Can Cranberries Contribute to Reduce the Incidence of Urinary Tract Infections? A Systematic Review with Meta-Analysis and Trial Sequential Analysis of Clinical Trials

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Abbreviations and Acronyms

PAC = proanthocyanidin
RCT = randomized controlled trial
rUTI = recurrent UTI
TSA = trial sequential analysis
UTI = urinary tract infection
WRR = weighted risk ratio

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Purpose: We sought to clarify the association between cranberry intake and the prevention of urinary tract infections.

Materials and Methods: This systematic review, which complies with the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) statement, was done as a meta-analysis and trial sequential analysis of clinical trials.

Results: The findings clearly showed the potential use of cranberries for the clinical condition of urinary tract infection. Cranberry products significantly reduced the incidence of urinary tract infections as indicated by the weighted risk ratio (0.6750, 95% CI 0.5516–0.7965, p <0.0001). The results of subgroup analysis demonstrated that patients at some risk for urinary tract infections were more susceptible to the effects of cranberry ingestion.

Conclusions: The results of the current study could be used by physicians to recommend cranberry ingestion to decrease the incidence of urinary tract infections, particularly in individuals with recurrent urinary tract infections. This would also reduce the administration of antibiotics, which could be beneficial since antibiotics can lead to the worldwide emergence of antibiotic resistant microorganisms.

Key Words: urinary tract infections, fruit and vegetable juices, disease susceptibility, proanthocyanidins, study publication bias

Urinary tract infections are common and among the most frequent medical conditions requiring outpatient treatment.[1] Approximately 80% of all UTIs occur in women and 20% to 30% of women with a UTI will experience recurrence.[1] rUTIs, defined as at least 3 UTI episodes in the last 12 months or 2 episodes in the last 6 months, can develop in susceptible individuals and they are a significant source of patient morbidity and health care costs.[2] In individuals with rUTIs low dose antibiotic prophylaxis for several months can be recommended.[1] However, antibiotics are the main cause of the development of antibiotic resistance and such prolonged treatments can lead to increased resistance.[1] The increasing prevalence of *Escherichia coli* isolates resistant to antimicrobial agents has stimulated interest in nonantibiotic methods to prevent UTIs.[1]

Prophylaxis with cranberries is a potential prevention strategy with health benefits associated with the high concentrations of polyphenols

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such as PACs in these berries.[3,4] PACs are stable phenolics with antiadhesion activity against *E. coli*.[3] They act as receptor analogues and inhibit *E. coli* adhesion to cells by binding to the fimbrial tips.[3]

The effects of cranberry ingestion in the prevention of UTIs were systematized in 2 previous reviews with meta-analyses.[5,6] The most recent one suggested that there is insufficient evidence that cranberries decrease the number of UTIs since the pooled findings were based on a small number of studies.[5] Considering this together with the results of recent clinical trials evaluating cranberries to prevent UTIs we performed this systematic review, which complies with the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) statement. The review was followed by meta-analysis and TSA (http://www.ctu.dk/tsa/), a newer approach that can assist in decreasing the likelihood of a type I error, to clarify the association between cranberry intake and the prevention of UTIs.

METHODS

Search Strategy

The search was performed in September 2016 in several electronic databases, including PubMed®, Scopus®, SciELO (Scientific Electronic Library Online), Cochrane Library and Web of Science™ using the terms (cranberr* OR Vaccinium) AND (urinary tract infections OR UTI) AND clinical trial AND human. According to the PRISMA statement, titles and abstracts of the records retrieved were screened and the full texts of those considered relevant were analyzed. Two of us independently performed the literature search with disagreements resolved by consensus with another of us. To be included in this work studies had to be clinical trials in humans, present a true control group and report the number of patients who experienced at least 1 UTI at the end of followup period (outcome of interest).

Data Extraction

Two of us independently assessed and extracted the data. Information was collected on the proportion of patients with at least 1 UTI and on study characteristics (supplementary table 1, http://jurology.com/). The RR served as the measure of effect for the outcome of interest.

Bias Assessment Risk

The bias risk of each included RCT was assessed with the Cochrane Library tool. This risk, which was classified according to 7 domains, was independently assigned by 2 of us with discrepancies resolved through discussions (fig. 1). Results were presented as a risk of bias summary and a risk of bias graph, which were sketched with RevMan, version 5.3.5 (http://community.cochrane.org/).

