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DEFEAT Cancer

ADVANCED SPECIALTY CARE

E&N News *September 2008*

EXERCISE & NUTRITION during/after CANCER

CURRENT PEER-REVIEWED MEDICAL LITERATURE and EXPERT COMMENTARY from RELIABLE SOURCES and DR. BLEYER

A reminder: the January-June 2008 compendium on ***E&N*** *News* is available for downloading on the DEFEAT Cancer website: www.defeatcancer.info. It is fully indexed and bookmarked.

The Second Expert Report website, www.dietandcancerreport.org, featuring the WCRF/AICR Expert Report, *Food, Nutrition, Physical Activity and the Prevention of Cancer: a Global Perspective*, includes errors and omissions in the report that have been identified since the launch of the report and new material on their continuous review project and policy report

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Exercise

Said the doctor to the cancer patient: Hit the gym

The bandwagon of exercise programs for cancer patients and survivors is rolling

New York Times - August 14, 2008
By ANAHAD O'CONNOR
AS the group of women trickled into the aerobics studio at the Bendheim Integrative Medicine Center in Manhattan on a recent Thursday morning, there were subtle signs that this was no ordinary fitness class. One woman told the instructor that she had missed a string of previous classes because she was grappling with fatigue, a side effect of her new cancer medication. Others wore colorful wraps on their arms, containment sleeves meant to protect against lymphedema, a painful swelling of the arm stemming from breast cancer surgery.

Sponsored by **Memorial Sloan-Kettering Cancer Center**, this class for cancer patients has been around for some time, mostly in a league by itself. But in recent years, following studies that found exercise to be beneficial in combating the effects of cancer, the class has gained some company.

Gyms and fitness centers have begun stepping in to meet a small but growing demand for programs designed to not only hasten recovery but to address the fatigue of chemotherapy, the swelling of lymphedema and the loss of muscle tone.

There have always been athletically inclined patients who stayed active, even competitive, in the wake of a diagnosis. A recent high-profile example is Eric Shanteau, an American Olympic swimmer who decided to put off testicular-cancer surgery until he had competed in Beijing.

But most of the roughly 10 million cancer survivors in the United States are not amateur Lance Armstrongs. Many, though, are inspired by celebrities like Mr. Armstrong, seeing them as models for how to come out on the other side of often-debilitating treatment regimens.

A new program from the **Y.M.C.A., in partnership with the Lance Armstrong Foundation**, offers cancer fitness classes at more than a dozen Y's in 10 states. At the women's gym **Curves International, researchers from Fox Chase Cancer Center in Philadelphia** are looking at whether overweight breast-cancer patients can keep to a five-day-a-week Curves routine for six months. And survivors are organizing their own classes.

"There used to be this understanding that if you're getting treatment you're supposed to be in your bed," said Pam Whitehead, an architect and survivor of uterine cancer who started the Triumph Fitness Program at gyms in Modesto and West Sacramento, Calif.

In some cases, oncologists are prescribing exercise, gently prodding patients to tackle whatever activity they can manage: light walking, simple stretches, exercise with resistance bands.

"I started in 1992 and that was really a time when not as many patients were exercising," said Dr. Alexandra Heerdt, a breast surgeon at Sloan-Kettering who is conducting a pilot program involving exercise. "If a patient came to me back then and asked about exercise, I would have said there wasn't really any information."

But now, she added, "they have a lot of options."

Wendy Rahn, 46, an associate professor of political science at the University of Minnesota, knows this well. After a double mastectomy, her shoulders hurt so much that she was often hunched in pain. Then, while researching her illness, she discovered a 2005 study on cancer and exercise.

"The effects — what we call effect sizes in statistical research — were enormous," she said, "and I was like 'How come no one is talking about this?' " She had given up exercise a decade earlier, but the study inspired her to go back to the gym.

"I started feeling so much better," she said. "And it struck me that if I'm feeling this good, then every cancer survivor should."

So she founded a nonprofit group called Survivors' Training, and in January opened a fitness studio in White Bear Lake, Minn., offering yoga, strength training, Pilates and Nia, which combines dance and martial arts. "I like to think of it as a support group that moves," she said.

