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On The COVER

Media Bias, Conflicts of Interest Distort Study Findings on Supplements

By Lyle MacWilliam, MSc, FP

Sloppy reporting, distorted editorial sensationalism, and conflicts of interest by researchers are unnecessarily alarming the public and threatening to destroy our trust in complementary health care. These injustices must be addressed before irreversible harm is done to an industry committed to natural approaches to wellness and to a public increasingly confused about where to turn for sound advice on preventing disease and achieving optimal health and well-being.



On February 23, the venerable New York Times—long regarded as an icon of journalistic integrity—trumpeted the headline, “2 Top-Selling Arthritis Drugs Are Found to Be Ineffective.” The “drugs” mentioned in the article are not drugs at all, but glucosamine and chondroitin, two popular, natural nutritional supplements successfully used by millions of people worldwide. Despite the fact that the study authors came to a distinctly different conclusion, this one article quickly raised questions in the public’s mind. The Associated Press and its Canadian counterpart, Canadian Press, also picked up the story and parroted the headline that glucosamine and chondroitin sulfate were “...no better than dummy pills” in relieving knee pain associated with osteoarthritis. The findings of the \$12.5 million study, published February 23 in the *New England Journal of Medicine*, provide a very different view.

Preceding this was another egregious headline in New York Times that likely sold a lot of newspapers. On February 16, the Times declared, “Big Study Finds No Clear Benefit of Calcium Pills.” Reporting on an \$18 million study conducted by the Women’s Health Initiative on the protective effect of calcium and vitamin D, the Times article dismissed the finding that those women who actually adhered to their supplementation regimen experienced a 29% reduction in hip fractures. Such a reduction is rarely achieved with the strongest pharmaceuticals, yet here was a natural supplement producing enviable results and the media failed to report it accurately.



A week prior, on February 9, an Associated Press newswire declared, “Palmetto No Help for Prostate.” Reporting on a study conducted by researchers at the San Francisco VA Medical Center, news media throughout the US and Canada regurgitated the story that the popular herbal remedy saw palmetto is of no help in relieving symptoms of an enlarged prostate. According to the New York Times, the study found “no benefit from saw palmetto by a variety of different measures.” Canada’s national daily, the *Globe and Mail*, condemned the extract as “no more effective than dummy capsules in easing symptoms.” The Los Angeles Times advised that men “might be better off taking FDA-approved medications.” Nowhere in these superficial and slanted accounts was there any more than a passing mention of the study’s substantial limitations.

On February 8, the New York Times reported on two related Women’s Health Initiative studies claiming that low-fat diets do not cut health risks. The studies, part of a multifaceted \$415 million federal research project involving nearly 49,000 postmenopausal women, investigated the effects of a low-fat diet in reducing the risks of cardiovascular disease and colon cancer.

According to the Times article, low-fat diets have virtually no effect on invasive colon cancer, heart attacks, or strokes. No attention was paid to the studies’ numerous design weaknesses, the most obvious of which are their common failure to discriminate between different types of fat and their handicapped ability to detect change—known as the power of a test—due to actual reductions in fat intake that were far less than anticipated. These considerations, along with the fact that the studies were based on generally overweight postmenopausal women, render the findings inapplicable to the general population and belie the implications of articles describing the study results.

Not to be outdone, the February 28 edition of Canada’s *Globe and Mail* followed up on the findings of the Women’s Health Initiative fat-loss studies. Declaring “everything you know about your health is wrong (again),” journalist Margaret Wentz espoused her bias that “despite everything you’ve been told for umpteen years by countless experts, the experts were wrong.”

According to Wentz, low-fat diets are of no benefit at all and the only people who benefit from calcium and vitamin D are those who work in the supplements industry. “Salads and supplements are useless in warding off the deadly diseases we all dread,” noted Wentz. “Give up health advice,” she further advised. “You’ll feel 100% better in no time.”

JUMPING TO FALSE CONCLUSIONS

A journalist’s obligation is to tease fact from hyperbole and truth from innuendo—particularly when it comes to issues of public health. In this regard, the articles just described are seriously wanting. That said, the media cannot be held solely accountable for the needless confusion and fear sown by these distorted accounts. Also to blame are those within the scientific community whose desire for 15 minutes of fame—not to mention future research funding from Big Pharma—displaces their scientific judgment.

