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MEN'S HEALTH

ABSTRACT & COMMENTARY

The Pitfalls of Herbal Viagra

By Luke Fortney, MD

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

SYNOPSIS: Be wary of and avoid over-the-counter products that claim to boost libido and sexual function, particularly for erectile dysfunction, which are often of spurious quality and contaminated with PDE-5 analogues.
SOURCE: ElAmrawy F, ElAgouri G, Einoweam O, et al. Adulterated and counterfeit male enhancement nutraceuticals and dietary supplements pose a real threat to the management of erectile dysfunction: A global perspective. *J Diet Suppl* 2016;13:660-693.

Erectile dysfunction (ED) prevalence globally is high, and it is the most common sexual problem among men.[1] ED is defined with relative subjectivity as the inability to achieve or maintain a sufficient erection for satisfactory sex. Normally, an erection is stimulated by a combination of neurovascular, hormonal, and environmental factors beginning with sexual interest and desire (which is mediated predominantly by testosterone). Through parasympathetic activation, nitric oxide (NO) synthase in endothelial cells is activated to produce NO from the amino acid precursor L-arginine. With NO present, the corpus cavernosum is engorged with arterial blood as a result of smooth muscle endothelial relaxation while venous return is simultaneously restricted. Most ED treatments ultimately make use of this biological pathway and mechanism.

Although psychosocial factors, hormonal disorders, recreational drug abuse, and adverse effects from prescribed medications contribute to ED, the overall

Editor's Note

Dr. Fortney's review highlights the problems with mislabeled and/or adulterated dietary supplements. In the case of "herbal Viagras," it can be a common and dangerous problem. A further shame of this illegal marketing and distribution is to overshadow some of the legitimate work being done (and published) on some dietary supplements that may have efficacy for erectile dysfunction, including *Panax ginseng*, L-arginine, *Coryananthe yohimbe*, pycnogenol, and *Ginkgo biloba*.

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Summary Points

- In general, erectile dysfunction (ED) supplements are less effective and often less safe than cardiovascular lifestyle modifications and appropriate use of quality-controlled pharmaceutical options. However, there is some evidence that supports the judicious use of specific high-quality supplements in appropriate situations.
- The FDA continues to update and re-issue statements warning consumers to avoid ED supplements.
- Given the common practice of adulteration of over-the-counter ED proprietary products and for safety concerns, healthcare providers should counsel patients to avoid email promotions, internet advertisements, and convenience store products that claim to enhance male libido and sexual function. Quality products, proven by third-party certification and accompanied by expert medical supervision, should be the focus of prescribing and use.
- Recent developments in quality testing have revealed rampant adulteration of "natural" herbal supplements with synthetic PDE-5 analogues.

prevalence increases with age and, in many cases, is associated with poor cardiovascular health. With an aging population worldwide, a recent review by ElAmrawy et al highlighted the growing concern about counterfeit and adulterated nutraceuticals that claim to be effective, safe, and of natural origin.[2] Given the flood of products that have invaded global markets with little or no safety and quality control, great effort has been undertaken in recent years to develop cost-effective but efficient and effective laboratory techniques that test quality and determine adulteration of these nutraceuticals products.

■ COMMENTARY

The review article by ElAmrawy et al highlights a concerning trend among "natural" ED products that are now widely available via the internet.[2] In particular, trans-national pharmacies have aided the widespread sale and availability of various spurious products. What is alarming is that most (> 60%) of these products are adulterated with active pharmaceutical ingredients but are mislabeled as "natural," which is a significant health hazard for consumers.[3] For example, *Eurycoma longifolia*, an herbal product from a flowering plant native to Indonesia and Malaysia, has been marketed as an "herbal Viagra," but this and many other "natural" products have been found to contain sildenafil (Viagra) or similar synthetic analogues.[4] That said, one recent meta-analysis of 139 participants concluded that daily use of *Eurycoma* over the 12-week study may improve mild ED symptoms but failed to show improvement in more severe cases.[5]

Another recent product analysis study found that three different nutraceutical products contained unregistered synthetic phosphodiesterase type 5 inhibitor (PDE-5) analogues.[6] These contaminants are variants of sildenafil, in particular dimethylsildenafil, thiodimethylsildenafil, and thiomethisosildenafil. Another recent analysis study of one "all-natural" product found similar results.[7] Not only was the product adulterated with PDE-5 synthetic analogues, but different capsules also contained unreliable and varying concentrations. Another analysis study from 2013 found that among 20 different dietary supplements for ED, eight contained actual sildenafil while another was found with nor-acetildenafil (another synthetic sildenafil analogue).[8]

Similarly, in 2013, a study coordinated by Pfizer Global Security obtained and analyzed 91 different "herbal" or "natural" ED supplements from various convenience stores and gas stations in the United States.[9] Sixty-two products claimed to be manufactured in the United States, while 15 were from unspecified "Asian" origin. The remaining 14 products did not clearly identify the country of manufacturing origin. Although

no product made claim to inclusion of synthetic PDE-5 substances, 74 (81%) were found to contain pharmaceutical PDE-5 ingredients or synthetic analogues. What was particularly frightening is that 18 of these products contained more than 110% of the highest FDA-approved medication strength of sildenafil or tadalafil (Cialis). There was also pronounced variability of contents between samples of the same product, indicating poor quality control. Perhaps most concerning, only 14 products warned against concomitant nitrate medication use.[9]

NUTRACEUTICAL OPTIONS

In the context of a healthy lifestyle the following supplements can be considered adjunctive treatment options for some men.[10] Look for GMP (good manufacturing practice) and USP (United States Pharmacopeia) quality assurance labels on reputable products):

- Yohimbine: 5 to 10 mg daily as needed
- *Panax ginseng*: 500 to 1000 mg daily as needed
- L-arginine: 1000 to 2000 mg daily as needed
- Propionyl-L-carnitine: 1000 mg daily as needed

ED PREVENTION PRESCRIPTION[10]

