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A Review of the Clinical Effects of Green Tea: Up-to-date Reasons to Imbibe

By David Kiefer, MD

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WE ALL KNOW THAT WE SHOULD BE DRINKING MORE GREEN TEA; every few days, either the media or medical journals are touting a new use for the Asian staple. Can it really cure breast cancer while preventing liver disease, simultaneously increasing knee range of motion in people suffering from osteroarthritis? The answer is "possibly, yes," but an evidence-based review refines the glowing reports with some clinical pearls, dosing specifics, and hopeful avenues of future research, as detailed below.

Botany and Pharmacology

Green tea is one of several forms of tea made from the tea plant, *Camellia sinensis*, Family Theaceae. Two varieties are used for most tea production: *Camellia sinensis* var. *sinensis* and *Camellia sinensis* var. *assamica*, the former accounting for most green tea production. Variety *assamica* has a higher content of polyphenols, which makes green tea taste excessively bitter.[1]

The tea plant is an evergreen shrub or small tree and reaches a height of up to 35 feet, but is often trimmed to 6 feet when cultivated for the tea production. The alternate leaves are blade elliptic or oblong, measuring approximately 14 cm in length and 7.5 cm in width. Their surface is dark green, leathery, and shiny while the bottom side is pale green. The white blossoms appear from October to February solitarily or up to three in a cluster. The fruits ripen from August through October and contain two brown round seeds.[2]

Camellia sinensis is known for a high content of polyphenols, including the well-known epigallocatechin-3-gallate (EGCG); polyphenols are a family of phytochemicals with numerous physiological effects as detailed below.[1] On average, green tea contains 20-45%

polyphenols by weight; a subset of polyphenols, catechins, comprises 60-80% of the polyphenol composition.[3] In addition, green tea contains a variety of vitamins, minerals, and other phytochemicals, such as the flavonol quercetin, in varying amounts depending on location and processing. Two methylxanthine compounds, caffeine and theophylline, are responsible for tea's stimulating effect.[4]

The relative polyphenol content depends on how the leaves are processed before drying; fermentation and heating of the leaves can affect the catechin content and resultant properties.[4] For example, black and oolong tea contain less EGCG than green tea. Also, instant preparations and iced teas contain fewer catechins.[1]

Other factors influencing the phytochemical composition of tea are the geographical location, growing conditions, the preparation of the infusion, and the age of the leaves. Young leaves contain more methylxanthines, but less EGCG compared to older leaves. Methylxanthine content varies only slightly between green, black, and oolong teas.[5,6]

Mechanisms of Action and Clinical Effects

There is a long list of clinical conditions purportedly affected by the therapeutic use of green tea (see *Table 1*).[1,3] It is beyond the scope of this article to address them all in detail, but the conditions with the greatest quantity and quality of data are reviewed below.

Cancer Prevention

During the last few decades, a large number of studies examined the cancer preventive effects of whole green tea and isolated EGCG, mostly through in vitro and animal research. Animal studies have shown the potential of green tea to inhibit carcinogenesis of the lung, esophagus, skin, liver, prostate, kidney, and stomach.[7,8] EGCG seems to act by targeting cycle proteins, apoptotic proteins, growth factors, anti-apoptotic proteins, transcriptions factors, and protein kinases.[7,8] Epidemiological research has looked at the cancer preventive effects of green tea on numerous types of cancer, though gastrointestinal cancers have been studied more than other cancers.[1] A range of green tea consumption has been examined, from 1-2 cups daily to more than 10 cups daily. Overall, there has been little to no effect on the relative risk of cancer, an accurate assessment or one confounded by the structure of the study, the demographics of the population being studied, and the particular type of cancer involved. A recent Cochrane review on green tea and cancer found some evidence for lower prostate cancer risk in men consuming "higher amounts" of green tea; slight evidence was found for the prevention of liver, lung, pancreatic, and colorectal cancers; no or conflicting evidence was seen for other types of cancer.[9]

This is an area of great interest in research circles; expect a refinement of these results in coming years as new and more well-designed studies are published. For example, one recent paper suggests that the 2-3 cups of green tea analyzed in most human research provides about about 0.5 μM of EGCG daily, much less than the 20-200 μM used in basic science research, and may account for the equivocal research results of some studies; clearly a variable that could be improved upon.[10] Also, EGCG has poor bioavailability when ingested with calcium and magnesium such as in hard water or milk, another confounding variable that, when corrected, may provide a better glimpse into the true cancer prevention effects of green tea.

Cardiovascular Health and Hyperlipidemia

The consumption of green tea has positive effects on cardiovascular structures and function, including improving arterial compliance and endothelial function, and attenuating the development of atherosclerosis (possibly from decreased LDL oxidation), presumably from the antioxidant effects of the polyphenolic compounds.[1,11] Whether these mechanisms of action translate into tangible improvement in cardiovascular conditions has been debated, with some researchers showing improvements in blood pressure, prevention of blood pressure increases, and decreased risk of myocardial infarction or cardiovascular mortality, while other researchers have failed to corroborate these effects.[1,3,11,12] Again, dosing, demographics, and confounding variables are thought to account for the different research results. At a minimum, some of the tri-

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Please contact Executive Editor **Leslie Coplin**, at leslie.coplin@ahcmedia.com.

