

The study was a 24-wk multicenter, double-blind, randomized, placebo-controlled trial that was designed to assess the effects of the consumption of a cranberry beverage on episodes of clinical (symptomatic) UTI in healthy women. The study was conducted at 17 clinical research sites in the United States and at one clinical

[1] Supported by Ocean Spray Cranberries Inc. Beverages were provided by Ocean Spray Cranberries Inc.

*To whom correspondence should be addressed. E-mail: kmaki@mbclinicalresearch.com.

Received January 11, 2016. Accepted for publication March 17, 2016.
doi: 10.3945/ajcn.116.130542.

research site in France between February 2013 and March 2015. The protocol was approved by an institutional review board in the United States (Quorum Review IRB, Seattle, Washington) and by the National Security Agency for Medicines and Health Products and an Ethical Research Committee (Committee for Personal Protection) in France. Procedures were followed in accordance with the Declaration of Helsinki of 1975 as revised in 1983. Written informed consent was obtained from all subjects.

Subjects

Eligible subjects included women who were 20–70 y of age with BMI (in kg/m^2) <40.0 and a recent history of a UTI, which was defined as ≥2 episodes of a UTI that were treated by a health care professional in the past year (self-report) of which ≥1 UTI had been treated ≤6 mo of the screening visit. Women who were using prophylactic antibiotics for a UTI were not enrolled, but a 2-wk washout period from antibiotic use was allowed before screening. Individuals with an active infection or signs or symptoms of a UTI or other active infection were excluded. If a clean-catch urine sample at screening was positive for asymptomatic bacteriuria (≥10^5 CFU for a uropathogen), the woman was rescreened ≥2 wk later.

Subjects agreed to avoid the consumption of *Vaccinium* products (blueberries, cranberry juice, cranberries, dried cranberries, and cranberry or blueberry powders, pills, or supplements) and probiotic dietary supplements and to limit the consumption of all probiotic-containing foods or yogurt, soda, and energy drinks within 2 wk before screening and through week 24. The daily consumption of carbonated beverages and fermented milk products has been associated with a reduced risk of recurrent UTI in some studies, although this finding has not been universal (15–18). In the current study, subjects were allowed to consume carbonated beverages, energy drinks, and yogurt but were asked to avoid intakes that were far above mean US intakes to allow the results to be generalizable while minimizing the potential for confounding by extreme intakes of these products. Subjects received a stipend for their participation in the study, which included 5 clinic visits (screening and baseline visits at weeks −1 and 0, respectively, and 3 treatment visits at weeks 8, 16, and 24) and 9 telephone contacts at weeks 2, 4, 6, 10, 12, 14, 18, 20, and 22 to improve study compliance by reminding subjects to record data in their daily diaries.

Individuals were excluded from participation in the study if they used a bladder catheter or had polycystic disease, interstitial cystitis, previous urologic surgery, stones, anatomical abnormalities of the urinary tract, a spinal cord injury, conditions that produce immunocompromise, severe renal impairment, or multiple sclerosis. Additional exclusionary conditions included diabetes mellitus with glycated hemoglobin ≥8.0%, diabetes mellitus treated with insulin, a history or presence of cancer in the previous 2 y (except nonmelanoma skin cancer), a recent (within the past 3 mo) major trauma or surgical event, or the use of oral anticoagulants ≤4 wk before screening. Women were also excluded from participation if they had an abnormal laboratory test of clinical importance. Women who were pregnant, planning to be pregnant during the study, or lactating were excluded from the study, and women of childbearing potential had to commit to the use of a medically approved form of contraception throughout the study.

Subjects were instructed to maintain a stable body weight, adhere to habitual exercise patterns, and avoid the consumption of foods that are high in polyphenols for the 24 h before and during the 24-h urine collection periods. Cigarette smokers were instructed to abstain from tobacco products 1 h before and during clinic visits.

Study products

Subjects were randomly assigned (1:1 ratio) to consume one 8-oz (240-mL) bottle of cranberry or placebo study beverage per day throughout the 24-wk treatment period. The randomization sequence was generated with SAS for Windows software (version 9.1.3; SAS Institute Inc.) by a blinded statistician with the use of a seed number and random allocation in blocks by research site. The randomization module of the DATATRAK Electronic Data Capture system (DATATRAK ONE UX, versions 13.0.0 to 13.3.5) was used for coded treatment allocation at each research site by a study coordinator or investigator.

Beverages were provided by Ocean Spray Cranberries Inc. and were stored at room temperature and refrigerated before consumption. Cranberry and placebo beverages each provided ∼35 kcal (∼146 kJ)/240-mL serving. The placebo beverage contained filtered water, fructose, dextrose, citric acid, quinic acid, malic acid, natural flavors, pectin, potassium citrate, sodium citrate, red 40, blue 1, acesulfame-potassium, and sucralose. The active study beverage contained filtered water, cranberry juice from concentrate, fructose, natural flavors, pectin, sodium citrate, acesulfame-potassium, and sucralose. The analytic composition of the study

TABLE 1
Study-product composition[1]

Component	Cranberry beverage	Placebo beverage
Energy,[2] kcal	36	34
Carbohydrates,[3] g	9	8
Sugars,[4] g	6.3 ± 0.1[5]	6.9 ± 0.3
Organic acids,[6] g	2.0 ± 0.1	1.9 ± 0.2
Vitamin C,[7] mg	ND	ND
Proanthocyanidins, mg		
DMAC-method I[8]	41.1 ± 7.1	ND
DMAC-method II[9]	119 ± 16.9	ND
Anthocyanins,[4] mg	1.3 ± 0.8	ND
Phenolic acids,[10] mg	5.4 ± 0.8	ND
Flavanols and flavonols,[10] mg	8.3 ± 3.6	ND
Total phenolics,[11] mg	135 ± 30.7	17.0 ± 5.4