Figure 1. Results of review author judgments of risk of bias assessment regarding methodological quality of included studies. *A*, summary of each risk of bias item for each included study.[2–4,7–10,13–30] *B*, each risk of bias item shown as percent across all included studies.

Statistical Analysis

Data statistical analysis was performed using Comprehensive Meta-Analysis, version 2.0 (https://www.meta-analysis.com/). A forest plot was generated to illustrate study specific RRs and the WRR estimate along with the 95% CIs using the random effects model. The I^2 statistic served as a measure of inconsistency across the findings of the studies.

Three analyses were performed to assess the potential impact of publication bias on the meta-analysis. One analysis was a funnel plot in which the log of RR was plotted against the corresponding SE. In the absence of publication bias the studies would have been symmetrically distributed about the WRR. Since interpretation is largely subjective, the Egger regression test was also performed. Finally the trim and fill approach was applied, which uses an iterative procedure to remove the most extreme small studies from the positive or negative side of the funnel plot and recalculate the RRs to yield an unbiased estimate of WRR.

Sensitivity analysis was performed by removing 1 study at a time to evaluate result stability. Furthermore, subgroup analysis was done according to patient mean age and gender, and intervention duration and type.

Trial Sequential Analysis

TSA is a methodology in which the evidence required is quantified, providing a value for the required information size. To adjust CIs due to sparse data and repeat testing on the cumulative meta-analysis we used TSA, version 0.9.5.5 beta. If the cumulative *Z*-curve crosses the trial sequential monitoring boundary or enters the futility area, it can be concluded that a sufficient level of evidence for the anticipated intervention effect may have been reached and no further trials are needed. TSA was performed at the level of an overall 5% risk of a type I error and with 80% power.

RESULTS

Included Studies

In compliance with the PRISMA statement the initial search identified 157 articles with the potential to be included in this meta-analysis. Figure 2 shows the progression of the database search regarding the effects of cranberries to prevent UTIs. After all steps 25 studies were considered suitable for qualitative and quantitative analyses. Among the reasons to exclude studies were an absent