Table 1: Clinical Conditions with Varying Evidence for Efficacy of Treatment with Green Tea

- Cancer prevention
- Obesity
- Hyperlipidemia
- Hypertension
- Cardiovascular event prevention
- Sustaining weight loss
- Skin aging and counteracting photo-oxidation
- Anogenital warts
- Oral health

als have demonstrated that 5 or more cups daily is what has led to decreased cardiovascular disease mortality or incidence of stroke; it appears that green and black tea may have a similar magnitude of effect in this category.[3,11]

The effects on serum lipids also have been been variable. Some, but not all, clinical trials have found that green tea is able to lower total cholesterol and LDL-cholesterol, with minimal to no effects on HDL-cholesterol and triglycerides.[3,11] The quantity of the effect, not surprisingly, depends on the green tea dose and form; four representative studies, chosen among the few that are available for their variety, are shown in Table 2.

Arthritis

There are both in vitro and in vivo research results demonstrating positive effects of green tea and EGCG on arthritis.[17] The oral administration of EGCG in collagen-induced arthritis in mice leads to the inhibition of COX-2, IFN-γ and TNF-α, decreasing the severity of the disease.[18] EGCG can also regulate cytokines, chemokines, reactive oxygen species, and nitric oxide in the pathogenesis of osteoarthritis and rheumatoid arthritis, leading to cartilage protection, regulation of synovial fibroblast activity, and bone-preserving activity through osteoclast inhibition.[19,20] The relevance of these mechanisms of action on humans remains to be seen; to date there have been no clinical trials examining the effect of green tea on people with arthritis.

Weight Loss

Barring the research on cancer, most of the clinical research on green tea has been done as a weight loss aid, as well as a maintenance treatment helping people to prevent weight gain after weight loss efforts. The catechins and methylxanthines in green tea likely synergize to cause an increase in overall metabolism, as well as a shift to fat oxidation in place of carbohydrate or protein metabolism.[21] Green tea catechins, usually in a dose of 270-1200 mg daily, may lead to body weight loss of 1.31 kg over 3 months, according to one meta-analysis.[22] The research is in its infancy; numerous factors, such as changes in fat metabolism (i.e., loss of fat mass vs body weight loss), demographics, and phytochemical ratio (catechins vs caffeine), are surfacing in trials that probably account for divergent research results.

With respect to the maintenance phase after weight loss, clinical trials have used a variety of doses in a variety of demographics. In one double-blind study, 46 women with an average body mass index (BMI) of 27.7 kg/m^2 on a low-energy diet were given a green tea extract (1125 mg catechins and 225 mg caffeine daily) or placebo.[23] The green tea group had less of a drop in resting energy expenditure, but no difference in body weight nor body composition compared to placebo. Another study randomized 104 moderately obese people, after 4 weeks on a very low energy diet (resulting in an average of 6.4 kg weight loss), to either 13 weeks of green tea extract (104 mg caffeine, 573 mg catechins daily) or placebo.[24] The green tea group and the placebo group each gained weight in equal amounts during this maintenance phase. However, people who were used to drinking high amounts of caffeine regularly gained weight more than habitual low caffeine users. Related to this, another study found improved weight maintenance and higher resting energy expenditure in 76 people who were habitual low-caffeine users.[25]

Topical

Extracts of green tea are showing promise in several areas of topical treatment.[1] An ointment standardized to 15% sinecatechins and a cream standardized to 10% inhibit viruses and stimulate the immune system, two effects that make it effective against external genital and perianal human papillomavirus (HPV).[3,26] In addition, green tea extracts are used in combination to make conventional antibacterials more effective against methicillin-resistant *Staphylococcus aureus*,[27] and there are dozens of research articles documenting the use of green tea as a photoprotectant, decreasing the adverse skin effects of ultraviolet radiation that may lead to aging or skin cancer.[28] A variety of topical green tea products have been studied, ranging in concentration from 5-90% polyphenols.[29]

Dosing

One cup (250 mL) of brewed green tea (one teaspoon of dried leaves) has, on average, 30-40 mg of caffeine and 50-100 mg of catechins.[22] "Typical" consumption varies, but it may be in the range of three cups daily, leading to 240-320 mg polyphenols ingested per day.[3,5] However, some studies have looked at people ingesting greater than 10 cups daily, and one research group mentions a "desirable" green tea intake of 3-5 cups (approximately 1200 mL daily) providing at least 250 mg of polyphenols.[9] Green tea extracts, some of which have been decaffeinat-

Table 2: Green Tea Effect on Lipids as per Three Clinical Trials and One Review Article

Authors (year)	Study type*	Green tea form	Effect on lipids
Maron (2003)[13]	DBRCT	375 mg once daily theaflavin-enriched green tea extract	LDL decrease 16.4%; total cholesterol decrease 11.3%
Nantz (2009)[14]	DBRCT	100 mg L-theanine, 200 mg catechin green tea extract in a capsule: two capsules daily	Total and LDL cholesterol each decreased by 9 mg/dL
Frank (2009)[15]	Placebo-controlled, parallel	714 mg daily of green tea polyphenols in aqueous form	No change in total nor HDL cholesterol
Kim (2011)[16]	Review and meta-analysis	145-3000 mg daily green tea catechins	LDL decrease by 5.3 mg/dL; total cholesterol decrease by 5.46 mg/dL