[1]DMAC, 4-dimethylaminocinnamaldehyde; ND, not detected.
[2]Determined with the use of Atwater factors (Covance Laboratory) (19).
[3]Determined with the use of the carbohydrate by difference method (20).
[4]Measured with the use of HPLC (21).
[5]Mean ± SD where applicable per 240-mL serving (all such values).
[6]Measured with the use of ion chromatography (21).
[7]Measured with the use of an iodiometric titration method (22).
[8]Determined with the use of a DMAC colorimetric method with procyanidin A2 as a standard (23).
[9]Determined with the use of a modified DMAC colorimetric method with the cranberry proanthocyanidin standard isolated and purified from cranberry juice concentrate (21, 24).
[10]Determined with the use of HPLC (25).
[11]Determined with the use of the Folin-Ciocalteu reagent colorimetric method (21).

beverages is shown in **Table 1** (19–25). The placebo beverage was designed to look, smell, and taste like the cranberry beverage (27% juice), and a separate sensory study showed no difference in the proportions of subjects who correctly guessed if they were randomly assigned to receive either the cranberry beverage (51%) or the placebo beverage (40%) (n = 167; parallel design; P = 0.20). The cranberry juice cocktail study beverage used was similar to commercially available low-calorie products in its juice content (27% cranberry juice) although additional measures were taken to minimize the variability in the contents of proanthocyanidins and other bioactives. These additional measures included production from a single lot of cranberry concentrate and the use of a shorter time to expiration than is used for beverages that are produced for commercial use.

Compliance with study beverage consumption was assessed by having subjects return all unused bottles of dispensed study product and empty bottles of study product that had been consumed to the clinic. This information was checked against diary data, and subjects were queried to evaluate any discrepancies.

Measurements

Subjects completed a validated daily diary in which they recorded their consumption of the study beverage and captured any UTI symptoms (26). Daily diaries were reviewed at each post–random assignment clinic visit, and subjects were queried during telephone calls between clinic visits regarding their compliance with the consumption of the study product as well as whether symptoms or adverse experiences had occurred. If symptoms occurred at any time during the study, the subject was instructed to call the research clinic to arrange for a UTI-evaluation visit, which included a pelvic examination. A clean-catch urine sample was also collected, and a clinical (symptomatic) UTI was diagnosed by the investigator on the basis of ≥1 of the following symptoms: dysuria, urinary frequency, urinary urgency, or suprapubic pain in the absence of other potential etiologies such as vaginal infection or discharge. Investigators treated a clinical UTI with a standardized antimicrobial therapy regimen, and subjects continued to consume the study beverages during treatment. Clean-catch urine samples were also collected at weeks −1, 0, 8, 16, and 24 for urinalysis and culture. The presence or absence of pyuria in clean-catch urine samples was determined by a leukocyte esterase dipstick result (27). In the United States, the urine culture at the screening visit and the urinalysis from all visits were analyzed by Johnson City Medical Center (Johnson City, Tennessee), and urine cultures from nonscreening visits were tested by The General Clinical Research Center (University of Washington, Seattle, Washington). In France, the urine culture at the screening visit and urinalysis from all visits were analyzed by Synevo Central Laboratory Poland (Gdansk, Poland), and urine cultures from nonscreening visits were tested in Barcelona, Spain, by Servei de Microbiologia, Hospital Universitari Vall d'Hebron. At weeks 0, 8, 16, and 24, subjects completed questionnaires that assessed sexual history, food and beverage consumption, and the presence and severity of gastrointestinal symptoms.

Statistical analyses

The primary outcome variable was the clinical (symptomatic) UTI incidence density, which was defined as the number of clinical UTI events in each group (including multiple events per subject when applicable) per unit of observation time. The incidence density was selected as the primary outcome variable because UTI episodes often cluster in time (28, 29). The selection of a clinical UTI as the primary outcome in the current study was consistent with guidelines for UTI management (30) because initial treatment decisions are generally made before the availability of culture results, and the presence of multiple symptoms in the absence of vaginal discharge in women with a history of UTI is highly predictive (UTI probability >90%) (7, 31).

The following 3 classifications were used for clinical UTI analyses: investigator-diagnosed UTIs, probable UTIs, and possible UTIs. Investigator-diagnosed clinical UTIs were those for which the investigator evaluated the subject and made the UTI diagnosis. Probable UTIs were those for which the investigator did not examine the subject, but a nonstudy health care provider did examine the subject and prescribed antibiotics. Possible UTIs were those that did not fall into either of the other 2 categories including those in which the subject self-treated and instances when it was not clear whether an episode was a new UTI or a continuation of a previous infection that had not cleared (e.g., when a subject's symptoms stopped and recurred within 2 wk with no intervening test-of-cure visit). Results for investigator-diagnosed UTIs are presented in detail, and results from analyses that included probable and possible UTIs are described as sensitivity analyses.

Secondary and exploratory outcome variables included the incidence density for a clinical UTI with pyuria, the time from random assignment to a first clinical UTI, the time from random assignment to a first clinical UTI with pyuria, and the time from random assignment to a first symptomatic UTI with culture positivity ($\geq 10^3$ CFU/mL) for any uropathogen and for *Escherichia coli*. Safety was assessed by an evaluation of treatment-emergent adverse events, the frequency and severity of gastrointestinal signs and symptoms, and the measurement of vital signs, body weight, and clinical laboratory values.

Fisher's exact test with the use of G*Power software (free software available at http://www.gpower.hhu.de) was used to complete power calculations (32). Because the incidence density was to be used as the primary outcome variable, it was anticipated that the study power would be greater than that reflected by this calculation (29), which did not account for the occurrence of multiple UTIs during the treatment period in some women. On the basis of the assumption that the proportion of women who would experience a UTI episode in the placebo group would be 32% (5), a sample size of 145 subjects/group was expected to provide ≥80% power (α = 0.05; 2 sided) to detect a reduction to 17.8% in the treatment group. An enrollment of 300 subjects (150 subjects/group) was initially planned, but a decision was later made to increase the enrollment by an additional 40 subjects because a blinded review showed that the rate of a first UTI was slightly below initial projections.

Statistical analyses were conducted with the use of SAS for Windows software (version 9.1.3). All tests for significance were performed at α = 0.05 (2 sided). The baseline comparability of treatment groups for subject characteristics was assessed with the use of ANOVA and chi-square tests. Analyses were performed in all randomly assigned subjects (intent-to-treat population) with the observation time censored at the time that the study product was discontinued for subjects who did

not complete the full treatment period. Assumptions of normality of residuals were investigated for each response measurement. In cases in which the normality assumption was rejected at the 1% level with the use of the Shapiro-Wilk test (33), an analysis with the use of ranks was performed.

