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CANCER

That Fish You Ate Might Protect Against Colorectal Cancer

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Dr. Kiefer reports no financial relationships relevant to this field of study.

The consumption of fish, supplementation with fish oil, and their effects on cardiovascular and pain conditions are common headline-makers in the mainstream media as well as this publication. A more recent line of inquiry involves the effects of omega-3 fatty acids on tumorigenesis, cancer prevalence, and mortality. The literature on cancer, all types, is too large a scope for this article; however, taking advantage of some recently published articles, the focus here will be on the effect of dietary fish intake and, to a lesser extent, fish oil supplementation on colorectal cancer rates and associated morbidity/mortality.

PHYSIOLOGY

Fish and fish oil are sources of the omega-3 fatty acids (n-3), one group of fatty acids that comprise the polyunsaturated fatty acids (PUFAs).[1,2,3] Furthermore, fish oils contain the long-chain omega-3 fatty acids: eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). EPA and DHA compete with arachidonic acid (AA; from omega-6 fatty acids) as substrates for metabolism by cyclo-oxygenase and lipoxygenase enzymes;[1,4] whereas AA leads to more inflammatory cytokines through the actions of these enzymes, downstream n-3 fatty acids form series 3 prostaglandins, series 5 leukotrienes, and thromboxane A3, all of which are less inflammatory.[1,3,4] This anti-inflammatory effect is one mechanism by which n-3 fatty acids are thought to be cancer protective; these less-inflammatory signaling molecules can be ligands for a number of nuclear receptors relevant to the control of the cell cycle and apoptosis.[1,5] More specifically, EPA and DHA can regulate transcription factors, serving themselves as ligands of the peroxisome proliferator-activated receptors leading to antiproliferative effects in colon cancer cells.[1] Another proposed mechanism is that fish oils actually might increase oxidative stress via reactive oxygen species in precancerous cells,

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causing them to become apoptotic.[5]

In addition, fish is known to contain selenium, vitamin D, and taurine in varying amounts, all of which have some proposed anti-neoplastic actions.[5] The overall cancer-protective effect of fish oil, therefore, could be a combination of the effect from the n-3 fats and these micronutrients.

Some other interesting mechanisms relevant to n-3 fatty acids and cancer have been mentioned in the medical literature. For example, the anti-inflammatory effects of n-3 fatty acids that positively affect those with inflammatory bowel disease (IBD) could likewise lessen the connection between IBD and colorectal cancer.[6] Also, more relevant to cancer treatment, n-3 fats may increase the antitumor effects of 5-fluorouracil (5-FU) and the radiosensitivity of colorectal adenocarcinoma cell lines.[6]

PRECLINICAL RESEARCH

Expanding on the biochemical n-3 fatty acid research described above, researchers have looked at fish and fish oil as part of the diet of animals and cancer-related outcomes. The Wistar rat has been studied in this context, with an 18% fish oil diet leading to less aberrant crypt foci (ACF) and lower incidence of colorectal tumors, as well as a more recent study using 4% lipids (closer to a normolipidemic human diet) from fish oil compared to flaxseed oil, olive oil, and soybean oil.[7] In this latter investigation, lower concentrations of ACF were found in the proximal colon in the fish and flaxseed oil groups (P = 0.011). Though outcomes were similar for both fish and flaxseed oil, other indications from the preclinical literature are that plant-derived n-3s are less bioactive with respect to cancer.[5]

CLINICAL TRIALS

The clinical trials fall into several categories, including numerous prospective cohort studies and case-control studies.[6] For example, one case-control study looked at the n-3 fatty acid content of red blood cells (RBC), thought to be a more accurate representation of n-3 intake than dietary recall, in 74 incident colorectal cancer cases and 221 controls without cancer.[8] The results showed no connection with dietary intakes of fish, meat, fat, or fatty acids, but colorectal cancer rates were inversely correlated with RBC DHA, AA, and PUFA content (odds ratios 0.36, 0.42, and 0.15, respectively). A predictable direct correlation between colorectal cancer and RBC saturated fatty acid content also was seen. The inverse relationship with AA was a bit of a red herring, no pun intended; AA, representative of omega-6 fatty acid intake and a competitive substrate with n-3s for the same enzyme systems, presumably would have led to increased colorectal cancer rates. The authors discuss the complicated data surrounding AA, including conflicting epidemiological evidence, and put forth a request for further research to explore the AA and colorectal connection, perhaps beyond the current paradigm.

A prospective cohort study, and one that impressively lasted 22 years using the Physicians' Health Study data, followed 22,071 men and their fish intake and looked for correlations for 500 who had a confirmed diagnosis of colorectal cancer.[9] The highest (≥ 5 times weekly) vs the lowest (< 1 time weekly) category of fish intake was inversely correlated with a lower risk of colorectal cancer (relative risk, 0.60 [0.40-0.91]). An estimate was made from the type of fish for n-3 fatty acid content, and this value also was inversely related to colorectal cancer risk (relative risk, 0.74 [0.57-0.95]). Some of the subgroup analyses bring up the complexities of doing a dietary recall study, as well as understanding the exact type of fish that is most beneficial in the context of participant demographics.

