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Integrative Medicine

The Clinician's Evidence-Based Resource on Complementary Therapies [ALERT]

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Moving Forward with a New Name: See page 74

CANCER

Exercise During and After Cancer Treatment

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Dr. O'Mathúna reports no financial relationships relevant to this field of study.

As of 2010, about 14 million cancer survivors were living in the United States, with the number projected to increase to 18 million by 2020.[1] All people diagnosed with cancer are considered cancer survivors for the rest of their lives.[2] As cancer treatments become more successful physiologically, more attention is being given to survivors' quality of life during and after treatment. Many cancer survivors are highly motivated to seek information about lifestyle factors that may influence their recovery and long-term quality of life.[3] This includes the role of physical activity and exercise.

Various cancer treatments may have adverse effects that exercise theoretically could counteract, including pain, fatigue, impaired cardiorespiratory capacity, reduced quality of life, and suppressed immune function.[4] However, rates of exercise decline considerably during chemotherapy and may not return to prediagnosis levels when treatment is concluded.[3] A single-blind, randomized, controlled trial (RCT) found that an oncologist's 30-second verbal recommendation to exercise led to breast cancer patients significantly increasing their levels of exercise.[3] The evidence to support such recommendations will be reviewed here. This evidence base has been growing rapidly, leading to new clinical guidelines from the American College of Sports Medicine (ACSM) in 2010[5] and from the American Cancer Society (ACS) in 2012.[2]

BACKGROUND

Research on exercise and cancer is challenging to review because it involves many variables. Studies have focused on patients with many different cancer types, and at various stages of diagnosis and treatment. Many different activity and exercise regimens have been studied, and at least 60 diverse outcomes measured.[6] Various study designs have been used, and carried out with varying levels of methodological rigor.

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Introducing *Integrative Medicine Alert*

The term "alternative medicine" conjures different perceptions, often emotional in nature, among patients and health care providers alike. As such, the term has been useful in drawing attention to the wide variety of treatments available to patients — the proven, the promising, and the potentially dangerous — and yet the term largely has worn out its utility. Most practitioners do not practice alternative medicine, which inherently implies non-use of conventional medicine. No, most providers use a coherent blend of conventional medicine and select complementary therapies to support physical, emotional, and even spiritual well-being for the people they care for. In other words, they practice integrative medicine, where the focus is primarily on diet and lifestyle practices that patients can use to better take control of their health, and select modalities to support overall healing.

With this background, let us introduce our newly renamed publication — ***Integrative Medicine Alert***, where the focus will continue to be evidence-based reviews of complementary approaches to good conventional medical care with an eye toward primary prevention of illness and optimizing health. The name change reflects reality — there is no good alternative to individualized care that attends to body, mind, and spirit and that is founded in good science and compassion. The way forward is not alternative — it is integrative.

All these factors lead to complexity and variability in the design of research studies and the interpretation of their results. Such factors must be taken into account when making recommendations for individual patients and survivors.

MECHANISM OF IMPACT

Exercise can counteract some of the symptoms caused by cancer and some of the adverse effects associated with treatment. These can include unintended loss or gain of body weight, loss of muscle mass, nausea, vomiting, and difficulties eating or digesting food.[2] Mood changes, fatigue, and other psychological disturbances frequently occur and may be affected by exercise. Cancer or its treatment may require periods of rest or bed rest, which can result in reduced fitness, endurance, or muscle strength that exercise at a later time could counteract. In addition, there is growing interest in the role exercise may play in preventing cancer recurrence and improving long-term survival.

CLINICAL STUDIES

An increasing number of studies have found that exercise is feasible and safe while patients are undergoing chemotherapy. Although many observational studies have been conducted, a growing number of RCTs have measured specific outcomes. A 2005 meta-analysis of this topic was updated in 2010 and found three times as many studies were now available for review.[6] A wide range of outcomes have been measured, as can be seen in Table 1.

General physical activity, aerobic exercise, and resistance training have consistently shown benefits in outcomes including cardiopulmonary fitness, muscle strength, body composition, and balance.[2] Exercise has also been shown to improve quality-of-life outcomes, such as fatigue, sleep quality, depression, and self-esteem. For example, one meta-analysis identified 78 studies examining the impact of exercise on quality-of-life outcomes in cancer survivors.[7] About half the studies involved breast cancer survivors. Overall, the exercise groups reported significantly higher quality-of-life scores than the comparison group, whether this was measured in pre-post studies or against a control group. The effect size was larger at the long-term follow-up assessment (0.35; 95% confidence interval [CI], 0.27-0.44) than immediately after the exercise intervention stopped (0.24; 95% CI 0.20-

0.28). Subgroup analysis showed that interventions with small amounts of aerobic exercise (like short walks) were associated with little or no quality-of-life change, while those with longer, larger amounts of aerobic activity (like moderately intense cycling) led to significant quality-of-life improvement. However, many of the studies provided few details about the exercise interventions.

