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EXERCISE & NUTRITION during/after* CANCER

**CURRENT PEER-REVIEWED MEDICAL LITERATURE and EXPERT COMMENTARY
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▶ **Exercise & Nutrition**

More hints at BMI to breast cancer survival

[Overweight women with breast cancer do not benefit as much as normal-weight women from the newer hormonal treatments and are better off taking the older drugs](#)

By Robert H. Carlson

Oncology Times | 32(18, September 25):38-39, 2010

CHICAGO—More tantalizing evidence has been found linking African-American race and also high body mass index (BMI) to worse outcomes in women with breast cancer, but still nothing definitively practice changing was gleaned from two retrospective studies presented here at the ASCO Annual Meeting.

Researchers from the Breast Cancer Intergroup of North America took an exploratory look at a genomic profiling subset of postmenopausal African-American women with early-stage estrogen receptor (ER)-positive breast cancer in clinical trials, and suggested that worse survival was due in large part to tumors with higher proliferation rates of five genes leading to more aggressive disease, and not to differences in hormone levels or degree of endocrine responsiveness.

From Austria, a study showed that **BMI has a significant impact on the efficacy of anastrozole but not tamoxifen, in adjuvant endocrine treatment of premenopausal breast cancer patients.** The researchers speculated this was probably due to the influence of aromatase availability in fat tissue. **Georg Pfeiler, MD**, a staff assistant physician in the Department of Obstetrics and Gynecology at **Medical University of Vienna**, reported that **overweight premenopausal patients with breast cancer and endocrine-responsive disease do worse when treated with anastrozole compared with tamoxifen.**

He described the hypothesis for this retrospective study, that **overweight patients have higher levels of aromatase enzyme availability so BMI might have an impact on the efficacy of aromatase inhibitors.**

The subset data were from on the Austrian Breast and Colorectal Cancer Group (ABCSCG) 12 trial, which studied the effect of adding zoledronic acid to a combination of either goserelin and tamoxifen or goserelin and anastrozole in premenopausal women with endocrine-responsive early breast cancer. That trial—reported in May 2009—showed that the addition of zoledronic acid increased disease-free survival (NEJM 2009;360:2367-2370).

In this analysis, **overweight patients treated with anastrozole were found to have had a significantly shorter disease-free survival (hazard ratio 1.60) and overall survival (hazard ratio 2.284) at five years** compared with normal-weight patients receiving anastrozole, and compared with overweight women receiving tamoxifen.

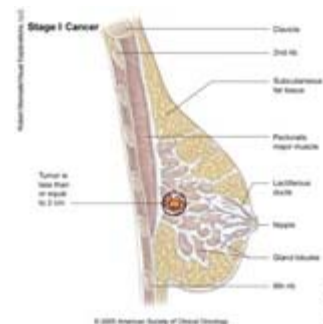
And no differences were seen in disease-free or overall survival between overweight and normal-weight patients treated with tamoxifen, Dr. Pfeiler said.

The session Discussant, **Pamela Jean Goodwin, MD, Chair in Breast Research and Professor of Medicine** at the **University of Toronto**, said that the biologic plausibility of a BMI-survival connection is strong and that the topic is worthy of further study.

Dr. Goodwin said she had reservations, though, about the strength of the study's conclusions, since it was a retrospective, post-hoc analysis, and because of an imbalance in age: overweight subjects taking anastrozole were more likely to be under age 40.

In addition, the BMI-related effect was much less for disease-free survival than for overall survival, “which raises the question of whether BMI contributed to mortality in ways independent of breast cancer,” she said, also noting there were only two non-breast cancer related deaths in this study.

Dr. Pfeiler acknowledged the limitations.



“It's the right thing to do, to step a bit back [for a closer look at the data],” he said. “But I think we and others are going to confirm the data, and then perhaps put it into clinical practice.

In the meantime, Dr. Pfeiler recommended that clinicians keep the effect of BMI in mind when treating premenopausal breast cancer patients with anastrozole or tamoxifen.

Dr. Goodwin, in her discussion, said she did not consider this a practice-changing report. But after reviewing several important studies on aromatase inhibition, she said that the data raise the question of whether “aromatase inhibitors, ‘given at one-size-fits-all’ doses in overweight and obese women, are associated with optimal breast cancer outcomes.”

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Dr. Bleyer:

- ☑ We now have, as one of the first biologically-plausible explanations, a laudible hypothesis for how being overweight reduces the benefit of chemotherapy
- ☑ Practically, the results of the study reported suggest that depending on the patient's BMI, oncologists may have to be selective in choosing which therapy to use
- ☑ For hormonal therapy of breast cancer, the new agents (aromatase inhibitors) are capable of nearly doubling the time to recurrence of breast cancer in normal-weight patients in comparison to overweight women
- ☑ In terms of survival time, the new agents (aromatase inhibitors) are capable of quadrupling the time to death in normal-weight patients versus overweight women
- ☑ Obese patients thereby also have fewer treatment options, which puts them in double jeopardy

Colon cancer: 'Abnormal' body weight linked to increased mortality

[Obesity, particularly abdominal obesity, in women with colon cancer is associated with a shorter time to death from cancer](#)

Oncology Times | 32(18, September 25):20,2010

Postmenopausal women diagnosed with colon cancer may be at increased risk of death if they fail to maintain a healthy body weight before cancer diagnosis, according to a study published in the September issue of *Cancer Epidemiology, Biomarkers & Prevention*.