* DBRCT: double-blind, randomized controlled trial

ed, are available as capsules or liquids ranging from 250-725 mg (230-290 mg EGCG) per capsule. The dosing range for green tea and green tea extracts varies widely depending on the clinical condition. Of note, green tea for weight loss and weight loss maintenance should remain caffeinated for optimal effects. Also, bioavailability may be enhanced through dry and cool storage, ingesting green tea during fasting, or co-administration of vitamin C or fish oil.[10]

Adverse Effects

When used in moderation, and especially as a hot water infusion, green tea is generally considered safe for most adults.[3] Some people can feel stimulant effects (nervousness, restlessness, insomnia, palpitations) from the caffeine content of green tea or mild gastrointestinal upset.[30] There have been cases of hepatotoxicity with the use of green tea and green tea products, prompting a review by the U.S. Phamacopeia (USP).[31] Some of the cases were difficult to causally tie to green tea, but others seemed probable, especially when a challenge/re-challenge situation occurred. The USP concluded that concentrated green tea extracts might cause liver damage, especially when ingested under fasting conditions. However, it also emphasized "the wide usage of green tea as a beverage and the low incidence of a causal relationship to hepatotoxicity."[31]

Other possible adverse effects and interactions may exist. For example, some green tea extracts inhibit the cytochrome P450 system 3A4, a common point of metabolism for many pharmaceuticals and botanicals.[31] Also, green tea catechins can inhibit the efficacy of sunitimib and bortezomib, two cancer pharmaceuticals; in high doses can counteract the effects of warfarin because of small amounts of vitamin K; again, in high doses, possibly may have anti-folate activity due to dihydrofolate reductase inhibition; and may cause allergic skin reactions with topical preparations.

Conclusion

From the long list of purported health effects for green tea, research is starting to refine the recommendations with both basic science and clinical research trials. Green tea contains both methylxanthines, such as caffeine and theophylline, and a family of compounds called polyphenols, one class of which are the catechins, such as EGCG. These medicinally active compounds vary in concentration in any given tea product, whether it be loose green tea or green tea extracts, and seem to have strong antioxidant, immunomodulatory, and antimicrobial effects. The most convincing data for clinical efficacy is for topical antiviral (HPV) effects. More modest results have been seen for weight loss, maintenance of weight loss, prevention of some but not all cancers, and lowering of total and LDL cholesterol. Dose recommendations vary, but the consumption of 3-5 cups of green tea daily meets many of the expert recommendations; more is probably needed for some weight loss effects (and it should be caffeinated), possibly for cancer prevention and cholesterol lowering. Caution is warranted in people with pre-existing liver disease, especially when ingesting more than 5 cups of green tea daily or taking green tea extracts. In addition, there are some drug interactions and other clinical scenarios to keep in mind, even though this plant is likely very safe for most of the population when used in moderation.

Recommendation

Prescribe green tea extracts topically for HPV, and counsel your patients interested in weight loss how to incorporate a moderate amount of green tea into their lives. For people with a family history of cancer, until research says otherwise, 3-5 cups of green tea daily may be a simple and tasty way to address that issue. Use cautiously, especially green tea supplements, in people with pre-existing liver disease. ■

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Tea Totaling: Green Tea and Cholesterol

ABSTRACT & COMMENTARY

By Russell H. Greenfield, MD

Synopsis: *A well-done meta-analysis showed that green tea, either as a beverage or as a supplement, could help lower total and LDL cholesterol levels in a statistically significant manner, but has no effect on HDL. The degree of clinical impact is debatable; what*

is not debatable is the poor quality of most studies on green tea and cholesterol.

Source: Zheng X-X, et al. Green tea intake lowers fasting serum total and LDL cholesterol in adults: A meta-analysis of 14 randomized controlled trials. *Am J Clin Nutr* 2011;94:601-610.

The authors performed a meta-analysis of randomized, controlled trials to ascertain the effect of regular green tea ingestion, in the form of tea or green tea extract, on total cholesterol (TC), LDL cholesterol, and HDL cholesterol in adults. A comprehensive, systematic literature search of English-language reports of clinical trials was performed. Articles were located in PubMed (1967-2010), Embase (1977-2010), and the Cochrane Library database, and from reviews and reference lists of relevant articles. The authors state that attempts also were made to contact investigators for access to unpublished data.

Inclusion criteria were strict; only studies in which subjects consumed green tea or its extract for > 2 weeks, were randomized and of a parallel or crossover design, where pre- and post-intervention lipid levels were retrievable, where food intakes between active and control groups were similar, where a supplement was not given as but one component of a multi-pronged supplement, and where fasting blood samples had been obtained were considered. Study quality was assessed using Jadad score, and publication bias was determined using funnel plots and the Egger's regression test. Search, data extraction, and quality assessment duties were completed independently by two reviewers, and discrepancies resolved through discussion (presumably amicably). Study characteristics (including sample size, study design, study duration, dose, and type of intervention), population information, baseline and final concentrations or net changes of TC, LDL, and HDL were extracted.