Such is the case in a recent study showing that modest reductions in homocysteine did not reduce heart attack risk in those with significant pre-existing arterial disease. Last September, at the 2005 European Society of Cardiology Congress held in Stockholm, Dr. Kaare Bonaa’s pronouncement that “the homocysteine hypothesis is dead”¹ certainly drew everyone’s attention. According to Dr. Bonaa, the study results “tell doctors that prescribing high doses of B vitamins will not prevent heart disease or stroke.”¹

At the time of Dr. Bonaa’s pronouncement, the trial had been neither peer reviewed nor published. A detailed critique of this study is provided in this issue in the article, “Mainstream Doctors Still Confused About Homocysteine.” If we are to believe the conclusions of Dr. Bonaa, the homocysteine hypothesis is dead. The question is, should we believe Dr. Bonaa when scores of published studies suggest the exact opposite conclusion?

FACTORS BEHIND THE STUDY RESULTS

So what is going on here? Why the sudden blizzard of published studies that appear to refute the majority of the scientific evidence on the benefits of natural approaches to wellness?

For one thing, several long-term Women’s Health Initiative dietary intervention studies, developed in the early 1990s, are now coming to fruition. These studies failed to separate “good fats” (omega-3 fats and monounsaturated oils, such as fish oil and olive oil) from “bad fats” (trans fats), although much about their differences was known even at the time of the studies’ design. Furthermore, the studies make no attempt to reconcile the balance of omega-6 and omega-3 fatty acids, believed by many health experts to be a critical factor in inflammatory disease risk. According to these studies, fat is fat, and reducing fat means cutting down on all fat. If anything, the studies’ mixed findings simply serve to demonstrate the folly of such an indiscriminate approach.

Second, when testing an association or effect, statistics tell us that one time out of every twenty times the association or effect may seem to be real, but in fact is not. There is always bound to be a statistical fluke in the bunch.

Third, it is not unusual that clinical studies investigating a particular effect will not have the needed number of subjects to show a statistically significant result. This occurs because in most clinical trials, the probability of detecting a difference between variables, known as the “power” of a test, is set at 90%, usually with a minimum “power” of 80%. Consequently, there may be a 10% or 20% chance of missing your mark and failing to find a difference when one in fact exists. This is merely the gremlin of statistical probability at work.

Finally, some investigations are just bad science—improperly conducted, poorly reported, and inadequately reviewed. As has been the case lately, it is these studies that attract the undue attention of a news media hungry for sensational headlines.

Just what do the latest studies tell us? To find their real message, we need to look beyond the headlines, the skewed media spin, and the superficial analyses that pad these “news” stories.

UNDERSTANDING STATISTICAL “POWER”

Statistical power refers to the probability that one can detect an effect if, in fact, there is one. It is influenced by the size of a study (the number of subjects) as well as the variable measured (the endpoint of the study). Sometimes studies are discounted if they show elevated, but not statistically significant, effects. Therefore, one should be careful of dismissing a possible association on the basis of negative study results alone.²



NEWS MEDIA MISSES THE POINT

A recent headline in the OB/Gyn News declared, “Vitamin E Shown Not to Reduce Cardiovascular Disease.” The article discussed the findings of a recent study of vitamin E, as reported in the *Journal of the American Medical Association* in July 2005.

The study's objective was to test whether vitamin E supplementation decreased the risks of cardiovascular disease and cancer among healthy women. According to the article, the study concluded, "vitamin E showed neither benefit nor harm in all clinical parameters examined."

However, if you read the study's fine print, an entirely different picture emerges. The study also found that for cardiovascular death, there was a markedly significant 24% reduction in risk. This is a huge decrease in death!

So why was this finding not heralded as a significant discovery and headlined in all the major dailies? Because cardiovascular death was not one of the pre-specified clinical parameters set up by the study (although it was a component of a composite parameter). Instead, the authors concluded that vitamin E supplementation is not recommended for cardiovascular disease prevention, despite the fact that it reduced cardiovascular disease death by 24%.