The researchers found that women considered “underweight” or “obese,” or who had increased abdominal obesity prior to cancer diagnosis seemed to face a greater risk of mortality.

“Maintaining a healthy body weight is beneficial for postmenopausal women. This may also be beneficial for those diagnosed with colon cancer later in life. It looks like abdominal obesity may be a useful indicator of higher colon cancer mortality,” **Anna E. Prizment, PhD, MPH**, a postdoctoral fellow in the division of epidemiology and community health at the **University of Minnesota, Masonic Cancer Center**, said in a news release.

“It is too early to say whether a decrease in weight characteristics after diagnosis will also decrease mortality risk; at that point it may be too late. Therefore, it's best to maintain a normal, healthy body weight throughout life.”

Dr. Prizment and colleagues extracted data from the **Iowa Women's Health Study**, which included **1,096 women diagnosed with colon cancer** who were **observed over a maximum 20-year period**. During that time, 493 died, 289 of whom died from colon cancer.

Women classified as obese, with a BMI of at least 30 kg/m², had a 45% increased overall mortality rate. The few women classified as underweight, with a BMI less than 18.5 kg/m², had an 89% increased mortality rate compared with those with a normal BMI.

Furthermore, women with a high waist-to-hip ratio had a 30% to 40% greater risk of colon cancer related death.

“The exact mechanisms underlying the link between obesity and higher mortality of colon cancer patients are unknown—obese people may be diagnosed at a later stage, have different treatment, or more comorbidities,” Dr. Prizment said.

However, the **facts that the increased abdominal obesity was associated with colon cancer mortality and that those associations persisted after correcting for age, stage at cancer diagnosis, and comorbidities suggest that obesity could have a direct biological effect.**

Obese women, especially those with higher abdominal obesity, have higher hormone levels and may have more aggressive cancer. These women have been already known to have a higher risk of developing colon cancer.

Dr. Prizment urged further investigation of the potential effect of obesity—in particular, abdominal obesity—on the prognosis after colon cancer diagnosis.

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Dr. Bleyer:

- ☑ This study also adds the observation that being too underweight also is associated with an increased cancer mortality, a correlation previously shown for other cancers including leukemia in children
- ☑ That abdominal (pear-shaped) obesity, the kind most associated with diet and exercise, is a particularly bad prognostic sign is further documented in this study

Doctor's orders: Eat well to be well

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By KATRINA HERON | New York Times | September 21, 2010

OAKLAND, California DR. PRESTON MARING was striding along a hospital corridor at double speed on a recent Friday morning, his tall frame, white hair and frequent gesticulations prompting waves of greetings from colleagues, who also took care to sidestep his forward momentum. His destination was the weekly farmers' market he started in 2003, just outside the front door at the **Kaiser Permanente** medical center here.

"Since it's mine, I made the rules — all organic," he said as he skimmed by a line of stalls where fresh fruits and vegetables are sold to hospital workers, passers-by and even, he said, those bringing patients to the emergency room.

Dr. Maring, 64, a gynecologist and obstetrician with three decades as a surgeon, is well known as a former physician in chief at the hospital, the man who spearheaded the creation of its new pediatric neurosurgery unit.

But increasingly, his reputation and perpetual motion revolve around his conviction that in the health professions, the kitchen must become as crucial as the clinic. Food is at the center of health and illness, he argues, and so doctors must make all aspects of it — growing, buying, cooking, eating — a mainstay of their medical educations, their personal lives and their practices.

Though Dr. Maring blithely refers to himself as "that food nut around the hospital," he is serious about the role he believes doctors should play in creating awareness of healthy food choices. To that end, he has worked to obtain fresh local food for hospital trays and in cafeterias. He began a Web site and blog that offers recipes and advice on meal planning and budgeting. He spent the summer working on a series of three-minute Web videos to explain the basics of shopping for healthful foods and efficient preparation techniques.

He also created a kind of culinary road show, which regularly takes him to health care institutions around the country, toting a PowerPoint presentation, a couple of plastic vegetable knives ("one of the great technological breakthroughs"), some salad ingredients and the makings of a vinaigrette.

"I like to put doctors on the spot," he said, referring to his penchant for hauling a senior clinician up to the front of the room to chop vegetables with him. "We tend to be exalted, and I want to show the staffs that many of us don't know how to mince garlic."

If there was ever a time when doctors need to be as handy with a peeling knife as they are with a scalpel, this may be it. **The draft version of the federal government's 2010 Dietary Guidelines**, which will be formally released in December, identifies **obesity as the nation's greatest public-health threat**. It also notes **the relationship of fast food (and physical inactivity) to unhealthy weight gain and emphasizes the importance of plant-based foods** in the diet.