The UTI incidence density was analyzed with the use of Poisson regression with terms of treatment, site, country (United States or France), time since last UTI category (≤30, 31–89, or ≥90 d), and age category (<50 or ≥50 y) as well as an offset variable for the log of time (woman-years) under observation. The model was reduced until treatment and any significant terms ($P < 0.05$) remained with the use of a backward-elimination method. The appropriate fit and overdispersion were assessed for each model (34), and comparisons of results from full and reduced models were completed to assess whether the model-reduction procedure materially altered the point estimates and 95% CIs for the treatment effect. An adjustment for the susceptible time under observation to account for antibiotic use was calculated with the use of a subtraction of 7 d from the susceptible time for each instance of antibiotic use regardless of the reason for use. The incidence density is presented with and without this adjustment.

Time-to-event outcome variables were analyzed with the use of Cox proportional hazards models with the same covariates and approach as previously described. HRs with 95% CIs and model variable P values were determined. Assumptions of a constant relative hazard were verified with the use of the Schoenfeld residuals goodness-of-fit test (35). Continuous variables were analyzed with the use of an ANCOVA and a model with a term for the treatment and baseline included as a covariate.

RESULTS

A total of 373 subjects were randomly assigned to consume the cranberry beverage (n = 185) or placebo beverage (n = 188), and 322 subjects [cranberry: n = 160 (86.5%); placebo: n = 162 (86.2%)] completed through week 24 of the study (**Figure 1**). Two subjects in the cranberry group were randomly assigned in error (one subject had asymptomatic bacteriuria and another subject did not have sufficient literacy to understand the consent form). Both subjects were discontinued from treatment once the errors were discovered. Three subjects withdrew consent because of adverse events that were unrelated to the treatment (cranberry group: oral thrush and dizziness; placebo group: stomach complaints).

Demographic and baseline characteristics are shown in **Table 2**. Subjects had a mean age of 40.9 y, and the majority of subjects were white (67.0%) and of non-Hispanic or non-Latino ethnicity (75.6%). The mean ± SEM compliance with daily study-beverage consumption was 98.1% ± 0.6% and 98.2% ± 0.5% in the cranberry and placebo groups, respectively.

A total of 53 UTI-assessment visits were completed for subjects in the cranberry group, and 82 UTI-assessment visits were completed in the placebo group. These visits resulted in the diagnosis by study investigators of 39 clinical UTIs in the cranberry group and 67 clinical UTIs in the placebo group (**Table 3**). The fractions of clinical UTI diagnoses for which the subject reported ≥2 UTI symptoms at the assessment visits were 97.4% (38 of 39 diagnoses) for the cranberry condition and 99.0% (66 of 67 diagnoses) for the placebo condition, and for ≥3 UTI symptoms at the assessment visits, these values were 97.4% (38 of 39 diagnoses) for the cranberry condition and 91.0% (61 of 67 diagnoses) for the placebo condition. The annualized UTI incidence density was significantly reduced in the cranberry compared with

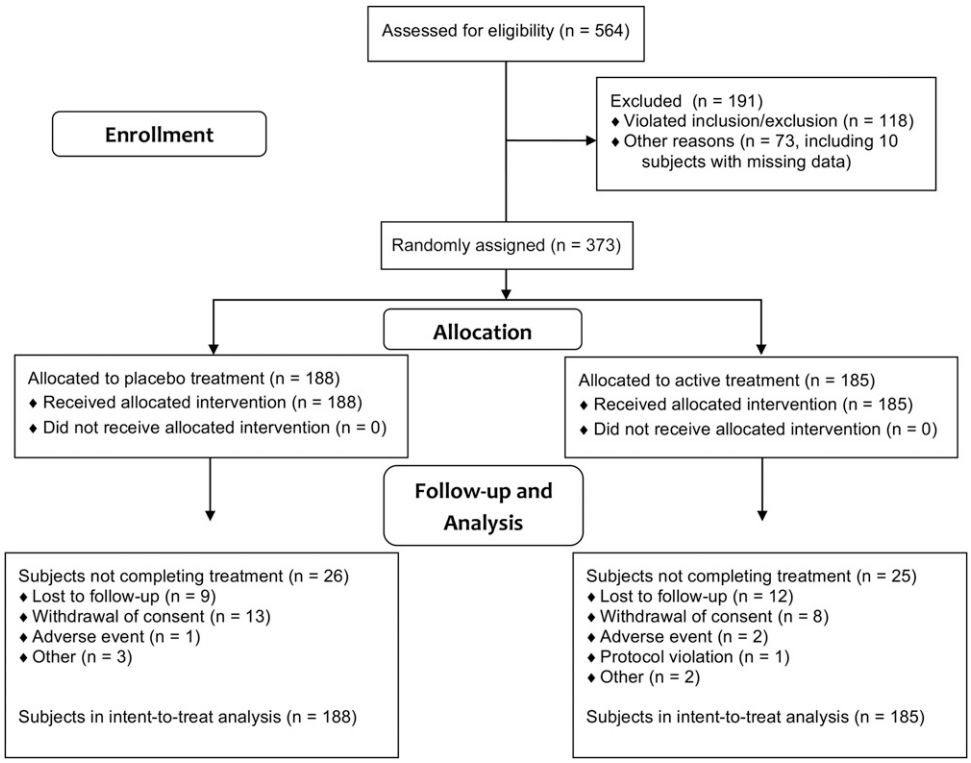

FIGURE 1 Subject disposition throughout the trial (Consolidated Standards of Reporting Trials flow diagram).