GLUCOSAMINE/CHONDROITIN FINDINGS IGNORED

The Glucosamine/chondroitin Arthritis Intervention Trial (GAIT),³ hailed as the largest-ever clinical study of these supplements, was supposed to be the definitive word on the effectiveness of glucosamine and chondroitin in reducing the pain of osteoarthritis. Instead, the study results have only generated more controversy, due, in part, to poor experimental design and the media's misrepresentation of the findings.

The trial was a randomized, double-blind, placebo- and celecoxib (Celebrex®)-controlled intervention trial with 1,583 patients with symptomatic osteoarthritis of the knee. The primary outcome was a 20% reduction in knee pain over 24 weeks. From a clinical perspective, the study appears well designed, with a projected 85% probability of detecting change and high adherence to the treatment protocol.

Unfortunately, an inordinately high placebo effect of 60.1%, which almost doubled the expected rate of 35%, virtually destroyed the trial's validity. The fact that 6 of 10 patients in the placebo group found significant pain relief from a dummy pill is an enormous placebo effect!

Another issue is the form of glucosamine used in the study. While glucosamine sulfate is the standard form used in supplements, the type used in this study was glucosamine hydrochloride. This form of glucosamine does not contain the sulfur moiety, found in the sulfate part of the glucosamine sulfate molecule, which may amplify its analgesic properties.

Finally, little was mentioned about the potential confounding effects of the use of pain relievers such as aspirin and acetaminophen. Despite the well-known fact that acetaminophen enhances the efficacy of osteoarthritis treatment, researchers allowed patients to take up to 4000 mg of acetaminophen daily, a decision that likely contributed to the outsized placebo effect noted previously.

IMPORTANCE OF SULFUR FOR THE JOINTS

One of the flaws of the *New England Journal of Medicine* study may have been that the form of glucosamine used did not provide any sulfur.³

Animal studies have shown that joints affected by osteoarthritis have lower sulfur content,⁴ and that arthritic mice given the sulfur-containing nutrient MSM (methylsulfonylmethane) experience less joint degeneration.⁵ In a double-blind trial in people with osteoarthritis, study participants who received MSM alone experienced significant pain relief.⁶

In a study published in 2004, the combination of glucosamine and MSM was more effective in improving the signs and symptoms of osteoarthritis than either agent alone.⁷ After 12 weeks of treatment, the average pain score in the glucosamine-only group dropped from 1.74 to 0.65, a 63% reduction. In the MSM-only group, it fell from 1.53 to 0.74, a 52% reduction. However, in the group taking glucosamine and MSM, the average pain score dropped from 1.7 to 0.36—an astounding reduction of 79%! The researchers also found that the combination therapy had a faster effect on pain and inflammation than either glucosamine or MSM alone.

Despite these limitations, the study did find that for those individuals with moderate-to-severe knee pain, the combination of glucosamine and chondroitin sulfate provided a 25-26% improvement in pain relief—a response that exceeded the projected 20% design measure to prove efficacy. According to the study authors, "treatment with chondroitin sulfate was associated with a [statistically] significant decrease in the incidence of joint swelling, effusion, or both."

In fact, for those participants with moderate-to-severe pain, the only treatment that bore significant benefit was the combination of glucosamine and chondroitin sulfate, which outpaced the anti-arthritis drug Celebrex® by a large margin.

Despite these findings, newswire coverage of the study chose to celebrate the positive effects of Celebrex®. In fact, Celebrex® did not relieve arthritis pain in those needing it the most—patients with moderate-to-severe pain—whereas the combination of glucosamine and chondroitin was effective in this group of patients. At the same time, these news articles claimed that “nutritional supplements show no overall benefit in treating arthritis.”

It appears that the news media took its cue from an editorial appearing in the same issue of the *New England Journal of Medicine*.⁸ Not once did the news coverage mention that the author of this editorial criticizing the use of glucosamine and chondroitin is someone who has received financial compensation from Pfizer, the maker of Celebrex®. Nor did the news media explore the disclosure that a number of the authors of the GAIT study received compensation from Pfizer and McNeil Pharmaceuticals (the maker of Tylenol®).