Despite evidence that doctors have a greater life expectancy than average, they don't necessarily look after their own dietary health, said **Dr. Walter Willett**, chairman of the nutrition department at the **Harvard School of Public Health**. "You'll have a pretty hard time these days finding a doctor who smokes, but not nearly as hard a time finding one who eats terrible food." He recalled a major breakfast

gathering he attended several years ago: “I came in a bit late and was struck by the surreal image of senior scientists feeding on junk while discussing solutions to national nutritional problems.”

Dr. Willett cited surveys showing that during examinations of obese patients, doctors often don’t remark on overweight as a health issue. “Many of them just avoid it,” he said, either because they doubt their counsel will be heeded or because they don’t know the issues well enough themselves, leading the patient to underestimate the gravity of the situation.

For many doctors, an uneasy relationship with nutrition starts as early as medical school. Long hours and ready access to fast food, often on the hospital grounds, tends to undermine students’ best dietary intentions, said **Dr. Robert F. Kushner**, a professor at **Northwestern University Feinberg School of Medicine**, where he directs the Center for Lifestyle Medicine. “Even the ones who come in excited about eating well and exercise find that good habits are harder and harder to maintain as time goes on,” Dr. Kushner said.

Dr. Maring’s son, Ben, 30, a fourth-year medical student at New York University School of Medicine, hopes to change that. Mr. Maring has developed a series of cooking classes that incorporate salient aspects of nutrition and clinical medicine. He named his scheme CHEF — for Cook Healthy, Eat Fresh. In 2009, he began lugging duffel bags filled with cooking implements and ingredients from his Brooklyn apartment to the medical school campus on East 31st Street in Manhattan, where he commandeered a spare lounge and taught fellow students simple preparation techniques, introduced guest speakers in specialties like diabetes and endocrinology, and handed out reams of recipes.

“I thought it was important for medical students to learn how to cook and eat well,” he said. “I also thought it was important for us to walk the walk when it comes to counseling patients about the importance of diet. We get so little training in nutrition that I wanted to provide some basic knowledge.”

Dr. Maring said: “You should have seen him trying to drag a convection oven into a taxicab. We cooked together as a family when he was a kid, but he blew past me a long time ago. Now I’m his sous-chef.”

Ben Maring, who has his father’s imposing build and forceful personality, but with a quieter, more scholarly mien, first planned on a career as a chef and did a post-culinary-school apprenticeship at Thomas Keller’s Per Se restaurant in Manhattan in 2005.

“It was very much like the world of a hospital, where you’re on your feet the whole time, you have to make the right decisions very quickly, and you have to be highly self-motivated while also working as part of a team,” Mr. Maring said. Nor was Mr. Keller’s keen appraisal of the neophyte’s technique unlike the scrutiny he now endures on hospital rotations. “I remember being at the pass” — the area closest to the dining room — “about to sauce a plate, and Keller came and stood right next to me,” Mr. Maring said. “I was so nervous. I was trying to artfully drizzle a broken foie gras vinaigrette, and my hand was just shaking. He jokingly asked if I had had too much caffeine.”

Mr. Maring is encouraged that CHEF’s feedback surveys show students are developing confidence in their cooking skills, making better food choices and feeling more comfortable talking to patients about the links between diet and health. He is developing recipes geared to the seasonal offerings at a new farmers’ market at Bellevue Hospital Center, adjacent to the N.Y.U. medical campus, which was begun in July by Aviva Regev, 24, a third-year student and CHEF participant.

Mr. Maring has another ally in Benjamin Navot, 25, a third-year student who entered medical school directly after graduating from the French Culinary Institute in Manhattan and has taught some CHEF classes. Mr. Navot acknowledged that, like Mr. Maring, his perspective on food is greatly influenced by his previous experience. But he, too, senses a widespread interest in food and healthy eating among his peers.

“This is a generation that cares a lot more and knows a lot more about the importance of diet,” he said.

“We need a system that educates physicians about nutrition, and we’re the ones who are going to have to fight for it.”

But the older generation can pick up a few new tricks, too. Preston Maring said that in some ways, his attempts to get more fresh local foods into hospitals have been reminiscent of his days as a young resident at Kaiser, particularly the need to climb a steep learning curve.

“I became the person who asks dumb questions constantly,” he said of the time he has spent over the last couple of years studying the technical aspects of food-distribution systems. “I just learned, for example, that cherry tomatoes with the stems still on are a no-go in an inpatient setting, and that at Kaiser there’s a specific size limit for an apple on a tray, because they’re stacked vertically for delivery.”

Kaiser Permanente, which is a provider and an insurer, is the largest nonprofit health care system in the country, with about 8 million members, 15,000 doctors and 170,000 employees, predominantly in western states. The sheer scale of Kaiser, which holds farmers’ markets at 30 sites, makes changing the way food is bought a challenge, but also an opportunity.

“We can leverage our size to create greater demand for healthy food,” Dr. Maring said. Kaiser Permanente Oakland, for example, serves 6,000 inpatient meals a day, 80 percent of which have no special restrictions.