- Exercise at least three hours a week to maintain a body mass index < 30 kg/m^2.
- Follow a healthy, calorie-controlled, Mediterranean-style diet that is rich in fruits and vegetables, omega-3 fatty acids, whole-grains, nuts, seeds, and legumes.
- Reduce stress through exercise, rest, meditation, breathing exercises, yoga, journaling, etc.
- Maintain healthy sexual relationships with good communication.
- Avoid tobacco, heavy alcohol use, marijuana, and recreational drug use.
- Avoid highly processed foods that contain high amounts of "anti-nutrients" (e.g., high-fructose corn syrup, trans-fats, artificial sweeteners/colors/preservatives, etc).
- Avoid over-exposure to pesticides and herbicides, and overuse of chemical or cleaning products.
- Avoid heating or storing food in plastics (e.g., endocrine and hormone disruptors such as bisphenol-A). ■

RESOURCES

http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm048386.htm

REFERENCES

1. Bacon CG, et al. Sexual function in men older than 50 years of age: Results from the health professionals follow-up study. *Ann Intern Med* 2003;139:161-168.
2. ElAmrawy F, et al. Adulterated and counterfeit male enhancement nutraceuticals and dietary supplements pose a real threat to the management of erectile dysfunction: A global perspective. *J Diet Suppl* 2016;13:660-693.
3. Cohen PA, Venhuis BJ. Adulterated sexual enhancement supplements: More than mojo. *JAMA Intern Med* 2013;173:1169-1170.
4. Said MM, et al. Rapid detection of sildenafil analogue in *Eurycoma longifolia* products using a new two-tier procedure of the near infrared (NIR) spectra database. *Food Chem* 2014;158:296-301.
5. Kotirum S, et al. Efficacy of Tongkat Ali (*Eurycoma longifolia*) on erectile function improvement: Systematic review and meta-analysis of randomized controlled trials. *Complement Ther Med* 2015;23:693-698.
6. Bortolini C, et al. "One-shot" analysis of PDE-5 inhibitors and analogues in counterfeit herbal natural products using an LC-DAD-QTOF system. *Anal Bioanal Chem* 2015;407:6207-6216.
7. Schramek N, et al. Pyrazolopyrimidines in "all-natural" products for erectile dysfunction treatment: The unreliable quality of dietary supplements. *Food Addit Contam* 2015;32:127-140.
8. Shi F, et al. Application of a high resolution benchtop quadrupole-Orbitrap mass spectrometry for the rapid screening, confirmation and quantification of illegal adulterated phosphodiesterase-5 inhibitors in herbal medicines and dietary supplements. *J Chromatogr A* 2014;1344:91-98.
9. Campbell N, et al. Adulteration of purported herbal and natural sexual performance enhancement dietary supplements with synthetic phosphodiesterase type 5 inhibitors. *J Sex Med* 2013;10:1842-1849.
10. Fortney L. Erectile Dysfunction. In: *Integrative Medicine*, 3rd ed. Rakel D, ed. Philadelphia: Saunders/Elsevier; 2012.

SPECIAL FEATURE

The Effects of Coffee Consumption on Health Outcomes

By Nancy J. Selfridge, MD

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

Worldwide, coffee is the second most consumed beverage after water. Chosen because of its rich complex flavors and pleasant stimulating effects, recent research suggests potential health benefits, including risk reductions for cardiovascular disease, cancers, diabetes, and Parkinson's disease. The global consumption statistics suggest that the public health effect of coffee consumption could be significant, even if the effect on an individual consumer is small.

Summary Points

- Brewed coffee contains many biologically active substances with antioxidant and other putative positive effects on human physiology.
- Meta-analyses of pooled data have shown mostly inverse associations of moderate coffee consumption of 2-5 cups/day and risk of all-cause mortality, cancers, cardiovascular disease, and several other diseases.
- Higher levels of coffee consumption appear to be associated with increased fracture risk, increased risk of bladder cancer, and an increased risk of gastric cancer in U.S. consumers.

Roasted coffee beans and the various brews derived from them contain many bioactive substances with potentially beneficial and detrimental effects on health. A summary of the biologically active classes of compounds and their putative effects is shown in Table 1.[1] Varying concentrations of substances in the variety of coffee preparations available, confounded by the fact that most of the substances are highly metabolized after consumption and do not reach significant plasma concentrations, dictate that the mechanisms of any observed beneficial effects remain obscure.

It is clear that describing coffee's benefits as primarily due to antioxidant effect is an oversimplification.[1] Coffee has been touted as an unhealthy beverage in the past based on epidemiologic studies published between 1980 and 2000, suggesting a possible association with increased risk of fractures, hypertension, and some cancers. However, more recent research has not supported these early conclusions. Several analyses of cumulative data form the focus of this review.

COFFEE CONSUMPTION AND ALL-CAUSE MORTALITY

Numerous epidemiological studies have investigated the effect of coffee consumption on health and disease. Analyzing pooled data often helps clarify or confirm statistical associations when an effect size is small and individual studies are not adequately powered or differ in methodology. Four recent publications have done just this, looking at coffee consumption and all-cause mortality. Malerba et al analyzed data from 23 prospective cohort studies comparing relative risk (RR) of all-cause mortality of the lowest coffee consumption (≤ 1 cup per day) to moderate (1-3 cups/day) and high (> 3 cups/day) consumption, using random-effects models for the heterogeneity in the studies.[2] The RR of highest consumption vs. lowest consumption categories was 0.88 (95% confidence interval [CI], 0.84-0.93) for all studies and was 0.87 (95% CI, 0.82-0.93) for the 19 studies that adjusted for smoking.[2]

