Recurrent Urinary Tract Infection and Urinary *Escherichia coli* in Women Ingesting Cranberry Juice Daily: A Randomized Controlled Trial

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Abstract

Objective: To compare the time to urinary tract infection (UTI) and the rates of asymptomatic bacteriuria and urinary P-fimbriated *Escherichia coli* during a 6-month period in women ingesting cranberry vs placebo juice daily.

Patients and Methods: Premenopausal women with a history of recent UTI were enrolled from November 16, 2005, through December 31, 2008, at 2 centers and randomized to 1 of 3 arms: 4 oz of cranberry juice daily, 8 oz of cranberry juice daily, or placebo juice. Time to UTI (symptoms plus pyuria) was the main outcome. Asymptomatic bacteriuria, adherence, and adverse effects were assessed at monthly visits.

Results: A total of 176 participants were randomized (120 to cranberry juice and 56 to placebo) and followed up for a median of 168 days. The cumulative rate of UTI was 0.29 in the cranberry juice group and 0.37 in the placebo group ($P=.82$). The adjusted hazard ratio for UTI in the cranberry juice group vs the placebo group was 0.68 (95% confidence interval, 0.33-1.39; $P=.29$). The proportion of women with P-fimbriated urinary *E coli* isolates during the intervention phase was 10 of 23 (43.5%) in the cranberry juice group and 8 of 10 (80.0%) in the placebo group ($P=.07$). The mean dose adherence was 91.8% and 90.3% in the cranberry juice group vs the placebo group. Minor adverse effects were reported by 24.2% of those in the cranberry juice group and 12.5% in the placebo group ($P=.07$).

Conclusion: Cranberry juice did not significantly reduce UTI risk compared with placebo. The potential protective effect we observed is consistent with previous studies and warrants confirmation in larger, well-powered studies of women with recurrent UTI. The concurrent reduction in urinary P-fimbriated *E coli* strains supports the biological plausibility of cranberry activity.

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Urinary tract infection (UTI) is an exceedingly common outpatient problem among young, healthy women, resulting in considerable morbidity and health care costs.[1,2] In addition to the cost burden, increasing antibiotic resistance is making treatment of these infections more problematic.[3,4] Thus, safe and effective nonantimicrobial prevention strategies are needed. One preventive approach that has been used for generations is ingestion of cranberry products.[5,6] In vitro data have shown that cranberry inhibits primarily P-fimbriated uropathogenic strains of *Escherichia coli* from adhering to uroepithelial cells, which is a critical step in the development of UTI.[7-9] However, these findings have not been correlated directly with clinical outcomes or verified in clinical studies.

Cranberry products have been evaluated as a UTI-preventive agent in several patient populations, including children and adults with neuropathic bladders, elderly men and women, pregnant women, and healthy, nonpregnant women.[10-17] The results from some, but not all, of these trials suggest that cranberry may reduce the incidence of bacteriuria and UTI, particularly in healthy women with acute, uncomplicated cystitis.[6]

In 2003, the National Center for Complementary and Alternative Medicine provided a standardized, well-characterized cranberry juice cocktail and matching placebo juice for conduct of studies that evaluated potential health benefits of cranberry products. The aim of this current study was to conduct a phase 2, proof-of-principle clinical trial assessing the ability of cranberry to reduce the rates of UTI, asymptomatic bacteriuria, and urinary P-fimbriated *E coli* in premenopausal women with a history of recent UTI.