Cancer experts say the shift in thinking began in the mid-1980s, coinciding with a greater awareness of health and fitness. Oncologists were faced with questions about exercise that they had never heard before: how much was allowable and when?

Scientists also took notice of studies showing that those who were physically active and eating well were less likely to develop cancer. They then asked what impact exercise and diet would have on those with the disease, said **Dr. Charles Fuchs**, an oncologist at the **Dana-Farber Cancer Institute** in Boston who studies cancer and exercise.

In the last eight years, a dearth of research has become a flood of studies. Among them is one sponsored by the National Cancer Institute in 2006 that looked at the effects of moderate exercise on groups of breast and prostate cancer patients undergoing radiation therapy for six weeks.

Those assigned to a daily program — taking walks of increasing distance and doing exercises with a resistance band — had less fatigue, greater strength and better aerobic capacity than those who were not instructed to exercise. This finding, and similar ones, has been replicated many times.

Other studies indicate that moderate exercise has additional benefits like strengthened immune function and lower rates of recurrence. **Studies at Dana-Farber found that non-metastatic colon cancer patients who routinely exercised had a 50 percent lower mortality rate during the study period than their inactive peers, regardless of how active they were before the diagnoses**.

Dr. Fuchs, a study author, said it influenced his advice. "I am counseling all of my patients to increase their activity," he said, "or if they were regularly exercising before their diagnosis, to continue."

But every recommendation has its caveats. There will be days during treatment when meaningful activity is not possible, oncologists say, and that's fine. The American Cancer Society promotes moderate exercise but encourages patients to discuss their exercise plans with their oncologists, and lists on its Web site 13 precautions (cancer .org/docroot/MIT/MIT_0.asp).

In the biweekly Focused Fitness class at the Bendheim Integrative Medicine Center in New York, the instructor, Donna Wilson, seeks to ease her charges back into exercise after, and often during, physically draining treatments. Arm extensions and other range-of-motion exercises that can help relieve lymphedema were first on the agenda on a recent morning, followed by heart-pumping lunges and core exercises. A woman who had breast cancer slogged through a set of isometric exercises. "It looks easy," she said, "but try keeping your arms up all the time when your nerves have been cut."

Ms. Wilson, a registered nurse, encouraged the woman to keep pushing. Then she looked at the class and turned to a visitor. "They're amazingly strong," she said.

Dr. Bleyer:

☑ **Therapeutic Associates** have been offering personal fitness training programs for ***DEFEAT Cancer*** participants at both their Bend and Redmond facilities since the beginning of the ***DEFEAT Cancer*** program, at no charge

☑ The LAF Program at YMCA is very similar to ***DEFEAT Cancer***'s program.

☑ ***DEFEAT Cancer*** been a pace setter!

Nutrition

Mortality and cardiovascular events in patients treated with homocysteine-lowering B vitamins after coronary angiography: A randomized controlled trial [Prevention]

Folic acid and vitamin B12 therapy did not reduce heart attacks after coronary angiography but may have increased cancer incidence

