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Can Fish Oil Interfere with Chemotherapy?

ABSTRACT & COMMENTARY

By Randy Horwitz, MD, PhD

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

Synopsis: *This basic science paper explores the role of the tumor microenvironment in the development of tumor resistance to chemotherapy. Two distinct fatty acid molecules, endogenously produced by cancer cells in response to platinum-based chemotherapy drugs, were found to confer significant tumor chemoresistance. Remarkably, these two fatty acids also were shown to be present in several commercial fish oil products, and, of potential import to clinicians, the oral administration of small amounts of these fish oils induced tumor resistance to cisplatin in a mouse tumor model.*

Source: Roodhart JM, et al. Mesenchymal stem cells induce resistance to chemotherapy through the release of platinum-induced fatty acids. *Cancer Cell* 2011;20:370-383.

Tumor resistance to chemotherapeutic agents presents a major obstacle in the successful treatment of cancer. Two types of chemoresistance have been described: an intrinsic, tumor cell-initiated event that develops slowly, and a more rapid, reversible resistance thought to be mediated by the tumor's surrounding stromal cells and associated molecules — the tumor's "microenvironment." This latter effect has remained an enigma until recently.

Evidence presented in this paper points toward the mesenchymal stem cell (MSC) as the cell that is directly responsible for the tumor's microenvironment. The MSC is pluripotent, and as such is capable of becoming an adipocyte, osteoblast, chondrocyte, or fibroblast under certain stimuli. MSCs are recruited in large numbers to the stroma of developing tumors, where they can stimulate tumor

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growth, angiogenesis, and metastatic spread. Their power to impart tumor resistance is significant, since as few as 50,000 of these cells, when administered intravenously, are sufficient to abolish the antitumor effects of cisplatin in two different murine tumor models. Their influence appears to be mediated by something other than local cellular interactions: if the MSCs are injected subcutaneously at a site distant from the tumors, as few as 1000 MSCs were sufficient to induce partial resistance to cisplatin, suggesting that there is a soluble or hormonal factor produced by the stimulated MSCs that is responsible for the action (i.e., cell-to-cell contact was not needed). This was reinforced by the observation that the injection of "conditioned media" (cell-free media made from MSCs co-cultured with a platin drug) inhibited the tumoricidal activity of cisplatin in tumor-bearing mice.

In addition, the researchers showed that the resistance conferred by MSCs can be extrapolated to other platinum-based drugs, including oxaliplatin and carboplatin, but not to other non-platinum based chemotherapeutic drugs (5-FU or irinotecan).

So what is this magic "chemo-resistance factor" secreted by the MSCs? It appears to be a fatty acid named KHT (12-oxo-5,8,10-heptadecatrienoic acid), as well as its precursor, KKT (hexadeca-4,7,10,13-tetraenoic acid). As little as 2 pM of either one of these injected into tumor-bearing mice will rapidly induce complete resistance to platin chemotherapy. Further, when MSCs are incubated with platin-containing compounds, their endogenous production of KHT and KKT goes up 3-fold. The authors call these 2 fatty acids "platinum-induced polyunsaturated fatty acids" (PIFAs).

They report some fascinating human correlates: Elevated levels of MSCs are seen in humans with metastatic tumors relative to lone tumors. In addition, it appears that platin-stimulated MSCs obtained from humans can induce resistance to chemo when used in the mouse model.

Now, on to the alternative medicine-relevant focus. It turns out that the PIFAs are abundantly represented in commercial fish oil products and algae extracts. They don't specifically name which ones were used in the experiments, but an oral dose of 100 ul (10-6 liters, or about 2 drops) of commercial fish oil (or algae extract) fed to tumor-bearing mice was sufficient to inhibit the activity of cisplatin significantly. In fact, fish oil neutralized the effect of the chemotherapeutic drug in two different murine tumor models. However, when the researchers used a purified EPA preparation (as opposed to "whole" fish oil), the EPA alone did not affect the antitumor effects of cisplatin. In fact, the purified EPA seems to actually make the cisplatin more tumoricidal (but not significantly so).

The researchers state that both commercial fish oil and the algae-derived product induced a "complete resistance to chemo at doses similar to the advised daily dose in humans."

■ COMMENTARY

This is a complex basic science paper with clinical implications, especially for those of us involved in the care of patients with cancer. There are clearly differences between the experimental mouse tumor models used in this study and human cancers, but the data presented in this study are provocative and deserve attention.

A plethora of research has explored omega-3 (specifically fish oil) intake and the incidence of malignancy in humans. Many studies showed no association. One exception, the EPIC (European Prospective Investigation into Cancer and Nutrition) study, followed more than 475,000 Europeans for an average of 5 years, and attempted to correlate meat or fish intake with malignancy. Fish intake was inversely associated with colorectal cancer. Those consuming 3 ounces of fish daily reduced their risk of colon cancer by nearly a third, relative to those averaging less than 0.5 ounces of fish daily.[1] (In case you are wondering, red meat was positively associated with colon cancer.)