Another meta-analysis examined the impact of exercise interventions on cancer-related fatigue.[8] This review identified 44 studies of various designs involving 3254 survivors with different cancer types. Exercise interventions were used that varied in type, intensity, and duration. Overall, the cancer survivors in the exercise groups had greater reductions in fatigue levels (0.31; 95% CI, 0.22-0.40). The improvement in fatigue levels was significantly related to exercise intensity ($P = 0.01$) and was greater among older cancer survivors ($P = 0.04$).

Research into the impact of physical activity on cancer disease outcomes and secondary cancer prevention is a relatively new and rapidly growing area. A 2012 systematic review found that almost all controlled studies had been published since 2000, and all were case-control or cohort studies.[1] The first RCT of a physical activity intervention where overall and disease-free survival are primary outcomes began recruiting subjects (colon cancer survivors) in 2009.[1]

Prospective, observational studies have found that physical activity after cancer diagnosis is associated with reduced risk of cancer recurrence and improved mortality with several types of cancers, including breast, colorectal, prostate, and ovarian.[2] For example, a 2011 meta-analysis of six studies involving more than 12,000 breast cancer survivors found that post-diagnosis physical activity reduced breast cancer deaths by 34% (95% CI, 0.57-0.77, $P < 0.00001$), all-cause mortality by 41% (95% CI, 0.53-0.65, $P < 0.00001$), and disease recurrence by 24% (95% CI, 0.66-0.87, $P = 0.00001$).[9] A more recent systematic review identified 43 studies in this area, with 27 being observational studies of cancer-related outcomes, five being observational studies involving cancer biomarkers, and 11 being RCTs measuring cancer biomarkers.[1] The studies varied considerably in design, interventions, and outcomes. However, the reviewers concluded that "there is fairly consistent evidence that physical activity either before or after breast cancer diagnosis is associated with a reduction in both breast cancer-specific mortality and overall mortality."[1] Other cancers have been studied much less frequently, but the results similarly find that physical activity is associated with improvements in all-cause and cancer-specific mortality. RCTs measuring biomarkers suggest that exercise may have beneficial effects on insulin and IGF in breast cancer survivors, and on C-reactive protein and natural killer cells in cancer survivors.[1]

Summary Points

- Growing numbers of studies show that exercise can be beneficial for cancer patients during and after treatment.
- Exercise positively affects cancer survivors' quality of life, fatigue levels, cardiorespiratory fitness, biomarker levels, and symptom management.

ADVERSE EFFECTS

Many of the RCTs and systematic reviews have explicitly collected data on adverse effects and concluded that exercise among cancer survivors is safe. For example, the ACSM guidelines gave the evidence for safety an A rating, defined as "overwhelming data from randomized controlled trials."[5] One particular area of concern is lymphedema, a common adverse effect of breast cancer treatment. Women historically have been discouraged from upper body exercise for fear of exacerbating lymphedema after axillary lymph node removal or radiation. However, seven RCTs all have shown that upper body aerobic or resistance training does not lead to the development or worsening of lymphedema.[5] These studies typically involve a supervised exercise program that gradually increases in intensity over 8 weeks with the women wearing a compression garment.[10]

Although exercise is not contraindicated for most cancer patients, particular individuals may be at higher risk of adverse effects. The ACS guidelines include some cautions.[2] Cancer survivors:

- with severe anemia should delay exercise beyond activities of daily living until the anemia is improved.
- with compromised immune function should avoid exercising in public until their white cell count returns to safe levels.
- with severe fatigue from therapy should approach exercise cautiously.
- undergoing radiation should avoid chlorinated swimming pools.
- with indwelling catheters or feeding tubes should be cautious about or avoid swimming and resistance training of muscles that might dislodge the catheter.
- with multiple or uncontrolled comorbidities

Table 1. Overview of evidence regarding the efficacy of exercise interventions for specific outcomes in cancer survivors (numbers reflect studies with a significant positive effect on the outcomes listed).[5]

Outcome	Type of Cancer (and Treatment)						
	Breast (during treatment)	Breast (after treatment)	Prostate	Colon	Adult Hematologic (no HSCT*)	Adult Hematologic (with HSCT*)	Gynecologic
Total number of RCTs reviewed	21	32	12	4	4	11	1
Safety (no exercise-related adverse events)	13	15	6		1	6	
Safety (lymphedema-related)	2	7					
Physical function	2	4	4			1	
Physical fitness							
Aerobic	10	10	5	1	3	5	
Muscle strength	5	6	4			2	
Flexibility		5	1				
Physical activity level	5	8	4	1		1	1
Body size (weight, BMI, etc.)	4	8	6		1	2	1
Bone health	2	1					
Quality of life	4	12	6	1	3		
Energy level, vigor		3	1				
Fatigue	4	4	5		3	3	
Sleep	1				1		
Depression		3			1		
Anxiety	3	3					
Physiological outcomes (biomarkers, blood lipids, PSA)	3	6	2	2			
Cancer-related symptoms (incl. pain)	3	3	1	1			

*HSCT = hematopoietic stem cell transplantation

should consult their physicians to consider the most appropriate exercise program.