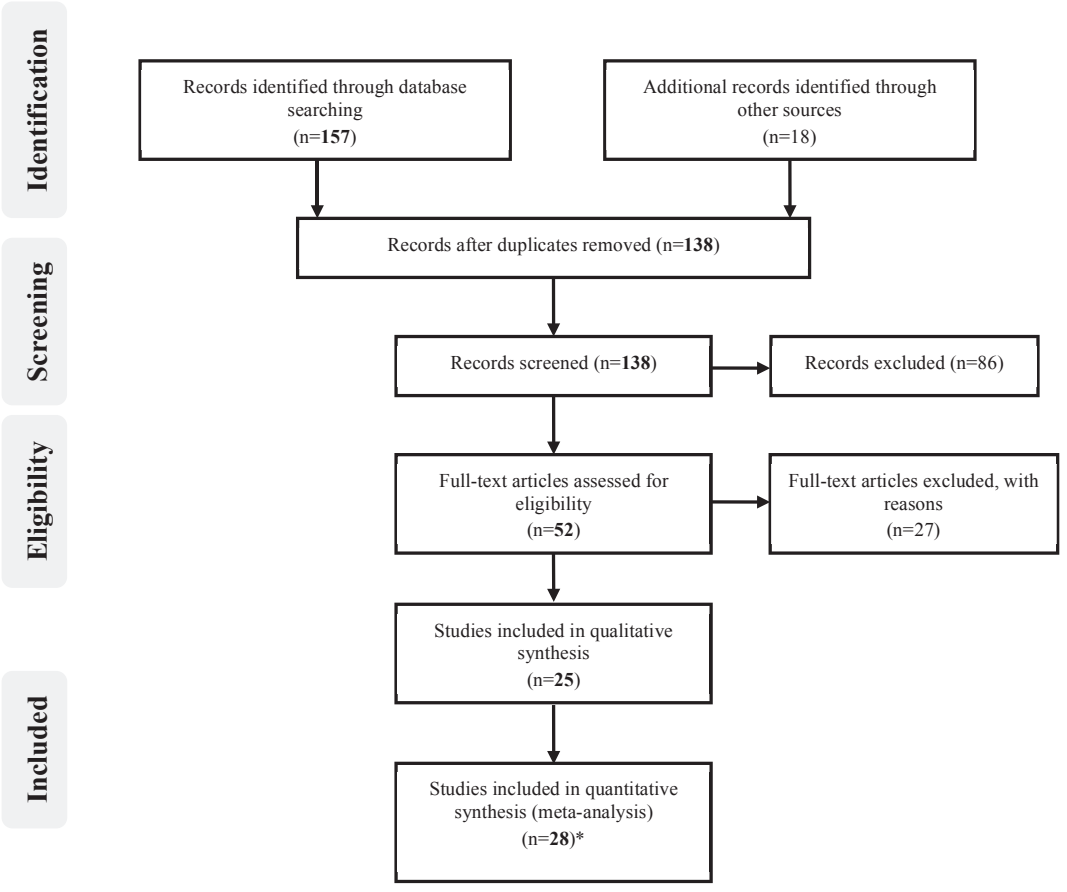

Figure 2. Flow diagram of database search, trial selection and articles included in systematic review with meta-analysis. Asterisk indicates that studies by Caljouw et al,[3] Stothers[7] and Wing et al[8] were each divided into 2 trials.

Random model effects of cranberry ingestion on UTI incidence

Outcome	UTI Incidence
No. trials	28
No. pts	4,947
Required information size	4,875
WRR (95% CI):	
Observed	0.6750 (0.5516–0.7965)
Adjusted	0.8334 (0.6976–0.9956)
p Value	<0.0001 (significant)
% I^2	58.1740

control group and lack of results in terms of the outcome of interest.

Three of the 25 included studies were divided into 2 trials for a total of 28 studies in 4,947 patients included in this meta-analysis. The study by Caljouw et al was divided since it presents patients at high and low UTI risk.[3] Stothers described 2 ways of orally administering cranberry products, that is tablets of concentrated cranberry juice and pure unsweetened cranberry juice.[7] Wing et al administered 2 doses of PACs, including a high dose (240 mg PACs per day) and a low dose (80 mg PACs per day).[8]

During the search 2 previous meta-analyses were also found on the prevention of UTIs by cranberries.[5,6] The 2012 study by Jepson et al, which focused on the effectiveness of cranberry and blueberry products to prevent symptomatic UTIs, included 13 trials in the meta-analysis.[5] In 2012 Wang et al evaluated products containing cranberry to prevent UTI and examined the factors influencing effectiveness in 10 clinical trials.[6] The current meta-analysis includes 28 clinical trials, which strengthened the statistical analysis to allow for better understanding of the effects of cranberry ingestion in the prevention of UTIs.

Supplementary table 1 (http://jurology.com/) lists the studies included and their characteristics. All represented individuals at certain risk for repeat UTIs, including children and elderly patients, long-term care facility residents, patients with cancer or spinal cord injury, and patients on clean intermittent catheterization. Followup in the included trials varied from 2 weeks to 12 months. Patients enrolled in the intervention groups ingested cranberries in several oral forms ranging from juices, capsules, tablets and extracts for different PAC doses per day.

Bias Risk

Figure 1 shows the results of the assessment of bias risk in the included RCTs. The nonrandomized study by Bonetta and Di Pierro,[9] the observational study by Burleigh et al,[2] and the registry, supplement and pilot study by Ledda et al[10] were not classified by bias risk since the Cochrane tool can only be applied to RCTs. In general the included RCTs satisfied the 7 domains of bias. The RCTs claimed to be randomized but only 13 trials detailed the randomization process and were classified as