“It’s difficult for farmers to crack the institutional supply chain,” he said. “We need a ‘universal adapter’ that can pair small producers with big customers.” Toward that end, he helped start a regional growers’ cooperative and joined the board of the nonprofit entity that administers it, the Community Alliance With Family Farmers.

Dr. Maring also envisions Kaiser’s role expanding into areas like environmental stewardship, and he has carved out a kind of subspecialty in institutional real estate, with the goal of eventually putting some of Kaiser’s undeveloped land into agriculture.

“As someone who relies on evidence-based medicine, it bothers me that we don’t have clear metrics to guide these food-related initiatives,” he said. “But for now, I remind myself of the enduring value of another care-giving principle: common sense.”

Dr. Bleyer:

- ☑ As previously reported by **DEFEATcancer**, oncologists infrequently discuss body weight control vis-à-vis nutrition and exercise
- ☑ This report identifies the medical school experience as a major reason for this deficit
- ☑ It also illustrates how physicians can make a difference, especially with the new generation of doctors who are more interested in nutrition than prior generations
- ☑ Nonetheless, cancer patients, survivors and family members should not wait until their oncologist does or does not raise the issue
- ☑ As mentioned in the Comment to the next article, waiting may be too late to overcome bad habits

► Exercise

New guidelines for cancer patients from American College of Sports Medicine: Exercising during & after treatment brings health benefits

30 minutes a day, five days a week, of moderate-paced activity such as walking recommended for the general population is beneficial for cancer patients, even during treatment

By Laino, Charlene

Oncology Times | 32(17, September 10):16, 2010

Avoid inactivity—That’s the main message a roundtable convened by the American College of Sports Medicine (ACSM) wants oncologists to get across to their patients. While clinicians have historically advised cancer patients to rest and avoid activity, emerging research challenges that recommendation, said **Kathryn H. Schmitz, PhD, MPH**, lead author of the new guidelines and Associate Professor of Epidemiology and Biostatistics at the **Abramson Cancer Center of the University of Pennsylvania School of Medicine**.

Cancer patients should be as physically active as possible both during and after treatment, said Dr. Schmitz. The guidelines appear in the July issue of ACSM’s journal, *Medicine & Science in Sports & Exercise* (2010;42:1409-1426).

“**We have to get past the idea that exercise is harmful for cancer patients,**” said Dr. Schmitz, who also presented the guidelines at this year’s ASCO Annual Meeting.

Exercise is not only safe for most patients, but also can improve physical fitness and strength, decrease fatigue, improve quality of life, and improve body image, she said.



With roughly 12 million cancer survivors alive in the US today, the recommendations have far-reaching implications, said the moderator of the ASCO discussion on the guidelines, **Jennifer A. Ligibel, MD**, Instructor in Medicine at **Harvard Medical School** and a medical oncologist at **Dana-Farber Cancer Institute**.

Many cancer patients who stop being physically active during treatment and early recovery never start up again, she said. “If we can prevent people from becoming inactive in the first place, we can stop them from going down that slippery slope.”

On the plus side, there are more and more articles in the literature regarding cancer and exercise, she noted. **“If you had done a search between 1950 and 1979 using the words ‘exercise’ and ‘cancer,’ you would have found a dozen references. By 2009, there were almost 500.”**

Moderate Activity Recommended

The 13-person ACSM panel came up with the exercise recommendations after reviewing published studies looking at the safety and effectiveness of physical activity during and after cancer therapy. The panel focused on breast, prostate, hematologic, colon, and gynecologic cancers, although most of the studies have been in breast cancer, Dr. Ligibel noted.

In general, the same 30 minutes a day, five days a week, of moderate-paced activity such as walking recommended for the general population is beneficial for cancer patients, even during treatment, according to the guidelines.

But it's not a one-size-fits-all prescription, and regimens should be tailored to individuals, taking into account their overall fitness, diagnoses, and other factors that could affect safety, the panel said.

Although stress testing is generally not needed prior to starting a moderate-intensity exercise program, some medical assessments are recommended, Dr. Schmitz said.

For example, evaluation for musculoskeletal morbidities and peripheral neuropathies secondary to treatment is recommended, regardless of how long it's been since the patient underwent treatment.

Patients who have undergone hormonal therapy should be evaluated for fracture risk, and patients whose disease has metastasized to the bone should have medical clearance before starting an exercise program.

Patients with cardiac conditions, whether related to their cancer or not, as well as those who are morbidly obese, may require additional supervision and exercise modifications, the guidelines state.

Specific Concerns

It may be advisable to tell patients with gastrointestinal cancers as well those whose cancers have metastasized to the bone to avoid heavy weight-training, Dr. Schmitz said.

Yoga generally appears safe, and as for Pilates, she noted, there was no published evidence for the panel to review, so a recommendation could not be made one way or the other.

Women with breast cancer can do upper body training—“but it should be done very slowly, which is not how many people approach it,” Dr. Ligibel said.