Je and Giovanucci included 20 of the same studies in their analysis,[3] all controlling for smoking, and as well as two earlier studies not considered in the Malerba analysis. These authors indicated that their pooled studies included 973,904 participants and 129,538 deaths. They similarly defined lowest coffee consumption as < 1 cup/day and moderate intake as 1-2 cups/day, but they stratified high consumption as 2-4 cups per day and 5-9 cups per day based on the variations in this definition in the original research publications. Pooled RR for total mortality comparing high vs. low consumption was 0.86 (95% CI, 0.80-0.92), and this result did not vary at all using the two different definitions of high consumption. Moderate coffee consumption was associated with a weak inverse association, RR 0.92 (95% CI, 0.87-0.98). Interestingly, these authors noted that associations differed according to geographical region, with European studies showing the strongest inverse association, followed by Japan, and finally by the United States.[3]

Crippa et al conducted a similar analysis of 21 prospective cohort studies, including four studies not included in the analyses above.[4] Again, all chosen studies adjusted risk for smoking and assessed risk based on three categories of coffee consumption. But unlike the other analyses, which assessed highest to lowest category relative risks, these authors performed a dose-response meta-analysis and reported risk reductions for total mortality, cardiovascular disease, and cancer deaths. Pooled data included 997,464 participants and 121,915 deaths. The authors reported strong evidence of a nonlinear inverse association between coffee consumption and mortality due to all causes and cardiovascular disease ($P < 0.001$). In the dose-response analysis, 4 cups/day showed the largest risk reduction for all-cause mortality (16%; 95% CI, 13-18) and 3 cups/day showed the largest risk reduction for cardiovascular disease mortality (21%; 95% CI, 16-26). There was no association between coffee consumption and cancer mortality.[4]

Ding et al examined associations between coffee consumption and total and cause-specific mortality in pooled data from three large cohort studies: the Nurses' Health Study, the Nurses' Health Study II, and the Health Professionals Follow-up Study. Total participants numbered 124,821 and there were 31,956 deaths over 4,690,072 person years of follow-up. Hazard ratios were reported instead of RRs, and these data sets included periodic updates of coffee consumption through food frequency questionnaires. Compared to no coffee consumption, hazard ratios for death were as follows: 0.95 (95% CI, 0.91-0.99) for ≥ 1 cup per day, 0.91 (95%

Table 1: Major Compound Classes in Coffee and Their Characteristics[1]

Compound Class	Qualities/Mechanisms	Putative Physiologic Effects
Chlorgenic acids	Powerful antioxidants in vitro; may modulate cell-signaling pathways, increasing phase II enzyme activity; effects may be due more to metabolites and catabolites than to original compounds in coffee	Anticarcinogenic; antithrombotic; anti-inflammatory; enhanced endothelial function; altered glucose metabolism; antimicrobial
Melanoidins	Produced by roasting process; behave as dietary fiber: largely indigestible and fermented in gut	Antioxidant; metal chelating; antimicrobial; anticariogenic; modulate colonic microflora; antihypertensive; antiglycative
Caffeine	Concentration in coffee beverages varies significantly; rapidly absorbed in the gut and distributed to all tissues; adenosine receptor antagonist (stimulates release of dopamine); synergistic interactions with epinephrine and norepinephrine; may protect cell membranes against oxidative stress	Increases metabolic rate and energy expenditure; increases lipid oxidation and lipolysis; increased heart rate and blood pressure; CNS stimulation enhances alertness, perception, memory consolidation, may cause sleeplessness; possible reduced fetal growth at higher levels of intake
Trigonelline	Absorption starts in stomach; pass through body to be excreted in urine without substantial phase II metabolism; regulates key enzymes of glucose and lipid metabolism	Hypoglycemic; neuroprotective; anti-invasive; estrogenic; antimicrobial
Diterpenes (cafestol and kahweol)	Abundant in boiled and unfiltered coffees, absent in filtered coffees; fatty acyl esters; may induce phase II detoxifying enzymes	Raise serum cholesterol; chemopreventive; enhance defense against oxidative damage

CI, 0.88-0.95) for 1.1-3 cups/day, 0.93 (95% CI, 0.89-0.97) for 3.1-5 cups/day, and 1.02 (95% CI, 0.96-1.07) for > 5 cups/day. This non-linear association changed to a linear inverse association when restricting the analysis to never smokers ($P < 0.001$).[5]

Recently, several meta-analyses looking at the associations between coffee consumption and specific disease risk have been published. These are summarized below.

CARDIOVASCULAR DISEASE

Ding at al performed a dose-response meta-analysis on 36 prospective cohort studies (including many of the studies cited in the analyses of all-cause mortality, above) investigating the relationship between coffee consumption and risk of cardiovascular disease, including coronary heart disease, heart failure, stroke, and cardiovascular disease mortality. The pooled data included 1,279,804 participants and 36,352 cases of cardiovascular disease. RR of developing cardiovascular disease compared to the lowest intake category (< 1 cup/day) was 0.95 for 5 cups per day (95% CI, 0.87-1.03), 0.85 for 3.5 cups per day (95% CI, 0.80-0.90), and 0.89 for 1.5 cups/day (95% CI, 0.84-0.94).[6] Mostofsky et al looked at coffee consumption and heart failure risk, performing a dose-response meta-analysis on five prospective cohort studies that consisted of 140,220 participants and 6,522 incidents of heart failure. They found an inverse relationship for coffee consumption up to 9-10 servings per day, with the lowest risk for 3-4 servings per day, RR 0.89 (95% CI, 0.81-0.99). More than 10 servings per day was associated with RR > 1.0.[7] Thus, even high coffee intake of up to 10 servings per day appears to have a protective effect for cardiovascular disease, with 3-4 cups per day associated with the lowest risk.