PATIENTS AND METHODS

Study Population

This was a multicenter study, with simultaneous enrollment at the Hall Health Primary Care Center at the University of Washington, Seattle, and at the

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Yale–New Haven Hospital General Clinical Research Center, New Haven, CT. The study began on November 16, 2005, and ended on December 31, 2008. Premenopausal women 18 to 45 years of age with a history of one or more clinician-diagnosed UTIs in the past 12 months were eligible to participate. In addition, women had to agree to avoid all foods containing cranberries or other *Vaccinium* species (eg, blueberries) other than the study product for the 6-month duration of the trial. Women were not eligible if they had prediagnosed anatomical abnormalities of the urinary tract, a history of kidney stones, diabetes mellitus, malignant neoplasm other than skin disease, known allergy or intolerance to cranberry products, symptoms of vaginitis or cystitis, or asymptomatic bacteriuria ($\geq 10^5$ colony-forming units (CFU)/mL of the same uropathogen on 2 consecutive cultures on 2 separate days); were pregnant, lactating, not regularly using contraceptives, using prophylactic antimicrobials, or taking warfarin; or had used antibiotics in the past 7 days or investigational drugs in the past 30 days. All study procedures were approved by the local institutional review board at each site.

Study Procedures

Recruitment methods included advertisements in the local area and clinician referral at the time of a UTI visit to one of the clinics. After written informed consent, women provided a urine sample for testing for asymptomatic bacteriuria and pregnancy. Women with a positive test result for pregnancy or asymptomatic bacteriuria were not eligible for enrollment and randomization. Participants complying with all inclusion and exclusion criteria and consenting to study participation were randomized to 1 of the 3 groups (4 oz of cranberry juice, 8 oz of cranberry juice, or placebo) in a 1:1:1 ratio. The biostatistician (S.C.) produced the randomization code and scheme through a computer-generated process. Randomization was stratified by site. Identification numbers were randomly preassigned to study participants, and the corresponding treatment group was stored and assigned from our Web-based system to ensure concealment of intervention allocation. At enrollment, women completed a brief questionnaire, provided a midstream clean catch specimen for urinalysis and culture, and self-collected vaginal and rectal swabs.

The active and placebo juices were manufactured and provided by Ocean Spray Cranberries Inc under National Center for Complementary and Alternative Medicine contract NOTCA-02-014 and approved for investigational use under Food and Drug Administration Investigational New Drug No. 67,799. The active juice contained 27% cranberry juice and sucralose (Splenda), similar in composition to the commercially available low-calorie Ocean Spray cranberry juice cocktail. The placebo juice was of similar color and taste but did not contain cranberry juice. Women returned for follow-up on a monthly basis for 6 months and whenever they experienced symptoms of a UTI.

Primary Outcome Assessment

The primary outcome was time to a symptomatic UTI event that met criteria for clinical or culture-confirmed UTI. Individuals with acute onset of urinary symptoms were assessed by study staff for dysuria plus one or more of the symptoms of frequency, urgency, suprapubic pain, hematuria, and pyuria (white blood cell count $>10/\mu$L in unspun urine by hemocytometer or a positive leukocyte esterase dipstick result). Women who met both the symptom and pyuria criteria were diagnosed as having symptomatic UTI. If the urine culture result was positive ($\geq 10^3$ CFU/mL of a uropathogen), the episode was categorized as culture-confirmed UTI. If the urine culture result was negative, alternate diagnoses were excluded (detailed below), and if symptoms resolved with therapy, the episode was categorized as a clinical UTI. Women with symptoms of UTI but no pyuria and a negative urine culture result were not treated and were evaluated via examination and urine nucleic acid testing for alternate diagnoses, including vaginitis or cervicitis caused by *Chlamydia trachomatis* or *Neisseria gonorrhoeae*.[18] Women with symptomatic UTI during the study period continued to drink the juice and remained in the study for the full 6 months unless they were lost to follow-up or elected to discontinue.

Secondary Outcomes

Asymptomatic bacteriuria was defined as 10^5 CFU/mL or more of a uropathogen in a woman without symptoms of UTI and was assessed at the monthly follow-up visits. *E coli* isolates from baseline vaginal and rectal cultures and from symptomatic UTI and asymptomatic bacteriuria episodes occurring during the study were further evaluated in the laboratory for the presence of functional P fimbriation, as described below. Adherence and adverse effects were captured by a structured questionnaire administered by direct interview at every follow-up visit. Adherence to the study product dosing regimen was calculated by dividing the reported number of ingested doses by the expected number of doses per month. Weighted monthly means were calculated for each treatment group.