Ebbing M, Bleie O, Ueland PM, et al
JAMA. 2008;300(7):795-804.
Context Observational studies have reported associations between circulating total homocysteine concentration and risk of cardiovascular disease. Oral administration of folic acid and vitamin B12 can lower plasma total homocysteine levels.
Objective To assess the effect of treatment with folic acid and vitamin B12 and the effect of treatment with vitamin B6 as secondary prevention in patients with coronary artery disease or aortic valve stenosis.
Design, Setting, and Participants Randomized, double-blind controlled trial conducted in the 2 university hospitals in western Norway in 1999-2006. A total of 3096 adult participants undergoing coronary angiography (20.5% female; mean age, 61.7 years) were randomized. At baseline, 59.3% had double- or triple-vessel disease, 83.7% had stable angina pectoris, and 14.9% had acute coronary syndromes. Interventions Using a 2 x 2 factorial design, participants were randomly assigned to 1 of 4 groups receiving daily oral treatment with folic acid, 0.8 mg, plus vitamin B12, 0.4 mg, plus vitamin B6, 40 mg (n = 772); folic acid plus vitamin B12 (n = 772); vitamin B6 alone (n = 772); or placebo (n = 780).
Main Outcome Measures The primary end point was a composite of all-cause death, nonfatal acute myocardial infarction, acute hospitalization for unstable angina pectoris, and nonfatal thromboembolic stroke.
Results Mean plasma total homocysteine concentration was reduced by 30% after 1 year of treatment in the groups receiving folic acid and vitamin B12. **The trial was terminated early because of concern among participants due to preliminary results from a contemporaneous Norwegian trial suggesting adverse effects from the intervention**. During a median 38 months of follow-up, the primary end point was experienced by a total of 422 participants (13.7%): 219 participants (14.2%) receiving folic acid/vitamin B12 vs 203 (13.1%) not receiving such treatment (hazard ratio, 1.09; 95% confidence interval, 0.90-1.32; P = .36) and 200 participants (13.0%) receiving vitamin B6 vs 222 (14.3%) not receiving vitamin B6 (hazard ratio, 0.90; 95% confidence interval, 0.74-1.09; P = .28).
Conclusions This trial did not find an effect of treatment with folic acid/vitamin B12 or vitamin B6 on total mortality or cardiovascular events. Our findings do not support the use of B vitamins as secondary prevention in patients with coronary artery disease.

Dr. Bleyer:
☑This report is included because secondary endpoints, not mentioned in the abstract, included cancer incidence, for which had a slight increase with the vitamin therapy that was not statistically significant
☑See the next report for additional information

Dietary supplements may pose risk to older cancer survivors
It's unclear if pills help keep them healthier or put them in danger of disease recurrence

The risks of antioxidants and other supplemental vitamin consumption, is particularly evident in older cancer survivors, and may not only be unnecessary but also put the survivor at increased risk of cancer recurrence

HealthDay News - Aug. 21, 2008
Older cancer survivors need to listen to warnings about the potential risks of dietary supplements, say Duke University Medical Center researchers and colleagues.
They noted that many older cancer patients who've survived five years or more take vitamins, minerals and other dietary supplements in an effort to remain disease-free. However, this supplement use may backfire.
"One of the most common behavioral changes cancer survivors make -- sometimes without a doctor's advice, often on their own -- is using dietary supplements in hopes of bolstering their health," researcher **Denise Snyder**, clinical trials manager at the **Duke School of Nursing**, said in a university news release. "Still, it's unclear whether supplements really help keep cancer survivors healthier or put them at further

risk. They, like many other people today, use the Internet, and you can find a lot of false hope out there with supplements targeted at cancer survivors."
Snyder and colleagues at **Pennsylvania State University** and the **University of Texas M.D. Anderson Cancer Center** studied 753 cancer survivors, age 65 and older. About 75 percent of them were taking dietary supplements, including multivitamins (60 percent), calcium/vitamin D (37 percent), antioxidants (30 percent), and herbs, amino acids and glandular extracts.
"In our study, we see people taking supplements who have good diets and who are relatively healthy. While they may need a particular vitamin because they don't get enough of it, they may not need a multivitamin or supplement because of the increased risk of cancer recurrence or secondary cancer," Snyder said.
Before they start to take supplements, older cancer survivors should talk with their health care provider or a registered dietitian, she advised.
The study was published in the Journal of Cancer Survivorship.

Dr. Bleyer:
☑ The caution expressed is reasonable, but lack sufficient evidence to warrant recommdation
☑ DEFEAT Cancer would prefer to supplement physical activity with exercise, for which abundance evidence for benefit exists, than with more vitamins, herbs, amino acids or glandular extracts for which there is little to no evidence for benefit and a scientific basis for concern that risk of recurrence may actually be increased (see next report)

Vitamin B, folate supplements won't help heart [Prevention]
In fact, new study hints they might be hazardous

Why the vitamin B12 - folic acid trial in the prior report was stopped and commentary from reliable experts