STROKE

Larsson and Orsini analyzed 11 prospective studies to assess the association between coffee dose and stroke risk. Pooled data included 479,689 participants and 10,003 cases of stroke. Risk for each category of consumption was compared to no consumption. RR was 0.86 (95% CI, 0.78-0.94) for 2 cups/day, 0.83 (95% CI, 0.74-0.92) for 3-4 cups/day, 0.87 (95% CI, 0.77-0.97) for 6 cups/day, and 0.93 (95% CI, 0.79-1.08) for 8 cups/day.[8] Kim at al arrived at similar risks comparing only highest to lowest intake categories for nine studies, six of which were included in Larsson's analysis above: RR 0.83 (95% CI, 0.76-0.91).[9]

FRACTURE RISK

Lee et al performed a dose-response meta-analysis to assess coffee consumption and risk of fracture. Nine prospective cohort studies and six case-control

studies were included with pooled data from 253,514 participants and 12,939 fracture cases. They found that the RR of fracture comparing highest to lowest categories of consumption was 1.14 (95% CI, 1.05-1.24) for women and 0.76 (95% CI, 0.62-0.94) for men. RR for women increased from 1.02 (95% CI, 1.01-1.04) to 1.54 (95% CI, 1.19-1.99) for 2 cups/day and 8 cups/day, respectively.[10] Li et al assessed 10 prospective cohort studies (five in common with Lee, above) for coffee and hip fracture risk. Highest coffee consumption (2-9 cups/day) compared to lowest (never to seldom) was associated with an RR of 1.13 (95% CI, 0.86-1.48).[11] Both of these analyses included studies involving participants who were middle-aged and elderly, so menopausal women, a cohort with significant osteoporosis and fracture risk, were included. Although coffee consumption is associated with an increase in urinary calcium excretion, it appears that there is no increased risk of fracture for men, and a negligible risk for women at around 2 cups/day, which may increase with higher daily doses.

CANCER

Since cancers are much less common than cardiovascular events, the large participant and event numbers from pooled data have been especially helpful in determining how coffee consumption may be associated with risks.

Gastric cancer: Five recent meta-analyses of coffee consumption and gastric cancer risk concluded that there was no association or a low positive association.[12,13,14,15,16] All of these authors included most of the same prospective cohort studies in their analyses. Results by Li et al were representative: comparing to lowest coffee consumption (< 1 cup/day), RR was 1.13 (95% CI, 0.94-1.35).[16] Two of these papers included subgroup analyses indicating that RR for participants from the United States was higher, 1.36 (95% CI, 1.06-1.75), despite the known fact that coffee consumption is much higher in European countries.[12,13] Authors believed that these differences might be due to genetic factors influencing gastric cancer risk or to artifact due to limited statistical power for the sub-analyses and that further studies were warranted. Coffee consumption may be associated with an increased risk of gastric cancer in the United States, but not in other countries included in these studies.

Breast cancer: Li et al analyzed pooled data from 26 published articles including 863,096 participants and 49,497 breast cancer cases from both prospective cohort and case-control studies. Results of this and previous meta-analyses were similar. RR of breast cancer comparing lowest and highest consumption of coffee was 0.96 (95% CI, 0.93-1.00), an insignificant association.[17] They noted that RR was slightly higher for premenopausal cancers (1.00) and slightly lower for postmenopausal cancers (0.92). A more recent meta-analysis of 37 studies yielded similar results, but the authors noted that an inverse association of coffee consumption with breast cancer risk was found for BRCA1 mutation carriers (RR = 0.69; $P < 0.01$).[18]

Prostate cancer: Cao et al included 10 prospective cohort studies with 206,096 participants and 8,973 cases of prostate cancer in their recent meta-analysis.[19] An inverse association between coffee consumption and prostate cancer was noted with pooled RR, compared to non- or seldom drinkers, of 0.88 (95% CI, 0.82-0.95). Thus, coffee consumption appears to slightly reduce the risk of prostate cancer.

Pancreatic cancer: A recent meta-analysis of 20 cohort studies by Ran et al reported a RR for highest vs. lowest coffee consumption and pancreatic cancer of 0.75 (95% CI, 0.63-0.86).[20] This analysis included three more studies than a previous publication by Turati et al, in which the pooled RR for cohort studies was 1.04 (95% CI, 0.80-1.36).[21] Despite a sentinel case-control study published in 1981 showing a positive association between coffee consumption and pancreatic cancer, cumulative data consistently demonstrate no increased risk and possibly a protective effect.

Colorectal cancer: Gan et al analyzed 19 prospective cohort studies (2,046,575 participants and 22,629 cases of colorectal cancer) to assess risk associated with coffee consumption. Pooled RR for highest vs. lowest consumption categories was 0.98 (95% CI, 0.90-1.06). However, dose-response analysis demonstrated that higher levels of consumption were associated with lower risk: RR was 0.93 (95% CI, 0.89-0.99) for 6 cups/day, 0.90 (95% CI, 0.85-0.97) for 7 cups/day, and 0.87 (95% CI, 0.80-0.95) for 8 cups/day.[22]

Other cancers: Liu et al reported a pooled RR of 0.81 (95% CI, 0.68-0.97) in an analysis of five cohort studies and two case-control studies assessing coffee and melanoma risk. This inverse association existed only for caffeinated coffee.[23] Oral cancer RR was reported to be 0.69 (95% CI, 0.54-0.88) in an analysis of 12 prospective cohort and case-control studies.[24] Sang et al assessed 16 case-control and prospective cohort studies for liver cancer risk. Pooled RR for highest vs. lowest coffee consumption was 0.50 (95% CI, 0.42-0.59). Of interest is that the RR was 0.39 (95% CI 0.28-0.54) with no adjustment for a history of liver disease and 0.54 (95% CI, 0.46-0.66) after adjusting for a history of liver disease, indicating a potentially protective effect even for those patients at higher risk of developing liver cancer.[25] Wu et al analyzed 34 case-control and six cohort studies to assess risk of bladder cancer. Odds ratios were reported due to the large number of case-control studies. Pooled OR for highest vs. lowest consumption was

