

Brief description of patient problem/setting (summarize the case very briefly):

46 y.o female presents with complaints of dysuria, urinary frequency, lower abdominal pain, and a minimal grade fever for the past 2 days. She reports that she is sexually active and has an extensive history of urinary tract infections.

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Search Question: Clearly state the question (including outcomes or criteria to be tracked)

In women with recurrent urinary tract infections, does cranberry extract compared to placebo reduce the frequency of urinary tract infections?

Question Type: What kind of question is this? (boxes now checkable in Word)

- Prevalence Screening Diagnosis
Prognosis Treatment Harms

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Assuming that the highest level of evidence to answer your question will be meta-analysis or systematic review, what other types of study might you include if these are not available (or if there is a much more current study of another type)?

Please explain your choices.

- If meta-analysis or systematic review are not available, I would include a randomized controlled study as it would create a well-organized study reducing bias. It would allow me to compare a control group and experimental group and a cause an effect relationship that cranberry extract would have on UTI prevention.

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PICO search terms:

P	I	C	O
Women with recurrent UTI's	Cranberry extract	Placebo	Frequency of UTI's
Women with UTI's	Cranberries		Prevalence of UTI's.
Urinary Tract Infections			Reduction of UTI's.

Search tools and strategy used:

Please indicate what data bases/tools you used, provide a list of the terms you searched together in each tool, and how many articles were returned using those terms and filters.

Explain how you narrow your choices to the few selected articles.

Results found:

PubMed:

- women cranberry urinary tract infection frequency-57
- women cranberry urinary tract infection frequency-31
Filter= within 10 years
- women cranberry urinary tract infection frequency
- Filter= randomized control trials, within 10 years - 11

Science Direct:

- prevention of UTI's women cranberry - 513
- prevention of UTI's women cranberry - 110
Filter= within 5 years

Google Scholar:

- UTI women cranberry recurrence – 6,560
- UTI women cranberry recurrence – 1,700
Filter= since 2020
- UTI women cranberry recurrence - 418
Filter= since 2020, review articles

- I was able to narrow my choice down to the articles that I selected by looking for randomized control trials that were based in the USA as well as meta analysis/systematic reviews for the highest level of evidence. I also tried to find articles that were directly relevant and answering the pico research question that I was examining.

Identify at least 4 articles (or other appropriate reputable sources) that answer your specific question with the highest available level of evidence (you will probably need to look at more than 4 articles to get the 4 most focused and highest level articles to address your question). Please make sure that they are Medline indexed.

Please post the citation and abstract for each article (to include the journal and authors' names and date) and say why you chose it.

Please also note what kind of article it is (e.g. meta-analysis, cohort study, or independent blind comparison with gold standard of diagnosis, etc.).

At the bottom of each abstract, please comment on what your key points are from this article (including any points or concepts included in the article, but not present in the abstract – i.e. make the concepts understandable to the reader)

Please note that if the evidence is not in the abstract, you must clearly summarize the evidence in your posting.

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Citation:

Stapleton, A. E., Dziura, J., Hooton, T. M., Cox, M. E., Yarova-Yarovaya, Y., Chen, S., & Gupta, K. (2012). Recurrent urinary tract infection and urinary Escherichia coli in women ingesting cranberry juice daily: a randomized controlled trial. *Mayo Clinic proceedings*, 87(2), 143–150.
<https://doi.org/10.1016/j.mayocp.2011.10.006>

Type of article:

Randomized Controlled Trial

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 & 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.

Key points:

- Randomized controlled trial of 176 participants (120 cranberry juice & 56 placebo), patients followed up for mean of 168 days.
- 72 total UTI's in follow up occurring in 50 women. Cumulative ratio of women with a culture-confirmed UTI at 6 months was .29 in the cranberry group and .37 in the placebo group. There was no significant difference in the time to first UTI in either group. There was a reduced hazard ratio of .68 for the incidence of UTI in women ingesting cranberry juice vs those ingesting placebo, this was not considered statistically significant.
- Proportions of women having more than one UTI were similar 10 women (8.3%) in cranberry group and 4 women (7.1%) in placebo group.

Why I chose it:

I chose this article because it was a randomized controlled study conducted in the USA. It directly looked at what I was looking to examine in the use of cranberry extracts vs placebos in preventing recurrent UTI's. The results of the article showed that there was not a significant reduction noticed in UTI's in the cranberry experimental group when compared to the placebo group. There was potential for a protective effect observed but this was not considered significant and further larger well powered studies are recommended according to this trial.