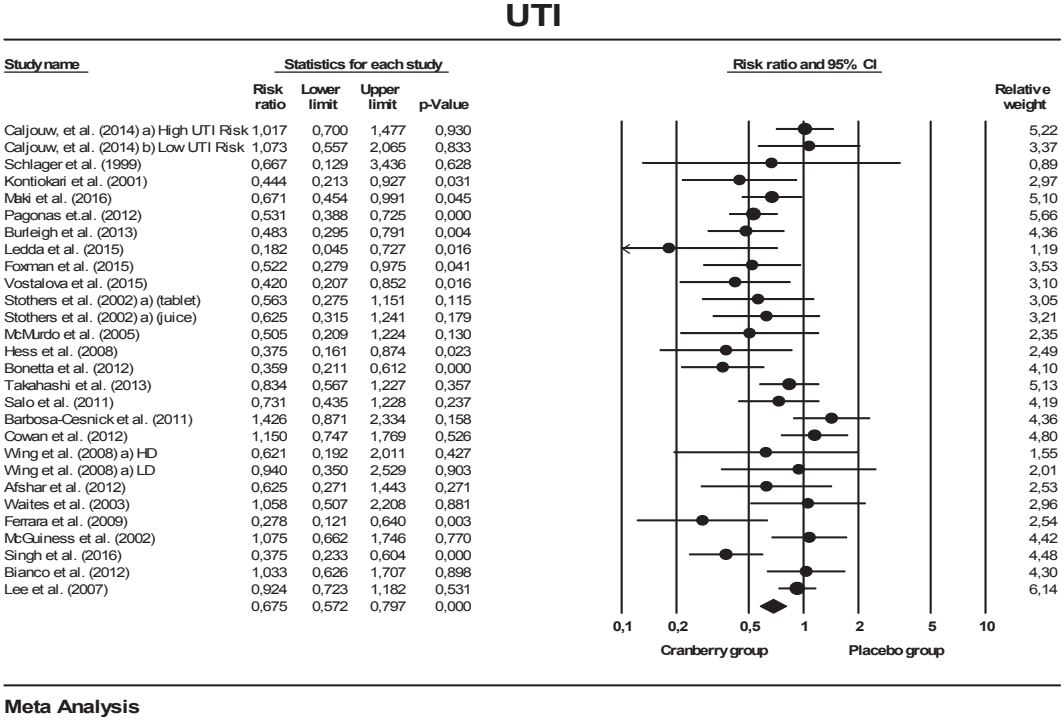

Figure 3. Forest plot of comparisons of cranberry ingestion effects on UTI incidence.[2–4,7–10,13–30] *HD,* high dose. *LD,* low dose.

low risk in the random sequence generation domain. Concerning the performance and detection types of bias, which are related to blinding of participants and personnel, and blinding to outcome assessment, respectively, 3 studies were classified as high risk since the investigators were not clear about the blinding process. Other sources of bias were also identified, namely the payment of a stipend to trial participants or sponsorship and financial support, which are factors that can skew the results.

Cranberry Ingestion Effects

The table summarizes meta-analysis results and figure 3 shows a forest plot of the results. Overall the estimated WRR showed a significant reduction in the risk of repeat UTIs with cranberry treatment compared to placebo (WRR = 0.6750, 95% CI 0.5516−0.7965, p <0.0001). There was a moderate degree of heterogeneity (I^2 = 58.1740%). TSA resulted in a required information size of 4,875, which was reached, and the cumulative *Z*-curve crossed the boundaries (fig. 4). Therefore, it was possible to reach a conclusion with no need for additional trials. To our knowledge the TSA of cranberry ingestion on the incidence of UTIs was applied for the first time, strengthening the conclusions achieved.

Subgroup and Sensitivity Analyses

To evaluate the influence of mean patient age, intervention duration and type, and patient gender on the effectiveness of cranberries in the prevention of UTIs a subgroup analysis was performed (supplementary table 2, http://jurology.com/). Although there was evidence of the benefit of cranberries in reducing UTIs overall, the subgroup analysis showed that compared with placebo cranberries did not significantly decrease repeat UTIs in any of the subgroups, including clean intermittent catheterization (WRR = 0.887, 95% CI 0.676−1.165, p = 0.384), young and older adults (WRR = 0.824, 95% CI 0.443−1.533, p = 0.542 and WRR = 0.833, 95% CI 0.697−1.119, p = 0.304, respectively), pregnant women (WRR = 0.792, 95% CI 0.371−1.687,