Few studies, however, have examined the interaction of fish or fish oils in patients undergoing active chemotherapy, especially with platinum-based agents. One animal study did investigate the effect of omega-3 fats and cisplatin on the level of pulmonary tumor load in a mouse model of lung carcinoma.[2] Mice were injected with a murine lung cancer cell line in the foot pad, and several days later, the lungs were assessed for metastatic tumor load.

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Mice were given diets containing either fish oil or soybean oil (isocaloric). Those mice fed the fish oil diet exhibited significantly less tumor spread to the lungs relative to those fed a soybean oil diet, suggesting a protective effect of the fish oil.

When the soybean oil-fed mice were treated with cisplatin, the metastatic tumor load was unaffected; the cisplatin had virtually no effect. This was interesting, as the tumor previously had been shown to be cisplatin-sensitive. When the fish oil-fed mice were treated with cisplatin, the metastatic spread decreased moderately relative to soybean-fed animals (no statistical significance was reported).

However, when we compare metastatic tumor spread in the fish oil-fed mice with the cisplatin-treated fish oil-fed mice, we see a marked attenuation of this anticancer effect of the cisplatin. That is, the results with the fish oil diet alone were significantly better than with the fish oil diet plus cisplatin. This suggests that fish oil alone inhibits metastatic spread somewhat, while the addition of cisplatin to fish oil attenuates this desired result. Perhaps this observation represents a similar phenomenon to that seen in the Roodhart paper. Taken as a whole, these papers certainly give pause to the potential interactions between fatty acid ingestion and tumor growth/chemotherapy responsiveness.

So what lessons can we glean? Many naturally derived substances prescribed in integrative medicine are used with impunity, owing to the benign nature of the source. Fish oil is a good example; a daily supplement dose often is equated with a large serving of a fatty fish (i.e., salmon), and thus is regarded as very safe. However, there are several challenges in making sweeping recommendations for fish oil use in patients with cancer: First, many oncologists are choosing therapeutic protocols based upon results from clinical studies conducted in populations that are typically *not* using regular doses of fish oil — most individuals do not eat daily servings of fish as a matter of course. In addition, there are few controlled studies looking at the potential interactions between foods or food components and biochemical therapeutics. In fact, I suspect that even among prescient observers, few would have predicted this profound effect of fish oil in a tumor model.

Until we have more details and corroborating studies, I would not recommend fish oil as an adjunctive therapy to patients receiving platinum-based chemotherapy. If a patient is considering fish oil supplementation during platin-based chemotherapy, it would be important to contact the manufacturers of commercial fish oil products to inquire about the KHT and KKT content of the oil. As described in the paper, very little PIFA is required to negate the chemotherapeutic effect of the platinum-based therapy in vivo. ■

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Just the Flax – Lignans and Postmenopausal Breast Cancer

ABSTRACT & COMMENTARY

By Russell H. Greenfield, MD, Editor

Synopsis: *In a case-control study using a biomarker for lignan intake, women with breast cancer who had higher levels of the biomarker post-diagnosis had a reduced risk of mortality over a median follow-up period of 6 years compared to women with low levels of the biomarker.*

Source: Buck K, et al. Serum enterolactone and prognosis of postmenopausal breast cancer. *J Clin Oncol* 2011;29:3730-3738.

Estrogenic compounds called lignans are found in a variety of vegetables, fruits, seeds, and grains, and may possess both estrogen-dependent and estrogen-independent anticancer activity. The authors of this population-based case-control study sought to evaluate the relationship between post-diagnostic serum levels of enterolactone, the primary metabolite of dietary lignans and thus a biomarker of dietary lignan intake, and both distant disease-free survival (DDFS) and overall survival (OS) in postmenopausal women with breast cancer.

The study sample was made up of German women aged 50-74 years (mean age 63 years) with histologically confirmed primary invasive (stages I to IV) or in situ breast cancer diagnosed between 2002-2005 (n = 1,140). Personal interviews were conducted at baseline to collect demographic and other information, including possible risk and prognostic factors. At the same visit, non-fasting blood samples were obtained for measurement of enterolactone levels. The median time between breast cancer diagnosis and blood collection was 101 days (range 2 to 1,112 days; standard deviation, 179 days). The first 160 blood samples were measured in duplicate to assure minimal variation in results.

A subject's vital status through the end of 2009 was ascertained via local population registries. Data regarding development of cancer recurrence and secondary tumors were collected via self-report during follow-up telephone interviews conducted in 2009, or through clinical records and attending physicians, or both. Endpoints of interest were DDFS and OS. Only patients with early-stage disease (stages 0 to IIIA) were included in the analysis of DDFS.

Analyses were stratified by age at diagnosis (in 1-year categories). Multivariate analyses were adjusted for traditional prognostic factors including tumor size, node status, metastatic spread, grade, and ER/PR status. Body mass index, mode of tumor detection (self-examination vs. routine screening mammography, for example), history of hormone replacement therapy, diabetes, and leisure time physical activity since the age of 50 years were accounted for in the final multivariate models.