TABLE 2
Demographic and baseline characteristics of subjects receiving cranberry or placebo beverages[1]

Characteristic	Cranberry group (n = 185)	Placebo group (n = 188)	P
Age, y	40.9 ± 1.1[2]	41.0 ± 1.0	0.896
Age subgroup, y, n (%)			0.999
<50	131 (70.8)	133 (70.7)	
≥50	54 (29.2)	55 (29.3)	
Race,[3] n (%)			0.329
White	122 (65.9)	128 (68.1)	
Black/African American	30 (16.2)	29 (15.4)	
American Indian/Alaskan Native	0 (0.0)	2 (1.1)	
Asian or Pacific Islander	3 (1.6)	7 (3.7)	
Multiracial origin	2 (1.1)	1 (0.5)	
Other	3 (1.6)	0 (0.0)	
Missing[4]	25 (13.5)	21 (11.2)	
Ethnicity, n (%)			0.661
Hispanic/Latino	25 (13.5)	21 (11.2)	
Not Hispanic/Latino	136 (73.5)	146 (77.7)	
Missing	24 (13.0)	21 (11.2)	
Treated UTIs in past 6 mo, n	1.6 ± 0.1	1.7 ± 0.1	0.647
Most recent UTI history, d, n (%)			0.837
≤30	17 (9.2)	21 (11.2)	
31–89	80 (43.2)	79 (42.0)	
≥90	88 (47.6)	88 (46.8)	
Vaginal intercourse frequency in past 4 wk, n	4.9 ± 0.4	5.7 ± 0.6	0.434
Sexual partners in past 4 wk, n (%)			
0	58 (31.4)	50 (26.6)	0.399
1	123 (66.5)	135 (71.8)	
≥2	2 (1.1)	3 (1.6)	
History of diabetes,[5] n (%)	2 (1.1)	6 (3.2)	0.284
BMI, kg/m^2	27.0 ± 0.4	26.5 ± 0.4	0.346
Categorical BMI, kg/m^2, n (%)			0.116
<25	79 (42.7)	92 (48.9)	
25 to <30	57 (30.8)	40 (21.3)	
≥30	49 (26.5)	56 (29.8)	
Alcoholic drinks,[6] n/wk	0.5 (0.0, 10.0)	0.4 (0.0, 12.0)	0.962
Smoking status, n (%)			0.282
Nonsmoker	134 (72.4)	145 (77.1)	
Current smoker	19 (10.3)	11 (5.9)	
Past smoker	32 (17.3)	32 (17.0)	

[1]Baseline comparability of treatment groups for subject characteristics was assessed with the use of ANOVA and chi-square tests. UTI, urinary tract infection.

[2]Mean ± SEM (all such values).

[3]Race and ethnicity were self-reported by subjects as part of a medical history questionnaire that was completed at screening to allow comparison with the racial and ethnic compositions of the country.

[4]For clinical studies in France, data regarding ethnicity can only be collected if justified by the type of research. In this study of cystitis, there was no justification to investigate ethnicity, and therefore, this information was not collected from subjects enrolled at the clinical site in France.

[5]Previous history of a medical diagnosis of diabetes as recorded in the medical history. In the cranberry group, 2 subjects with diabetes were ≥50 y of age; in the placebo group, 2 subjects with diabetes were <50 y of age, and 4 subjects were ≥50 y of age.

[6]All values are medians; minimums, maximums in parentheses. These data were not normally distributed (normality assumption was rejected at the 1% level with the use of the Shapiro-Wilk test) and were ranked in the analyses.

in the placebo arm (incidence rate ratio: 0.62; 95% CI: 0.42, 0.92; P = 0.017). Adjustment for antibiotic use (139 instances in the control group and 111 instances in the cranberry group) for the susceptible time under observation did not materially alter the point estimate (incidence rate ratio: 0.61; 95% CI: 0.41, 0.91; P = 0.016). For every 3.6 woman-years (95% CI: 2.3, 15.8 woman-years) of the cranberry intervention, 1 symptomatic UTI event was prevented. After adjustment for antibiotic use, 1 symptomatic UTI was prevented for every 3.2 woman-years (95% CI: 2.0, 13.1 woman-years).

Results were not materially influenced by the model reduction (data not shown). There was no statistical heterogeneity in the treatment response for subjects <50 and ≥50 y of age (P-treatment by age-group interaction = 0.526).

The incidence density for symptomatic UTIs with pyuria (adjusted for antibiotic use) was significantly reduced in the cranberry arm compared with in the placebo arm (Table 3) (incidence rate ratio: 0.63; 95% CI: 0.40, 0.97; P = 0.037). With the use of the classifications of investigator-diagnosed plus probable symptomatic UTIs (47 and 72 UTIs in the cranberry

TABLE 3
Symptomatic episodes of UTI diagnosed and treated by study investigators and symptomatic UTIs with pyuria in subjects consuming cranberry or placebo beverages for 24 wk[1]

	Cranberry group (n = 185)	Placebo group (n = 188)	Incidence rate ratio (95% CI)[2]	P
Subjects reporting a symptomatic UTI, episodes, n (%)				
0	152 (82.2)	138 (73.4)	—	—
1	27 (14.6)	36 (19.2)	—	—
2	6 (3.2)	11 (5.9)	—	—
3	0 (0.0)	3 (1.6)	—	—
≥1	33 (17.8)	50 (26.6)	—	—
Total UTIs, n	39	67	—	—
UTI, annualized incidence density (95% CI)[2]	0.48 (0.33, 0.63)	0.75 (0.56, 0.94)	0.62 (0.42, 0.92)	0.017
Incidence density (95% CI) adjusted for antibiotic use[3]	0.54 (0.38, 0.70)	0.85 (0.65, 1.05)	0.61 (0.41, 0.91)	0.016
Subjects with a symptomatic UTI with pyuria, episodes, n (%)				
0	157 (84.7)	147 (78.2)	—	—
1	24 (13.0)	31 (16.5)	—	—
2	4 (2.2)	8 (4.3)	—	—
3	0 (0.0)	2 (1.1)	—	—
≥1	28 (15.1)	41 (21.8)	—	—
Total UTIs with pyuria, n	32	53	—	—
UTI with pyuria, annualized incidence density (95% CI)[2]	0.40 (0.39, 0.41)	0.59 (0.58, 0.61)	0.63 (0.41, 0.98)	0.041
Incidence density (95% CI) adjusted for antibiotic use[3]	0.43 (0.42, 0.45)	0.67 (0.65, 0.68)	0.63 (0.40, 0.97)	0.037

[1]UTI, urinary tract infection.
[2]Incidence rate ratios and P values for the number of UTIs (or UTIs with pyuria) per woman-year of observation were determined from the generalized linear model with the log link and Poisson distribution specified along with the offset log for observation time. The model was reduced until treatment, and any significant terms ($P < 0.05$) remained with the use of a backward elimination method.
[3]Observation time was adjusted by subtracting 7 d from the observation time for every instance of antibiotic use regardless of the indication.

and placebo groups, respectively) and investigator-diagnosed plus probable and possible symptomatic UTIs (48 and 74 UTIs in the cranberry and placebo groups, respectively), the antibiotic-adjusted incidence rate ratios at week 24 were 0.68 (95% CI: 0.47, 0.99; $P = 0.043$) and 0.68 (95% CIs: 0.47, 0.98; $P = 0.037$), respectively.