A STUDY DESIGN DESIGNED TO FAIL

Here's a plan: take \$18 million of taxpayer money and 36,000 postmenopausal women in various stages of osteoporosis. Divide them randomly into two groups and give one group a sugar pill and the other a pill containing low amounts of vitamin D and a poorly absorbed form of calcium.

Complicate the study design by mixing together women who are already taking calcium and still others who are on hormone replacement therapy and other forms of supplements.

Now, tell the intervention group to take their pills every day—but don't worry if they don't take them every day, because you'll include their results anyway.

What definitive study result do you get? None.

Are you surprised? You shouldn't be.

Media Bias, Conflicts of Interest Distort Study Findings on Supplements

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CALCIUM-VITAMIN D STUDY FLAWED

The \$18 million double-blind, placebo-controlled Women's Health Initiative study was designed to test whether postmenopausal women who were given calcium and vitamin D would have a lower risk of hip fracture.⁹ In this study, 1000 mg of calcium in the form of calcium carbonate and 400 IU of vitamin D (generally the same dosages recommended by most doctors to their elderly patients) were provided each day to the intervention group, which was followed for eight years.

While the women receiving calcium and vitamin D showed a greater preservation of hip-bone density, over all there was a non-significant 12% lower risk of fracture. What most media reports failed to disclose, however, is that by the study's end, compliance with the prescribed daily intake was only 59%. In other words, fully 41% of the study participants stopped taking the prescribed daily dosage of calcium and vitamin D. Moreover, 24% were no longer taking any of the supplements—a level of non-compliance that dramatically decreased the difference between the two groups.

This unexpectedly low compliance rate and a projected hip fracture rate that was more than twice the rate observed reduced the power of the study to a paltry 48%. Consequently, the trial, as designed, had insufficient power to detect anything but the largest of differences in fracture risk.

Despite this and other shortcomings, the data show that those women who mostly followed their prescribed regimen had a statistically significant 29% reduction in fractures, and women over the age of 60 experienced a statistically significant 21% reduction in the risk of fracture—a drop that the New York Times called a "hint" of gain.

MISSING INFORMATION, WRONG CONCLUSION

According to a February 16 New York Times article, the 29% reduction in fractures (for those women who mostly adhered to their prescribed regimen) suggests a mere "hint" of benefit.

To protect against osteoporosis, the Times advised, women should instead consider taking several prescription drugs that have been shown in clinical trials to prevent fractures.

The Times article fails to mention that for some of these drugs, the benefits are more modest than those obtained through simple vitamin D and calcium supplementation, while for others, the drugs work effectively only when adequate calcium and vitamin D are present.¹⁶

FATAL STUDY FLAW: EXCLUDING MAGNESIUM AND OTHER MINERALS

In designing the Women's Health Initiative study, the authors overlooked the fact that reducing fracture risk depends on factors other than calcium. Studies show that magnesium is equally important in treating and preventing osteoporosis, and its deficiency plays a central role in the development of the disease.¹⁰

Magnesium supplementation is believed to suppress excess bone turnover, which may help prevent age-related osteoporosis.¹¹ It also contributes to the fortification of the bone mineral matrix and is critical for the proper function of vitamin D. It is well established that magnesium intake should be about half that of calcium intake.¹²

In particular, postmenopausal women and those with osteoporosis generally have low bone magnesium content and exhibit other indicators of magnesium deficiency not seen in non-osteoporotic women.^{13,14} Studies show that osteoporosis-related magnesium deficiency is associated with low blood levels of the most active form of vitamin D (1,25-dihydroxy-vitamin D), which in turn inhibits calcium uptake in the gut and its resorption in the bone.¹⁴

Consequently, postmenopausal women who increase their calcium intake without also increasing their magnesium intake—as was the case in the Women’s Health Initiative study—can reduce absorption of magnesium because calcium competes for absorption with magnesium.¹⁵ Within this context, the failure of the researchers to include magnesium supplementation, along with calcium and vitamin D, strongly biased the findings in favor of harm—a glaring and irresponsible oversight for an \$18 million study.