A comparable trial was undertaken in Europe, following 478,040 men and women for 4.8 years and looking for dietary correlates for the cases of colorectal cancer.[10] Comparing people who consumed > 80 g of fish daily to < 10 g daily, there was an inverse relationship with colorectal cancer risk (hazard ratio, 0.69 [0.54-0.88]). The researchers found a positive relationship between red meat consumption and colorectal cancer risk; interestingly, when

Summary Points

- Regular fish intake, based on most but not all clinical trials to date, correlates with a decreased risk of colorectal cancer.
- Omega-3 fatty acids may affect cancer risk through both anti-inflammatory mechanisms and direct antiproliferative effects.
- The most convincing preventive effects against colorectal cancer were seen in people who consumed fish 5-7 times weekly, or approximately 3 ounces of fish (preferably cold-water fish) daily.

red meat consumption was removed as a possible confounding variable, it did not alter the association of fish consumption and decreased cancer risk.

A summary of many of the existing research trials was attempted by the authors of a recent meta-analysis.[11] The authors searched for epidemiological studies (case-control or cohort studies) that explored the relationship between colorectal cancer and fresh fish consumption, finding 41 articles (22 cohort, 19 case-control). Despite the heterogeneity among the studies, there was a statistically significant trend showing a reduction in colorectal cancer risk with the highest (vs lowest or non) fish consumption (odds ratio, 0.88; confidence interval, 0.80-0.95). The authors' calculations were that fish consumption may reduce the risk of colorectal cancer by 12%, though they were unable to comment on the quantity of fish intake necessary to reach this protective effect (due to significant heterogeneity in the methods and units of fish intake), nor to comment on the effect of fish oil supplementation or other types (i.e., salted) of fish.

Another meta-analysis considering all cancers failed to find a relationship (either positive or negative) between plant-based n-3 fats and colorectal cancer;[12] however, the authors did support the fact that limited evidence exists for a protective effect of the long-chain fatty acids, DHA and EPA, on colorectal cancer risk. As with the meta-analysis described in the prior paragraph, a serious challenge to interpreting the data in this meta-analysis is the lack of homogeneity in the studies analyzed, the multifactorial aspect of colorectal cancer, and the difficulties in pinning down the exact type of fish (and resulting n-3 content) consumed. One trial reviewed in this meta-analysis may offer a view into a more simple and accurate way to address these issues; using serum n-3 fatty acid levels and an endoscopy-based, case-control approach, which in this case found an inverse relationship between serum n-3 fatty acids and colorectal adenoma risk. Some, but not universal, benefits also were seen in yet another meta-analysis, with an inverse relationship between the highest vs lowest intake of n-3 on colorectal cancer incidence (relative risk, 0.88 [0.78-1.00]), but not for colorectal cancer mortality.[13] In this latter meta-analysis, when fish consumption was at least seven times monthly, the relative risk improved and became more significant. Furthermore, the authors estimate that each additional time per week that fish is consumed, or for each additional 100 g of fish eaten per week, there is a 3% or 4% lower risk of colorectal cancer, respectively.

Other trials related to colorectal cancer have looked at the effect of fish or fish oil in people already diagnosed or treated for colorectal cancer. For example, in one study, colorectal patients were given 900 mg DHA+EPA, which was found to help improve inflammatory markers and nutritional status,[14] though there are unclear ramifications regarding the cancer pathophysiology itself.

DOSE

In general, it is difficult to determine dose from the epidemiological research as described above, a parameter that is more convincingly established by prospective, randomized, controlled trials. That said, an optimal dose range for colorectal cancer protection can be estimated by aiming for the higher levels in the clinical trials with positive results on colorectal cancer risk. Examples would be fish consumption more than 5-7 times weekly, or more than 80 g of fish daily; 80 g of fish is approximately 3 ounces or a small fillet.

CONCLUSION

The connection between fish consumption and lower risk of colorectal cancer has grounds both in physiology and clinical research. Fish and fish oil, high in long-chain n-3 fatty acids, may prevent colorectal cancer through its well-known anti-inflammatory effects, as well as several direct antiproliferative effects as proposed in various cancer models. Most of the clinical research has employed either case-control or cohort methodologies, and there is general agreement that higher levels of dietary fish consumption are inversely related to a lower risk of colorectal cancer. Exact doses needed to achieve these effects remain to be determined, but extrapolation from the published research seems to indicate that almost once daily fish intake is ideal. There is debate about the type of fish and for which demographics this connection is most convincingly

shown. Preliminary results seem to indicate that plant-based n-3 fats have less of a protective effect against colorectal cancer.