People with compromised immune systems should be advised to avoid exercising in public gyms, she added, and if a patient has peripheral neuropathy, a stationary bike may be preferable to weight-bearing exercise.

Research Gaps

While large gains have been made regarding the benefits of exercise in certain cancers, particularly breast, there are still large research gaps, Dr. Schmitz said. For example, colon cancer is the third most common cancer and has a fairly good prognosis, yet few trials have examined the potential contributions of exercise toward recovery.

Also, most cancer survivors are over age 65, yet most exercise studies have been conducted in younger patients. There is also a need for assessing the benefits of alternative forms of exercise such as Pilates, Dr. Schmitz said.

Finally, because cancer treatments are increasingly customized according to specific tumor characteristics, fitness trainers who work with cancer survivors need to learn as much as possible about the specifics of patients' cancer diagnoses and treatments in order to make informed safe choices, she said.

Asked to comment on the panel's recommendations, prostate cancer specialist **Brant Thrasher, MD, Chairman of Urology** at the **University of Kansas**, said they were long overdue.

“No one is recommending people go out and take a run the day they are having chemo,” he added.

“Patients know their bodies best, so work with them to come up with an exercise program with which they feel comfortable.”

Echoing the panel's bottom line, Dr. Thrasher concluded: “The important thing is to **avoid inactivity.**”

ACSM's Exercise Guidelines for Cancer Survivors

The new guidelines stress that patients should avoid inactivity and engage in normal daily activities and exercise as much as possible **during** and after treatment, but clinicians need to be aware of certain risks and the potential need for exercise modifications in different populations of cancer patients.

Breast cancer: Be aware of fracture risk.

As far as resistance training, start the patient on a supervised program at very low resistance, with additional resistance added in small increments. Watch for arm/shoulder symptoms, including lymphedema, and reduce resistance or stop specific exercises according to symptom response. There is no upper limit on the amount of weight to which survivors can progress.

Yoga appears safe as long as arm and shoulder morbidities are taken into consideration. Dragon boat racing was not empirically tested, but the volume of participants provides face validity of its safety. There are no data on organized sport or Pilates.

Prostate cancer: Same situation, to be vigilant for the increased potential for fracture. As far as resistance training, pelvic floor exercises should be added for men who undergo radical prostatectomy.

Colon cancer: As far as aerobic activities, patients with an ostomy should be cleared by a physician prior to participation in contact sports.

With resistance training, start the patient at low resistance and progress resistance slowly to avoid herniation at the stoma.

Recommendations for flexibility training are generally the same as for the general population, but care should be taken to avoid excessive intra-abdominal pressure for patients with ostomies.

If an ostomy is present, modifications will be needed for swimming or contact sports.

Gynecologic cancers: There are no data on the safety of resistance training in women with lower limb lymphedema secondary to gynecologic cancer. This condition is very complex to manage.

Proceed with caution if the patient has had lymph node removal and/or radiation to lymph nodes in the groin.

General statement: For patients with metastatic bone disease, exercise programs need to be modified to avoid fractures. Patients with cardiac conditions, secondary to cancer or not, may require exercise modifications as well as greater supervision for safety.

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Dr. Bleyer:

- ☑ The benefit of exercising during therapy (chemotherapy, radiation therapy, soon after surgery) has been underemphasized, an unfortunate situation partially rectified by this report
- ☑ Even worse, **DEFEATcancer** offers, is that inactivity during therapy induces bad habits and leads to inactivity after therapy
- ☑ The cancer-specific guidelines, all in one resource, is also a meritorious feature of this report

▶ **Nutrition**

Vitamin D levels and survival in colorectal cancer

Vitamin D deficiency at diagnosis in patients with colorectal cancer is associated with a 50% worse survival than non-deficient patients

2010 ASCO Annual Meeting | J Clin Oncol | 28:15s, Abstract No: 3615, 2010

K. M. Wesa, G. Jacobs, D. Woo, A. Cronin, N. H. Segal, M. Coleton, L. Saltz, B. R. Cassileth
Memorial Sloan-Kettering Cancer Center, New York, NY

Background: Higher serum D levels are associated with decreased incidence of CRC. However, the prevalence of vit D deficiency at CRC diagnosis is not documented; most published studies measured vit D levels years prior to CRC diagnosis. We therefore conducted a retrospective study of baseline vit D levels in newly diagnosed stage IV CRC patients (pts) to determine whether serum vit D levels at diagnosis predict survival. Vit D levels of 40-60 ng/mL are considered optimal for bone health, and recent data suggest that levels near 40 ng/mL may increase survival in pts with breast cancer. The optimal level of vit D for CRC pts is not known.

Methods: MSKCC maintains an extensive bank of frozen sera. For this study, stored sera from CEA measurements obtained between February 2005 and March 2006 were screened for study inclusion. The first 250 pts with CEA drawn \pm 30 days of stage IV CRC diagnosis and for whom survival data were available were included in this analysis. Vit D levels were determined on all samples. Information regarding metastatic sites, chemotherapy received, body mass index and demographic data were obtained from patient charts.