Furthermore, emerging research suggests that additional minerals such as boron, zinc, and silicon may also be critical for maintaining healthy bones. (See “Osteoporosis: How Calcium Combines with Other Nutrients to Combat Bone Loss,” *Life Extension*, January 2005.) The failure of the Women’s Health Initiative study to examine the impact of these important mineral nutrients may have further compromised the study’s findings.

OTHER CRIPPLING DESIGN FAILURES

Several other factors conspire to erode the impact of the Women’s Health Initiative calcium trial. For one, the study’s prescribed dosage of 400 IU per day of vitamin D had already been shown to have a negligible effect on the risk of hip fracture.^{17,18} In fact, most of the studies supporting a benefit provide vitamin D at a dose of 600 IU per day or higher.¹⁹⁻²³

In addition, more than half the women in both the intervention and comparison groups were already taking estrogen hormone therapy, known to increase bone mineral density, confounding interpretation of the study intervention. Moreover, all the study participants, including those in the comparison group, were allowed to continue their personal use of calcium and vitamin D. Therefore, it is quite conceivable that some of the women (those who normally take a calcium-vitamin D supplement) in the control group were actually taking more calcium and vitamin D than many of those women in the intervention group who did not take the prescribed daily amount. No wonder the results were confusing!

Another significant weakness is the type of calcium used in the trial. Calcium carbonate has a low solubility and is one of the least bioavailable forms of calcium on the market. Absorption of this form of calcium greatly depends on stomach acidity. Even people with normal levels of stomach acid absorb only 22% of the calcium in calcium carbonate supplements.



Furthermore, studies show that as we age, our ability to produce copious amounts of stomach acid wanes. In postmenopausal women—the very group the Women’s Health Initiative study addressed—approximately 40% may be deficient in stomach acid.^{15,24} Studies in the 1980s revealed that patients with insufficient stomach acid absorb as little as 4% of the oral dose of calcium carbonate.²⁵ (When the form of calcium was changed to the more bioavailable calcium citrate, absorption in these same individuals increased to 45%.) Consequently, in the Women’s Health Initiative study, it can be estimated that up to 40% of the intervention group was absorbing as little as 4%, or 40 mg, of their daily calcium intake. This fact alone so severely compromises the study that it may be sufficient to disregard the findings altogether.

Despite the study’s glaring oversights and contrary to the media spin that the Women’s Health Initiative study dispels long-held beliefs about the benefits of calcium and vitamin D, the authors

conclude that the results do provide evidence of a positive effect of calcium and vitamin D on the bone health of older, postmenopausal women.

One can only image what might have been the result had this \$18 million boondoggle been properly designed in the first place.

DIETARY MODIFICATION TRIAL RESULTS MIXED

On February 8, 2006, the *Journal of the American Medical Association* (JAMA) published three studies based on data from the eight-year, \$415 million Women’s Health Initiative Dietary Modification Trial, one of the largest long-term trials ever conducted, involving 48,835 postmenopausal women.

This dietary modification trial was designed to test whether behavioral intervention intended to produce a dietary pattern low in total fat—along with increased intake of vegetables, fruits, and grains—would decrease the risks of cardiovascular disease, breast cancer, and colorectal cancer in postmenopausal women. Women aged 50-59 were randomly assigned to a dietary intervention or comparison group, in an attempt to reduce total dietary fat intake in the intervention group to 20% of daily calorie intake. The primary outcomes were fatal and non-fatal cardiac events or stroke,²⁶ invasive breast cancer,²⁷ and invasive colorectal cancer.²⁸ Each of these three primary outcomes was reported in a separate study.

The difference in fat intake between the intervention and comparison groups was expected to be 20%. However, the intervention group achieved only 70% of this design goal. This led to a substantial loss in the statistical power (ranging from 40% to 60%) of

the studies to detect a reduction in each of the three outcomes—which is about as good as flipping a coin. In other words, despite its unusually large sample size, the Women’s Health Initiative study was dramatically underpowered and not particularly capable of detecting a difference, if one existed.

Studies like these require highly powered trials with large sample sizes and clear discrimination between the intervention and comparison groups in order to detect relatively rare events. (It is not every day, after all, that a person dies of a heart attack or cancer.) Consequently, in the Women’s Health Initiative trial, only a very large effect of decreased fat intake would have rendered the changes statistically significant. Put another way, the lack of evidence of a protective benefit does not mean there was none. Although these limitations were clearly reported in all three studies, the implications were either not understood or disregarded by the news media.