A total of 805 potentially eligible articles were initially identified, 778 of which subsequently were excluded either because they were not clinical trials or the interventions were not relevant to the meta-analysis. Thus, 27 articles were selected for detailed evaluation, 13 of which were excluded due to a variety of methodological shortcomings including short trial duration and lack of relevant outcomes. In the end, 14 randomized controlled trials providing data from 1136 subjects were analyzed. Trial size ranged from 20-240 subjects, duration from 3 weeks to 3 months (median 12 weeks), and dose of green tea catechins from 150 to 2500 mg/d (median: 625 mg/d). Five trials were conducted in healthy adults with another five focusing primarily on overweight and obese adults. A green tea beverage was tested in half of the trials, an extract in the remaining half. Twelve trials used a parallel group study design, two employed a crossover design. Twelve studies were double-blinded, and 10 were placebo-controlled (how double-blinding was maintained using a green tea beverage was not explained). In most of the trials investigators attempted to maintain participants' usual lifestyles, but in two studies a low-fat diet was used, and a low-energy diet in another.

Study quality was very disappointing, with only three of 14 studies assessed as being of high quality based on Jadad score. Two studies received industry funding.

Primary outcome measures of interest were pre- and post-intervention changes in TC, LDL, and HDL. Results for TC were reported in 14 comparisons from 13 studies (n = 949). Mean change in TC concentration was significantly reduced in subjects receiving green tea compared with controls (-7.20 mg/dL; 95% confidence interval [CI], -8.19 to -6.21 mg/dL; $P < 0.001$). Mean change in LDL concentration was reported in 11 comparisons from 10 studies (n = 853) and was significantly decreased by 2.19 mg/dL in the intervention groups compared with controls (95% CI, -3.16 to -1.21 mg/dL; $P < 0.001$). HDL results were calculated in 12 comparisons from 11 studies (n = 998), and in the intervention groups a favorable trend was identified that was not statistically significant (+ 0.25 mg/dL; 95% CI, -0.73 to 1.23 mg/dL; $P = 0.62$).

Subgroup analyses were conducted to explore methodological impacts such as dose-effect relationships and differences between drinking green tea and the taking of green tea extracts. Catechins intake was divided into low dose (< 625 mg/d) and high dose (≥ 625 mg/d). Time to follow-up varied from 3 weeks to 3 months; a subgroup analysis was performed by dividing the follow-up duration into a shorter-term subgroup (< 12 wk) and a longer-term subgroup (≥ 12 wk). These analyses showed that the reported reductions in TC and LDL were not influenced by type of intervention (drinking green tea or taking a supplement), and that TC and LDL were significantly decreased in both lower- and higher-catechin consumption groups. Green tea significantly reduced TC and LDL in both healthy subjects and in participants with cardiovascular risk factors. Short- and longer-term intervention subgroups experienced significant reductions in TC and LDL cholesterol.

Neither study heterogeneity nor publication bias was identified. Removal of the two trials associated with industry funding did not change the final results. The authors did not pool data on safety, stating that no serious side effects were reported in the trials they examined.

The authors concluded that the regular ingestion of green tea, whether through drinking or the taking of supplements, results in significant reductions in TC and LDL concentrations, but no significant effect on HDL.

■ COMMENTARY

Cardiovascular disease is a multifaceted disorder, but the contribution of dyslipidemia to increased risk of heart

attack and stroke is universally accepted. Diet and exercise remain the mainstays of therapy, often are very successful, and may help to negate the need for medical therapy or at least lessen the dosage required to attain healthier cholesterol levels. Any easy, widely available intervention that could add to the success of dietary means of lowering cholesterol would be welcome, especially in the form of a beverage. Therein lies the value of this meta-analysis.

Green tea (*Camellia sinensis*) is one of the most widely consumed beverages in the world and is viewed by many as a health-promoting powerhouse with demonstrated antioxidant, anticancer, anti-inflammatory, and antithrombotic activity. Animal data suggest it also may help lower cholesterol levels. The majority of human trials also suggest a lipid-lowering effect of regular green tea consumption, but not all, and that was the stated reason for the researchers to embark on this meta-analysis: to try and make sense of the available human data on green tea and its potential cholesterol-lowering action. And they did, but only to a point, with the shortcomings occurring through no fault of their own.

The authors suggest that the positive results they report point to a potentially significant role for green tea as part of a public health dietary policy to help improve cardiovascular health. This is over-stated. Green tea indeed may offer health benefits, including beneficial effects on lipids, but the current study does not add in a compelling way to the discussion. Even though study quality did not affect the results of meta-analysis, the majority of reviewed trials were of poor quality and short duration. In addition, the researchers rightly note that no definitive recommendation regarding proper dose of green tea catechins to promote cardiovascular health can be drawn from their investigation due to the wide range of doses employed across studies. However, it is reassuring to know that the positive effects of green tea on TC and LDL were consistent across varied methodologies. Then again, some might argue that the impact of green tea on cholesterol levels reported here may not be clinically relevant.

This meta-analysis is somewhat helpful in that it suggests green tea may hold promise as a mildly effective adjunct in the management of hyperlipidemia. Perhaps more importantly, it serves notice on the poor state of research regarding that promise. The good news is that practitioners should generally feel comfortable recommending green tea to their patients with high cholesterol, especially as a beverage, considering both safety and clinical utility. Optimal dosing has yet to be agreed upon, but most authorities suggest 3-5 cups (1-2 mugs) daily. Questions regarding the regular use of green tea extracts persist, however, in light of reports suggesting the potential for hepatotoxicity. The tea tastes way better, anyway. ■

Further Research Warranted on Low-fat Diets with Fish Oil Supplementation for Prostate Cancer Patients

ABSTRACT & COMMENTARY

By Dónal P. O'Mathúna, PhD

Dr. O'Mathúna is Senior Lecturer in Ethics, Decision-Making & Evidence, School of Nursing and Human Sciences, Dublin City University, Ireland; he reports no financial relationship to this field of study.