Results: Of the 250 pts, 153 had died as of April 2009. On univariate analysis vit D was significantly associated with survival when analyzed as continuous variable ($p = 0.036$). **Patients with vit D deficiency (< 30 ng/mL) had survival outcomes approximately 1.5 times worse than those with normal levels.** The median vit D level for all 250 patients was 21.5 ng/mL; 207 patients (83%) were vit D deficient (defined as < 30 ng/mL). Only 7 patients had serum vit D levels > 40 ng/mL. Vit D levels were not significantly associated with age, gender, BMI or race.

Conclusions: A majority of patients with newly diagnosed stage IV CRC are vit D deficient at the time of diagnosis. For patients with stage IV CRC, higher vit D levels at diagnosis are associated with better overall survival. Whether aggressive vit D repletion would improve outcome in vit D deficient CRC patients remains unknown. Clinical trials addressing this question are warranted. We are about to initiate such a study.

Dr. Bleyer:

- ☑ A logical conclusion is that vitamin D therapy may overcome the survival disadvantage but, as warned by the investigators, this has to be determined and it may well be too late for benefit to occur
- ☑ **DEFEATcancer** would expect that a single nutrient is unlikely to overcome the deficit and that a more fundamental (broader) change in diet would be required
- ☑ **DEFEATcancer** further submits, of course, that nutrition plus exercise (**E&N**) is more likely to prolong survival

Colorectal cancer patients with vitamin D deficiency see worse outcomes

[Further comment on the original report, with comments from the principal investigator that cautions against vitamin repletion as therapeutic](#)

By Shalmali Pal | Oncology Times International | August 10, 2010

Investigators at Memorial-Sloan Kettering plan to tease out exactly how much vitamin D is enough to improve survival prospects

Numerous epidemiological studies have strongly suggested that vitamin D has a protective effect against cancer, including breast, prostate, and colon. But the data for these studies were gathered before the cancer diagnosis. Researchers at New York's **Memorial-Sloan Kettering Cancer Center** have, for the first time, documented levels at the time of cancer diagnosis.

Kathleen Wesa, MD, and colleagues conducted a retrospective study of baseline vitamin D levels in newly diagnosed, stage IV colorectal cancer (CRC) patients to determine if serum levels at diagnosis could predict survival. Dr. Wesa is a physician-scientist in the integrative medicine service at MSKCC. One of her co-authors is Barrie Cassileth, PhD, chief of the integrative medicine service.

"Vitamin D levels of > 40 ng/ml are considered optimal for bone health, and recent data suggest that levels near 40 ng/mL may increase survival in patients with breast cancer. The optimal serum level of vitamin D for CRC patients is not known," wrote Dr. Wesa and colleagues (ASCO 2010 abstract 3615). Frozen sera samples from the MSKCC sera bank were used for this analysis. The first 250 patients with serial plasma carcinoembryonic antigen (CEA) drawn within 30 days of a stage IV CRC diagnosis, and

with survival data available, were included and vitamin D levels were measured. CEA measurements were obtained between 2005 and 2006.

According to the results, of the 250 patients, 153 had died as of April 2009. The median vitamin D level for all patients was 21.5 ng/mL, but the majority of patients (83%) were vitamin D deficient, which was defined as levels below 30 ng/mL. Only seven patients had serum vitamin D levels above 40 ng/mL. Two recent neurological studies found that high levels of vitamin D may protect against Parkinson's disease while low levels were associated with substantial cognitive decline in the elderly. This research builds on the body of literature that has also identified vitamin D as a protective agent in the heart—low levels seem to predispose people to hypertension and chronic vascular inflammation—and in the skeletal system (Arch Neurol 67:808-811, 2010; Arch Intern Med 170:1135-1141, 2010; Recent Prog Med 101:202-211, 2010; Clin Biochem online, June 17, 2010). In univariate analysis, vitamin D was significantly associated with survival ($P = .036$). Patients with low vitamin D levels had survival outcomes that were about 1.5 times worse than those with normal levels. The authors concluded that most patients with newly diagnosed stage IV CRC are vitamin D deficient at the time of diagnosis and that higher vitamin D levels are associated with better survival.

Whether aggressive vitamin D repletion would improve outcomes in deficient CRC patients is not known, the authors stated. Dr. Wesa pointed out that **trials using other isolated vitamin supplementation, or in mega-doses have not necessarily shown benefit and in some cases have been detrimental, such as with beta-carotene supplementation in male smokers.**

"I don't know that it is necessarily appropriate for everyone to take high levels of vitamin D supplementation," she said. "We do not yet know what optimal serum vitamin D levels are for the cancer patient. Certainly low levels are associated with worse outcomes in many cancers, but the only way to answer the question of whether normalizing low vitamin D levels improve cancer outcomes is with a clinical trial. **What may be most beneficial is for people throughout their lifetime to maintain normal levels of vitamin D for promoting health and wellness.**"

Dr. Wesa's group is currently enrolling vitamin D-deficient CRC patients in an ongoing phase II clinical trial that will look at what dose of vitamin D is required to achieve and maintain adequate vitamin D levels. Dr. Wesa said that they anticipate having preliminary results in approximately the next 12 months.