RECOMMENDATION

Eating fish regularly may help to lessen a person's risk of colorectal cancer, so it should be one dietary consideration for preventing this disease process. This intervention may provide benefits regardless of other aspects of the diet, but further benefits in colorectal cancer prevention could be achieved by eating less red meat, exercising regularly, and probably eating more fiber.[1,15] Given that one-half of diagnosed cases of colorectal cancer may be related to diet,[11] this is an important line of investigation for researchers, clinicians, and patients alike. In most studies, n-3 fatty acid content of the ingested fish correlates with improved colorectal cancer rates, but not always, so it is unclear whether fish oil provides the same protection or how many mg of fish oil is necessary to match the benefits seen in consuming fish 5-7 times weekly. There are minimal risks associated with a recommendation to eat more cold-water fish; it is becoming increasingly important, however, to find sustainable sources of fish, as well as fish that is free of contaminants, such as mercury and PCBs, in order to meet the intake guidelines suggested by the results of recent investigations. ■

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CANCER

Lycopene and Prostate Cancer: No Magic Bullet

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Prostate cancer is the most commonly diagnosed non-dermatologic cancer and the second leading cause of cancer-related death in U.S. men.[1] Its etiology and predisposing factors are inadequately characterized, but probably include some combination of older age, north American and northern European residence (perhaps a diet-related issue), African American race, and genetic similarities within families. Oxidative stress is also a common etiologic element suggested for many kinds of cancer. Antioxidant-rich foods and supplements are marketed widely as having protective properties with respect to cancer, but few have rigorous scientific evidence to back up such claims.

Lycopene (one of the carotene family of antioxidants) came to be of interest early in the study of diet and cancer. It is present in meaningful quantities in tomatoes and tomato products, watermelon, pink grapefruit, and red bell peppers,

Summary Points

- Lycopene is naturally found in tomatoes and tomato-based products, watermelon, pink grapefruit, and red bell peppers.
- Most of the data around lycopene relates to consumption of whole foods, not supplements.
- Little positive evidence exists that lycopene offers meaningful protection against prostate cancer, but significant exposure may have to occur at a young age to be protective.

and is known to be taken up by human prostate tissue.[2] However, its precise mechanism of anticancer action is still mostly speculative. It might function by scavenging intracellular free radicals, by mediating programmed cell death (apoptosis), by inhibiting specific growth factors, or by some combination of these.[2] This uncertainty, combined with the attractive prospect of a chemoprotective agent with virtually no side effects and the general difficulty of assessing the impact of any single factor in so multifactorial a process as cancer, has kept lycopene on the research agenda.

The available published research is divided into observational and experimental studies. The former are usually larger and include most of the evidence for lycopene as contained in whole foods. The latter are smaller, but often have more precisely controlled estimates of exposure (through the use of supplements with known contents). Some studies avoid the exposure measurement issue altogether by using serum lycopene levels. This produces greater efficiency for the researchers, but at the expense of providing less useful information for clinicians.

OBSERVATIONAL EVIDENCE

Much of the early evidence for lycopene was in the form of observational studies that looked first at lycopene-rich whole foods and later at supplements containing lycopene.[3] A comprehensive meta-analysis of this body of research included both prospective and retrospective studies, and covered a wide range of definitions of lycopene intake. These included raw and cooked tomato products, and dietary and serum lycopene (measured in mg). There was general agreement among the studies included that a serving of raw tomatoes was about 200 g, but there was no similar agreement about cooked tomatoes. Because of this and other definitional issues, intake of both kinds — food and supplements — was divided arbitrarily into quintiles, and then further consolidated into high (the fifth [highest] quintile), moderate (the second and third; or second, third, and fourth quintiles, depending on the study), and low. The common outcome derived from all studies was the "risk" of prostate cancer. This could be estimated directly in the prospective studies because all participants were prostate cancer-free when those studies started. In the retrospective studies, risk was inferred indirectly from the difference in prior experience (of lycopene exposure) between those with and without prostate cancer.

Summing across all studies, there was a small but not statistically significant reduction in the risk of prostate cancer with higher consumption of raw tomatoes (relative risk [RR] = 0.94; 95% confidence interval [CI], 0.88-1.01). When the analysis was limited to the higher-quality evidence of the prospective studies, the effect was more pronounced (RR = 0.78; 95% CI, 0.66-0.92). There appeared to be a small and significant increase in risk with increasing intake of cooked tomatoes (RR = 1.07; 95% CI, 1.06-1.08), but this must be seen in light of the disagreement among studies about units of consumption mentioned above. Dietary lycopene levels showed a similar pattern to raw tomatoes — a nonsignificant reduction in risk when all studies were included, and a more dramatic reduction (RR = 0.38; 95% CI, 0.34-0.42, for a change in lycopene consumption of 12.7 mg/day) in an analysis restricted to prospective studies. Findings were also positive and statistically significant when comparing the highest quintile of intake with the four lower quintiles of consumption.

Since the publication of the first meta-analysis, a few other researchers have reported observational results. For example, one study reported finding no significant association between serum lycopene levels and prostate cancer risk (odds ratio [OR] = 0.98; 95% CI, 0.68-1.43).[4] This study, conducted in Australia, had a relatively strong design — a case-control study nested in a larger prospective study — and avoided the complexities of intake quantification by using serum levels, but was small in size. It falls well within the range of prior results and does little to support any therapeutic claim for lycopene.