The overall median enterolactone level was 20.8 nmol/L (interquartile range, 34.6 nmol/L), with levels differing significantly between participants who had died (median, 17.0 nmol/L) and those who were still alive (median, 21.4 nmol/L; $P = 0.04$). High enterolactone levels were associated with tumors that were smaller, lower grade, hormone receptor-positive, and physician-detected compared with participants with lower enterolactone levels. Those with high enterolactone levels were more likely to have used hormone replacement therapy, not to have received chemotherapy, have a lower BMI, and have a never/past smoking history.

During a median follow-up time of 6.1 years after diagnosis (range, 0.2 to 7.7 years), 162 deaths occurred in the sample, 124 (76.5%) of which were from breast cancer. In the 962 patients with early-stage disease included for the DDFS analysis, 124 distant recurrences or deaths occurred. Higher serum enterolactone levels were associated with a significantly reduced hazard ratio (HR) for overall mortality (multivariate HR per 10 nmol/L increment, 0.94; 95% confidence interval [CI], 0.88-1.00; $P = 0.04$). The highest vs the lowest enterolactone quartile was associated with a significantly reduced risk for death (multivariate HR, 0.58; 95% CI, 0.34 to 0.99). Serum enterolactone level also was associated with a non-statistically significant reduction in HR for distant disease (multivariate HR, 0.94; 95% CI, 0.87-1.01; $P = 0.08$ per 10 nmol/L increment and 0.62; 95% CI, 0.35-1.09 for the highest quartile).

In the subgroup of 902 early-stage (stages I to IIIA) patients with breast cancer who receive standardized adjuvant treatment, the HR for death associated with highest vs lowest enterolactone levels was not substantially different compared with that for the total population (P for heterogeneity = 0.94), but the finding did not achieve statistical significance (multivariate HR, 0.95; 95% CI, 0.88-1.02 per 10 nmol/L increment and HR, 0.56; 95% CI, 0.27-1.14 for the highest quartile).

The association between enterolactone and overall mortality was not significantly heterogeneous for time between diagnosis and blood collection below or above the median, with HRs for death for the highest compared with the lowest quartile of 0.60 (95% CI, 0.27-1.32) and 0.59 (95% CI, 0.26 to 1.34), respectively (P for heterogeneity = 0.98). Significant heterogeneity was not found between the 827 subjects who did not receive chemotherapy or with blood collected before chemotherapy (73%) and patients with blood collected after the start of chemotherapy (multivariate HR, 0.56; 95% CI, 0.25-1.25 and HR, 0.38; 95% CI, 0.16-0.90 for the highest quartile; P for heterogeneity = 0.57). Looking at ER/PR status, the association between enterolactone level and overall mortality was statistically significant only for ER-negative tumors in the highest compared with the lowest quartile (HR, 0.27; 95% CI, 0.08-0.87). Effect heterogeneity by tumor size or by grade was also not observed.

The researchers concluded that postmenopausal patients with breast cancer who have high post-diagnostic serum enterolactone levels may have improved survival.

■ COMMENTARY

Once ingested as food, lignans are metabolized by the gut microbiota to enterolignans and subsequently absorbed. They have features in common with estrogens and can bind to estrogen receptors, thus blocking the body's estrogen from interacting with those same receptors. In this way, lignans potentially could confer a cancer protective effect. In addition, animal data suggest non-estrogen dependent inhibition of tumor growth and spread. A number of human studies have suggested a beneficial role for lignans in the setting of ER negative breast cancer.

The current study measured enterolactone levels as a biomarker of lignan ingestion and metabolism, thereby avoiding the pitfalls of recall bias inherent with dietary questionnaires; however, levels were obtained only once and only after the diagnosis of breast cancer had been made. Results speak only to the degree of short-term lignan intake, and the study authors state their results may not reflect enterolactone levels pre-diagnosis.

A very good commentary found in the same edition of the journal[1] cautions that it is far too early to jump on the flaxseed wagon with respect to women with breast cancer (flaxseeds contain a high concentration of lignans). The author notes that many variables have yet to be fleshed out, including the bioavailability of lignans from different food sources, and the impact of changes in the colonic microenvironment on lignan metabolism. Plus, we are discussing a phytoestrogen, and there is much that

needs to be better understood about the activity of different plant-based estrogens in the body. In addition, the data discussed here are observational in nature.

Keeping all this in mind, however, any intervention that might provide a 40% reduction in risk of death, as found in this study, should get people's attention and be re-examined as soon as possible.

Adding a tablespoon of ground flaxseed to one's cereal, smoothie, or salad has long been a general health recommendation proffered by some health care practitioners, and may be a reasonable option for women who have been diagnosed with breast cancer, especially ER negative breast cancer. But ingesting lignans as part of a healthy diet is very different from the taking of supplemental lignans, and the latter cannot be supported on the basis of this study's findings alone. ■

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15 to Life – Limited Exercise and Mortality Risk

ABSTRACT & COMMENTARY

By Russell H. Greenfield, MD, Editor

Synopsis: *Data from this large observational trial with an average follow-up of over 8 years suggest that even 15 minutes a day of moderate-intensity exercise, such as taking a brisk walk, provides significant health benefits in terms of lowered mortality risks and life extension.*

Source: Wen CP, et al. Minimum amount of physical activity for reduced mortality and extended life expectancy: A prospective cohort study. *Lancet* 2011;378:1244-1253.