Dr. Bleyer:

- ☑ The principal investigator cautions against expecting vitamin D therapy after a cancer diagnosis to eliminate the survival disadvantage, citing the detriment that has been found for other nutrients [see also next report]
- ☑ Like Parkinson's disease, vitamin D may be associated with an increased incidence but not therapeutic when administered after diagnosis

Selenium fails to prevent secondary lung cancer tumors

[A randomized prospective placebo-controlled trial not only found that selenium did not prevent recurrence of or the development of new cancer in patients with lung cancer, it may have worsened the outcome](#)

By Mary Beth Nierengarten | Oncology NEWS International | 19(7. July 13), 2010

Results of a long-term intergroup study on the effect of selenium in early non-small-cell lung cancer highlight the differences between smokers and nonsmokers, and support the thesis that "good" supplements may be harmful in the presence of carcinogens.

The double-blind study (E5597) included 1,522 patients with stage IA and IB NSCLC who were randomized 2:1 to receive selenium yeast (200 µg daily) or placebo for four years. All patients had undergone surgical resection of their primary tumor, were cancer-free for at least six months after surgery, were not taking excessive vitamin supplements, and had normal liver function and normal chest x-ray. Prior to randomization, patients were stratified by smoking status (active, former, never), gender, and disease stage/prior treatment (1A, 1B no chemotherapy, 1B prior chemotherapy).

Conducted between October 2000 and November 2009, the nearly 10-year study was halted early at the four-year median follow-up mark because the patients in the selenium group showed a poorer progression-free survival (PFS) than did those in the placebo group.

Differences in PFS began to appear at about 28 months, and at 5 years, PFS was 78% in the control group vs 72% in the selenium group ($P = .15$), reported lead investigator Daniel Karp, MD, a professor of thoracic/head and neck medical oncology at Houston's M.D. Anderson Cancer Center. Overall, 216 second primary tumors of any type developed in 190 patients, occurring in 4.1% of patients treated with selenium and 3.7% in the placebo group. The selenium group also had a higher incidence of secondary lung cancer tumors. Overall, 84 of the 216 second primaries (38.9%) were lung cancers, occurring in 1.9% of patients treated with selenium and 1.4% in the placebo group. Overall survival was about 5% lower at three and five years in the selenium group, compared with placebo (ASCO 2010 abstract CRA7004).

Although the poorer outcomes in the selenium group were not statistically significant, Dr. Karp emphasized that they certainly weren't better, and a futility analysis showed that, over time, these results would not revert to a positive outcome for selenium.

Asked why the patients treated with selenium did worse, Dr. Karp drew on prior data that has shown a poorer outcome in patients with lung cancer who smoke and take large amounts of beta-carotene.

"Roughly 80% of lung cancer patients will be current or former smokers, and we saw in the beta-carotene study that patients with lung cancer taking beta-carotene in large amounts did worse," he said. "This was confirmed with a variety of data showing that these antioxidants may be harmful in the presence of carcinogens."

Learn more about smoking cessation and lung cancer in the Oncology News International article "Smoking cessation requires unremitting reinforcement". The poorer outcome with selenium supports these data, Dr. Karp said, emphasizing that the association was observational and not based on any "ironclad" evidence. But the take-home message is that lung cancer is a different disease in people who smoke and that lung cancer patients need to be stratified by smoking status, he said.

Dr. Bleyer:

☑ As previously reported by **E&N News** and now joins beta-carotene as another supplement that at least for lung cancer dietary supplements can worsen survival

☑ The critical role of clinical trials in sorting out what works and what doesn't (and may even make things worse), despite popular opinion and premature conclusions, is reaffirmed by this report

Food fortification: Now B12 too?

[The reports of increased cancer incidence after the B vitamin folic acid was added to the food supply, the proposed vitamin B12 fortification must be approached with caution](#)

by Ralph Green, MD, PhD, FRCPath | HemOnc Today | August 25, 2010

Fortification of the U.S. diet with several essential nutrients has occurred, both voluntarily and because it was mandated by the federal government. The usual vehicle is flour because of its widespread consumption, but salt (iodine) and the water supply (fluoride) have also been used.

At least **two of the nutrients added to flour — iron and folic acid — are of more than a passing interest to hematologists and oncologists**. Now, there is discussion about introducing vitamin B12 fortification. What are the reasons, and what, if any, are the risks?

Pros and cons

When a nutrient is added to the food supply, two issues dominate the discussion. First, what is the target group and purpose? And second, what are the possible side effects, and are there segments of the population that potentially could be harmed? In the case of iron, the target population was women, particularly the young and pregnant, as well as infants and young children.

The leading concern was that iron accumulation would be hastened in individuals carrying genes for hereditary iron overload who could phenotypically express hemochromatosis. A fine print theoretical possibility was that iron fortification might result in generation of free radicals that are implicated in a variety of degenerative diseases. Yet another concern was that the diagnosis of "silent" colonic cancers, which often first reveal their presence through symptoms of iron deficiency anemia due to occult bleeding, could be delayed by larger iron stores.