Kristal et al also conducted a case-control study nested in a clinical trial of a prescription drug for the prevention of prostate cancer.[5] This virtually guaranteed them a population free from prostate cancer until a known and recent date, as well as clear evidence of prediagnosis levels of lycopene in the form of frozen blood samples collected just before and just after random assignment in the

trial. Those diagnosed as cases during the trial were compared with a sample of trial participants who did not develop prostate cancer. The results showed no association of lycopene with reduced cancer risk (OR for a 10 mg/dL increase in lycopene were 0.99, 1.01, and 1.02 for rising grades of prostate tumors). This study also combines powerful methods with minimal findings.

Agalliu and colleagues examined dietary factors in a subgroup of men in a large Canadian study of cancer.[6] A sample of men stratified by age reported what they ate and what supplements they took at baseline using a food-frequency questionnaire. From this, their intakes of a variety of nutrients were calculated. The main outcome was time to a diagnosis of prostate cancer or the end of study follow-up (about 7 years), whichever came sooner. The study's main objective, to evaluate the joint effect of a group of pro- and anti-oxidant factors, proved to be unsupported statistically. However, there was a statistically significant reduction in the risk of prostate cancer with lycopene consumption under certain circumstances. Specifically, an effect was shown when the cases included in the analysis were restricted to those diagnosed 2 or more years after the start of follow-up. Men consuming higher levels of lycopene (second through fifth quintiles as compared with the first) had hazards (relative risks) of prostate cancer between 0.64 and 0.75. It should be noted, however, that there was no evidence of a trend to greater protection with greater consumption, and, in fact, the reduction in risk appeared to attenuate with rising lycopene levels. This study was large and had the virtue of measuring actual dietary patterns, but produced results that at best require further evidence to confirm.

Finally, Beydoun and colleagues took a slightly different approach, looking for associations between antioxidant intake and values for prostate specific antigen (PSA) commonly used as markers of prostate cancer.[7] Dietary and PSA data were abstracted from the records of 3800 men in three waves of the National Health and Nutrition Evaluation Survey (NHANES). Lycopene was divided into quartiles of consumption, and PSA was reported as total PSA > 10 ng/mL, > 4 ng/mL, and > 2.5 ng/mL, as well as free PSA as a proportion of total PSA (< 15% and < 25%). It was found in unadjusted analyses that rising levels of lycopene consumption were associated with a lower chance of being above the > 4 and > 2.5 ng/mL PSA threshold levels ($P = 0.007$ and 0.033, respectively). However, after adjusting for likely confounding factors such as age, race, education, and body mass index, these associations were no longer statistically significant. This study is interesting because it uses a common screening marker, still in use despite recent controversy, rather than the disease outcome itself, moving the association of interest further "upstream." However, the balance of observational research still does not give a clear answer about the role of lycopene in prostate cancer prevention.

EXPERIMENTAL EVIDENCE

Numerous experimental studies have focused on the effects of single or repeated doses of lycopene-rich foods (usually tomato products) in preventing DNA damage and other processes known or believed to play a role in the genesis of prostate cancer. Ellinger and colleagues reviewed this literature in 2006 and concluded that there is some evidence to support such a role.[8] They found that the bulk of the available evidence relates to lycopene consumed in the form of whole foods rather than in supplements, and characterized the strength of the collected findings (reviewed systematically but not meta-analytically) as, "the regular ingestion of tomatoes or tomato products *might prevent*" prostate cancer (emphasis added).

Another group reasoned that the antioxidant effects of lycopene might slow the progression of prostate disease that is already established.[9] The authors conducted a "Phase II" study in a group of 71 men with histologically proven prostate cancer who had rising PSA levels and were on no other therapies. Participants were randomly assigned to receive 15 mg of lycopene alone (in the form of a "tomato extract" capsule) or lycopene plus a soy isoflavone mixture, twice a day for up to 6 months. All participants showed continued increases in their PSA values, but a larger proportion of those in the lycopene-alone group than in the lycopene plus soy group showed enough slowing in the rate of rise to be classified as having stable disease (95% vs 67%, $P = 0.003$, though the test result was not reported in the paper).

In another study related to disease progression, Bunker and colleagues moved one step earlier in the disease process, assembling a group of Afro-Caribbean men considered to be at high risk for prostate cancer — those with high-grade prostatic intraepithelial neoplasia (HGPIN) or other cellular changes that often precede the development of cancer.[10] The men were randomly assigned to receive 30 mg/day of lycopene plus a multivitamin or the multivitamin only for 4 months. PSA was measured at baseline, and again 1 and 4 months later. The investigators found that PSA declined in both treatment groups between baseline and month 1, but then returned to prestudy levels by month 4. There was no significant difference in PSA between the treatment groups at any measurement.

Mohanty et al and Schwarz et al also considered lycopene's role in preventing or delaying progression to prostate cancer.[11,12] Mohanty began with men with HGPIN. The study was small (n = 40), and the lycopene dose was lower than in most other trials (4 mg/day), but the 1-year duration of follow-up was longer than that of the Bunker study. The results showed a reduction in average serum PSA in the lycopene group and an increase in average PSA in the comparison group (which received no active therapy). Curiously, no statistical tests were reported. Schwarz recruited 40 men with proven benign prostatic hyperplasia (BPH), but who were free from prostate cancer, and randomly assigned them to receive 15 mg/day of lycopene or placebo for 6 months. PSA level, measured at 6 months and 1 year, was the main outcome. The lycopene group showed a significant ($P < 0.05$) reduction in serum PSA, while the placebo group did not. However, the magnitude of the difference between the two groups over time was not statistically significant.