Laboratory Methods

All laboratory procedures were performed with the investigators masked to the treatment group. Urinalyses and cultures were performed using standard methods, as previously described.[19] Vaginal and rectal

swabs from both study sites were transported in Amies swabs to the University of Washington Research Laboratory. *E coli* were identified using standard microbiological procedures[20, 21] and were frozen at −80°C for later determination of P fimbriation. P-fimbriated *E coli* isolates were defined as demonstrating a multiplex polymerase chain reaction positive for *papA*, *papC*, *papEF*, and one or more of the *papG* alleles, as well as being capable of mediating mannose-resistant hemagglutination of human red blood cells.[20,22]

Sample Size

On the basis of previous studies from similar populations, we expected 35% of women with a history of UTI to have a symptomatic UTI recurrence within 6 months.[18] Originally, we planned enrollment of 350 women to give a sample size of 210 in the cranberry group (105 taking 4 oz and 105 taking 8 oz) and 105 in the placebo group, allowing for a 10% dropout rate, to provide 80% power to detect an absolute reduction of 15% in the rate of symptomatic UTI recurrence.

Statistical Analyses

Data management and analyses were performed at Yale University School of Medicine. As part of the a priori analysis plan to control type I error, a hierarchical testing procedure was used to first examine differences between the cranberry and placebo groups (combined 4- and 8-oz doses in each group) at the 2-sided .05 significance level and, if significant, test for differences between the doses. The latter was not performed because the combined dose comparison was not significant. The analysis was performed on the modified intent-to-treat population, which included any individual with at least one postrandomization assessment. Continuous variables were presented as mean ± SD. Categorical variables were presented as number (percentage). Continuous variables were compared using the *t* test. Categorical variables were compared using the χ^2 test. Time to first UTI was assessed using the Kaplan-Meier method. The treatment arms were compared using the log-rank test. Cox proportional hazards regression was adjusted for age, frequency of sexual activity, race, site, history of kidney infection, and number of bladder infections. All analyses were performed using SAS statistical software, version 9.2 (SAS Institute Inc, Cary, NC).

RESULTS

Among 345 women screened, 136 were ineligible and 23 declined participation (Figure 1). The study was terminated in December 2008 before the target sample size could be achieved because of administrative and budget issues. Thus, 186 women (100 from Seattle and 86 from New Haven) were enrolled and randomized. After enrollment, 10 women dropped out before the first follow-up visit (Figure 1), leaving 176 women (120 in the cranberry juice group and 56 in the placebo group) in the modified intent-to-treat population. The median follow-up time for each participant was 168 days. Reasons for early withdrawal included being too busy, moving away from the area, wanting antibiotic prophylaxis, becoming pregnant, and being diagnosed as having a kidney stone (1 individual in the placebo arm).

The demographics and baseline characteristics of the 176 randomized women were similar across treatment groups and sites (Table 1). The mean age was 25 years, 133 (75.6%) were white, and almost 100% were sexually active. The mean number of UTIs in the past year was 1.8 in the placebo group and 2.1 in the cranberry group (*P*=.37). A history of pyelonephritis was more frequent in the placebo group and was further evaluated in the regression models.

Proportions, Cumulative Rates, and Time to First UTI

There were 72 UTIs (18 clinical and 54 culture confirmed) in follow-up, occurring in 50 women. No differences were found in the proportions of women having a clinical or culture-confirmed UTI in the cranberry group (33/120, 27.5%) or placebo group (17/56, 30.4%) (*P*=.70). The proportions of women having more than one UTI during the study period were also similar: 10 women (8.3%) in the cranberry group and 4 women (7.1%) in the placebo group.