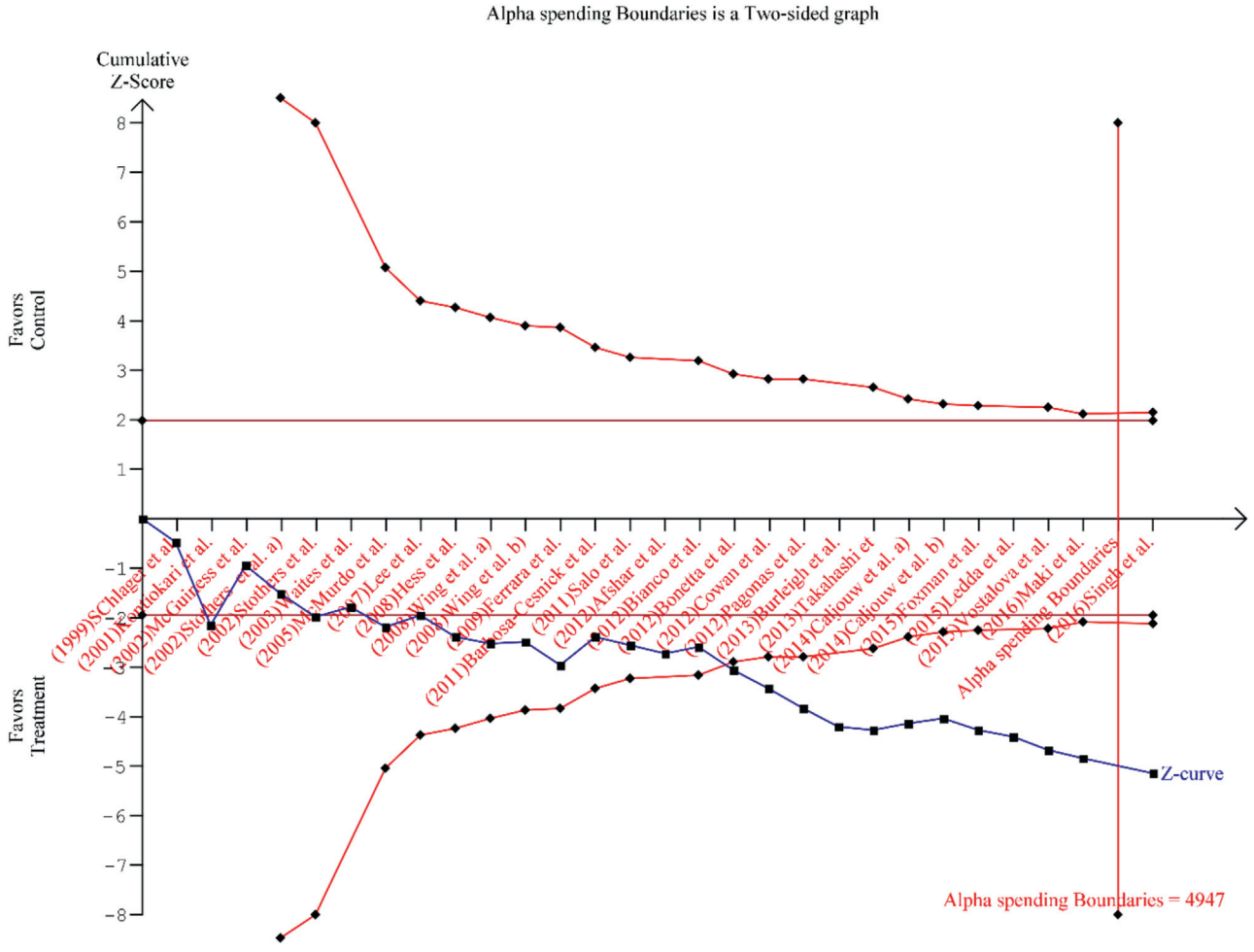

Figure 4. Trial sequential analysis of pooled result of effects of cranberry ingestion on UTI incidence.[2–4,7–10,13–30]

p = 0.545) and patients with bladder or cervical cancer (WRR = 1.150, 95% CI 0.747−1.796, p = 0.526).

The sensitivity analysis was performed by excluding 1 or more studies from analysis to determine how this would affect the results (fig. 5). This analysis showed that the pooled effects of cranberry ingestion on the incidence of UTIs did not change substantially whether a single study or a few studies were omitted. Overall the sensitivity analysis demonstrated that the findings of the current meta-analysis were robust.

Publication Bias

The funnel plot, which was generated for the defined outcome and considered the trim and fill adjustment, included observed studies and the imputed studies necessary to achieve the absence of bias (fig. 6). Because there were more studies on the left side than on the right side, 9 studies were imputed on the right to adjust the funnel plot for the absence of publication bias. The key finding that the RR had substantive importance did not change (adjusted WRR = 0.8334, 95% CI 0.6976−0.9956).

In addition to visual inspection of the funnel plot, publication bias for the impact of cranberry ingestion on the UTI incidence was explored using the Egger regression test (95% CI −2.81222−0.07500, t = 1.94874, df = 25, p = 0.0623). Results did not indicate evidence of publication bias.