DOSE

It is worth summarizing briefly the forms and doses that have been tested to date. Supplement doses as low as 4 mg/day and as high as 30 mg/day have been tested. The most common dose used for research appears to be 15 mg/day. None of the experimental studies reviewed used whole foods as part of the dosing regimen. An analogous statement about the studies that used whole foods is difficult to make. It can be said that one cup of a concentrated tomato product (like soup or sauce) contains about 25 mg of lycopene, and a serving of fresh tomato contains about 4 mg.[13]

CONCLUSION

On balance, there seems to be little in vivo evidence that lycopene produces a clinically meaningful amount of protection against prostate cancer. This appears to be the case regardless of the form in which the lycopene is consumed and regardless of the presence or absence of early cancer precursors. None of the studies identified for this review presented consistent, statistically significant results that withstand adjustment for known or suspected confounding factors.

Caution is required when speculating about why this may be the case, but a few possibilities may be noted. First, it may genuinely be the case that lycopene does not play a role in preventing prostate cancer. With lingering uncertainty as to its mechanism of action, it is difficult to know exactly what to test and how. A related possibility is that lycopene's main role in disease prevention takes place earlier in the life course. All of the studies reviewed here focused on men in the age range in which prostate cancer typically presents. If lycopene's function has more to do with inhibiting initiation than promotion of disease, it may be necessary to look for exposure to it among younger men (or further in the past for those currently in the prostate cancer window). This possibility cannot be ruled in or out on the basis of the available literature, though a clear majority of the studies reviewed are based on the assumption that lycopene can and does have value later in the natural history of prostate cancer.

As with many phytochemicals, it is also important to consider dosing and the vehicle of delivery. It is a common observation that constituents of whole foods that appear to have desirable properties often show disappointing results when they are extracted and delivered in isolation. The limited positive evidence for lycopene comes mostly from studies measuring its consumption in whole foods. All of the experimental studies included here used supplements of some kind, although with some variation in the dose delivered. It may be that careful research with prolonged exposure to a controlled dietary exposure (as difficult as that may be) is needed to settle the question definitively.

RECOMMENDATION

There appears to be little support for clinicians to recommend or endorse their patients' use of lycopene as part of a prostate cancer prevention strategy. Although there appears to be virtually no risk of toxicity with lycopene use at conventional levels, and the possibility of benefit cannot be ruled out definitively, it is not possible to say how much benefit there might be or for whom. It is important that the availability and promotion of this and other supplements not distract patients from other strategies, such as PSA screening and digital rectal exams, which can aid in the detection and early treatment of prostate cancer. These are "secondary" forms of prevention (that is, means to detect disease early rather than prevent it from starting), but they are of proven value. Clinicians should also emphasize the value of consuming a wide variety of nutrients in whole foods, since the research seems to show that if there is any benefit to be had from phytochemicals, it is most likely to come in that form. ■

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WOMEN'S HEALTH

ABSTRACT & COMMENTARY

Probiotics vs. Antibiotics for Prevention of UTIs: Inferiority Complex?

By Donald J. Brown, ND

Managing Director, Natural Product Research Consultants, Seattle, WA

Dr. Brown reports no financial relationships relevant to this field of study.

SYNOPSIS: In this non-inferiority clinical trial, 1-year prophylaxis with an oral lactobacilli probiotic combination proved less effective than trimethoprim-sulfamethoxazole for preventing recurrence of urinary tract infections in postmenopausal women. However, although women in the antibiotic group had a dramatic increase in antibiotic resistance, there was no increase noted in the probiotic group.

SOURCE: Beereport MAJ, et al. Lactobacilli vs. antibiotics to prevent urinary tract infections: A randomized, double-blind, noninferiority trial in postmenopausal women. *Arch Intern Med* 2012;172:704-712.

Growing concerns about antibiotic resistance have led to increased interest in non-antibiotic therapies for recurrent urinary tract infections (UTIs). In this randomized, double-blind, non-inferiority clinical trial, postmenopausal women with a history of at least three self-reported UTIs in the year preceding the study were recruited through advertisements or referred by Dutch family physicians. Women were randomized to: 1) trimethoprim-sulfamethoxazole (TMP-SMX), 480 mg, one tablet at night and one placebo capsule twice daily or 2) one capsule containing *Lactobacillus rhamnosus* GR-1 and *Lactobacillus reuteri* RC-14 (1 x 10^9 colony forming units [CFU] of each strain) twice daily and one placebo tablet at night. The treatment period was 12 months. Immediately before the study medication was started and monthly thereafter, until 3 months after discontinuation of the study medication, the women were asked to collect urine and fecal samples and also a vaginal swab specimen. During these times, women also completed a questionnaire regarding UTI symptoms, adverse events, infections other than UTIs, and antibiotic use. In case of a symptomatic UTI, women were instructed to collect urine using a dipslide and to send it to the study laboratory for culture. Urine and stool samples were used to measure antibiotic resistance of commensal *Escherichia coli*, and urine samples also were tested for antibacterial activity associated with TMP-SMX or other antibacterial substances.