Evidence suggesting the health benefits of regular exercise and associated guidelines are commonplace, with authorities calling for a minimum of 30-60 minutes of fitness activity on most days of the week to help support optimal health. There has long been a sense that lesser amounts of physical activity do not offer significant health benefits, but this perspective has largely gone unchallenged. The researchers behind this Taiwanese historical prospective cohort trial assessed the impact of a range of different volumes of physical activity on health.

More than 400,000 people (199,265 men and 216,910 women) who participated in a standardized medical screening program in Taiwan from 1996-2008, and were followed for an average of slightly more than 8 years, formed the basis for this historically prospective cohort study. At enrollment, each participant completed a questionnaire addressing lifestyle information and their personal medical history. Participants were encouraged to return annually for evaluations, at which times the questionnaires would again be completed, but only the answers supplied during the initial visit were used for the purposes of the study.

Individual leisure time physical activity (LTPA) was determined via another questionnaire where subjects were asked to classify the types, intensities, and duration of weekly LTPAs they had performed during the previous month, with examples of types of exercise activities given under four intensity categories: light (walking), moderate (brisk walking), medium-vigorous (jogging), or high-vigorous (running). Metabolic equivalents (METs) were assigned to the activities based on existing guidelines.

The product of intensity (MET) and duration of exercise (h) was calculated for each subject, who were then classified into one of five different activity categories: inactive (< 3.75 MET-h), low (3.75–7.49 MET-h), medium (7.50–16.49 MET-h), high (16.50–25.49 MET-h), or very high (≥ 25.50 MET-h). The amount of physical activity done at work was also assessed, and on the basis of individual responses participants were classified into one of four different activity levels, ranging from low (mainly sedentary work) to a high level characterized by hard physical labor. Hazard ratios (HR) were calculated to compare mortality risks between individuals in different exercise groups (grouped by volume of exercise) and those in the inactive group.

Results were impressive — compared with individuals in the low-volume activity group, those in the inactive group had a 17% increased all-cause mortality risk (HR 1.17, 95% CI 1.10–1.24) and an 11% increased cancer mortality risk (1.11, 1.01–1.22). Participants in the low-volume activity group, who exercised for an average of 92 minutes per week or about 15 minutes a day, were found to have a 14% reduced risk of all-cause mortality (0.86, 0.81–0.91) and a longer life expectancy compared with subjects in the inactive group by 3 years. Every additional 15 minutes of daily exercise beyond the minimum volume of 15 minutes a day up to 100 minutes daily (after which no additional health benefits accrued) further reduced all-cause mortality by 4% (95% CI 2.5–7.0) and all-cancer mortality by 1% (0.3–4.5). Of note, vigorous-intensity exercise yielded similar or greater health benefits in terms of all-cause mortality reduction when compared with moderate-intensity exercise at similar or greater volumes of activity. The mortality benefits identified were applicable to all age groups and both sexes, even to those with cardiovascular disease risks, and remained consistent after controlling for numerous potential confounding factors.

The study authors conclude that as little as 15 minutes a day of moderate-intensity exercise might provide significant health benefits, even for those at risk for cardiovascular disease, and lessen the risk of death due to cardiovascular disease, cancer, and diabetes.

■ COMMENTARY

Prior to the publishing of this paper, the minimum exercise threshold above which mortality benefits reasonably could be expected could only be guessed at. "Guestimates" were usually in the range of 30-60 minutes performed on most days of the week; while reasonable on the surface, many people nonetheless find these fitness goals difficult to meet due to time constraints, health issues, and lack of commitment, among other reasons. In addition, the message that exercise can prevent heart disease and other illnesses is true and somewhat effective, but does not universally motivate people to get moving. But what if the message changed and was made easier to embrace and understand? Imagine if health professionals could honestly report to their patients that lesser but still regular amounts of physical activity, perhaps just 15 minutes a day, and requiring only moderate levels of exertion, could help them live 3 years longer than if they continued to be sedentary — that might be more likely to get a person's attention and light a fire under them. The exercise goal is easily attainable, the association between inactivity and mortality risk easily understandable, and the desire to put off death as long as possible remains pretty popular.

The minimum duration of exercise recommended on the basis of this study's results are 50-75% less than standard fitness guidelines, but additional minutes provide for additional health benefits. The researchers believe their data can be used to motivate people to exercise, and that once they begin they actually might increase the amount of time spent in fitness activities over time. For the relatively fit person who is pinched for time, and in agreement with the findings of a number of other studies, the researchers also found that higher intensity exercise performed for short periods may offer the same or even better health benefits than more moderate fitness activities of longer duration.

It would be great if we could interpret the results of this study as a slam dunk, but it was an observational trial, so cause (a limited amount of exercise) and effect (less risk of death) cannot be solidly defined. The results of observation need to be tested, but in this instance they can be safely promoted even as we await definitive evidence.