Citation:

Fu, Z., Liska, D., Talan, D., & Chung, M. (2017). Cranberry Reduces the Risk of Urinary Tract Infection Recurrence in Otherwise Healthy Women: A Systematic Review and Meta-Analysis. *The Journal of nutrition*, 147(12), 2282–2288. <https://doi.org/10.3945/jn.117.254961>

Type of article:

Systematic Review & Meta Analysis

Abstract:

Background- Cranberry (*Vaccinium* spp.) has been advocated for treatment of urinary tract infection (UTI); however, its efficacy is controversial. Women have a 50% risk of UTI over their lifetime, and ;20–30% experience a subsequent UTI recurrence

Objective- We conducted this meta-analysis to assess the effect of cranberry on the risk of UTI recurrence in otherwise healthy women.

Methods- Literature published before January 2011 was obtained from 2 published systematic reviews, and we conducted updated searches in EMBASE and MEDLINE (through July 2017). We included randomized controlled trials that were conducted in generally healthy nonpregnant women aged 18 y with a history of UTI, compared cranberry intervention to a placebo or control, and reported the outcome as the number of participants experiencing a UTI. Two researchers conducted abstract and full-text screenings, data extractions, and risk of bias assessments independently, and discrepancies were resolved by group consensus. Meta-analyses were performed by using Stata SE software (version 13). We employed a fixed-effect model using the Mantel-Haenszel method to estimate the summary risk if the heterogeneity was low to moderate ($I^2 < 50\%$). Otherwise, we applied a random-effects model using the DerSimonianLaird method.

Results- We identified 7 randomized controlled trials conducted in healthy women at risk of UTI ($n = 1498$ participants). Results of the meta-analysis showed that cranberry reduced the risk of UTI by 26% (pooled risk ratio: 0.74; 95% CI: 0.55, 0.98; $I^2 = 54\%$). Risk of bias indicated that 2 studies had high loss to follow-up or selective outcome reporting. Overall, the studies were relatively small, with only 2 having >300 participants.

Conclusion- These results suggest that cranberry may be effective in preventing UTI recurrence in generally healthy women; however, larger high-quality studies are needed to confirm these findings.

Key points:

- 7 randomized controlled trials conducted in healthy women at risk of UTI assessed.
- Trials included healthy nonpregnant women at least 18 years of age with a history of UTI.
- Cranberry intervention to placebo intervention was examined with the outcome as the number of participants experiencing UTI's.
- 1498 participants across 7 trials with 798 in cranberry group and 702 in placebo group. Cranberry experimental group showed a reduction in UTI recurrency by 26% when compared to the placebo group.
- However, risk reduction was not statistically significant with large uncertainty and heterogeneity among women who were enrolled with confirmed active UTI and treated with antibiotics prior to UTI recurrence assessment, making a more ambiguous study.
- The article similar to my first shows potential of cranberry extract as an aid for UTI recurrence prevention but also mentions the need for further studies.

Why I chose it:

I chose this article because it was a high level of evidence study based in the USA. It was systematic review and meta analysis of randomized controlled trials. There was a large number of patients studied in the examination (1498). It was conducted looking to evaluate the same research that I was

curious about (the use of cranberry extracts as an aid to recurring UTI's). It also included a placebo group which was mentioned in my PICO search elements. One downfall to the article was mentioned in my key points, the ambiguity and uncertainty of women previously treated with antibiotics for an active UTI infection prior to recurrence assessment.

Citation:

Maki, K. C., Kaspar, K. L., Khoo, C., Derrig, L. H., Schild, A. L., & Gupta, K. (2016). 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. *The American journal of clinical nutrition*, 103(6), 1434–1442. <https://doi.org/10.3945/ajcn.116.130542>

Type of article:

Randomized double-blind controlled trial

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.

Key points:

- 24-wk multicenter double-blind randomized placebo-controlled trial assessing effects of cranberry beverage consumption on clinical UTI infections in healthy women. Study was performed in 17 clinical research sites in USA and 1 in France.
- Eligible participants included women 20-70 y.o with BMI <40, and a recent history of UTI (2 or more episodes treated by a health care professional in the past year).
- Total of 322 subjects (160 cranberry beverage group, 162 placebo group) completed through the 24 week study. Subjects recorded symptoms in daily diaries were reviewed at each post-random assignment clinic visit. If any symptoms occurred subjects were instructed to call the clinic and arrange for a UTI evaluation visit which included a pelvic exam, and a clean catch urine sample. A clinical UTI was diagnosed with the presence of 1 or greater of the

following symptoms : dysuria. Urinary frequency, urinary urgency, suprapubic pain in the absence of other etiologies such as vaginal infection or discharge.