The primary clinical outcomes were the mean number of symptomatic UTIs (clinical recurrences [CR]) during 12 months, the proportion of patients with at least one CR during 12 months of prophylaxis, and the median time to the first CR. The primary outcome evaluating the development of antibiotic resistance was the percentage of TMP-SMX-resistant *E. coli* isolates from asymptomatic women at 1 and 12 months. Additionally, antibiotic susceptibility of these *E. coli* isolates to trimethoprim, nitrofurantoin, amoxicillin, amoxicillin-clavulanic acid, gentamicin, ciproflaxin, and norfloxacin was analyzed. An additional analysis of these measures was repeated 3 months after discontinuation of the study medications. Secondary outcomes included the mean number of microbiologically confirmed UTIs (microbiological recurrences [MRs]) during the 12 months of prophylaxis and in the 3 months after its discontinuation, the proportion of women with at least one MR during this period, and the time to the first MR. An MR was defined as a UTI

Summary Points

- Probiotics and cranberry are non-antibiotic options women frequently choose in trying to prevent recurrent UTIs.
- This study strongly suggests that suppression therapy with TMP-SMX is more effective than oral probiotic therapy against recurrent UTI in postmenopausal women.
- Development of antibiotic resistance was significant in those receiving TMP-SMX, but not in the group taking probiotics.

based on the combination of clinical symptoms and bacteriuria (≥ 10^3 CFU/mL bacteria in midstream urine). Preplanned subgroup analyses included the mean number of CRs in women with complicated vs uncomplicated UTIs. To establish non-inferiority of the probiotics compared to TMP-SMX, the upper limit of the 95% confidence interval (CI) for the between-groups difference in the mean number of CRs at 12 months had to lie below a predefined 10% non-inferiority margin.

The study included 252 postmenopausal women, with 127 randomized to receive TMP-SMX (mean age 65.4 years) and 125 to receive probiotics (mean age 63.2 years). After 12 months of prophylaxis, the mean number of CRs was 2.9 (95% CI, 2.3 to 3.6) in the TMP-SMX group and 3.3 for the probiotic group (95% CI, 2.7 to 4.0). The between-group difference in the mean number of CRs after 12 months was 0.4 (95% CI, -0.4 to 1.5), which equated to a difference of 13.8%. The percentage of women with at least one CR at 12 months was 69.3% in the TMP-SMX group and 79.1% in the probiotic group. The median times to first recurrence were 6 and 3 months, respectively (P = 0.02). The number of CRs during the 3 months following discontinuation of prophylaxis did not differ significantly between groups. After 1 month of TMP-SMX prophylaxis, resistance to TMP-SMX and amoxicillin increased from approximately 20-40% to approximately 80-95% in the feces and urine of asymptomatic women. After 12 months of TMP-SMX, all urinary *E. coli* isolates of asymptomatic women were resistant to TMP-SMX and trimethoprim. Resistance rates for ciproflaxcin and norflaxacin in urinary *E. coli* isolates increased from 16-18% at baseline to 34% 1 month after TMP-SMX prophylaxis was stopped. Resistance remained unchanged in the probiotic group.

After 12 months of prophylaxis, the mean number of MRs was 1.2 (95% CI, 0.9 to 1.6) in the TMP-SMX group and 1.8 (95% CI, 1.4 to 2.3) in the probiotic group. The percentage of women with at least one MR at 12 months was 49.4% in the TMP-SMX group and 62.9% in the probiotic group. Median times to first MR were 12 and 6 months, respectively (P = 0.02). The number of MRs 3 months after treatment discontinuation did not differ significantly between groups. Resistance percentages of *E. coli* isolates in these symptomatic women were similar to that found for asymptomatic women. At 1 month, 39.6% of women in the TMP-SMX group and 44.7% of those in the probiotic group had asymptomatic bacteriuria. At 12 months, these percentages were 38.5% and 53.2%, respectively. The mean number of CRs after 12 months of prophylaxis in women with uncomplicated UTIs was 1.9 (95% CI, 1.4 to 2.6) in the TMP-SMX group and 3.2 (95% CI, 2.5 to 4.2 in the probiotic group. In women with complicated UTIs, these numbers were 4.4 (95% CI, 3.4 to 5.7) and 3.4 (95% CI, 2.6 to 4.5), respectively (P < 0.001). No significant differences in AEs were noted between the two groups.

COMMENTARY

Approximately 50-60% of women have a UTI during their lifetime, and recurrence occurs in approximately 25-30%.[1] Recurrent UTIs are most common in sexually active women 20-40 years old and postmenopausal women. Standard therapy for postmenopausal women with at least three UTIs per year is vaginal application of estrogens or low-dose antibiotic prophylaxis.[2] The first choice is increasingly unpopular with women and the second, while an effective prevention, has led to an increased prevalence of antibiotic resistance. Probiotics have joined cranberry as one of the popular, non-antibiotic alternatives for women with recurrent UTIs.