With folic acid, the target group was pregnant women at risk for having a neural tube defect (NTD) pregnancy. The chief concern was that high folate intake might mask megaloblastic anemia in people with pernicious anemia, which could result in irreversible neurological damage. Interference with antifolate drugs such as methotrexate was another possible undesired consequence.

Now, 30 years after the second round of iron fortification and 12 years after folic acid fortification, we can take stock. Iron fortification has dramatically lowered the prevalence of iron deficiency and its associated anemia, and there is no clear evidence of adverse effects of the increased iron intake, although reports have appeared that show a higher HR for various cancers and for cardiovascular disease in those with higher levels of iron. Regarding folate, results are less cut and dried, although there has been a substantial reduction in the incidence of NTDs — about 20% to 30%.

It was widely expected that folic acid fortification would result in a lowering of homocysteine levels in the population, which it did. **Because of the association of hyperhomocysteinemia with cardiovascular disease, some predicted that this would also result in a significant reduction in deaths from cardiac disease, but this has not been observed.** However, some additional benefits appear to have been reaped. Most convincing has been an observed and significant reduction in fatal stroke in North America, coinciding with the implementation of folic acid fortification; that has not been the experience in the U.K., where fortification has not been introduced.

On the negative side of the balance sheet have been **reports of an increased incidence of certain cancers, notably of the colon, following folic acid fortification in the USA and Canada. Another report from Norway found that co-administration of folic acid (0.8 mg) and vitamin B12 (0.4 mg) daily supplements for 7 years were associated with an overall increase of cancer mortality, due mainly to lung cancer.** There is a plausible cause for concern regarding the safety of high folate as a possible risk factor for cancer, although this likely arises from nutritional supplements rather than through the food supply.

More recently, there have been studies pointing to a possible adverse effect of high folate levels in those with low B12 status. Although there has been no evidence of the classical masking of megaloblastosis in these individuals, there has been evidence of more marked interference in the metabolic pathways requiring B12, including higher homocysteine and methylmalonic levels when low B12 is associated with high folate. One study also reported lower hemoglobin values and more neurocognitive decline in the low B12 with high folate group.

Target groups

This brings us to the question of B12 fortification, which is now being contemplated at the CDC and elsewhere. Supporters of B12 fortification point to evidence that a subset of remaining NTDs may relate to B12 deficiency. Although this may be the case, there has been no demonstration of efficacy of B12 supplementation in either incidence or recurrence rates of NTDs, as was clearly the case with folate and NTDs that led to the folic acid fortification initiative.

A second target group is the elderly. In addition to autoimmune pernicious anemia, which has an estimated prevalence of 1% to 2% in the population older than age 65 years in the U.S., there is a larger segment of the growing elderly population with varying degrees of “subclinical B12 deficiency.” This somewhat nebulous entity associated with low normal B12 and raised homocysteine and methylmalonate has been attributed to food B12 malabsorption, caused by gastric atrophy and a variety of other conditions. It is uncertain whether any of these conditions progress to frank clinical B12 deficiency.

The problem with population-wide B12 fortification is that at the levels of B12 deemed practical, pernicious anemia sufferers and other malabsorbers of the soluble vitamin would not benefit, and it is questionable whether any useful purpose is served by providing B12 for the elderly with subclinical deficiency states. As for potential harmful effects, no safe upper limit for B12 is defined because there is little or no evidence of toxicity for the vitamin. However, new evidence is emerging that B12 can be degraded in the gastrointestinal tract with the generation of B12 analogues. The possibility that these analogues, if produced in sufficient amounts, could enter the body raises the concern that there could be interference with B12 metabolic pathways.

The bottom line is that **the flimsy justification for B12 fortification, its dubious benefits and the possibility that it may have undesirable side effects all add up to a risk-benefit ratio that argues against further tinkering with the national food supply** before gathering much more information.

For more information: Allen RH. Am J Clin Nutr. 2008;87:1324-35; Ebbing M. JAMA. 2009;302:2152-3; Mason JB. Cancer Epidem Bio Prev. 2007;16:1325-9; Miller JW. Am J Clin Nutr. 2009;90:1449-50; Selhub J. Am J Clin Nutr. 2009;89:702S-706S; Yang Q. Circulation. 2006;113:1335-1343.

Dr. Bleyer:

- ☑ The increased incidence of cancer with folic acid supplementation is not surprising since folic acid was noted to stimulate leukemia, an observation that led to the development of folic acid antagonists (methotrexate, pemetrexed, aminopterin) that are used to treat a variety of cancers, including breast cancer, lymphoma, and lymphoblastic leukemia
 - ☑ Not mentioned in the report is the benefit of iodine supplementation (via salt) in preventing thyroid insufficiency (hypothyroidism) and tumors (goiters) and flourine (via toothpaste) has been an effective preventer of tooth decay
 - ☑ Nonetheless, the adverse effect of folic acid supplementation raises real concern about fortification of our food supply with another B vitamin.
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