Table 2: Associations Between Coffee Consumption and Various Conditions

Condition	Effect Compared to Little or No Consumption	Optimal Dose*
All-cause mortality	Reduced risk, benefits may diminish at > 5 cups/day for women	3-4 cups/day
Cardiovascular disease	Reduced risk up to 10 cups/day	3-4 cups/day
Stroke	Reduced risk up to 8 cups/day	3-4 cups/day
Fracture risk	Reduced risk for men up to 8 cups/day Insignificant risk for women up to 2 cups/day Increased risk for women > 2 cups/day	N/A
Gastric cancer	Small increased risk, greatest in consumers in the United States	N/A
Breast cancer	Reduced risk in BRCA1 mutation carriers Risk otherwise not affected	N/I
Prostate cancer	Reduced risk	N/I
Pancreatic cancer	Reduced risk	N/I
Colorectal cancer	Reduced risk	8 cups/day
Melanoma	Reduced risk[§]	N/I
Oral cancer	Reduced risk	N/I
Liver cancer	Reduced risk	N/I
Bladder cancer	Increased risk[¥]	N/A
Endometrial cancer	Reduced risk	N/I
Type 2 diabetes	Reduced risk	6 cups/day
Urolithiasis	Reduced risk	N/I
Parkinson's disease	Reduced risk	N/I
Depression	Reduced risk	N/I
Alzheimer's disease	Reduced risk	N/I

*Where coffee consumption is associated with a reduced risk, the dose associated with the lowest risk is presented when provided in analyses
N/A = Not applicable; N/I = Not indicated; [§]Only noted for caffeinated coffee intake; [¥]Greatest risk noted in non-smokers

1.33 (95% CI, 1.19-1.48). In this analysis, odds ratios were actually higher in non-smokers, 1.72 (95% CI, 1.25-2.35), vs. smokers, 1.24 (95% CI, 0.91-1.70). The authors hypothesized that this might be due to smoking effects on caffeine metabolism.[26] Zhou et al explored coffee consumption and risk of endometrial cancer in a meta-analysis. Pooled RR from 13 studies including 1,534,039 participants and 10,100 cases of endometrial cancer comparing highest and lowest consumption categories was 0.66 (95% CI, 0.52-0.84) for caffeinated coffee and 0.77 (95% CI, 0.63-0.94) for decaffeinated coffee.[27]

Other diseases: An updated meta-analysis of 29 prospective studies, including 1,109,272 participants and 45,335 cases of type 2 diabetes, demonstrated an inverse association that was dose related. RR was reported at 0.92 (95% CI, 0.90-0.94) for 1 cup/day and 0.67 (95% CI, 0.61-0.74) for 6 cups/day. These findings were consistent with earlier meta-analyses.[28] Coffee consumption showed an inverse association with urolithiasis in a meta-analysis by Wang et al: odds ratio 0.70 (95% CI, 0.60-0.82).[29] An inverse association was also noted for Parkinson's disease: RR 0.72 (95% CI, 0.6-0.81).[30] Pooled RR for coffee and depression in a meta-analysis by Wang et al was 0.75 (95% CI, 0.62-0.91).[31] Habitual coffee consumption and dementia risk was reported by Liu et al, who noted a significant inverse relationship between highest levels of coffee consumption and Alzheimer's disease, RR 0.73 (95% CI, 0.55-0.97).[32]

The associations between coffee consumption and various conditions presented earlier is summarized in Table 2.

DISCUSSION

A plethora of meta-analyses have been published recently assessing the association of coffee consumption with risk of various disease and mortality. An inverse association (potentially protective effect) has been noted for all-

cause mortality, cardiovascular disease including stroke, breast cancer in BRCA1 mutation carrying women, prostate cancer, colorectal cancer, pancreatic cancer, oral cancer, liver cancer, melanoma, endometrial cancer, type 2 diabetes, Parkinson's disease, urolithiasis, depression, and Alzheimer's disease. No significant association has been noted for breast cancer in pre- and postmenopausal women and gastric cancer in non-U.S. consumers. A small increased risk of fracture in women is associated with coffee intake and it appears to increase at higher levels of consumption. Significant positive associations have been noted for gastric cancer in U.S. consumers and for bladder cancer.

Several meta-analyses have investigated the associations between coffee consumption and pregnancy outcomes, but these studies are beyond the scope of this present review. Omitting conclusions relevant to pregnant women, in general, coffee consumption is not associated with significant risk of adverse health outcomes or death, with the exceptions noted above, and it may have some protective effect against certain cancers and diseases. The reported studies all had similar limitations. Associations in observational studies tell us nothing about causation, and we can only hypothesize about reasons and mechanisms.

Moderate heterogeneity, which can influence the reliability of the analyses, frequently was reported in the studies. Adjustment for all possible confounders in the original studies could hamper results, although many did adjust for the significant confounder of smoking status, which has been strongly associated with high coffee consumption. In addition, patients with chronic diseases may reduce coffee consumption voluntarily, yet baseline health status would affect outcomes independent of coffee consumption. All studies used Food Frequency Questionnaires and self-reporting for stratifying coffee consumption, which was generally given in cups per day or cups per week, both contributing to potential measurement errors. Coffee type (Arabica vs. Robusta) and method of preparation (boiled, steeped, filtered, percolated) were not specified; these affect the quantities and proportions of biologically active substances in coffee and could affect outcomes. Finally, coffee consumption may have other confounding aspects that could affect health outcomes. Many people drink coffee in social settings or while "taking a coffee break" and experience true pleasure associated with the coffee drinking experience. There may be psychosocial aspects intrinsic to these contexts that contribute to a beneficial effect of coffee on health outcomes.