Americans have been reported to be more physically active than people living in East Asia where this study was conducted, but there are still too many of our patients who do not exercise regularly. In fact, too many health professionals could be classified as inactive, and we need to be good role models for healthy living. Committing to no less than 15 minutes a day of brisk walking, for example, should be a medical mantra. In a world where so much seems outside our control, how good it is to know, or at least assume reasonably, that such an easily attainable fitness goal may help give us some control over the length of our lives. ■

From Questions to Answers: How Research Is Designed

By Howell Sasser, PhD

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

THIS IS THE SECOND IN A THREE-PART SERIES ABOUT THE design and conduct of clinical research. The first installment discussed how research begins with the formulation of research questions (See *Alternative Medicine Alert*, September 2011). This article will look at the way the design of a study flows from the research question and from the available data. It also will consider briefly the most important potential problems in the design of research. It is intended not as a comprehensive review of study design, but rather as a reiteration of the key insights that research projects come in all shapes and sizes, and that each study must be designed in a way that is appropriate to its specific circumstances.

A research question can be answered reliably only with information collected in a systematic way. The details of a study design are really nothing more than a framework to ensure that the study's results allow for meaningful inference. A study's processes, the flow of what actually happens, should serve the question or questions it is trying to answer. In practical terms, this means that different kinds of questions will be best served by different kinds of studies. (*See Table 1.*)

In some situations, a rapid snapshot of conditions is all that is needed. If it is sufficient to know that when some characteristic is present in a population, another is also present some portion of the time, a cross-sectional study may be appropriate. In such a study, there is no a priori assumption that one thing causes another, only that they co-occur with a frequency that may suggest a relationship.

An example of this type of study is a survey of complementary and alternative medicine (CAM) use in an Irish hospital population by Chang and colleagues.[1] The authors distributed a questionnaire to cancer patients, pa-

Table 1. Strengths and Limitations of Observational and Experimental Studies

	Strengths	Limitations	Uses
Observational Studies			
Cross-Sectional Studies	Quickly completed Inexpensive	No risk estimate Bias likely Event sequence unclear	Opinion surveys Hypothesis generation
Case-Control Studies	Often quickly completed Good for rare outcomes	Bias possible Imperfect risk estimate	Studies of harm When latency is lengthy (i.e., cancer risk exposure)
Cohort Studies	Good for rare exposures Allow repeated measures Good estimate of risk	Lengthy and expensive Attrition likely	Long-term evaluation Studies with multiple outcomes of interest
Experimental Studies			
Clinical Trials	Best test of clinical interventions Least bias in risk estimate	Often very expensive Labor-intensive	Clinical settings Evidence for licensing of drugs and devices Development of clinical evidence base

tients with other diagnoses, and health care professionals. In addition to collecting information on use of various CAM modalities, they recorded demographic and social characteristics. From this, the authors reported the rate of CAM use (highest among health care workers, lowest among cancer patients) and various other factors that seemed to be associated statistically with CAM use (female sex, non-Christian faith, private health insurance). However, they did not suggest that any of these factors *caused* CAM use.

Other research questions have a clear element of causality — one factor precedes and is in some sense responsible for an outcome — but for any of several reasons, this causal sequence cannot be observed as it happens. This may be because the associated events are too far apart in time to make measurement practical or because the outcome event is rare, or even because the outcome is a negative event and observing it happen without intervening (and thus contaminating the study) would be unethical. When these issues arise, a common strategy is to use a case-control, or retrospective, design. In this type of study, a group of participants who already have the outcome of interest is assembled and compared with a group of participants who do not have the outcome. Any number of prior factors can be assessed for their possible association with the outcome, but a certain element of doubt as to which came first, the proposed risk factor or the outcome (an issue also called causal sequence), almost always tempers the strength of the conclusions in case-control studies.

An example of this design is Hedin and colleagues' study of prebiotic and probiotic use in a group of 234 patients with inflammatory bowel disease (IBD) as compared to such use in a group of 100 healthy controls.[2] Those with and without IBD were asked to recall their past use of pre/probiotics, and the comparative odds of use in the two groups were calculated. As compared with the healthy controls, the odds of prior probiotic use were more than four times as great among those with ulcerative colitis and more than three times as great among those with Crohn's Disease. Note that while this study design comes closer to addressing causality, its results are expressed in terms of the probability of earlier events among those with and without an outcome, not the probability of an outcome among those with and without an earlier event.

When possible, observing events in their "natural" sequence is a more reliable way to draw reasonable inferences about causality. In some situations, it is feasible to recruit a group of participants, determine that they have not yet had the outcome of interest, assess whether they have one or more other factors that may play a role in bringing about the outcome, and then follow them forward in time to see which do and which do not actually have the outcome. This is a cohort, or prospective, study design.

As an example, Sibbritt and colleagues studied a group of 14,701 randomly selected Australian women for the presence of asthma (seen here as the "risk factor") and the use of CAM modalities (seen here as the "outcome") over a 10-year period.[3] Participants completed questionnaires at baseline and three other times during the study. Those in the study population who were asthmatic were significantly more likely to use CAM overall than were those who were not asthmatic, but when CAM modalities were considered individually, a statistically significant relationship could only be shown for consultations with a

naturopath or herbalist.