Synopsis: *A prospective, randomized controlled trial measured the impact of a low-fat diet that included high levels of omega-3 fatty acids from fish oil on biomarkers for prostate cancer. No significant differences were found for the primary outcome during an interim analysis and the trial was stopped early. Analysis of secondary endpoints showed some significant differences between the groups, although other biomarkers did not differ.*

Source: Aronson WJ, et al. Phase II prospective randomized trial of a low-fat diet with fish oil supplementation in men undergoing radical prostatectomy. *Cancer Prev Res* 25 Oct 2011; Epub ahead of print; DOI:10.1158/1940-6207.CAPR-11-0298.

THIS PHASE 2 RANDOMIZED CONTROLLED TRIAL EXAMINED whether lowering dietary fat and decreasing the omega-6 to omega-3 fatty acid ratio would delay the progression of prostate cancer. The hypothesis arose from previous research showing such an effect in cell lines and mouse models. In addition, some, but not all, epidemiological studies have shown a correlation between intake of dietary fat in general or omega-3 fatty acids and risk of prostate cancer.[1]

The proposed mechanism of action for these effects is through reduced insulin-like growth factor (IGF) signaling and changes to omega-6 to omega-3 fatty acids ratios in cell membranes. For this reason, the primary outcome for the trial reported here was the change in fasting serum IGF-1 levels between the two groups. Several secondary outcomes (to be specified below) were examined by measuring biochemical markers.

Participants were recruited from patients diagnosed with localized prostate adenocarcinoma and scheduled for radical prostatectomy at least 4 weeks after entering the trial. Participants were excluded if they had taken 5-alpha reductase inhibitors or several other drugs that might interfere with the study's biomarkers, and had to

agree to stop all herbal remedies, nutritional supplements, and COX-2 inhibitors at least 1 week before the study.

The experimental intervention was designed to reduce overall fat consumption and shift the ratio of omega-6 to omega-3 fatty acids to 2:1. This was done via a low-fat diet (15% of calories from fat, 15% protein, 70% carbohydrate that included 39 g/d fiber) and supplementation with fish oil high in omega-3 fatty acids (five 1.1 gram fish oil capsules daily; each capsule contained 200 mg eicosapentaenoic acid and 367 mg docosahexaenoic). The control intervention was a Western diet, consisting of 40% of calories from fat, 15% protein, and 45% carbohydrate that included 15 g/d fiber. The omega-6 to omega-3 ratio was 15:1. All meals for both groups were prepared by the research team and delivered to the participants' homes. Unconsumed food and capsules were collected to measure compliance, which was excellent. Body weight and exercise levels were to remain unchanged. Participation lasted 4 to 6 weeks depending on when the prostatectomy was scheduled.

A power analysis was conducted which estimated that 70 participants were needed to detect a difference of 20% in serum IGF-1 levels between the groups with 80% power. After 48 subjects had completed the trial, an interim analysis showed that there was little chance that significant differences would be found for the primary outcome. Therefore, the study was ended early and secondary endpoint analyses carried out.

No significant differences were found between the groups in serum IGFBP-1, IGFBP-3, insulin, PSA levels, urine prostaglandin levels, COX-2 levels, or angiogenesis (CD-31). Comparing the Western diet and low-fat groups, respectively, triglyceride levels decreased by 13.6 and 56.5 mg/dL ($P = 0.03$) and cholesterol levels by 10.4 and 31.7 mg/dL ($P = 0.02$). Significant differences were found in the membrane levels of omega-6 and omega-3 fatty acids in benign and malignant prostate tissues and red blood cells. For example, the omega-6:omega-3 ratio in malignant tissues was 5.02 in the Western diet group and 2.68 in the low-fat group ($P < 0.001$). Proliferation of malignant cells was measured using Ki-67 and TUNEL methods. The former test showed significantly less proliferation in the low-fat group ($P < 0.05$), while the latter test showed no significant differences. Another proliferation test using subjects' serum and prostate cancer cell lines found significantly reduced proliferation in the low-fat group ($P = 0.039$).

The researchers concluded that the significant changes they found warranted further clinical trials with membrane omega-6:omega-3 ratios and malignant cell proliferation as the primary endpoints. Because these were not primary outcomes, however, they considered these results to be "hypothesis generating." If their current findings are validated, long-term trials of this low-fat, high omega-6 fatty acid intervention would be warranted.

■ COMMENTARY

As a Phase 2 trial, this study was relatively small and short, designed to show whether large-scale prospective trials were warranted. The study was rigorously designed and reported in great detail. The authors gave the rationale for their study design, based on preclinical studies conducted by their team and others. The lack of significant impact on IGF, COX-2, and prostaglandin outcomes raised questions about their postulated mechanism of action. The mechanism for the significant differences found in some of the cancer cell proliferation tests is unknown.