Finally, several of the participants in this three-part trial also participated in two other randomized studies. It is unclear whether the treatment regimens in these two other studies—the Women’s Health Initiative hormone replacement trial and Women’s Health Initiative calcium trial—confounded the effects of dietary intervention.

FAT INTAKE AND CARDIOVASCULAR DISEASE RISK

The Women’s Health Initiative study investigating the effect of total dietary fat reduction on the risk of cardiovascular disease²⁶ found that long-term reduction of total dietary fat did not affect the risk of coronary heart disease, stroke, or cardiovascular disease. It did, however, achieve a modest, yet significant, reduction in cardiovascular disease risk factors, including low-density lipoprotein (LDL) and diastolic blood pressure. There was also a trend toward reduction in cardiovascular disease risk among women who had the lowest intake of fat and the highest intake of fresh fruits and vegetables, as well as for women with no previous cardiovascular disease. Moreover, women in the intervention group who had the lowest fat intake had a lower risk of coronary heart disease than those in the control group.



The power of this trial, however, was crippled by its failure to lower the level of fat intake to that prescribed by the design criteria, and by an observed incidence of myocardial infarct (heart attack) and cardiovascular disease that was 30% lower than projected. Hobbled with a scant 40% chance of detecting a decrease in the cardiovascular disease rate, the chances of a positive finding were less than the flip of a coin. Consequently, it is not surprising that the trial failed to achieve a statistically valid reduction in cardiovascular disease risk. Nevertheless, what it does show is just how hard it is to achieve a dramatic reduction in total fat intake over the long haul through behavioral intervention.

The study was designed to reduce total fat intake without regard to the types of fat, a feature that has been harshly criticized by nutritional researchers and informed consumers alike. In a letter to the editor of the New York Times, one reader recalls her mother, who was involved in the Women’s Health Initiative studies, bemoaning the fact that the researchers “made no difference between lard and olive oil!” Given what we knew even back in 1991 (when the trial was designed) about the differences between “good” fats and “bad” fats, it appears an inexcusable oversight not to differentiate between healthy and unhealthy fats. However, within this context, the findings further our understanding that a nondiscretionary reduction of total fat is of limited value in reducing cardiovascular disease risk.

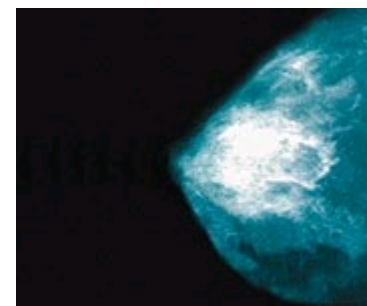
Far from being the “definitive answer” on the health effects of reduced dietary fat, as suggested by some “experts” and described by some reporters, the study only helps confirm what we already know—that simply eliminating all fats is not the answer to reducing cardiovascular risk.

LOW FAT AND RISK OF BREAST CANCER

Like the previous study, the Women’s Health Initiative investigation of fat reduction’s effect on invasive breast cancer²⁷ did not find a significant decrease in cancer rates. After eight years of follow-up, the dietary intervention group had a relative decrease of 9% in the incidence of invasive breast cancer compared to the control group—a level of risk reduction that approached, but did not achieve, statistical significance. Cancer can take years, even decades, to develop. Considering the study’s relatively short time frame, it is very likely that, given more time for the trial to proceed, it would have revealed evidence of a preventive benefit.

As in the companion studies, the intervention group's inability to reach the targeted level of fat reduction fatally compromised the trial's power. The study design was simply not robust enough to detect anything but the most dramatic of changes between the intervention and comparison groups.

The investigators take care to point out certain trends in their findings. While it can be misleading to read too deeply into subgroup analyses, women who had the highest levels of fat intake at the start of the trial showed a stronger trend toward breast cancer reduction than did the intervention group as a whole. Such variation would not have been expected if the dietary intervention had no effect on breast cancer. The researchers also found that the low-fat diet was associated with a 15% reduction in circulating levels of estradiol, the form of estrogen that increases the risk of breast cancer. This finding is consistent with the results of other clinical trials demonstrating the protective effect of estradiol reduction in breast cancer treatment.²⁹ Similarly, this would not have been expected if dietary intervention had no effect on cancer risk reduction.