- 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. 39 clinical diagnoses of UTI's in the cranberry group and 67 clinical UTI's in the placebo group.
- Consumption of cranberry juice beverage lowered the number of clinical UTI episodes in women with recent UTI history.

Why I chose it:

I chose this article because it was a USA based double-blind randomized placebo-controlled trial which is of high evidence. It was a well-organized study that evaluated the use of cranberry beverage compared to placebo in prevention of future UTI's in patients with a UTI history. The study was easy to evaluate and the article did a good job explaining the fine details regarding outcome measurement that increased its validity. The study concluded that cranberry juice beverage significantly reduced clinical UTI incidence and the need for antibiotic use associated with the treatment of UTI's.

Citation:

Barbosa-Cesnik, C., Brown, M. B., Buxton, M., Zhang, L., DeBusscher, J., & Foxman, B. (2011). Cranberry juice fails to prevent recurrent urinary tract infection: results from a randomized placebo-controlled trial. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*, 52(1), 23–30. <https://doi.org/10.1093/cid/ciq073>

Type of article:

Prospective randomized Double-Blind controlled trial

Abstract:

Background- A number of observational studies and a few small or open randomized clinical trials suggest that the American cranberry may decrease incidence of recurring urinary tract infection (UTI).

Methods- We conducted a double-blind, placebo-controlled trial of the effects of cranberry on risk of recurring UTI among 319 college women presenting with an acute UTI. Participants were followed up until a second UTI or for 6 months, whichever came first. A UTI was defined on the basis of the combination of symptoms and a urine culture positive for a known uropathogen. The study was designed to detect a 2-fold difference between treated and placebo groups, as was detected in unblinded trials. We assumed 30% of participants would experience a UTI during the follow-up period

Results- Overall, the recurrence rate was 16.9% (95% confidence interval, 12.8%-21.0%), and the distribution of the recurrences was similar between study groups, with the active cranberry group presenting a slightly higher recurrence rate (20.0% vs 14.0%). The presence of urinary symptoms at 3 days, 1-2 weeks, and at ≥ 1 month was similar between study groups, with overall no marked differences.

Conclusions- Among otherwise healthy college women with an acute UTI, those drinking 8 oz of 27% cranberry juice twice daily did not experience a decrease in the 6-month incidence of a second UTI, compared with those drinking a placebo.

Key points:

- 319 college women presenting with an acute UTI were followed up until a second UTI or for 6 months.
- Baseline, 3 month, and 6 month visits and visits with UTI symptoms were carried out where a clean-catch midstream urine specimen was collected, self-collected vaginal and rectal specimens and were cultured for the presence of UTI pathogens. Questionnaires regarding

UTI symptoms, risk and behavioral factors, diet, compliance, GI or other symptoms and medical history were also conducted.

- Of the 319 women 155 belonged to the cranberry group and 164 to the placebo group. 230 of the 319 women completed the study as 5 became pregnant and were excluded and 84 were lost to follow up or dropped out.
- 54 culture-confirmed recurrent UTI episodes (31 in cranberry and 23 in placebo) 19.3% recurrence rate in cranberry group and 14.6% recurrence rate in placebo group. Indicating no significant effect of cranberry juice in risk of recurrence in those with UTI history.

Why I chose it:

This article was a well organized randomized double-blind controlled trial. It examined my pico research directly and included all elements and outcomes I was looking to evaluate. One aspect of this study that made me want to include it in my research was the involvement and mention of other variables. It discussed patient sexual behavior, amount of previous UT's, birth control usage, marriage status, etc.. This all has a heavy influence on UTI prevalence. I thought this study was very well conducted and easy to assess.



What is the clinical “bottom line” derived from these articles in answer to your question?

After conducting my research, I do not feel comfortable stating that there is a definitive correlation regarding UTI prevention and the use of cranberry extract in patients susceptible to UTI's. Although there were potential for preventative results in three of the articles that I chose, 2 of them discussed the need for further large well powered studies. One of the articles that showed promising results stated that the outcomes were not statistically significant. The last article I chose showed that there was no difference in UTI recurrence rate in the placebo vs the cranberry beverage group. There was actually a higher recurrence rate (19.3%) in the cranberry group then the placebo group (14.6%). In my opinion further testing of high level evidence large-based studies are needed to confirm the benefits of cranberry extract in preventing future UTI's in patents with a history of UTI's.

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