The authors discussed the study's strengths and limitations. Foremost among these was the study's short duration and their failure to recruit sufficient subjects as determined by their power analysis. The combined nature of the intervention meant that the influence of either the low-fat diet or the fish oil supplements could not be separated. In addition, the difference in carbohydrate content of the two diets may have had an impact, especially as this led to significant differences in the groups' fiber intake. The low-fat diet led to significantly greater reductions in cholesterol levels, and this could affect prostate cancer growth.

The most serious limitation with this study is the complex interplay of multiple factors and what is called multiple hypothesis testing.[2] When statistical significance is set at $P = 0.05$, there is a 1 in 20 chance of getting a false-positive. The chance of a false-positive increases with each additional outcome tested. For example, with five outcomes, the calculated chance of a false-positive is almost 1 in 4.2 This study had numerous secondary outcomes, so it is not surprising that some were significantly different. Statistical tests (e.g., the Bonferonni Correction) are available to take account of these factors to minimize the risk of false-positives, but these were not reported.

Although the original study authors were cautious about the study's implications and limitations, other reports have been much more enthusiastic. The study was conducted by researchers at the UCLA Jonsson Comprehensive Cancer Center. The Center's website posted a news item about the study and this publication.[3] The headline read that the diet intervention "Slows Growth of Prostate Cancer Cells." Only the significant results found in the study were discussed, and there was no mention that the study was stopped early because its primary outcome was unlikely to show significant benefit. This highlights the importance of studying original publications and not relying on news summaries of reports. As the primary investigator has stated, dietary changes for

prostate cancer patients cannot be recommended on the basis of this study, although it does provide support for further research in this area. ■

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Vitamin E and Prostate Cancer

ABSTRACT AND COMMENTARY

By Howell Sasser, PhD

Dr. Sasser is a scientific review coordinator with Manila Consulting Group, and an adjunct member of the faculty of New York Medical College. He reports no financial relationships relevant to this field of study.

Synopsis: *The SELECT Trial investigators report on nearly 10 years of follow-up of participants in a study of selenium and vitamin E and the risk of prostate cancer. A small but statistically significant increased risk of prostate cancer appears to be associated with taking vitamin E supplements. These results are in disagreement with others in the literature, and the authors present no plausible biological explanation for them. Nonetheless, the balance of evidence does not appear to support any recommendation that physicians advise their middle-aged and elderly patients to begin vitamin E supplementation for prostate cancer prevention.*

Source: Klein EA, et al. Vitamin E and the risk of prostate cancer: The Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA* 2011;306:1549-1556.

The role of antioxidants in the prevention of a variety of diseases has been an active and controversial area of research for many years. Findings have been mixed and methodological issues have often affected their interpretation. Among these problems has been a lack of appropriately powered randomized studies with long enough periods of follow-up to permit assessment of clinically relevant endpoints. Such studies are especially important for cancer research because of the — usually — long latency period between initiation and the development of detectable disease. The newly published results of the SELECT trial go some way to meet this need in the case of prostate cancer.[1]

Briefly, 34,887 men were assigned in a parallel fashion to selenium (200 μg/d) plus placebo, vitamin E (400 IU/day) plus placebo, both active agents, or neither (double placebo). All had prostate-specific antigen (PSA) levels of no more than 4 ng/ml and normal digital rectal exam (DRE) findings. Recruitment began in 2001 and blinded follow-up continued through October 2008. At that point, an interim analysis of the study findings showed a small (13%) excess in the hazard (time-adjusted risk) of prostate cancer among those receiving vitamin E. This finding was not statistically significant (HR = 1.13, 99% CI, 0.95 to 1.35), but was of adequate concern to lead the investigators to end the experimental component of the study, inform all parties of study treatment assignments, and continue follow-up.[2]

The newest results update follow-up through July 2011. All treatment combinations (selenium, vitamin E, and selenium plus vitamin E) now show elevated hazards of prostate cancer as compared with placebo, and the hazard associated with vitamin E is statistically significant (HR = 1.17, 99% CI = 1.004 to 1.36). The authors interpret their findings as adding weight to the argument that consumers should be skeptical of the health claims made for products not regulated as medications.

There are a number of methodological reasons why these findings are compelling. First, the sample size is very large, and follow-up is lengthy. The SELECT study recruited on a population basis, from numerous sites in the United States, Canada, and Puerto Rico. This increases confidence that selection bias was minimized. The study's use of National Cancer Institute and Department of Veterans' Affairs research networks as mechanisms for recruitment also adds confidence that the study had access to a diverse group of potential participants. The original study design envisioned follow-up of between 8 and 12 years. The combined blinded and unblinded follow-up intervals cover nearly 10 years. Given that all participants were between 58 and 68 years of age on enrollment, follow-up included much of the period in the life course when prostate cancer is of greatest clinical significance.

Also worth noting is the study's naturalistic design and — paradoxically — its apparent lack of impact on the findings. Physicians were not instructed to perform PSA tests or DREs at specific intervals, but rather to do these and other tests as indicated by normal clinical pro-

tocol based on the patient's age and the presence of other risk factors. Replication of typical clinical conditions improves the study's generalizability. This would have been especially important had the experimental interventions shown a beneficial effect, but is worth noting even in the absence of such a result. Equally important is the reported finding that the rates of PSA and DRE tests did not change after unblinding. It might have been assumed that unblinding, combined with the nature of the study's initial findings, would have led to more frequent testing among men known to have been in the experimental treatment arms. Greater testing frequency, in turn, might have led to an apparent excess of new cases among those being tested more often. Because this does not seem to have been the case, it is possible to combine the blinded and unblinded phases of follow-up, adding to the study's case-finding power.

