

# In This Issue: Antiestrogen Withdrawal, Yoga, and a Reflection on Quality of Clinical Trials

Integrative Cancer Therapies  
2016, Vol. 15(3) 239–241  
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DOI: 10.1177/1534735416661418  
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This issue, the second-to-last printed issue of *Integrative Cancer Therapies* before the publication goes to fully online-only publication, contains some especially significant articles, and also notably includes 4 articles on the potential importance of yoga for cancer patients.

Appearing first in this issue is a pair of particularly interesting articles on the topic of the antiestrogen withdrawal response. One is a case report submitted by an alert naturopath, Walter Lemmo of Lemmo Integrated Cancer Care in Vancouver, Canada, who took the time to really listen to a patient and take her perceptions and intuitions seriously, as well as maintaining a wide acquaintance with the scientific literature. This equipped him to understand the potential importance of what she reported, which turned out to be the first clinical case of an antiestrogen withdrawal effect reported for raloxifene. The other article is a Guest Editorial commenting on this case by V. Craig Jordan, known as the “father of tamoxifen,” Professor of Breast Medical Oncology at MD Anderson Cancer Center, and the Dallas/Fort Worth Living Legend Chair of Cancer Research. We are honored to have Jordan explain for us in detail the real significance of and the biology behind the antiestrogen withdrawal response, an area of particular interest for him.

An antiestrogen withdrawal response is a phenomenon seen with antiestrogen drugs such as tamoxifen and, as Lemmo’s case demonstrates, raloxifene. It should be no surprise that prolonged treatment with an antiestrogenic drug like tamoxifen will eventually result in tamoxifen-resistant cells, which has been demonstrated in the laboratory. However, continued treatment with the antiestrogen finally leads to the evolution of a new population of cancer cells that, surprisingly, are highly susceptible to apoptosis when exposed to estrogen. Stopping antiestrogen treatment, and thus allowing these cells to be exposed to a patient’s naturally produced estrogen, can result in a 30% tumor response rate in breast cancer patients. The anticancer effects of antiestrogens, in other words, continue when the medications are stopped. A similar phenomenon underlies the clinical use of intermittent androgen deprivation in prostate cancer patients. Dr Jordan—not one to rest on his laurels after developing a drug that revolutionized breast cancer treatment—is now conducting further research into

exploiting this phenomenon to further improve the treatment of breast cancer patients. We urge all clinicians to read Lemmo’s case, keeping in mind the contributions to science that even a single clinician can make, as well as the importance of remaining appropriately open to their patients’ self-reports. Breast cancer clinicians are especially urged to read Jordan’s summary of the biology of antiestrogen withdrawal for a timely update on this very intriguing area of research.

The issue then turns from deep biology to the realm of mind-body medicine, or what we call biobehavioral medicine. Four studies on yoga have recently been accepted in the journal. The first of these also hails from MD Anderson, and is an examination by Lorenzo Cohen and colleagues of moderators and mediators of yoga’s effects in a trial previously conducted in breast cancer patients receiving radiotherapy. Their particular goal in this study was to determine yoga’s specific effects in patients who suffered from depression and sleep disturbance at the start of the trial. Michelle Janelsins and colleagues at the University of Rochester also examined moderators and mediators of yoga’s effects in a randomized trial that had shown that yoga improved memory in breast cancer patients. They were also concerned about sleep difficulties, and in particular, whether yoga might have affected memory because of an effect on sleep. Neha Vapiwala and colleagues report a feasibility study of yoga for prostate cancer patients, also undergoing radiation therapy. Yoga is usually offered to breast cancer patients, but its benefits need exploration beyond just female populations. Results reassuringly demonstrate the acceptability of yoga to prostate cancer patients. Finally, Lillian Sung of the Hospital for Sick Children in Toronto, along with her colleagues, explains the development of a yoga intervention for hospitalized pediatric cancer patients. The program aims to address the fatigue commonly observed as a treatment side effect through a yoga program acceptable to children

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that stresses safety, adaptability, environmental flexibility, and appeal to children—in other words, fun!

Among other subjects in this issue, Michael McCulloch of the Pine Street Foundation in San Anselmo, California, addresses the important topic of the ability of Chinese herbal formulas to prevent toxicity from fluorouracil-based chemotherapy regimens. The low quality of many of the older trials of traditional Chinese medicine that are used in published meta-analyses has been pointed out by other authors. McCulloch and coauthors take this caution seriously, and offer a quality-adjusted meta-analysis that sorts results according to the risk of bias evident in the trial designs. The results are sobering.

Evidence that exercise benefits breast cancer patients is increasing, but with it come questions—about safety as well as about efficacy. Prue Cormie of Edith Cowan University in Western Australia, along with colleagues explore a crucial question about safety in their study of the influence of resistance training on acute inflammation in breast cancer patients with lymphedema.