The cumulative rate of women with a clinical or culture-confirmed UTI at 6 months was 0.29 (95% confidence interval [CI], 0.21-0.38) in the cranberry group and 0.37 (95% CI, 0.25-0.54) in the placebo group (*P*=.82). The time to first UTI was not significantly different between the 2 groups (Figure 2). The unadjusted hazard ratio for UTI in the cranberry vs placebo group was 0.78 (95% CI, 0.43-1.41; *P*=.41). After adjusting for age, baseline sexual frequency, race, study site, pyelonephritis history, and number of bladder infections, the hazard ratio for UTI in the cranberry vs placebo group was 0.68 (95% CI, 0.33-1.39; *P*=.29). As per the a priori analysis plan, dose-specific analyses were not performed because the combined dose comparisons were not significant.

Asymptomatic Bacteriuria and Culture-Confirmed *E coli* UTI

Asymptomatic bacteriuria was identified at least once during the study period in 101 of 176 women (57.4%), including 75 of 120 women (62.5%) in the cranberry juice group and 26 of 56 women (46.4%) in the placebo group (*P*=.04). *E coli* was the causative organism of asymptomatic bacteri-

FIGURE 1. Study flow chart.
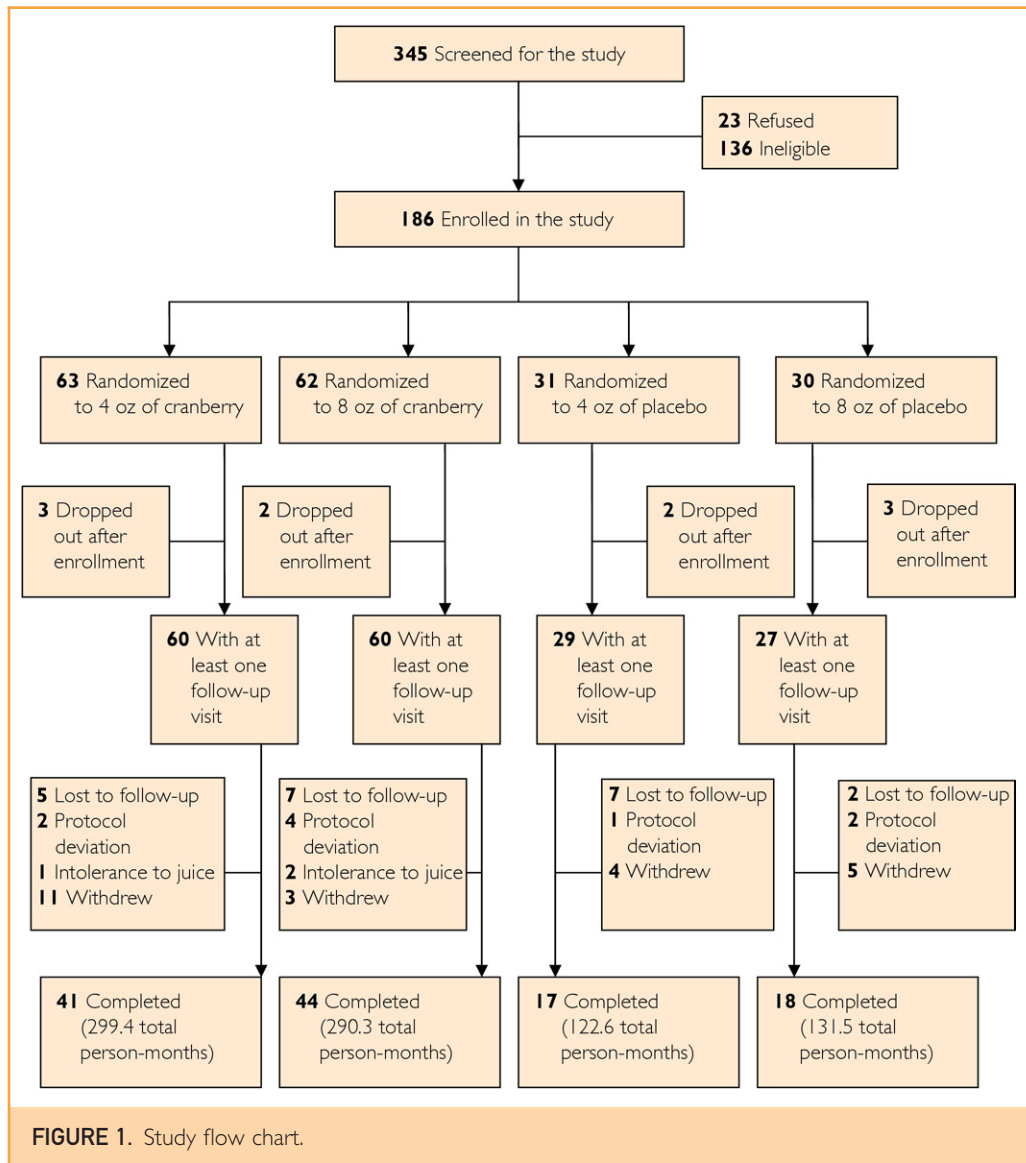
uria in 29 of 75 women (38.7%) women in the cranberry juice group and 11 of 26 women (42.3%) in the placebo group.