Like bacterial vaginosis, an imbalance in the normal vaginal flora is associated with recurrent UTIs. Vaginal colonization with *E. coli* has been linked to a depletion of vaginal H_2O_2-producing lactobacilli in women with recurrent UTIs.[3] Postmenopausal women have been found to have reduced concentrations of vaginal lactobacilli, most likely the result of decreased estrogen levels.[4] Research to date using probiotics as prophylaxis for recurrent UTIs has focused largely on premenopausal women using vaginal suppositories and primarily has been negative.[5] Promising results recently have been shown with the intravaginal application of a new probiotic strain, *L. crispatus* CTV-05, but the study focused only on premenopausal women following antibiotic treatment.[6] The current study is the first

to focus on postmenopausal women using an oral probiotic combination[7,8] and an active control. It did not address the effect of prophylaxis following standard antibiotic therapy for an acute UTI.

So, what to make of the results? Based solely on efficacy, one would conclude that TMP-SMX prophylaxis is superior to the oral probiotic combination in preventing UTI recurrence in postmenopausal women. The results correspond roughly to 1.5 additional UTIs in women choosing to take the probiotic combination instead of TMP-SMX. Interestingly, the only exceptions were those women with complicated UTIs, where probiotics outperformed TMP-SMX. However, it is important to factor in the difference in antibiotic resistance between the two treatments. Although the probiotic group showed no increase in resistance, the TMP-SMX group had a more than two-fold increase in resistance to both TMP-SMX and amoxicillin. The investigators sum it up best by stating, "Lactobacilli may be an acceptable alternative for prevention of UTIs, especially in women who dislike taking antibiotics." Unfortunately, that conclusion comes at the very end of the Discussion section of the paper. I look forward to an upcoming paper by the investigators that will offer an economic evaluation weighing the pros and cons of both regimens.

Non-inferiority clinical trials have a number of inherent weaknesses that superiority trials do not but are often used when a placebo group cannot be ethically included.[9] These weaknesses include lack of protection from bias by blinding and difficulty in specifying the non-inferiority margin. It is interesting to note that this is the second of these trials by this group from the Netherlands. The earlier study was a noninferiority study comparing cranberry (in capsules) and TMP-SMX in premenopausal women with recurrent UTIs.[10] The difference in recurrence was similar to that found in this probiotic study, while the antibiotic resistance findings at 1 month were similar for TMP-SMX but slightly higher for cranberry (approximately 28%) compared to the probiotic findings in the current study. Perhaps a combination of probiotics and cranberry might be superior when considering the downside of antibiotic prophylaxis for prevention of UTIs. ■

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DIABETES

ABSTRACT & COMMENTARY

Spice and Sugar: Curcumin and Type 2 DM

By Russell H. Greenfield, MD

SYNOPSIS: Results of this year-long intervention trial suggest that an ethanolic extract of curcumin could, together with appropriate dietary and lifestyle changes, play a role in slowing the progression from prediabetes to type 2 diabetes.

SOURCE: Chuengsamarn S, et al. Curcumin extract for prevention of type 2 diabetes. *Diab Care* 2012; Jul 6. [Epub ahead of print].

Strategies aimed at preventing type 2 diabetes mellitus (DM) typically focus primarily on diet and lifestyle changes, together with select drug therapy where appropriate. The rationale is reasonable, but results have been largely disappointing. An increasing number of people are diagnosed with type 2 DM each year and not just in industrialized nations. There is urgent need for safe, economical interventions that can effectively help prevent, or at least delay, further spread of this scourge. In an attempt to answer the need, the authors of this 12-month, randomized, double-blind, placebo-controlled, cohort trial explored the effects of an ethanolic extract of curcumin on Thai people

Summary Points

- The incidence of type 2 DM is increasing worldwide despite dietary and lifestyle preventive measures.
- Curcumin is a spice that possesses potent antioxidant and anti-inflammatory potential.
- None of the pre-diabetic subjects in this study who took an ethanolic extract of curcumin for 9 months developed DM, compared with 16% of those in the placebo group.

older than 35 years with known prediabetes. The study was performed at a major university medical center in Thailand where subjects (n = 240) with prediabetes based on American Diabetes Association (ADA) guidelines were screened for participation (n = 237 were enrolled). Exclusion criteria included the use of oral hypoglycemic agents as well as use of herbal remedies. Subjects were advised that the study aimed to compare two different interventions, and all began their participation by attending a 20- to 30-minute, one-on-one educational session with an instructor detailing the benefits of a healthy diet and lifestyle program they should try to follow. There was no further intervention for 3 months. Participants were randomly assigned to take either a) three placebo capsules twice a day, or b) three capsules of an extract of curcumin twice daily for a period of 9 months both beginning 3 months after the educational session. Compliance was determined via pill count at follow-up visits at 3, 6, and 9 months. Curcuminoid content of the curcumin extract capsules was 250 mg per capsule. Each batch of capsules containing curcumin extract was subjected to High Performance Thin Layer Chromatography (HPTLC) to ensure consistency over the 9-month course of treatment. Capsules containing the extract or placebo were identical in appearance and were manufactured by the Government Pharmaceutical Organization of Thailand.