It is also important to note a few limitations of the latest SELECT results. First, the authors' finding of an increased risk of cancer with vitamin E supplementation is in disagreement with other published findings and the authors are not able to present a biological rationale for it. As noted in the present paper, the Alpha-Tocopherol, Beta Carotene (ATBC) trial and the second Physicians' Health Study (PHS II) reported a reduction in risk and no change in risk with supplementation, respectively.[3,4] The ATBC dose was considerably smaller (roughly 75 IU/day as compared with 400 IU/day in SELECT) and the study population were all smokers. PHS II used the same dose as SELECT, but it was given only every other day. Nonetheless, all had populations of similar ages and studied supplementation of a similar duration, if not of the same intensity. This mix of similarities and differences makes a direct comparison of risk across studies difficult, but it does seem reasonable to conclude that the balance of evidence does not support the use of vitamin E in prostate cancer prevention.

A second issue also relates to biology and the theoretical model underlying the research question. All of these studies (SELECT, ATBC, PHS II) recruited participants who were at least 50 years of age — at least 58 in the case of SELECT. The most common proposed mechanism for antioxidants in cancer involves their role in preventing DNA damage through the scavenging of reactive oxygen species, a process that arguably begins much earlier in the life course. The role that antioxidants play late in the natural history of cancer may not be the same as, or as pronounced as, their role earlier on. SELECT did not collect information on earlier use of supplements or on diet, although care was taken to assure that participants were not taking concomitant doses of the agents in the study supplements.

This picture is further complicated by the apparent interaction of selenium and vitamin E observed in SELECT in the form of a smaller increased risk of cancer among those in the vitamin E plus selenium group as compared to that among those in the vitamin E only group. The authors hypothesized that selenium mitigated the negative effect of vitamin E but could offer no biological explanation for this either.

It can be argued that random assignment should have made most pre-trial and peri-trial factors irrelevant, but expected findings in any study should prompt questions about the assumptions on which it was built and around which randomization methods are designed.

Finally, from a statistical perspective, the finding of increased risk associated with vitamin E is significant but only by the smallest margin. In a large study, great precision is possible, but results must also be interpreted in light of the effect of the sample size on statistical outcomes. The lower bound of the relevant confidence interval (1.004) is expressed to a greater number of significant figures than any other in the paper. This undoubtedly represents an abundance of caution on the authors' part, but it should be noted that this would have been interpreted as a non-significant finding for any other reported measure.

Given all of this, what should a clinician recommend to his or her patients? There seems to be little evidence to suggest that vitamin E, consumed by men in the 50s and 60s, has much beneficial effect in preventing prostate cancer. The small, but marginally statistically significant, increase in risk associated with vitamin E in this study is of concern, but in the absence of a plausible biological rationale, should not be seen as alarming. If a patient is already taking vitamin E supplements for some other reason, it would be wise to discuss the potential risk it carries. If a patient is not taking vitamin E, this study provides no argument for why he should start, and at least a precautionary argument for why he should not. ■

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A Cool Head: Hypnosis and Hot Flashes

ABSTRACT & COMMENTARY

By Russell H. Greenfield, MD

Synopsis: *A randomized controlled trial of weekly clinical hypnosis sessions plus home self-hypnosis practice over 5 weeks for breast cancer survivors with hot flashes resulted in significant symptomatic improvement when compared to a matched group of women who received no additional treatment.*

Source: Elkins G, et al. Randomized trial of a hypnosis intervention for treatment of hot flashes among breast cancer survivors. *J Clin Oncol* 2011;26:5022-5026.

The authors of this prospective, randomized, controlled intervention trial had previously explored the potential for hypnotherapy to be an aid in the treatment of hot flashes in women. In response to promising pilot results they expanded their research, the result being the current examination.

Sixty adult women with a history of breast cancer and experiencing hot flashes were enrolled. Subjects had to have a history of primary breast cancer with no current detectable disease, ≥ 14 hot flashes per week for at least 1 month by self-report, and not receiving treatment for hot flashes, including mind-body therapies such as yoga. Women using anti-hormonal therapy (for example, tamoxifen) could participate provided drug dosage had remained stable over the previous month. Subjects were randomized to receive either clinical hypnosis (five weekly 50-minute sessions) or no treatment for 5 weeks. Subjects were then asked to complete a daily hot flash diary for 1 week prior to any intervention. Baseline and post-intervention (after 5 weeks) measures included the Hot Flash Related Daily Interference Scale (HFRDIS), Center for Epidemiologic Studies Depression Scale (CES-D), Hospital Anxiety and Depression Scale-Anxiety Subscale (HADS-A), and the Medical Outcomes Study Sleep Scale (MOS-Sleep Scale).