The study designs discussed so far are all observational. In other words, the investigator observes and records characteristics and events, but does not intervene to assign exposure to some factor to some participants and not to others. In many clinical settings, however, it is important to assess the value of exposures such as therapeutic approaches that plainly are assigned or applied. In such cases, one of several variations on the clinical trial study design may be indicated. Common features of clinical trials are random assignment to one of two or more study treatments, the concealment of treatment assignment when practical to prevent deliberate or inadvertent biasing of study findings, and careful control of as many extraneous factors as possible to increase the likelihood that observed results are due to the study treatment.

For example, Cherkin and colleagues conducted a clinical trial in which participants were assigned randomly to one of two types of massage or to usual care for the treatment of low back pain.4 Each treatment lasted 10 weeks, and participants completed questionnaires measuring disability and symptoms at 10, 26, and 52 weeks. It was not possible to conceal the treatment assignment from participants, but those assessing the study's outcomes were not aware of which treatment each participant had received. Results at 10 weeks were similar in the two massage groups and statistically better than in the usual care group, however most of the benefit appeared to have dissipated by 52 weeks.

It is commonly observed that there is a rising strength of evidence in the study designs as ordered here. The greater our certainty as to the temporal sequence of events, the more reliable our inferences will be. However, this is subject to two caveats. First, it bears repeating that not every study design will fit every question. In some cases, a design that is lower in the study "food chain" may be the best, or indeed the only, option. Second, the relative strength of any study design rests on assumptions about the way its population of participants was assembled and the way information was collected from them. If the results of a study are to be broadly applicable, the study population must be similar in demographic and other important characteristics to the larger population it represents. Also, the information collected from study participants must be as complete and accurate as possible. When either of these conditions is not met, statistical results may (indeed will) still be calculated, but they may not mean what they appear to. The difficulty is that there often is no way of comparing study results to "truth," since they often are the only available source of information about the state of nature. So it is all the more important that studies be carefully constructed and conducted.

In the third article in this series, we will consider how study results are interpreted and applied in clinical and other health practice. ■

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Constipation, Cardiovascular Disease, and the Connection

ABSTRACT & COMMENTARY

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Dr. Gupta reports no financial relationship relevant to this field of study.

This article originally appeared in the September 29, 2011 issue of Internal Medicine Alert. At that time it was peer reviewed by Gerald Roberts, MD, Assistant Clinical Professor of Medicine, Albert Einstein College of Medicine, New York. Dr. Roberts reports no financial relationships relevant to this field of study.

Synopsis: *In postmenopausal women, constipation is associated with having major risk factors for cardiovascular disease and increased cardiovascular risk.*

Source: Salmoirago-Blotcher E, et al. Constipation and risk of cardiovascular disease among postmenopausal women. *Am J Med* 2011;124:714-723.

Constipation is one of the most common presenting complaints in a primary care practice. Estimates of population-based studies conducted in North America reveal that up to 27% of individuals may experience constipation, with most estimates ranging from 12% to 19%.[1]

Managing constipation is often frustrating and associated with substantial economic costs to the health care system.[2] Constipation is often treated on the basis of a patient's impression that there is a disturbance in bowel function. However, I must admit that I have often enjoyed having medical students and residents struggle with attempting to define something as simple as constipation. This is because constipation often has wide-ranging interpretations for most people. In clinical practice, constipation is generally defined as fewer than three bowel movements per week. While the rates for constipation are on the rise, especially in women and the elderly, very little is understood about the pathophysiology of this common clinical disorder.[3] Many of the risk factors associated with constipation, such as diabetes mellitus, hormonal abnormalities, and neurologic diseases, also contribute to cardiovascular disease. Therefore, it is reasonable to explore whether there may be a direct link between constipation and cardiovascular disease in the adult population.

In their study, Salmoirago-Blotcher et al conducted an analysis in 93,676 women enrolled in the observational arm of the Women's Health Initiative. The duration of follow-up in this group of postmenopausal women was between 6 and 10 years and information about constipation was collected by means of a self-administered questionnaire. For this study, the authors defined constipation as "difficulty having bowel movements" over the previous 4 weeks, and this was rated using a scale ranging from none (symptom did not occur), mild (symptom did not interfere with usual activities), moderate (symptom interfered somewhat with usual activities), to severe (symptom was so bothersome that usual activities could not be performed). The study outcomes, identified by self-report, were coronary heart disease, stroke, breast and colorectal cancer, osteoporotic fractures, diabetes, and total mortality.

Due to exclusions, the final analysis included 73,047 women. Researchers found that women with moderate and severe constipation experienced more cardiovascular events (14.2 and 19.1 events/1000 person-years, respectively) compared with women with no constipation (9.6/1000 person-years). Researchers also found that constipation was associated with the following factors: increased age, African American and Hispanic descent, smoking, diabetes, high cholesterol, family history of myocardial infarction, hypertension, obesity, lower physical activity levels, lower fiber intake, and depression. However, after adjusting for these factors, constipation was no longer associated with an increased risk of cardiovascular events, except for the severe constipation group, which had a 23% higher risk of cardiovascular events.