Breast cancer.

All this leaves us with a study that lacked the diagnostic power to do the job it was designed to do, primary results that nudge the boundaries of statistical significance, and secondary findings that exhibit supportive trends for reduction in breast cancer risk. While it is disappointing that the results were not more definitive, it is hardly cause to “throw out the salad” and “give up health advice,” as one Canadian journalist suggested.

Media Bias, Conflicts of Interest Distort Study Findings on Supplements

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REDUCING FAT AND COLORECTAL CANCER RISK

Similar to the previous studies, the Women's Health Initiative colorectal cancer study²⁸ was designed to evaluate whether a diet low in total fat, with abundant intake of fresh fruits and vegetables, helps prevent colorectal cancer. The findings reveal that dietary intervention did not reduce the incidence of this cancer in postmenopausal women. As in its companion studies, the power of this study was heavily compromised because participants in the intervention group were simply incapable of reaching the targeted fat-reduction levels. At a power of 40%, the study had less probability of detecting a reduction in colorectal cancer risk than the flip of a coin. Consequently, the negative findings are not surprising.

The slight elevation of risk reported in the findings, while far from significant, is also not surprising. In this context, the authors acknowledge that the intervention was accompanied by a statistically significant decrease in total vitamin E and gamma tocopherol intakes, an outcome that does not appear to have been anticipated or controlled for. The study was designed in 1991, when the authors would not have been aware of the negative influence that a concomitant reduction of vitamin E, particularly gamma tocopherol, would have on cancer risk.³⁰

An across-the-board reduction in all fats, as mandated in the study, would inadvertently reduce blood levels of the fat-soluble tocopherols—precisely what was observed. Because of the important role played by gamma tocopherol in reducing the risk of colorectal cancer,³¹⁻³⁵ its concomitant reduction within the intervention group may have had the antagonistic effect of enhancing colorectal cancer risk.

The three studies that were spun out of the Women's Health Initiative fat-reduction trial had crippling design flaws that call their findings into question. Hobbled with statistical powers ranging from 40% to 60%, the authors would have been better off tossing a coin. At least that way they would not have squandered tens of millions of taxpayer dollars on studies that were simply incapable of doing the job.

SAW PALMETTO: ANOTHER STUDY DESIGNED TO FAIL?

At first blush, the results of a San Francisco study of saw palmetto's effects on enlargement of the prostate, published in the February 9 issue of the *New England Journal of Medicine*,³⁶ are puzzling. The negative finding that the plant extract was not effective in alleviating problems associated with an enlarged prostate is inconsistent with a large body of evidence that shows otherwise, including more than 20 studies demonstrating saw palmetto's ability to alleviate commonly associated symptoms.³⁷ One such study, a meta-analysis of 21 clinical trials involving over 3,000 men, concluded that saw palmetto showed a benefit versus placebo and showed benefits comparable to the drug finasteride (Proscar®), with significantly fewer side effects than the drug.³⁷

The San Francisco study was a well-designed, double-blind, placebo-controlled trial with clear inclusion and exclusion criteria. It adhered closely to the standard protocols for clinical trials and all participants were screened to have a 75% adherence rate to the daily supplementation regimen (the final adherence rate was 92%). The primary outcome was to determine whether the use of saw palmetto, at a dose of 160 mg twice daily, would reduce symptoms of benign prostatic hyperplasia (BPH).

So why were the findings at odds with other similar studies?

First, the study examined men with moderate-to-severe BPH.³⁷ The exclusion of patients with only mild disease may have limited the study's ability to detect benefits.