Kaplan-Meier curves are shown in **Figure 2**. By the end of the 24-wk treatment period, 33 subjects (17.8%) in the cranberry group had experienced a first symptomatic UTI compared with 50 subjects (26.6%) in the placebo group (HR: 0.67; 95% CI: 0.43, 1.05; $P = 0.078$). There were no significant differences between treatment groups in the time from random assignment to the first clinical UTI with pyuria (HR: 0.69; 95% CI: 0.43, 1.12; $P = 0.131$), with microbiological positivity (HR: 0.97; 95% CI: 0.56, 1.67; $P = 0.914$), or positive for *E. coli* (HR: 1.38; 95% CI: 0.73, 2.59; $P = 0.323$).

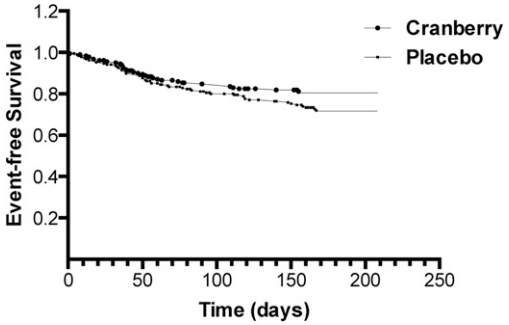

FIGURE 2 Time to first symptomatic UTI (week 24 survival time) in subjects receiving a cranberry beverage (n = 185) or a placebo beverage (n = 188). The HR for the difference between cranberry and placebo groups in the number of subjects who had experienced a first symptomatic UTI by the end of the 24-wk treatment period was 0.67 (95% CI: 0.43, 1.05; $P = 0.078$). UTI, urinary tract infection.

A total of 30 investigator-diagnosed clinical UTIs in the cranberry group and 34 investigator-diagnosed clinical UTIs in the placebo group were microbiologically positive. The bacterial species identified in the cultures that were positive for bacteria are shown in **Table 4**. A majority of the microbiologically positive infections in both treatment groups were positive for *E. coli* [27 infections (90.0%) and 24 infections (70.6%) in the cranberry and placebo groups, respectively]. Analyses of urine samples collected at the scheduled post–random assignment visits indicated no significant differences between treatment groups in the fractions of subjects with asymptomatic bacteriuria (for cranberry and control groups: at week 8, 4.3% and 3.7%, respectively; at week 16, 8.1% and 8.0%, respectively; and at week 24, 9.2% and 11.2%, respectively).

Adverse events that occurred in ≥5% of subjects in either treatment group included headache [cranberry group: n = 16 (8.6%); placebo group: n = 12 (6.4%)], sinusitis [cranberry group: n = 10 (5.4%); placebo group: n = 6 (3.2%)], and upper respiratory infection [cranberry group: n = 13 (7.0%); placebo group: n = 13 (6.9%)]. One subject in the cranberry group had a serious adverse event (chest pain), and 4 subjects in the placebo group had a serious adverse event (ischemic colitis leading to septic shock, miscarriage, in-patient hospitalization for appendicitis, and surgery for a rectal prolapse). All serious adverse events were classified as either unrelated or unlikely to be related to the treatment.

The only significant difference between treatment groups in the gastrointestinal tolerability questionnaire was at week 8 with 3 subjects (1.6%) in the cranberry group and 11 subjects (5.9%) in the placebo group reporting a nausea rating of "somewhat more

TABLE 4
Bacterial species identified in urine cultures collected when women who were consuming cranberry or placebo beverages reported a symptomatic UTI[1]

	UTIs positive for the microorganism, *n*	
Species	Cranberry group (*n* = 185)	Placebo group (*n* = 188)
Escherichia coli	27	23
Staphylococcus saprophyticus	1	1
Enterococci	0	3
Klebsiella spp.	0	2
Enterobacter spp.	1	0
Citrobacter spp.	0	2
Group B Streptococcus	0	2
Other gram-negative rods (*Escherichia vulneris*)	1	0
E. coli and *Enterococci*	0	1
Sum	30	34

[1]UTI, urinary tract infection.

than usual" or "much more than usual" ($P = 0.044$). There were no significant differences between treatment groups at baseline or during the study in systolic or diastolic blood pressures, heart rates, or body weights (data not shown).

DISCUSSION

In this randomized, double-blind, placebo-controlled, multicenter study in women with a recent UTI history, the daily consumption of a cranberry beverage for 24 wk produced a 39% (95% CI: 9%, 59%) reduction in clinical UTI episodes. The rate of clinical UTI with pyuria episodes was also reduced by 37% (95% CI: 3%, 60%) although no difference between the groups was observed for microbiologically positive UTIs. A course of antibiotic therapy for a clinical UTI was prevented for every 3.2 woman-years (95% CI: 2.0, 13.1 woman-years) (adjusted for antibiotic use) of the cranberry intervention.

To our knowledge, this is the largest study to date to evaluate the influence of cranberry-product consumption on UTI incidence in women and was designed to address some of the limitations of previous trials, which have included an inadequate statistical power because of low UTI-event rates, small sample sizes, poor compliance with study-product consumption, and high dropouts (13). The current study had greater statistical power to detect differences than did previous trials because of its larger sample size, the use of the incidence density to account for the tendency of clinical UTI events to cluster in time within an individual, a high average level of compliance with study-product consumption in both groups (~98%), and a comparatively large percentage of subjects in each group who completed the treatment period (~86%).