Symptomatic *E coli* UTI was diagnosed in 33 of 176 women (18.8%): 24 of 120 (20.0%) in the cranberry juice group and 9 of 56 (16.1%) in the placebo group (*P*=.53). Among the 38 women with a culture-confirmed UTI during the study period, *E coli* was the causative pathogen in 33 (86.8%).

P-Fimbriated *E coli*

Both treatment groups started out at baseline with no urinary *E coli* as per study inclusion criteria. *E coli* strains from 33 (23 in the cranberry juice group and 10 in the placebo group) of the 73 women with *E coli* asymptomatic bacteriuria or symptomatic UTI

events during the intervention period were available for testing for P fimbriae. The proportions of urinary *E coli* that were P fimbriated were 10 of 23 (43.5%) in the cranberry juice group and 8 of 10 (80.0%) in the placebo group (*P*=.07). Overall, the odds of having P-fimbriated *E coli* in the urine during the intervention period in the cranberry group were one-fifth the odds in the placebo group (odds ratio, 0.19; 95% CI, 0.03-1.11).

At baseline, vaginal colonization with P-fimbriated *E coli* was identified in 13 of 46 women (28.3%) in the cranberry group and 11 of 23 (47.8%) in the placebo group (*P*=.11). P-fimbriated rectal *E coli* from the baseline visit were isolated in 24 of 84 women (29%) and 17 of 45 women (37.8%) in the cranberry juice and placebo groups, respectively (*P*=.20).

TABLE 1. Demographics and Characteristics of Women Randomized to Cranberry vs Placebo Juice[a]

Variable	Placebo (n=56)	Cranberry juice[b] (n=120)	P value
Site			.98
Yale	26 (46.4)	56 (46.7)	
Washington	30 (53.6)	64 (53.3)	
Mean (SD) age (y)	26.4 (6.5)	25.3 (6.6)	.33
Race			.43
White	40 (71.4)	93 (77.5)	
Black	5 (8.9)	4 (3.3)	
Asian	9 (16.1)	17 (14.2)	
Other	2 (3.6)	6 (5.0)	
Lifetime UTIs			.10
≤2	12 (22.2)	43 (35.8)	
3-5	21 (38.9)	30 (25.0)	
≥6	21 (38.9)	47 (39.2)	
Mean (SD) No. of bladder infections last year	1.8 (1.2)	2.1 (1.4)	.37
Previous kidney infection	14 (26.9)	15 (12.7)	.02
Ever sexually active	51 (94.4)[c]	116 (96.7)	.49
Mean (SD) sexual partners in past year	1.5 (1.1)	1.4 (0.9)	.54
Sexual frequency[d]			.11
Weekly or more	32 (65.3)	85 (78.0)	
Less than weekly	17 (34.7)	24 (22.0)	
Using birth control pill	18 (35.3)	61 (52.1)	.04
Using spermicidal product	2 (3.9)	13 (11.1)	.15

[a] Data are presented as No. (percentage) of study participants unless indicated otherwise. UTI = urinary tract infection.
[b] Comparison of total cranberry and placebo groups as per a priori analysis plan.
[c] Denominator for this variable is 54.
[d] Denominator for this variable is 49 for the placebo group and 109 for the cranberry group.