RECOMMENDATIONS

Based on a significant amount of data, we can safely say that coffee consumption poses no significant health hazards for a given individual who is otherwise healthy, and where there is no concern for development of gastric cancer or bladder cancer. Women at risk for fracture, especially those with osteoporosis or osteopenia, should be informed of the increased risk of fracture associated with coffee consumption of > 2 cups/day. Statistics and what is known about the putative effects of the biologically active chemicals in coffee suggest that it may be a health-promoting beverage. People who enjoy their daily coffee consumption without suffering adverse effects, such as jitteriness, insomnia, dyspepsia or palpitations, can be reassured that they don't need to give this up, though moderate intake of 3-4 cups/day appears a most wise limit. However, it is premature to suggest coffee as a preventive or therapeutic intervention until more is understood about the mechanisms of its impact on health and disease. ■

REFERENCES

1. Ludwig IA, et al. Coffee: Biochemistry and potential impact on health. *Food Funct* 2014;5:1633-1978.
2. Malerba S, et al. A meta-analysis of prospective studies of coffee consumption and mortality for all causes, cancers and cardiovascular disease. *Eur J Epidemiol* 2013;28:527-539.
3. Je Y, et al. Coffee consumption and total mortality: A meta-analysis of twenty prospective cohort studies. *Br J Nutr* 2014;111:1162-1173.
4. Crippa A, et al. Coffee consumption and mortality from all causes, cardiovascular disease and cancer: A dose-response meta-analysis. *Am J Epidemiol* 2014;180:763-775.
5. Ding M, et al. Association of coffee consumption with total and cause-specific mortality in 3 large prospective cohorts. *Circulation* 2015;132:2305-2315.
6. Ding M, et al. Long-term coffee consumption and risk of cardiovascular disease: A systematic review and dose-response meta-analysis of prospective cohort studies. *Circulation* 2014;129:643-659.
7. Mostofsky E, et al. Habitual coffee consumption and risk of heart failure: A dose-response meta-analysis. *Circ Heart Fail* 2012;5:401-405.
8. Larsson SC, et al. Coffee consumption and risk of stroke: A dose-response meta-analysis of prospective studies. *Am J Epidemiol* 2011;174:993-1001.
9. Kim B, et al. Coffee consumption and stroke risk: A meta-analysis of epidemiologic studies. *Korean J Fam Med* 2012;33:356-365.
10. Lee DR, et al. Coffee consumption and risk of fractures: A systematic review and dose-response meta-analysis. *Bone* 2014;63:20-28.
11. Li S, et al. Effect of coffee intake on hip fracture: A meta-analysis of prospective cohort studies. *Nutr J* 2015;14:38-44.
12. Zeng SB, et al. Long-term coffee consumption and risk of gastric cancer. A PRISMA-compliant dose-response meta-analysis of prospective cohort studies. *Medicine* 2015;94:e1640.
13. Xie F, et al. Coffee consumption and risk of gastric cancer: A large updated meta-analysis of prospective cohort studies. *Nutrients* 2014;6:3734-3746.
14. Liu H, et al. Effect of coffee consumption on the risk of gastric cancer: A systematic review and meta-analysis of prospective cohort studies. *PLoS ONE* 2015;5:e0128501.
15. Shen Z, et al. Coffee consumption and risk of gastric cancer: An updated meta-analysis. *Clin Res Hepatol Gastroenterol* 2015;39:245-53.
16. Li L, et al. Coffee consumption and the risk of gastric cancer: A meta-analysis of prospective cohort studies. *BMC Cancer* 2015;15:733.
17. Li X J, et al. Coffee consumption and risk of breast cancer: An up-to-date meta-analysis. *PLoS One* 2013;8:e52681.
18. Jiang W, et al. Coffee and caffeine intake and breast cancer risk: An updated dose-response meta-analysis of 37 published studies. *Gynecol Oncol* 2013;129:620-629.
19. Cao S, et al. Coffee consumption and risk of prostate cancer: A meta-analysis of prospective cohort studies. *Carcinogenesis* 2014;35:256-261.

20. Ran HQ, et al. Coffee consumption and pancreatic cancer risk: An update meta-analysis of cohort studies. *Pak J Med Sci* 2016;32: 253-259.
21. Turati F, et al. A meta-analysis of coffee consumption and pancreatic cancer. *Ann Oncol* 2012;23:311-318.
22. Gan Y, et al. Association of coffee consumption with risk of colorectal cancer: A meta-analysis of prospective cohort studies. *Oncotarget* 2016; doi: 10.18632/oncotarget.8627. [Epub ahead of print]
23. Liu J, et al. Higher caffeinated coffee intake is associated with reduced malignant melanoma risk: A meta-analysis study. *PLoS One* 2016;11:e0147056.
24. Zhang Y, et al. Association between coffee consumption and the risk of oral cancer: A meta-analysis of observational studies. *Int J Clin Exp Med* 2015;8:11657-11665.
25. Sang LX, et al. Consumption of coffee associated with reduced risk of liver cancer: A meta-analysis. *BMC Gastroenterol* 2013;13:33-46.
26. Wu W, et al. Coffee Consumption and bladder cancer: A meta-analysis of observational studies. *Sci Rep* 2015;5:9051-9059.
27. Xhou Q, et al. Coffee consumption and risk of endometrial cancer: A dose response meta-analysis of prospective cohort studies. *Sci Rep* 2015;5:13410-13422.
28. Ding M, et al. Caffeinated and decaffeinated coffee consumption and risk of type 2 diabetes: A systematic review and dose-response meta-analysis. *Diabetes Care* 2014;37:569-586.
29. Wang S, et al. A meta-analysis of coffee intake and risk of urolithiasis. *Urol Int* 2014;93:220-228.
30. Qi H, et al. Dose-response meta-analysis on coffee, tea and caffeine consumption with risk of Parkinson's disease. *Geriatr Gerontol Int* 2014;14:430-439.
31. Wang L, et al. Coffee and caffeine consumption and depression: A meta-analysis of observational studies. *Aust N Z J Psychiatry* 2016;50:228-242.
32. Liu QP, et al. Habitual coffee consumption and risk of cognitive decline/dementia: A systematic review and meta-analysis of prospective cohort studies. *Nutrition* 2015;15:doi: 10.1016/j.nut.2015.11.015. [Epub ahead of print]

CANCER

ABSTRACT & COMMENTARY

Mediterranean Diet and Breast Cancer

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

SYNOPSIS: A Mediterranean diet supplemented with the consumption of one liter of extra-virgin olive oil per week may be beneficial in the primary prevention of breast cancer.

SOURCE: Toledo E, Salas-Salvado J, Donat-Vargas C, et al. Mediterranean diet and invasive breast cancer risk among women at high cardiovascular risk in the PREDIMED trial: A randomized clinical trial. *JAMA Intern Med* 2015;175:1752-1760.