Primary outcome of interest was the number of subjects who, by the end of the trial, developed type 2 DM according to ADA guidelines. Secondary outcomes of interest included changes in β-cell function, insulin resistance, adinopectin levels, and waist circumference, among others. Monitoring took place at baseline and at the 3-, 6-, and 9-month post-intervention follow-up appointments.

Two hundred one subjects completed the study (n = 234 subjects were included in the intention-to-treat analysis). Mean values for blood chemistries such as 2-hour OGTT, fasting glucose, and HbA_{1c} were significantly lower in those subjects who received the curcumin extract as compared to the placebo group at all follow-up visits ($P < 0.01$). Measures of insulin resistance declined significantly after 6 and 9 months in the active group compared with placebo, and those in the active group had higher adinopectin levels at 9 months. By trial's end, 19 (16.4%) in the placebo group had developed type 2 DM compared with none in the curcumin-treated group. No serious side effects were reported. The authors conclude that an ethanolic extract of curcumin may help prevent progression of prediabetes to type 2 DM.

COMMENTARY

Prevention trumps treatment in any discussion of health and disease, but preventing type 2 DM has proved a frustratingly difficult task. How crazy would it be if a simple herbal remedy might be part of the answer? Crazy, indeed, but don't jump on the bandwagon too quickly — there are devils in the details of this paper. For example, all subjects underwent a brief discussion on the importance of dietary and lifestyle measures for optimal health, emphasizing the impact of such measures on blood sugar and inflammation. Three months later the first capsules, placebo or curcumin, were taken. It is unlikely that such a brief intervention had a significant impact on the majority of participants, but there is no way of knowing whether people altered their daily habits to help prevent the development of DM, short- or long-term, because it was not monitored. Although the dropout rate (15%) was impressive for a year-long trial, the sample size was relatively small. In addition, the rate of conversion in the placebo group from prediabetes to frank type 2 DM was quite high (16.7%), higher than what is typically seen in industrialized countries. The authors believe that aspects of Thai culture may be to blame, but the argument falls short because the considerations described (older, overweight population with significant family histories for hypertension and DM) are not unique to Thailand. Finally, pill count is a notoriously inexact way to determine compliance.

On the upside, the researchers posed a unique question that was investigated over a significant time frame and explored through a variety of laboratory tests. Curcumin, derived from the rhizome (underground stem) of the turmeric plant (*Curcuma longa*), is commonly used as a spice in Asian cuisine and has been the focus of intense study in recent years due to its antioxidant and anti-inflammatory capacity. Studies suggest that curcumin may help in

the treatment and prevention of a variety of illnesses, including Alzheimer's and certain types of cancer. Results from the current study point to a possible role for curcumin in improving β-cell function and insulin sensitivity, like through anti-inflammatory actions.

This is a very interesting study that raises intriguing questions — could curcumin, a potent natural anti-inflammatory agent with additional physiologic actions, help stem the tide of type 2 DM? Would eating curry dishes on a regular basis have the same effect? If curcumin has a protective effect, is it independent of diet and lifestyle habits? It's too early to begin recommending curcumin to our patients at risk for type 2 DM, as the current study raises questions more than it provides answers, but it seems likely a novel line of inquiry and investigation has been opened as a result of the findings, making awareness of the trial important. ■

CME INSTRUCTIONS

To earn credit for this activity, please follow these instructions:

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CME QUESTIONS

1. To lessen one's risk of colorectal cancer, what level of omega-3 fatty acid intake is ideal?
a. One serving of fish weekly
b. 2 tablespoons of flaxseed (ground) daily
c. 5-7 servings of fish weekly
d. 1000 mg of fish oil daily

2. Dietary fish via its omega-3 fatty acid content seems to decrease colorectal cancer incidence by which of the following proposed physiological mechanisms?
a. Higher arachidonic acid levels and corresponding cytokines
b. Low selenium levels
c. Serving as ligands of the peroxisome proliferator-activated receptors leading to antiproliferative effects in colon cancer cells
d. Increased inflammation in people with inflammatory bowel disease

3. Lycopene is a phytochemical in the family of:
a. carotenes.
b. B vitamins.
c. amino acids.
d. trace minerals.

4. The best evidence for lycopene's efficacy as a cancer preventive is in studies that used:
a. lycopene supplements.
b. whole foods.
c. combination with soy products.
d. lipid-based delivery vehicles.

5. In the study comparing probiotics to antibiotics for prevention of UTIs in postmenopausal women, probiotic prophylaxis was found to:
a. be slightly less effective than antibiotics for the prevention of UTIs.
b. result in less antibiotic resistance compared to antibiotics.
c. result in significantly fewer adverse events compared to antibiotics.
d. Both a and b
e. None of the above

[IN FUTURE ISSUES]

Yoga and stroke

Chocolate and cardiovascular disease

The science behind fad diets