The authors conclude that in postmenopausal women, while evidence for an independent association or for a causal association between constipation and cardiovascular disease was not found, constipation is a marker for the major risk factors for cardiovascular disease and increased cardiovascular risk. Thus, they state that because constipation is easily evaluated in a primary care setting, it may be a helpful tool to identify postmenopausal women who may be at increased cardiovascular risk.

■ **COMMENTARY**

We know that although constipation is a common condition, only a proportion of the affected individuals will seek health care for their symptoms. However, this does not stop people from utilizing health care resources to attempt to self-treat the condition. On the other hand, cardiovascular disease remains one of the leading causes of morbidity and mortality in women in the United States. Women fare less well than men after a myocardial infarction or cardiac interventions. Their short- and long-term prognosis is worse and the likelihood for adverse events is higher than in men. The postmenopausal state itself renders a woman at higher likelihood for cardiovascular disease.

While the results of this study are not conclusive enough to warrant definitive recommendations, they may provide valuable information regarding health and lifestyle choices of the patients being seen. Along with recommending diet and lifestyle changes, physicians can potentially use constipation in postmenopausal women as another opportunity to discuss cardiovascular risks with the patients as well as to conduct an evaluation for factors such as hypertension, hyperlipidemia, obesity, and smoking status. ■

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Chinese Herbal Remedy for H1N1

By Carol A. Kemper, MD, FACP

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This article originally appeared in the October 2011 issue of Infectious Disease Alert. At that time, it was peer reviewed by Timothy Jenkins, MD, Assistant Professor of Medicine, University of Colorado, Denver Health Medical Center. Dr. Jenkins reports no financial relationship to this field of study.

Source: Wang C, et al. Oseltamivir compared with the Chinese Traditional Therapy Maxingshigan-Yinqiaosan in the treatment of H1N1 Influenza. *Ann Intern Med* 2011;15:217-225.

THOUSANDS OF CHINESE USED A COMPOUND CALLED MAXingshigan-yinqiaosan (MY) for treatment of flu symptoms during the 2009 H1N1 epidemic. MY is a concoction of 12 different herbs, including toasted Herba ephedra, as well as qinghao, gypsum fibrosum, and rhizoma.

To test the efficacy of this herbal remedy for influenza, the authors conducted an unblinded, randomized study of 410 adults (ages 15-59; average age, 19 years) with laboratory-confirmed influenza H1N1. Patients were randomly assigned in a 1:1 fashion to receive 5 days of either oseltamivir (OS), OS plus MY, MY alone, or nothing. Patients were excluded from study if they had pneumonia or abnormal chest radiographs, other significant underlying illness or HIV infection, or had received influenza vaccination in the past year. All of the participants were hospitalized for quarantine and close monitoring. Serial real-time PCR for viral RNA titers were conducted daily in a subset of 148 randomly selected patients.

The MY compound met Chinese safety standards and was tested for heavy metals, bacterial contamination, and pesticides, and was centrally distributed to the study sites. Antibiotics could be used at the discretion of the treating physician.

The median time from onset of illness to randomization was 35 hours (range, 18-48 hours), and was similar between the three active treatment groups and controls. The use of concomitant antibacterials was similar in the four groups prior to randomization. Following randomization, the control group received significantly more antibiotics than the three active treatment groups (34% vs. 15.7% for OS, 9.7% for MY, and 7.8% for OS + MY; $P < 0.001$). Time to resolution of fever was significantly less for all three treatment groups compared with the control group (median time, 15 hours for OS + MY, 16 hours for MY, 20 hours for OS, and 26 hours for the control group; $P < 0.001$). A borderline statistically significant difference in favor of the combined treatment group compared with the OS group was observed for time to resolution of fever. No difference in the reduction of other symptoms (cough, headache, fatigue) between the groups was observed. Only two patients developed nausea and vomiting with MY, and none reported side effects to OS.

Throat swabs demonstrated a rapid reduction in H1N1 viral shedding between baseline and day 5, although no significant difference between the treatment groups and controls was detected. By day 5 of illness, viral shedding was still detectable by PCR in 40% of the control group, 30% of the MY group, and 16-18% of the groups receiving OS. Further analysis revealed that this subgroup of patients had a lower symptom score compared with the other study patients.

The combination of this Chinese herbal remedy plus oseltamivir for influenza H1N1 appeared more effective than OS alone in the reduction of fever, and was well-tolerated. ■

Why You Should Outsource Your Weight Loss Treatment

ABSTRACT & COMMENTARY

By Barbara A. Phillips, MD, MSPH

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Dr. Phillips serves on the speakers bureaus for Cephalon, Resmed, and Respironics.

This article originally appeared in the September 29, 2011 issue of Internal Medicine Alert. At that time it was peer reviewed by Gerald Roberts, MD, Assistant Clinical Professor of Medicine, Albert Einstein College of Medicine, New York. Dr. Roberts reports no financial relationships relevant to this field of study.