Breast cancer is the leading cause of cancer among women. World estimates since 2008 have showed a 20% increase in breast cancer incidence and a 14% increase in mortality.[1] There is an inconsistent association between diet and breast cancer, with high alcohol consumption being the only convincing risk factor in women.[2]

The Mediterranean diet (MedDiet) consists of an abundance of plant foods, fish, and olive oil.[3] The potential benefits of a MedDiet may be partly explained by reduction in oxidative DNA damage. Olive oil has a high supply of monounsaturated fatty acids, mainly oleic acid and squalene. Additionally, extra-virgin olive oil (EVOO) has various biologically active compounds, such as the polyphenols oleocanthal, oleuropein, hydroxytyrosol, and lignans. In vitro studies have suggested that oleic acid has an antiproliferative effect by affecting the expression of human oncogenes.[4] The hydrocarbon squalene has been reported to have intracellular oxidative stress and DNA oxidative damage in mammary epithelia cells.[5] Oleocanthol has been associated with inhibition of tumor growth, proliferation, migration, and invasiveness in breast cancer cells in in vivo models.[6] Finally, lignans are phytoestrogens whose consumption has been associated with a lower risk of breast cancer in postmenopausal women.[7]

One secondary outcome of the Lyon Diet Heart Study showed a 61% lower risk of all subtypes of cancer in participants following a MedDiet compared to controls, who followed the American Heart Association diet.[8]

Summary Points

- Breast cancer incidence has increased by 20% since 2008.
- Dietary intervention involving a Mediterranean style diet supplemented with extra-virgin olive oil (1 L/week) may be a useful primary prevention strategy among white postmenopausal women.
- Longer term and larger studies with this intervention as a primary outcome are needed to confirm these findings.

Toledo et al sought to examine the effects of the MedDiet on breast cancer risk, and specifically, the effects of EVOO or nuts in the randomized intervention of the PREDIMED trial on the incidence of breast cancer.

The study was conducted within the frame of the PREDIMED trial, which was designed as a multicenter, single-blind, randomized, controlled trial to test the effects of MedDiet on the primary prevention of cardiovascular disease. The study was conducted between 2003-2009 at primary care clinics in Spain. The median follow-up was 4.8 years, and the trial was stopped because of early evidence of cardiovascular benefit. In this study, 4,282 women between 60 and 80 years of age who were at high risk of cardiovascular disease were randomly allocated to MedDiet supplemented with EVOO (1 L/week), a MedDiet supplemented with mixed nuts (30 g/day; 15 walnuts, 7.5 g hazelnuts, and 7.5 g almonds), or a control arm (advice to reduce dietary fat). Energy restriction or physical activity was not specifically promoted in any group. For this study, one woman was excluded due to prior diagnosis of breast cancer and seven others were excluded because of probable (unconfirmed) malignant breast tumors. Outcome was defined as first invasive breast cancer diagnosis using current ICD codes. Results of cytological or histological examination was considered as confirmation. Cancer incidence was defined as a secondary outcome in the original study protocol.

Thirty-five confirmed incident cases of malignant breast cancer were identified. There were no data available for 122 participants. The breast cancer rate per 1,000 person-years for the control group was 2.9. Among the intervention group, the lowest rate was found in the EVOO group (1.1), followed by the EVOO and nuts group (1.4), and then nuts alone (1.8). The multivariate hazard ratio (HR) followed a similar pattern when compared to control, with the EVOO group having the lowest risk 0.32 (95% confidence interval [CI], 0.13-0.79), followed by EVOO and nuts 0.43 (95 % CI, 0.21-0.88), and nuts alone 0.59 (95% CI, 0.26-1.35). Those who had a higher EVOO consumption during follow-up had an HR of 0.18 (95% CI, 0.06-0.57). Consumption of EVOO accounted for 22% of the total caloric intake in the MedDiet-EVOO arm, whereas nuts represented 10% of the total caloric intake in the MedDiet-nuts arm.

■ COMMENTARY

Toledo et al found that supplementation with EVOO (> 15% of total energy intake) as part of a Mediterranean-style diet that consists of plant foods, fish, and olive oil provided statistically significant decrease in the risk of developing breast cancer. A non-significant trend was also observed with a Mediterranean-style diet supplemented with 30 g of mixed nuts.

The strength of this study was the randomized, controlled design and large sample size, which the authors indicated likely balanced out certain potential residual confounding factors. These residual confounders included: 1) breast cancer not being the primary outcome of the original PREDIMED trial, which resulted in not all women having a documented baseline disease-free mammogram; 2) possible subclinical cases; and 3) data on reproductive factors associated with breast cancer not being available for further adjustment during the analysis.

Other limitations of the study included the small incident number of breast cancer cases. However, the authors argued that if any cases were missed, they would have been in the control group, which comprised the majority of cases lost to follow-up. This would have further increased the incidence rates in the control group and would not have affected the findings of the study. There was a very high rate of adherence to the MedDiet at baseline, which was speculated to be the reason for the small incident cases.

The study population consisted mainly of white postmenopausal women, so it may not be generalizable to other age groups or ethnicities.