HealthDay News - Aug. 19, 2008
By Ed Edelson
A study to determine whether folic acid and vitamin B supplements help the heart has been cut short, because the pills weren't doing any good and might have even caused participants harm.
"This confirms what a lot of recent studies have found -- no benefit of taking vitamin B supplements to reduce the risk of heart disease, and it raises a few red flags," said **Alice H. Lichtenstein**, Gershoff Professor of Nutrition at Tufts University, Boston.
In the new study, reported in the Aug. 20 issue of the Journal of the American Medical Association, physicians at Haukeland University Hospital in Bergen, Norway, enrolled almost 3,100 volunteers. Three-quarters of them took various doses of vitamin B and folic acid (which is chemically a B vitamin), while the others got a placebo, an inactive substance.
The study was ended early, after an average follow-up of 38 months, because "we could not detect any preventive effect of intervention with folic acid plus vitamin B12 or with vitamin B6 on mortality or major cardiovascular events," the researchers reported.
They did find a **slight reduction of stroke**, but also a **slight increase of cancer in those taking folic acid**, but **neither of these results reached statistical significance**. The study was ended, because **another Norwegian study of folic acid and vitamin B supplementation has also hinted at an increased incidence of cancer among users**.
But the real bottom line here, according to Lichtenstein, is that "there is no evidence that individuals should take B vitamins to decrease the risk of heart disease, and there may be some evidence that they shouldn't."
The trials were initiated, because observational studies did link high blood levels of a protein called homocysteine with an increased risk of cardiovascular disease. In the new study, homocysteine levels did go down by 30 percent over the course of three years in people taking folic acid and vitamin B. However, there was no related effect on the risk of cardiovascular events.
So, "the observational data was great, but the interventional studies were negative," Lichtenstein said.
Food in the United States is routinely fortified with folic acid, because it reduces the incidence of a specific class of birth defects called neural tube defects. Folic acid is a synthetic form of folate, a B vitamin found in many fruits and vegetables.
"We have been optimistic about the role of antioxidants such as vitamin B in preventing heart disease, yet many of these large trials have shown that there is no benefit," said Dr. **Suzanne Steinbaum**, director of women and heart disease at Lenox Hill Hospital in New York City.

It's hard to say whether the reduction in cardiovascular disease seen in some observational trials was caused by vitamin supplementation or because "people taking the supplements have good lifestyles in general," Steinbaum said.

It is also possible that the benefits of vitamin supplements show up only after many years, Steinbaum said. She does **recommend a daily multivitamin pill**. "But at this point, it is certainly hard to recommend extra supplements when we don't have proof of benefit," Steinbaum said. "What we can **recommend is a diet with fruits and vegetables that have antioxidant vitamins in them**," she said.

SOURCES: Alice M. Lichtenstein, D.Sc., Stanley Gershoff Professor, Nutrition, Tufts University, Boston; Suzanne Steinbaum, M.D., Director, Women and Heart Disease, Lenox Hill Hospital, New York City; Aug. 20, 2008, Journal of the American Medical Association

Dr. Bleyer:

- ☑ This report on two trials in Norway whose combined results suggested that vitamin B and folic acid supplementation increase cancer incidence, and led to a discontinuation of the trial, again lead to a caution of non-discriminate vitamin therapy
- ☑ DEFEAT Cancer points out that physical activity was not controlled or studied
- ☑ As the Director, Women and Heart Disease at Lenox Hill Hospital in NYC implied, fruits and vegetables and a daily multivitamin pill should not be further supplemented with extra vitamin supplements

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Vitamin C injections slow tumor growth in mice [Laboratory Study]

Very high doses of vitamin C that can only be achieved with parenteral (intravenous, intratumor, intracavitary) injection and not by diet or oral administration may have anti-cancer activity

High-dose injections of vitamin C, also known as ascorbate or ascorbic acid, reduced tumor weight and growth rate by about 50 percent in mouse models of brain, ovarian, and pancreatic cancers, researchers from the National Institutes of Health (NIH) report in the August 5, 2008, issue of the Proceedings of the National Academy of Sciences. The researchers traced ascorbate's anti-cancer effect to the formation of hydrogen peroxide in the extracellular fluid surrounding the tumors. Normal cells were unaffected.