Adverse Effects

No serious adverse events occurred in either of the study groups. Minor adverse effects included primarily gastrointestinal (constipation, heartburn, loose stool), vaginal (itching, dryness), and other (migraine) symptoms. The proportions of women who reported minor adverse effects were 29 of 120 (24.2%) in the cranberry juice group and 7 of 56 (12.5%) in the placebo group (*P*=.07). Three women in the cranberry group stopped taking the study product because of gastrointestinal symptoms thought to be related to the study product.

Adherence With the Study Products

The proportion of women who reported missing one dose or more of their study product was not different between treatment groups at any of the monthly follow-up assessments. The mean number of doses missed each month was 1 to 3, resulting in a mean monthly dose adherence of 27.1 of 30 (90.3%) and 27.5 of 30 (91.8%) in the placebo and cranberry groups, respectively. Adherence to use of

the study product was not independently associated with the time to first UTI (data not shown).

DISCUSSION

Regular ingestion of cranberry products is a popular strategy for preventing UTI. Our study used a standardized cranberry product and matching placebo and demonstrated an overall reduced hazard ratio of 0.68 for the incidence of UTI in women ingesting cranberry juice vs those ingesting placebo, a difference that was not statistically significant but in concordance with findings of previous studies.[6] The reduced proportion of urinary P-fimbriated *E coli* strains in women ingesting cranberry juice vs those ingesting placebo demonstrated in our study provides, for the first time to our knowledge, an in vitro correlate to the clinical outcome of symptomatic UTI.

Our study differs in both methods and results from that of a recently published trial using the same products and a similar population.[23] Barbosa-Cesnik et al[23] used a more frequent dosing regimen
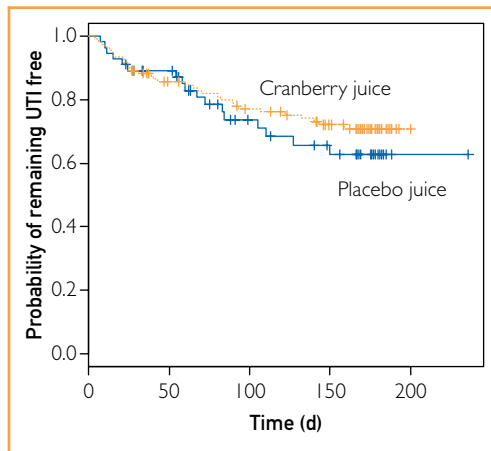
FIGURE 2. Kaplan-Meier curve for time to symptomatic urinary tract infection (UTI) in women ingesting cranberry juice (orange line) vs placebo juice (blue line). No significant difference was found in time to UTI between the groups (P=.41; log-rank test).

and studied a larger sample of predominantly college-age women. The major difference was in the definition of the primary outcome, symptomatic UTI, which in the study by Barbosa-Cesnik et al required culture confirmation. Diagnosis of acute cystitis without a urine culture in women who present with dysuria in the absence of vaginal discharge is consistent with the definition used in the studies forming the basis of the sample size estimates for both trials and with definitions used by international clinical practice guidelines.[18,24,25] The evidence for not requiring culture confirmation for this population is derived from well-designed studies that demonstrate that up to 15% to 20% of women have negative culture results or low-count bacteriuria but still respond to a short course of UTI-directed treatment and have no other diagnosis.[3,24] Requiring positive culture results could partly explain the lower-than-expected event rates. Our study did not suggest any activity of the placebo juice, as evidenced by a recurrent UTI rate exactly as predicted by previous studies.[18,25]