A 2008 Cochrane review of 10 clinical studies reported that the consumption of cranberry products (juice or tablets) significantly reduced UTI incidence compared with that from placebo consumption (RR: 0.65; 95% CI: 0.46, 0.90), which is a reduction that is similar in magnitude to the effect reported in the current study (36). Another meta-analysis of 13 trials reported a protective effect of cranberry consumption against recurrences of UTI (RR: 0.53; 95% CI: 0.33, 0.83) (5). However, a more recent Cochrane review reported a nonsignificant reduction in risk of repeat UTIs with cranberry treatment compared with a placebo or no treatment (RR: 0.74; 95% CI: 0.42, 1.31) but with substantial heterogeneity in the results ($I^2 = 65\%$) that were largely attributable to a single study that included only microbiologically positive UTIs in the analysis (37). When that study was omitted, the pooled RR was 0.58 (95% CI: 0.39, 0.86) (13).

Stapleton et al. (38) reported results from a randomized controlled trial of cranberry juice consumption that was similar in many respects to those of the current trial. The investigators showed a nonsignificantly reduced HR for the cranberry beverage compared with the placebo beverage of 0.68 (95% CI: 0.33, 1.39; $P = 0.29$) for the outcome of the time to a first clinical UTI event. Note that the point estimate for the effect was nearly identical to that observed in the current trial for the secondary outcome of the time to a first clinical UTI for which the HR was 0.67 (95% CI: 0.43, 1.05; $P = 0.078$), and significance was present for the primary incidence density outcome. Therefore, results from the current investigation are consistent in direction and magnitude with those from most previous studies of the effects of cranberry consumption on the prevention of clinical UTIs in women and are also concordant with those of Barbosa-Cesnik et al. (37) in showing no significant difference in culture-positive UTI incidence.

All subjects had a recent UTI history, and a large majority of participants had multiple symptoms in the absence of vaginal discharge or irritation at diagnosis, which was consistent with >90% probability of UTI (31). These results suggest a low likelihood of a substantial misdiagnosis, and because this was a double-blind study, the diagnostic criteria were unlikely to have been applied in a differential manner between treatment groups. A majority of microbiologically positive UTI events are typically due to *E. coli* infection (39). In the current study, 90.0% (cranberry) and 70.6% (placebo) of the microbiologically positive UTI events showed the presence of *E. coli*, which was very similar to the results reported by Barbosa-Cesnik (37) in which *E. coli* was present in 93.3% (cranberry) and 58.3% (placebo) of culture-positive UTIs. Because the 2 largest studies completed to date on cranberry use to reduce episodes of UTI have shown no evidence of a difference in the microbiologically positive UTI incidence, the mechanisms responsible may not have influenced this outcome.

Results from in vitro and ex vivo studies have suggested that cranberry interferes with the attachment of uropathogenic *E. coli* to epithelial cells in the bladder, periurethral region, and gastrointestinal tract (40–43). In addition, cranberry consumption appears to produce anti-inflammatory effects (44–46), which may help to explain the reduction in clinical UTI episodes without a difference in the incidence of microbiologically positive UTI events. One possible explanation is that cranberry consumption may reduce the proportion of asymptomatic bacteriuria episodes that progress to symptomatic UTIs (11). Cranberry may also suppress inflammation associated with the activation of intracellular bacterial communities during a recurrent UTI episode (44, 46). Anti-inflammatory activity has the potential to prevent the development of symptoms but also to lower intercellular bacterial propagation, and thus reduce the severity of a UTI episode as well as the propensity for a chronic infection (44, 46, 47). Such effects have been shown for anti-inflammatory agents such as cyclooxygenase inhibitors and

dexamethasone (48–50). Mechanistic studies are needed to more-clearly define the mechanisms through which cranberry is affecting clinical UTI recurrence.

One limitation of the current study is the evaluation of only a single level of once-daily cranberry beverage intake. An additional investigation will be necessary to evaluate other intakes and delivery forms such as powdered extracts. In addition, subjects were volunteers with a self-reported history of a recent UTI who may not have been fully representative of women who are treated in clinical practice, although the similarities in the sizes of the effects in the current and previous trials suggested that the results may be generalizable. The fraction of women in the placebo group with ≥1 UTI (50 of 188 women; 27%) was within the expected range of 25–35% (1, 5). The percentage of women with ≥1 UTI in France was somewhat lower (10%) but with wide confidence limits because of the small number of subjects ($n = 21$ assigned to receive the placebo in France).

In conclusion, the consumption of a cranberry juice beverage significantly reduced the clinical UTI incidence density in women with a history of ≥2 UTIs in the previous year. These results suggest that the consumption of cranberry is a useful strategy for reducing recurrent clinical UTI episodes and antibiotic use that is associated with the treatment of these events.

We thank the following individuals for assistance with this trial: Ann Stapleton, Marsha Cox, and Aurelio Silvestroni from the University of Washington, Seattle, Washington (specimen analyses); Antonio Andreau Domingo from the Servei de Microbiologia Hospital Universitari Vall d'Hebron, Barcelona, Spain (specimen analyses); Thomas M Hooton from the University of Miami Health Systems, Miami, Florida (study-design assistance); and Barbara Davis, who is currently with PLT Health Solutions, Morristown, New Jersey (study-design assistance). We also thank the following individuals who are affiliated with Biofortis Clinical Research, Addison, Illinois, for their assistance: Jennifer Baldwin (monitoring of clinical sites), Patti Shatkus (monitoring of clinical sites), DeAnn Liska (assistance with the analysis and interpretation of the data), Mary Dicklin (writing and editing assistance), and Mitchell Silverman (data management). The UTI Study Group included the following principal investigators and sites: Kathleen Kelley, Biofortis Clinical Research, Addison, Illinois; Jeffrey Geohas, Evanston Premier Healthcare Research, Evanston, Illinois; Rovena Reagan, Women's Health Care Research Corp., San Diego, California; Derek Muse, Jean Brown Research, Salt Lake City, Utah; Albert Tejada, Radiant Research, Scottsdale, Arizona; Randall Severance, Radiant Research, Chandler, Arizona; Michelle Reynolds, Radiant Research, Dallas, Texas; Douglas Schumacher, Radiant Research, Columbus, Ohio; Larry Kotek, Radiant Research, Edina, Minnesota; Stephen Halpern, Radiant Research, Santa Rosa, California; Michael Noss, Radiant Research, Cincinnati, Ohio; David Bolshoun, Radiant Research, Denver, Colorado; James Kopp, Radiant Research, Anderson, South Carolina; E William Parker Jr. and David Young, Physicians' Research Options/Central Utah Clinic Women's Health, Pleasant Grove, Utah; Khai Chang, Lakeview Medical Research, Summerfield, Florida; Susan Hole, Riverside Clinical Research, Edgewater, Florida; Miriam Lara, Apple Med Research Inc., Miami, Florida; and David Gendre, Biofortis SAS, France.