Consumption of grains and carbohydrates is a continuing point of controversy in cancer as well as in other illnesses. Reema Tayyem of Hashemite University in Jordan provides a case-control study examining the consumption of whole and refined grains, and their influence on colorectal cancer. The results, with whole grain consumers much less likely to contract colon cancer than those eating mainly refined grains, do not come as much of a surprise, but interestingly extend the range of populations in which this question has been tested.

Joshua Bauml and colleagues at the University of Pennsylvania conducted a feasibility study of acupuncture for dyspnea. Dyspnea is a distressing symptom for patients, and nonpharmacological methods of managing it would be welcomed by many. This feasibility study was notable for the high rate of completion of the 10-week acupuncture intervention, and encouraging signs of improvement in outcome variables.

Curcumin is a phytochemical of great interest in cancer research. Amirhossein Sahebkar of Mashad University of Medical Sciences in Mashad, Iran provides a brief summary of research on curcumin and its analog, 3,4-difluorobenzylidene curcumin (CDF) focused on potential use in pancreatic cancer. Both curcumin and CDF have potential bioavailability problems, for which several new technologies are currently being tried in preclinical settings, as Sahebkar discusses.

Luke McPherson and colleagues at the University of Western Sydney conducted a qualitative study with practitioners of traditional Chinese medicine (TCM) in Australia. Several themes emerged in discussions, with a notable emphasis on lack of understanding of TCM by conventional biomedical practitioners. Additionally, there is variability within the TCM community on best strategies of TCM diagnosis and treatment protocols.

As more hospitals add integrative treatment programs to their offerings, it is important to evaluate how well these programs serve patients, and what kinds of improvements in health could be expected by patients attending them. Chiu Jen-Hwey and colleagues at National Ming-Yang University in Taipei evaluated an outpatient integrative care center aimed at breast cancer patients that was attached to a major hospital. Patients could receive integrative consultations with or without acupuncture. The program is well-accepted by patients, a number of whom include acupuncture in their regimens.

Hepatocellular carcinoma (HCC) is the second leading cause of cancer death in men worldwide, and the sixth leading cause in women.<sup>1</sup> With the large number of patients receiving HCC treatment, especially in Asia where this cancer is most common, there is a need to help patients reduce treatment side effects. A common treatment is transcatheter arterial chemoembolization (TACE), which results in a short hospital stay as patients recover from the procedure. Zhigiang Meng and colleagues at Fudan University explored the use of a TCM decoction, Jian Pi Li Qi, for reducing symptoms and aiding recovery in a randomized trial. Their encouraging results suggest a possibility for further study of this agent.

A systematic review of flaxseed published in this journal in 2014<sup>2</sup> found a decreased risk of breast cancer with flax intake. This issue features an *in vitro* study of flaxseed oil as a chemopreventive agent for skin cancer, by Jyoti Sharma and colleagues at the University of Rajasthan. Their *in vivo* study indicated not only reduced tumor growth in the mouse model, but also reductions in lipid peroxidation, with increases in antioxidant activity and activity of phase II detoxifying enzymes. The ability of natural products to affect so many biologically relevant parameters continues to amaze us.

Another research group from Fudan University, led by Quan-Bao Zhang, studied an herbal compound for prevention of liver cancer metastasis in mice through an immunomodulatory mechanism. Most unusually, this animal study takes seriously the dictate of integrative cancer therapy that multiple lifestyle interventions are better for overall health, and combined the herbal therapy with moderate swimming, an exercise intervention for mice. Swim training for mice had previously been shown to inhibit the growth of liver tumors (hepatoma). Examination of the improvements in immune system variables for the combined intervention provides important data that may be useful in the development and evaluation of clinical integrative cancer treatment.

Bitter melon is known as an herb with antidiabetic effects. With the increasing recognition of the importance of diabetes as a risk factor for cancer, interest in antidiabetic natural products is rising. Metformin is a natural product derivative that is of major importance in diabetes treatment,

and increasingly being explored in cancer. Its anticancer activity may be derived from its stimulation of AMP-activated protein kinase (AMPK). David Chan at the University of Hong Kong, along with colleagues, examined bitter melon to see if it had AMPK-activating properties, and whether these might be useful in ovarian cancer in mice, including cancer cells with cisplatin resistance. Their exploration of molecular pathways involved in the tumor inhibition they observed provides additional impetus to the study of antidiabetic natural products in cancer.

The final article in the issue wrestles with the problem of poor bioavailability of anticancer phytochemicals. Icariside II is a flavonoid from a plant in the barberry family, with anticancer activity but with solubility problems. Xiaobin Jia

and Zhenhai Zhang of the Key Laboratory of Delivery Systems of Chinese Materia Medica in Jiangsu have formulated this phytochemical into micelles made of a phospholipid complex and a solubilizer. Their interesting results in a mouse model highlight the potentials of research in the area of drug delivery for natural products, which will be crucial in translating the potentials of nature into clinically useful medications.

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