Synopsis: *Participation in Weight Watchers resulted in a greater weight loss over a year than did clinical intervention in a primary care office.*

Source: Jebb SA, et al. Primary care referral to a commercial provider for weight loss treatment versus standard care: A randomised controlled trial. *Lancet* 2011; doi:10.1016/S0140-6736(11)61344-5.

THIS STUDY (WHICH WAS FUNDED BY WEIGHT WATCHERS) WAS a multicenter, randomized, controlled trial involving patients recruited from primary care practices in Germany, Australia, and the UK. To be included, patients had to have body mass index (BMI) of 27-35 kg/m^2 and at least one additional risk factor for obesity-related disease, including central adiposity, type 2 diabetes without insulin treatment, family history of diabetes, previous gestational diabetes, impaired glucose tolerance, dyslipidemia, hypertension, polycystic ovarian syndrome, lower-limb os-

teoarthritis, or abdominal hernia. People were excluded for a variety of reasons, including having had a weight loss of 5 kg or more in the previous 3 months, eating disorders, limitations to regular physical activity, untreated thyroid disease, ongoing or past surgical treatment for weight or appetite, and insulin-treated diabetes. Participants were randomized to receive 12 months of free access to a Weight Watchers program or 12 months of standard care, as defined by national treatment guidelines in the three participating countries.1-3 A total of 772 people were recruited, screened, and randomized, and were assessed at 2, 4, 6, 9, and 12 months with measurements of weight, fat mass, waist circumference, blood pressure, and biomarkers of cardiovascular risk, as well as self-reported data about food intake and physical activity. The Weight Watchers program was more intensive; participants attending assessment visits for standard care reported a mean of one appointment per month with their health care provider, but those assigned to the Weight Watchers group attended a mean of three meetings per month in the UK and Australia and two meetings per month in Germany.

The dropout rate was high, with only 61% of those in the Weight Watchers group and 54% of those in the "standard care" program completing the full 12 months of assessment. Notably, the patients from Germany were much less likely to drop out; 75% of them completed the study. Participants who completed the 12-month assessment were significantly older at baseline (mean, 50.2 years) than were those who did not (43.6 years), but there were no significant effects of sex, baseline weight, or diabetes status on whether individuals completed the 12-month assessment. Of those who completed the year of follow-up, those in the Weight Watchers group lost about twice as much weight as those in the usual care group: 5.06 kg (11 lbs) vs 2.25 kg (5 lbs). Those in the Weight Watchers program were also more likely to lose at least 5% or 10% of their weight. Participants randomized to the commercial program also had larger reductions in waist circumference, fat mass, insulin, and ratio of total to HDL cholesterol. There were small reductions in blood pressure in both treatment groups. No adverse events were reported by either group.

■ COMMENTARY

I found the results of this trial dismal, but not surprising. The most discouraging thing was that only slightly more than half of the people (who were motivated enough to enroll and go through screening) completed the trial. It is probably safe to say that those who didn't finish the study probably didn't lose any weight. Also discouraging is that those who did complete the most effective protocol only lost about 11 pounds on average. Obesity is a chronic, intractable disease. And dealing with it consumes a great deal of time and emotional energy in almost every

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aspect of medicine. This report confirms and extends other studies of commercial weight loss programs, including Weight Watchers and Jenny Craig, demonstrating that these types of programs are more effective in addressing the intractable problem of obesity than are interventions in clinicians' offices.4-8 As a physician who is confronted daily by the implacably obese, I find this to be powerful, time saving-information. Specific referral to a commercial weight loss program may result not only in greater weight loss for my patients, but also in reduced angst, wasted time, and reprimands by customer service personnel for me. ■

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c. 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.

CME Questions

1. Which if the following is true regarding fish oils, mesenchymal stem cells (MSC), and chemotherapy?

a. MSCs block tumor growth.
b. Neither the commercial fish oil or algae-derived products tested induced resistance to platinum-based chemotherapy.
c. PIFAs are commonly present in commercial fish oil products and algae extracts.
d. MSCs confer chemoresistance not only to platinum-based chemotherapy but also to drugs such as irinotecan and 5-FU.
e. Large amounts of PIFAs are required to induce chemoresistance.

2. Fifteen minutes of daily light exercise, such as slow walking, confers a potential life extension benefit of approximately 3 years.

a. True
b. False

3. In the relationship between constipation and cardiovascular disease in postmenopausal women, which of the following statements is false?

a. There is a causal association between constipation and cardiovascular disease.
b. Constipation is one of the most common chief complaints expressed by patients visiting their primary doctors.
c. Constipation is associated with having increased cardiovascular risk.
d. Both constipation and cardiovascular disease are common in postmenopausal women.

4. Regarding effects of weight loss strategies:

a. commercial programs are more successful than intensive advice.
b. women are generally more successful at weight loss than are men.
c. retention in a structured weight management programs is generally high, averaging 75-85%.
d. individuals who complete 12 months of a structured weight loss program typically lose 20-25 pounds.

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