Natural physiologic controls precisely regulate the amount of ascorbate absorbed by the body when it is taken orally. "When you eat foods containing more than 200 milligrams of vitamin C a day -- for example, 2 oranges and a serving of broccoli -- your body prevents blood levels of ascorbate from exceeding a narrow range," says **Mark Levine**, M.D., the study's lead author and **chief of the Molecular and Clinical Nutrition Section of the National Institute of Diabetes and Digestive and Kidney Diseases** (NIDDK), part of the NIH. To bypass these normal controls, NIH scientists **injected ascorbate into the veins or abdominal cavities** of rodents with aggressive brain, ovarian, and pancreatic tumors. By doing so, they were able to deliver high doses of ascorbate, up to 4 grams per kilogram of body weight daily. "At these high injected doses, we hoped to see drug-like activity that might be useful in cancer treatment," said Levine.

Vitamin C plays a critical role in health, and a prolonged deficiency leads to scurvy and eventually to death. Some proteins known as enzymes, which have vital biochemical functions, require the vitamin to work properly. Vitamin C may also act as an antioxidant, protecting cells from the damaging effects of free radicals. The NIH researchers, however, tested the idea that **ascorbate, when injected at high doses, may have prooxidant instead of antioxidant activity**. Prooxidants would generate free radicals and the formation of hydrogen peroxide, which, the scientists hypothesized, might kill tumor cells. In their laboratory experiments on 43 cancer and 5 normal cell lines, the researchers discovered that high concentrations of ascorbate had anticancer effects in 75 percent of cancer cell lines tested, while sparing normal cells. In their paper, the researchers also showed that these high ascorbate concentrations could be achieved in people.

The team then tested ascorbate injections in immune-deficient mice with rapidly spreading **ovarian, pancreatic, and glioblastoma (brain)** tumors. The ascorbate injections reduced tumor growth and weight by 41 to 53 percent. In 30 percent of glioblastoma controls, the cancer had spread to other organs, but the ascorbate-treated animals had no signs of disseminated cancer. "These pre-clinical data provide the first firm basis for advancing pharmacologic ascorbate in cancer treatment in humans," the researchers conclude.

Interest in vitamin C as a potential cancer therapy peaked about 30 years ago when case series data showed a possible benefit. **In 1979 and 1985, however, other researchers reported no benefit for cancer patients taking high oral doses of vitamin C in two double-blind, placebo-controlled clinical trials.**

Several observations led the NIH researchers to revisit ascorbate as a cancer therapy. "Clinical and pharmacokinetic studies conducted in the past 12 years showed that oral ascorbate levels in plasma and tissue are tightly controlled. In the case series, ascorbate was given orally and intravenously, but in the trials ascorbate was just given orally. It

was not realized at the time that **only injected ascorbate might deliver the concentrations needed to see an anti-tumor effect**," said Levine, who noted that new clinical trials of ascorbate as a cancer treatment are in the planning stages.

Data from Levine's earlier studies of the regulation and absorption of dietary vitamin C were used in the revision of the Institute of Medicine's Recommended Dietary Allowance for the vitamin in 2000. In the current study, Levine led a team of scientists from the NIDDK and the National Cancer Institute (NCI), both components of the NIH, as well as the University of Kansas. "NIH's unique translational environment, where researchers can pursue intellectual high-risk, out-of-the-box thinking with high potential payoff, enabled us to pursue this work," he said.

Dr. Bleyer:

- ☑ That very high concentrations of vitamin C may be pro-oxidant rather than anti-oxidant opens a more promising door to potential cancer therapy
- ☑ It's not clear why the investigators chose ovary, pancreas and brain cancer cell lines to test the effect of vitamin C instead of cell lines of the more common cancers (e.g. colon, breast, pancreas, lung); hopefully they will expand their screen before clinical trials are conducted in order to know where the highest rates of success are likely to be
- ☑ This lead has a long way to go before it can be clinical exploited, however
- ☑ Major obstacles include 1) demonstrating safety in people at the massive doses required (having "no toxicity" in mice is minimally reassuring); 2) non-specificity of the anti-tumor effect versus targeted approach of most of today's new anti-cancer agents; 3) the negative results of prior randomized trials, which despite the rationale of a higher dose strategy will impede patient accrual; and 4) requiring intravenous administration