Second, by design, the study investigated the effect of a single herbal ingredient, saw palmetto, even though many physicians find that moderate-to-severe BPH requires aggressive, multimodal treatment to achieve effective relief. From a scientific perspective, this approach cannot be faulted; however, from a clinical perspective, it is an example of where science's

GAMMA TOCOPHEROL AND COLORECTAL CANCER

Gamma tocopherol has recently been shown to play a central role in preventing colorectal cancer by acting as a chemoprotective agent in the colon. New evidence shows that both alpha tocopherol and gamma tocopherol can shield the cells lining the colon from cancerous growth. Gamma tocopherol and its water-soluble metabolite also quench oxidative stress in the colon.³⁰⁻³⁵

compulsion to isolate a single variable often misses the larger picture. Nutritional researchers have long known that when it comes to prevention, there is no single “magic bullet”—a fundamental truth that the drug industry has been loath to accept.

In this context, the study overlooked the established value of ancillary herbal remedies such as nettle root and pygeum, which may work synergistically with saw palmetto. Because nettle root and pygeum may be particularly effective in more aggressive cases of prostate enlargement, their inclusion in the San Francisco trial would have made perfect sense.³⁸⁻⁴¹

What can we conclude about the San Francisco study? Despite the trial’s solid fundamentals, the investigators’ decision to focus on only the more aggressive cases of benign prostatic hyperplasia, their use of a single moderate dose of saw palmetto (rather than a dosage range), and their disregard for the synergistic role of other herbal antagonists give it the appearance of failure by design.

Incidentally, none of the negative news articles reporting on the results of the study chose to mention that the researchers conducting the investigation have received consulting fees and financial support from major players in the drug industry. These include Merck, which manufactures the prostate drug Proscar®; GlaxoSmithKline, which makes Avodart®; and TAP Pharmaceutical Products, Inc., makers of Lupron®.

Consequently, when considering the study’s negative findings on an herbal supplement that cannot be patented, one should not disregard the considerable financial interests of the study’s authors.

CONCLUSION

It is no wonder that health-conscious readers are becoming frustrated and alarmed at the mixed messages promulgated by the mainstream news media. It seems one day we are told that something is good for us and the next day we are told that it is not. We could certainly be excused for wondering why scientists cannot get it straight for once.

If there is any consolation, it helps to understand that science never progresses smoothly—there will always be new findings that appear to refute long-held beliefs. Controversy is the crucible for change, and paves the road that science must travel to arrive at a final truth. Unfortunately, it does not help when media bias and conflicts of interest keep throwing up detours along the way.

In this respect, researchers and peer-reviewed journals bear a heavy responsibility and a fiduciary duty to report the results of clinical trials in a fair and unbiased manner. To their credit, the vast majority of investigators take great pains to ensure proper study design and unbiased reporting of their findings. As always, however, there are exceptions to the rule. Simply put, headline-grabbing pronouncements by the news media and by researchers elbowing for their 15 minutes of fame are not conducive to the advancement of science.

So, too, the national and local media has a public duty to ensure that their reporting of important scientific findings is balanced, accurate, and complete. Sensational headlines, disregard for study limitations, and—by design or otherwise—fundamental misrepresentation of the facts serves no good purpose, other than to bolster author Norman Mailer’s claim that “once a newspaper touches a story, the facts are lost forever.”

SYNERGISTIC EFFECTS OF NETTLE ROOT AND PYGEUM

Nettle root, which blocks the proliferative action of dihydrotestosterone on prostate cell growth, has been used successfully, alone or in combination with saw palmetto, for many years. Pygeum has been shown to reduce prostate swelling and block the proliferative effects of dihydrotestosterone.^{40,41}

Both herbal remedies are approved medicinals in Europe for the treatment of benign prostatic hyperplasia. These nutrients demonstrate a complementary effect when used in conjunction with saw palmetto.

CAN WE TRUST THE STUDIES?

Recent research highlights a frustrating aspect of science: it is rarely, if ever, a matter of black and white. In a sobering review of major studies published in three influential medical journals between 1990 and 2003—including 45 highly publicized studies—nearly one third of the original results did not hold up.

According to Dr. John Ioannidis, author of the critical review, “Contradictory and potentially exaggerated findings are not uncommon in the most visible and most influential original clinical research.”

The findings of his review serve as a reminder to physicians and the public alike that they should not put too much stock in a single scientific study. As Dr. Ioannidis notes about the refuted studies, “The general public should not panic ... we all need to start thinking more critically.”⁴²

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