The authors' responsibilities were as follows—KCM: designed and conducted the research, performed the statistical analysis, wrote the manuscript, and had primary responsibility for the final content of the manuscript; KLK and CK: designed and conducted the research and wrote the manuscript; LHD: conducted the research; ALS: performed the statistical analysis; KG: designed the research and wrote the manuscript; and all authors: read and approved the final manuscript. KCM, LHD, and ALS received research grant funding from Ocean Spray Cranberries Inc., and KLK and CK are employees of Ocean Spray Cranberries Inc., which is the manufacturer of the product studied. KG reported no conflicts of interest related to the study.

REFERENCES

1. Foxman B, Barlow R, D'Arcy H, Gillespie B, Sobel JD. Urinary tract infection: self-reported incidence and associated costs. Ann Epidemiol 2000;10:509–15.
2. Litwin MS, Saigal CS, Yano EM, Avila C, Gescgwind SA, Hanley JM, Joyce GF, Madison R, Pace J, Polich SM, et al. Urologic Diseases in America Project: analytical methods and principal findings. J Urol 2005;173:933–7.
3. Foxman B. Urinary tract infection syndromes: occurrence, recurrence, bacteriology, risk factors, and disease burden. Infect Dis Clin North Am 2014;28:1–13.
4. Schappert SM, Rechtsteiner EA. Ambulatory medical care utilization estimates for 2007. Vital Health Stat 13 2011;169:1–38.
5. Wang CH, Fang CC, Chen NC, Liu SS, Yu PH, Wu TY, Chen WT, Lee CC, Chen SC. Cranberry-containing products for prevention of urinary tract infections in susceptible populations: a systemic review and meta-analysis of randomized controlled trials. Arch Intern Med 2012;172:988–96.
6. Beerepoot MA, ter Riet G, Nys S, van der Wal WM, de Borgie CA, de Reijke TM, Prins JM, Koeijers J, Verbon A, Stobberingh E, et al. Cranberries vs antibiotics to prevent urinary tract infections: a randomized double-blind noninferiority trial in premenopausal women. Arch Intern Med 2011;171:1270–8.
7. Hooton TM. Uncomplicated urinary tract infection. N Engl J Med 2012;366:1028–37.
8. Trautner BW, Gupta K. The advantages to second best: comment on Lactobacilli vs antibiotics to prevent urinary tract infections. Arch Intern Med 2012;172:712–4.
9. Gupta K. Emerging antibiotic resistance in urinary tract pathogens. Infect Dis Clin North Am 2003;17:243–59.
10. World Health Organization. Antimicrobial resistance global report on surveillance [Internet]. 2014 (cited 2015 Apr 14). Available from: http://apps.who.int/iris/bitstream/10665/112642/1/9789241564748_eng.pdf.
11. Cai T, Nesi G, Mazzoli S, Meacci F, Lanzafame P, Caciagli P, Mereu L, Tateo S, Malossini G, Selli C, et al. Asymptomatic bacteriuria treatment is associated with a higher prevalence of antibiotic resistant strains in women with urinary tract infections. Clin Infect Dis 2015;61:1655–61.
12. Wagenlehner FME, Naber KG. Treatment of asymptomatic bacteriuria might be harmful. Clin Infect Dis 2015;61:1662–3.
13. Jepson RG, Williams G, Craig JC. Cranberries for preventing urinary tract infections. Cochrane Database Syst Rev 2012;10:CD001321.
14. Eells SJ, McKinnell JA, Miller LG. Daily cranberry prophylaxis to prevent recurrent urinary tract infections may be beneficial in some populations of women. Clin Infect Dis 2011;52:1393–4.
15. Foxman B, Freichs RR. Epidemiology or urinary tract infection: II. Diet, clothing, and urination habits. Am J Public Health 1985;75:1314–7.
16. Foxman B, Geiger AM, Palin K, Gillespie B, Koopman JS. First-time urinary tract infection and sexual behavior. Epidemiology 1995;6:162–8.
17. Foxman B, Gillespie B, Koopman J, Zhang L, Pallin K, Tallman P, Marsh JV, Spear S, Dobel JD, Marty MJ, et al. Risk factors for second urinary tract infection among college women. Am J Epidemiol 2000;151:1194–205.
18. Kontiokari T, Laitinen J, Jarvi L, Pokka R, Sundqvist K, Uhari M. Dietary factors protecting women from urinary tract infection. Am J Clin Nutr 2003;77:600–4.
19. United States Department of Agriculture. Composition of foods. In: Agriculture handbook no. 8. Beltsville (MD): USDA; 1975. p. 159–160.
20. United States Department of Agriculture. Energy values of foods. In: Agriculture handbook no. 74. Beltsville (MD): USDA; 1973. p. 2–11.
21. Martín MA, Ramos S, Mateos R, Marais JPJ, Bravo-Clemente L, Khoo C, Goya L. Chemical characterization and chemo-protective activity of cranberry phenolic powders in a model cell culture. Response of the antioxidant defenses and regulation of signaling pathways. Food Res Int 2015;71:68–82.
22. United States Pharmacopeial Convention. Food chemical codex. Baltimore (MD): United Book Press Inc.; 2010.
23. Prior RL, Fan E, Ji H, Howell A, Nio C, Payne MJ, Reed J. Multilaboratory validation of a standard method for quantifying proanthocyanidins in cranberry powders. J Sci Food Agric 2010;90:1473–8.
24. Krueger CG, Chesmore N, Chen X, Parker J, Khoo C, Marais JPJ, Shanmuganayagam D, Crump P, Reed JD. Critical reevaluation of the 4-(dimethylamino)cinnamaldehyde assay: cranberry proanthocyanidin standard is superior to procyanidin A2 dimer for accurate quantification of proanthocyanidins in cranberry products. J Funct Foods 2016;22:13–9.