DISCUSSION

Several studies have presented the effects of cranberries in subgroups of the population at increased risk for UTIs. The current systematic review with meta-analysis demonstrates the effectiveness of cranberry products in the prevention of UTIs. The addition of further studies to previous meta-analyses allows us to conclude that there exists strong evidence that cranberries decrease the number of UTIs, particularly in patients with rUTIs.

Single UTI episodes are common, especially in women, with a 50-fold higher rate of infection than men.[11] Subgroup analysis of patient gender was performed to verify whether the effects of cranberry ingestion are gender dependent. It was observed that for both genders the incidence of UTIs was

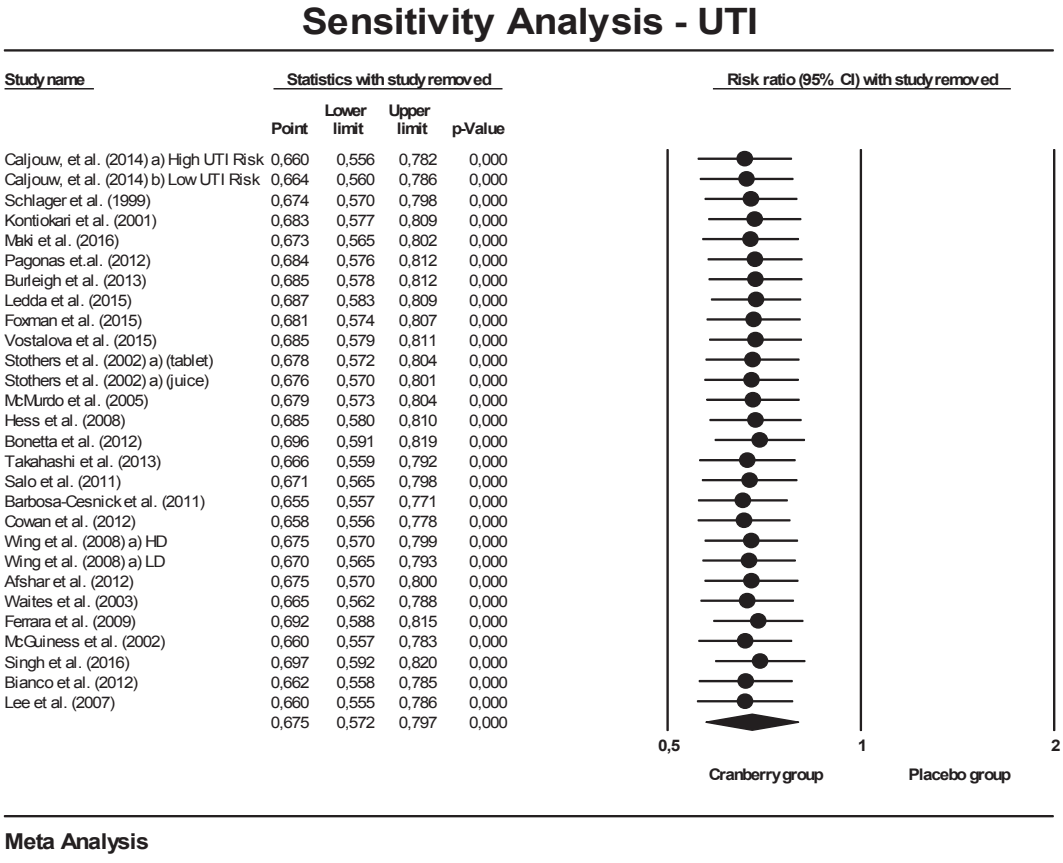

Figure 5. Sensitivity analysis results.[2−4,7−10,13−30] *HD*, high dose. *LD*, low dose.