Despite these differences, the overall conclusion that cranberry juice did not demonstrate a statistically significant reduction in the rate of recurrent UTI compared with placebo in women with recent acute cystitis is similar in both studies. Neither study was adequately powered to evaluate a 50% reduction, given the smaller sample sizes and lower event rates than those assumed in the original power calculations.[26] Interestingly, a recent Cochrane meta-analysis found a significantly reduced incidence of UTIs at 12 months with a relative risk of 0.66 (95% CI, 0.46-0.90) in cranberry juice vs placebo/control groups, similar to the hazard ratio of 0.68 that we report here; albeit, the 95% CI in our study is wider and spans a nonsignificant difference.[6]

The most intriguing and novel finding in our study is the strong, although not statistically significant, trend toward lower rates of urinary P-fimbriated *E coli* isolated from women who received cranberry juice compared with those who received placebo juice. Our findings are strengthened by the fact that both groups started out without any urinary *E coli* at baseline because inclusion criteria required the absence of asymptomatic bacteriuria. The prevalence rates of P fimbriation among rectal and vaginal *E coli*, the most likely sources of urinary isolates, were lower in women ingesting cranberry juice vs placebo by 10% to 20% at the baseline visit and were not measured during the intervention phase. These differences were not statistically significant and were of smaller magnitude compared with the differences among the urinary isolates but could have contributed in part to the lower rate of urinary *E coli* in the cranberry arm during the intervention phase. Although the mechanism of cranberry activity in the prevention of UTI is not fully elucidated, one leading hypothesis is that a cranberry component, or a direct metabolite, inhibits P-fimbriated *E coli* from attaching to the bladder epithelium.[27] In vitro studies have demonstrated this adherence inhibition with proanthocyanidin extract from cranberries, human urine collected after cranberry ingestion, and growth of *E coli* on cranberry-containing media.[9,27,28] None of these previous in vitro studies longitudinally evaluated clinical outcomes. Similarly, none of the clinical studies correlated observed patient outcomes with in vitro findings. Our data are the first, to our knowledge, to report on both clinical and in vitro outcomes and suggest a concurrent but nonsignificant reduction in the cumulative rate of symptomatic UTI and urinary P-fimbriated *E coli* in women ingesting cranberry juice vs placebo juice. The lack of statistical significance in the results warrants caution in making definitive conclusions, and future well-powered studies will be needed to further evaluate the correlations between clinical and in vitro effects.

Tolerability of cranberry juice has been problematic in previous reports. Even though we used a lower volume of juice than most previous studies, women in the cranberry juice arm had a higher rate of minor adverse events compared with women in the placebo arm. Despite the adverse effects, adherence to ingestion of the cranberry and placebo juices was high compared with what previous studies have found, likely related to the once-daily dosing regimen. The optimal balance between a high cranberry juice concentration and tolerability may be best

achieved with cranberry solids, which have shown promising effects in previous studies and are probably a more viable option for continuous daily prophylaxis.[11]

The main limitation of our study is that we did not achieve our desired sample size and thus were not powered to show a significant effect of cranberry on the cumulative rate of UTI. Adherence was based on self-report rather than measurement of an active urinary metabolite because the latter was not available during the trial. Overall, the limitations of our study highlight some of the limitations of real-life use of cranberry juice for prevention of UTI. Consistent daily ingestion of a glass or more of cranberry juice cocktail may not be feasible or tolerated for prolonged periods.

CONCLUSION

The strengths of this double-blinded, randomized, controlled study include the use of well-characterized and standardized cranberry and placebo products, multicenter enrollment, and evaluation of clinical and bacterial virulence outcomes. Our data demonstrated a potentially protective effect of cranberry with a hazard ratio for UTI of 0.68 compared with placebo, but it was not statistically significant, and the wide CIs do not exclude the possibility of a lack of risk reduction. However, the observation that this therapy reduced infection with P-fimbriated E coli strains suggests a cohort that may benefit from cranberry juice therapy. This observation should be pursued with additional mechanistic and perhaps clinical study in patients infected with this organism type.

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