25. McKay DL, Chen CY, Zampariello CA, Blumberg JB. Flavonoids and phenolic acids from cranberry juice are bioavailable and bioactive in healthy older adults. Food Chem 2015;168:233–40.
26. Clayson D, Wild D, Doll H, Keating K, Gondek K. Validation of a patient-administered questionnaire to measure the severity and bothersomeness of lower urinary tract symptoms in uncomplicated urinary tract infection (UTI): the UTI Symptom Assessment questionnaire. BJU Int 2005;96:350–9.
27. St John A, Boyd JC, Lowes AJ, Price CP. The use of urinary dipstick tests to exclude urinary tract infection: a systematic review of the literature. Am J Clin Pathol 2006;126:428–36.
28. Nosseir SB, Lind LR, Winkler HA. Recurrent uncomplicated urinary tract infections in women: a review. J Womens Health (Larchmt) 2012; 21:347–54.
29. Salo J, Uhari M, Helminen M, Korppi M, Nieminen T, Pokka T, Kontiokari T. Cranberry juice for the prevention of recurrences of urinary tract infections in children: a randomized placebo-controlled trial. Clin Infect Dis 2012;54:340–6.
30. Gupta K, Hooton TM, Naber KG, Wult B, Colgan R, Miller LG, Moran GJ, Nicolle LE, Raz R, Schaeffer AJ, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis 2011;52:e103–20.
31. Bent S, Nallamothu BK, Simel DL, Fihn SD, Saint S. Does this woman have an acute uncomplicated urinary tract infection. JAMA 2002;287:2701–10.
32. Faul F, Erdfelder E, Lang AG, Buchner AG. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 2007;39:175–91.
33. Shapiro SS, Wilk MB. An analysis of variance test for normality (complete samples). Biometrika 1965;52:591–611.
34. Stokes MA, Davis S, Koch GG. Categorical data analysis using the SAS system. 2nd ed. Cary (NC): SAS Institute Inc.; 2000.
35. Kleinbaum DG, Klein M. Survival analysis. A self learning text. 2nd ed. New York: Springer; 2005.
36. Jepson RG, Craig JC. Cranberries for preventing urinary tract infections. Cochrane Database Syst Rev 2008;1:CD001321.
37. Barbosa-Cesnik C, Brown MB, Buxton M, Zhang L, De Busscher J, Foxman B. Cranberry juice fails to prevent recurrent urinary tract infection: results from a randomized placebo-controlled trial. Clin Infect Dis 2011;52:23–30.
38. Stapleton AE, Dziura J, Hooton TM, Cox ME, Yarova-Yarova Y, Chen S, Gupta K. Recurrent urinary tract infection and urinary *Escherichia coli* in women ingesting cranberry juice daily: a randomized controlled trial. Mayo Clin Proc 2012;87:143–50.
39. Zhang L, Foxman B. Molecular epidemiology of *Escherichia coli* mediated urinary tract infections. Front Biosci 2003;8:e235–44.
40. Lavigne JP, Bourg G, Combescure C, Botto H, Sotto A. In-vitro and in-vivo evidence of dose-dependent decrease of uropathogenic *Escherichia coli* virulence after consumption of commercial Vaccinium macrocarpon (cranberry) capsules. Clin Microbiol Infect 2008;14:350–5.
41. Harmidy K, Tufenkji N, Gruenheid S. Perturbation of host cell cytoskeleton by cranberry proanthocyanidins and their effect on enteric infections. PLoS One 2011;6:e27267.
42. Feliciano RP, Meudt JJ, Shanmuganayagam D, Krueger CG, Reed JD. Ratio of "A-type" to "B-type" proanthocyanidin interflavan bonds affects extra-intestinal pathogenic *Escherichia coli* invasion of gut epithelial cells. J Agric Food Chem 2014;62:3919–25.
43. Krueger CG, Reed JD, Feliciano RP, Howell AB. Quantifying and characterizing proanthocyanidins in cranberries in relation to urinary tract health. Anal Bioanal Chem 2013;405:4385–95.
44. Huang Y, Nikolic D, Pendland S, Doyle BJ, Locklear TD, Mahady GB. Effects of cranberry extracts and ursolic derivatives on P-fimbriated *Escherichia coli*, COX-2 activity, pro-inflammatory cytokine release and the NF-kappa-beta transcriptional response in vitro. Pharm Biol 2009;47:18–25.
45. Vasileiou I, Katsargyris A, Theocharis S, Giagninis C. Current clinical status on the preventive effects of cranberry consumption against urinary tract infections. Nutr Res 2013;33:595–607.
46. Denis MC, Desjardins Y, Furtos A, Marcil V, Dudonne S, Montoudis A, Garofalo C, Delvin E, Marette A, Levy E. Prevention of oxidative stress, inflammation and mitochondrial dysfunction in the intestine by different cranberry phenolic fractions. Clin Sci (Lond) 2015;128:197–212.
47. Robino L, Algorta G, Zunino P, Vignoli R. Detection of intracellular bacterial communities in a child with *Escherichia coli* recurrent urinary tract infections. Pathog Dis 2013;68:78–81.
48. Finer G, Landau D. Pathogenesis of urinary tract infections with normal female anatomy. Lancet Infect Dis 2004;4:631–5.
49. Hannan TJ, Mysorekar IU, Hung CS, Isaacson-Schmid ML, Hultgren SJ. Early severe inflammatory responses to uropathogenic *E. coli* predispose to chronic and recurrent urinary tract infection. PLoS Pathog 2010;6:e1001042.
50. Hannan TJ, Roberts PL, Riehl TE, van der Post S, Binkley JM, Schwartz DJ, Myoshi H, Mack M, Schwendener RA, Hooton TM, et al. Inhibition of cyclooxygenase-2 prevents chronic and recurrent cystitis. EBioMedicine 2014;1:46–57.

The American Journal of Clinical Nutrition