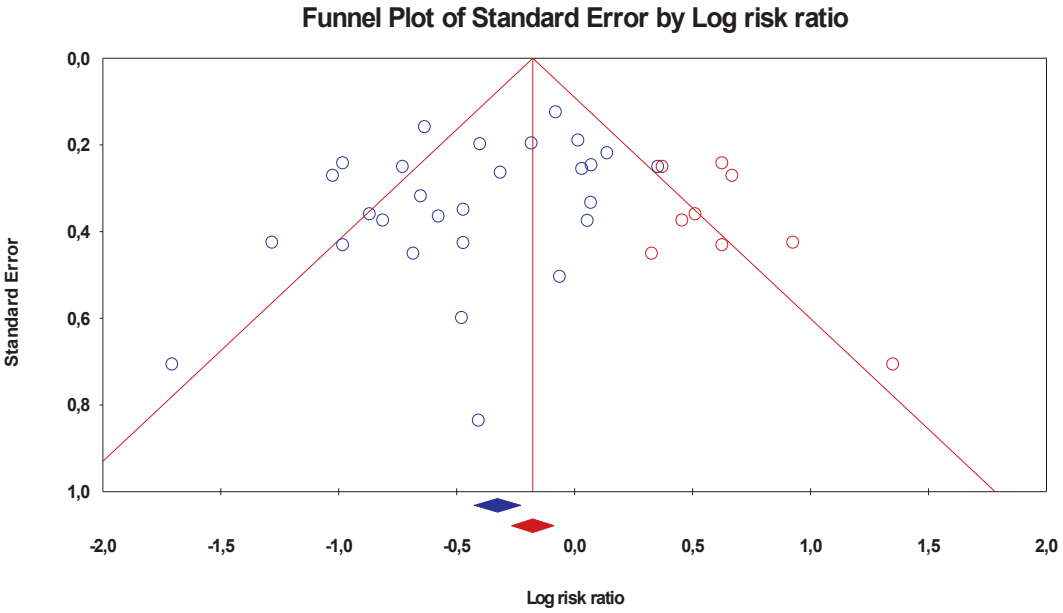

Figure 6. Funnel plot of SE by log RR for publication bias tests of cranberry ingestion effects on UTI incidence. Blue symbols represent observed studies. Red circles represent imputed studies necessary to achieve absent bias.

significantly decreased in the cranberry treated group.

It is known that the prevalence of UTIs is also age dependent.[11] During the first year of life the rate of UTIs is less than 2%. The incidence among males remains relatively low after age 1 year to approximately age 60 years, when prostate enlargement interferes with bladder emptying.[11] To take this into consideration a subgroup analysis concerning mean patient age was performed. Results enabled us to conclude that in children 2 to 17 years old and in middle-aged adults 36 to 55 years old cranberry ingestion significantly decreases the incidence of UTIs.

The results of subgroup analysis of patient type revealed that those with rUTIs and those who had undergone gynecologic surgery were more protected by cranberry intake with a significant reduction in the incidence of UTIs in those groups. This interesting result reinforces the importance of the ingestion of cranberries by patients at some risk for UTIs.

Although EAU (European Association of Urology) recommends continuous use of cranberries as an alternative method to prevent UTIs, the data are not conclusive because the available studies were performed for periods of up to a year. Thus, there is no evidence to support the efficacy of cranberry products for chronic use. Future trials may need to cover much longer periods.

The effectiveness of cranberry products is likely to depend on the concentration of PACs, which are the polyphenols associated with the amelioration of UTIs. The most accepted mechanism of action for preventing UTIs by cranberries is based on its interference with bacterial adhesion in the urinary tract.[12] An antiadhesion response is caused in urine after cranberry consumption, preventing uropathogenic P-fimbriated *E. coli* from adhering to bladder cell receptors.[12] If the bacteria are not able to adhere to cells, they cannot grow and cause infection.[12] The daily recommended amount of PACs to decrease the number of UTIs is at least 36 mg. A limitation of the findings is the lack of consistency among the administered doses of PACs in the considered studies.

Another limitation found during the preparation of this report was the absence of uniformity in the definition of UTI among the included trials. All trials used the term UTI while in fact some referred specifically to *E. coli* UTI. The differentiation between UTI and *E. coli* UTI makes a clinical difference. For example, cranberry would likely not be effective in patients with other uropathogens but it would be expected to be effective in patients with *E. coli* UTI since cranberry inhibits the adhesion of *E. coli* pili.

CONCLUSIONS

The current systematic review with meta-analysis could be used by physicians to recommend the ingestion of cranberries to decrease the incidence of UTIs, particularly in patients with recurrent UTIs. This alternative treatment could also help reduce the widespread use of antibiotics, which is leading

to the worldwide emergence of antibiotic resistant microorganisms. Future research should focus on clarifying the underlying mechanisms that contribute to the efficacy of cranberry PACs in decreasing UTIs and the standardization of quantities of cranberries and/or doses of ingested cranberry PACs along with the duration of the treatment required to be effective.

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