Hypnosis sessions followed a treatment manual developed specifically for the study, and were delivered by a PhD clinical psychologist who had completed > 40 hours of training with the principal investigator. Hypnotic suggestions for each session included hypnotic induction following a standardized script; "mental imagery" and suggestions for relaxation; mental imagery for coolness; deepening hypnosis and dissociation from hot flashes; positive suggestions and imagery for the future; self-hypnosis; and the alert, "In a few moments, return to conscious alertness." Subjects were instructed in home self-hypnosis and provided with a cassette tape recording of a hypnotic induction and guided in-home practice. While hypnotic induction followed a transcript, specific imagery for relaxation and imagery for coolness were individualized.

The major outcome of interest was a combination of hot flash frequency and hot flash score. Participants' number and severity of hot flashes per day was computed for the baseline and final week, as was severity of hot flashes (one point was given for each mild hot flash, two points for each moderate hot flash, three points for each severe hot flash, and four points for each very severe hot flash). Hot flash score was calculated by multiplying the week's severity average times the week's hot flash frequency. Self-report of the impact of hot flashes on daily activities was a secondary outcome measure.

Eight-six patients were screened, of which 26 either did not meet eligibility criteria or did not want to participate; thus, a total of 60 women were randomized. Some participants who had enrolled were either lost to follow-up (n = 3) or withdrew (n = 6); three had been assigned to the treatment group, six to the control group. Reasons for not completing the study included being too busy/no desire to continue for personal reasons (n = 7), and not able to be reached (n = 2). Baseline average number of hot flashes in the two groups was balanced, and the two groups were otherwise similar save for the fact there were a greater number of subjects with graduate degrees in the treatment group than would be expected by chance (P = 0.04); however, educational levels were evenly distributed between treatment and control groups among those who completed the study.

Using the HFRDIS scale, women rated the degree that hot flashes interfered with 10 different aspects of their lives (work, social activities, leisure activities, sleep, mood, concentration, relations with others, sexuality, enjoyment of life, overall quality of life). Overall impact was statistically significant ($F[10,29] = 4.73$; $P < 0.001$); at post-test, hot flashes interfered significantly less in the lives of women in the treatment group compared with those in the control group. Follow-up analyses of each item showed that all items were statistically significantly less interfering ($P < 0.05$) for those in the experimental group, with the exception of an item asking about interference with sexuality ($P = 0.124$). Those in the hypnosis group showed statistically significant improvements for both hot flash and interference score. Hot flash scores (frequency X average severity) decreased 68% from baseline to endpoint in the hypnosis arm ($P < 0.001$). The final measures of hot flashes in the hypnosis group when compared with controls revealed statistically significant lower scores on the multivariate hot flash outcome measure in the inter-

vention group, with an effect size of 0.479 (deemed high magnitude using conventional criteria). Results of the MOS-Sleep Scale at baseline and trial's end were statistically significant, with the hypnosis group experiencing improved sleep compared with both their own baseline scores and controls. Results from HADS-A and CES-D showed that subjects in the hypnosis arm had statistically significant improvements in both anxiety and depression compared with the control group.

The study authors concluded that hypnosis reduces hot flashes in female breast cancer survivors, and may also help relieve anxiety, enhance mood, and improve sleep.

COMMENTARY

The search for an effective non-hormonal approach to relieving hot flashes continues, and this time with some promising results. The background for the study is the widely acknowledged impairment in quality of life often associated with menopausal or medication-induced vasomotor symptoms. What some readers may not know is the extent to which women being treated for breast cancer may experience hot flashes — the study authors cite data suggesting the numbers are 78% of those receiving chemotherapy and 72% who take tamoxifen.[1] Imagine the cumulative impact of loss of sleep, mood changes, and impairment in concentration, to name but a few of the many stresses associated with hot flashes, on a woman trying to heal from breast cancer. Practitioners desperately try to help their patients find relief but candidate therapies that are both safe and generally effective have been far and few between. An intervention that not only works but that might also enhance self-reliance could be invaluable; in this regard, clinical hypnosis deserves further attention.

The placebo effect accompanies any intervention designed to relieve hot flashes. When teased out, however, the placebo effect does not typically exceed 30-40%; the current trial showed a 68% reduction in hot flash scores with hypnosis.

Not that the results are cut and dried. The fact that the intervention group had added attention and instruction alone might have a positive influence on symptoms, especially if the interactions were perceived to be caring in nature. There was also no placebo control, but the authors have begun a new trial to address this limitation.

A growing number of practitioners have attained certification in clinical hypnotherapy so the approach is becoming widely available. Hypnotherapists offer a therapy that is potentially effective, generally enjoyable for patients, and that within a short period of time can be performed by patients on their own. Trained hypnotherapists also recognize the contraindications to hypnosis, such as schizophrenia. Yes, further study is warranted, but this low-risk approach to relieving hot flashes and their troubling set of associated symptoms seems a therapeutic investment worth making. ■

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   a. 1 cup
   b. 2 cups
   c. 3-5 cups
   d. 6-8 cups
   e. > 10 cups

2. Some research on green tea (various forms) has found benefits for which of the following lipid parameters?
   a. Total cholesterol
   b. HDL cholesterol
   c. Triglycerides
   d, All of the above
   e. Both a and b

3. The SELECT trial showed an elevated risk of prostate cancer with:
   a. vitamin E alone.
   b. selenium alone.
   c. vitamin E plus selenium.
   d. neither vitamin E nor selenium.