This is the first randomized trial on the effect of a long-term dietary intervention on breast cancer incidence. The study found a beneficial effect of a MedDiet supplemented with EVOO in white postmenopausal women. However, the role of nuts in primary prevention of breast cancer remains ambiguous, although there was a non-statistical risk reduction found with consumption of nuts. Longer-term studies are needed with higher number of incident cases to improve the strength of evidence in terms of breast cancer prevention. However, the MedDiet pattern has been shown to have cardioprotective effect. Therefore, it is reasonable for clinicians to recommend it as part of a healthy heart diet, which includes plant foods, fish, and EVOO. ■

REFERENCES

1. Ferlay J, et al. Cancer incidence and mortality patterns in Europe: Estimates in 40 countries in 2012. *Eur J Cancer* 2013;49:1374-1403.
2. WHO International Agency for Research on Cancer IARC monographs on the evaluation of carcinogenic risks to humans. Vol 96. Alcohol consumption and ethyl carbamate.
3. Willett WC, et al. Mediterranean diet pyramid: A cultural model for healthy eating. *Am J Clin Nutr* 1995;6(Suppl):14025-14065.
4. Menendez JA, et al. A genomic explanation connecting "Mediterranean diet," olive oil and cancer. *Eur J Cancer* 2006;42:2425-2432.
5. Warleta F, et al. Squalene protects against oxidative DNA damage in MCF10A human mammary celsl but not in MCF7 and MDA-MB 231 human breast cancer cells. *Food Chem Toxicol* 2010;48:1092-1100.
6. Akl MR, et al. Olive phenolics as c-Met inhibitors: Olecanthol attenuates cell proliferation, invasiveness and tumor growth in breast cancer models. *PLoS One* 2014;9:e97622.
7. Buck K, et al. Meta-analysis of lignans and enterolignans in relationship to breast cancer risk. *Am J Clin Nutr* 2010;92:141-153.
8. De Lorgeru M, et al. Mediterranean dietary pattern in a randomized trial: Prolonged survival and possible reduced cancer rate. *Arch Intern Med* 1998;158:1181-1187.

SHORT REPORT

Interval Training for Cardiovascular Health: Less is More?

By David Kiefer, MD, Editor

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Dr. Kiefer reports he is a consultant for WebMD.

SYNOPSIS: Sedentary men achieved similar cardiometabolic improvements after 12 weeks of either short-duration, high-intensity exercise or the standard 45 minutes of sustained moderate-intensity exercise.

SOURCE: Gillen JB, Martin BJ, MacInnis MJ, et al. Twelve weeks of sprint interval training improves indices of cardiometabolic health similar to traditional endurance training despite a five-fold lower exercise volume and time commitment. *PLoS One* 2016;11:e0154075.

It almost sounds too good to be true. We can exercise less and still reap the cardiovascular benefits of extended moderate-intensity aerobic effort? Sign me up! Gillen et al, in a study that received widespread media coverage, compared sprint interval training to moderate-intensity training; the former involved one minute of intense exercise (3 x 20 seconds at 100% maximum heart rate) within 10 minutes, whereas the latter was the standard 45-minute continuous exercise (70% maximum heart rate) regimen, often recommended for preventive health and therapeutic interventions. Twenty-seven sedentary men (nine in the intense group, 10 in the moderate group, six controls) exercised three times weekly for 12 weeks.

Summary Point

- One minute of maximum exercise in 10 minutes (three 20-second maximum cycling efforts separated by two minutes of low-intensity cycling) is comparable to 45 minutes of sustained cycing (70% maximum exercise) with respect to cardiovascular and metabolic parameters.

Cardiometabolic parameters were tested pre- and post-intervention, and are listed and resulted in Table 1. Essentially, the improvements in the measurements were comparable (significant *P* values for intra-group comparison and no difference for inter-group comparisons) between the intense and moderate exercise groups. The researchers also measured skeletal muscle mitochondrial content, estimated mostly by the activity of citrate synthase (mmol/kg protein/hr), and found that the intense group increased by 48% and the moderate group increased by 27%, both of which were higher than the control group ($P < 0.001$).

The authors tie their results into the greater picture of how to improve cardiovascular risks (measurements of cardiovascular fitness have some correlates with this) and insulin resistance, and albeit a short duration, these results are intriguing. With an ever more sedentary population, the demographic studied here is likely relevant to our patients, and the intervention produced results that were meaningful, certainly in the short term, and, hopefully follow-up research will show in the long

Table 1: Cardiometabolic Parameters for the Intense and Moderate Exercise Groups and Control Group

	Intense Exercise		Moderate Exercise		Control	
	Pre	Post	Pre	Post	Pre	Post
Peak oxygen uptake (mL/kg/min)	32	38	34	40	32	"no change"; value not given
Insulin sensitivity index (microU/mL)	4.9	7.5	5.0	6.7	7.4	7.0

term. Encouraging lifestyle change can be a challenge, but perhaps this high-intensity, short-duration approach will appeal to some people, and help them along the road to better cardiometabolic health. Obviously, this regimen would need to be tailored to someone's physical abilities (a swift move from sedentary to high-intensity could lead to injury or worse), probably best done, at first, under the supervision of a professional. This could be the breakthrough that people need to be more active in their busy lives. Overall, although it appears that less is not actually *more*, at least less duration (more intensity) of exercise leads to the *same* outcomes. ■

CME INSTRUCTIONS

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

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CME QUESTIONS

1. **Which of the following is false about managing erectile dysfunction?**
   a. All over-the-counter herbal and supplement products for erectile dysfunction are safe and natural.
   b. Therapy should begin with an assessment of lifestyle medicine.
   c. Pharmaceutical PDE-5 medications are a reasonable option for most men with erectile dysfunction who do not use nitroglycerine for angina.
   d. Erectile dysfunction has many causes, and cardiovascular disease should be considered in men with risk factors.

2. **Moderate coffee consumption has been a reduced risk of all of the following *except*:**
   a. endometrial cancer.
   b. stroke.
   c. bladder cancer.
   d. Alzheimer's disease.
   e. liver cancer.

3. **In the study by Gillen et al, which of the following cardiometabolic measurements improved from baseline in the high-intensity exercise group?**
   a. Peak oxygen uptake (mL/kg/min)
   b. Insulin sensitivity index (microU/mL)
   c. Skeletal muscle mitochondrial content
   d. All of the above

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- present evidence-based clinical analyses of commonly used alternative therapies;
- make informed, evidence-based recommendations to clinicians about whether to consider using such therapies in practice; and;
- describe and critique the objectives, methods, results, and conclusions of useful, current, peer-reviewed, clinical studies in alternative medicine as published in the scientific literature.

[IN FUTURE ISSUES]

Seafood consumption and brain mercury level

Integrative treatments for restless legs syndrome

Health benefits of cocoa flavonols

Integrative approaches for autism