- with peripheral neuropathy or dizziness should engage in exercise that takes account of their restricted balance and coordination.

EXERCISE PROTOCOLS

Guidelines consistently note that the particular exercise program and when it is initiated should be individualized to the patient's condition and personal preferences.[6] A person's level of exercise before diagnosis and treatment must be taken into account. In some cases, increased physical activity prior to

surgery or radiation may have beneficial effects on recovery. Inactivity should be avoided.[5] The 2012 ACS guidelines recommend that adults should engage in at least 150 minutes per week of moderate intensity activity or 75 minutes per week of vigorous activity, or an equivalent combination of both levels (*see Table 2*). Moderate activities are those that can be done while talking (e.g., gardening, biking on the flat, walking briskly), while vigorous activities are difficult to do while talking (e.g., hiking uphill, jogging, digging, aerobic dancing).[1]

For those exercising prior to diagnosis, maintaining exercise levels or returning to earlier levels should be the goal, where appropriate. However, lower intensities or shorter durations may be necessary during treatment. For those who were not exercising before diagnosis, a program of low-intensity exercise that is tailored to the individual should be developed and gradually advanced. Account must be taken of other symptoms and conditions, along with patients' individual interests and enthusiasm for exercise. To develop and monitor individualized exercise programs, people should be referred to a physical therapist or personal trainer with expertise working with cancer survivors.

CONCLUSION

Growing numbers of studies show that exercise can be beneficial for cancer patients during and after treatment. Most studies have been conducted with breast cancer survivors, with other types of cancer each having relatively few trials. Caution is needed in applying the results from breast cancer to other cancers.[6] In general, exercise positively affects cancer survivors' quality of life, fatigue levels, cardiorespiratory fitness, and other outcomes. Improvements with exercise were also noted on some biomarker levels and with symptom management. However, many other exercise outcomes have been inadequately researched to allow evidence-based recommendations. Exercise programs were tolerated well with few adverse events reported.

RECOMMENDATION

Evidence increasingly supports encouraging cancer survivors to continue and improve physical activity levels during and after treatment. The evidence is most clear for women with breast cancer, but the few studies with other cancers have had positive results. Exercise recommendations must be tailored to individual patients depending on their activity levels prior to diagnosis and other limitations imposed by their disease or treatment. Guidance should be sought from physical therapists or personal trainers with expertise working with cancer survivors.

Evidence regarding the impact of exercise on secondary cancer prevention and long-term mortality comes primarily from observational trials, but is positive. RCTs in this area are only just beginning, but should provide more clear-cut evidence.

Larger and better designed studies may reveal more specific guidelines for all cancer patients and those with specific types of cancer. Guidelines for specific exercise programs are generally not available as studies have used a wide variety of programs. However, general recommendations from the American Cancer Society are shown in Table 2.[2] ■

Table 2. American Cancer Society Guidelines on Nutrition and Physical Activity for Cancer Survivors[2]

Achieve and maintain a healthy weight.
■ If overweight or obese, limit consumption of high-calorie foods and beverages and increase physical activity to promote weight loss.
Engage in regular physical activity.
■ Avoid inactivity and return to normal daily activities as soon as possible following diagnosis. ■ Aim to exercise at least 150 minutes per week. ■ Include strength training exercises at least 2 days per week.
Achieve a dietary pattern that is high in vegetables, fruits, and whole grains.
■ Follow the American Cancer Society Guidelines on Nutrition and Physical Activity for Cancer Prevention.

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ABSTRACT & COMMENTARY

Improving *H. pylori* Eradication Rates Naturally

By Donald Brown, ND

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Dr. Brown is a consultant to the supplement industry. He reports no financial relationships relevant to this field of study.

SYNOPSIS: Results from this small open-label trial out of Turkey suggest that vitamins C and E decrease *Helicobacter pylori* (*H. pylori*) intensity and possibly local inflammation in patients with *H. pylori*-positive non-ulcer dyspepsia. The results provide added support to results from an earlier clinical trial by the investigators that found adjunctive use of vitamins C and E improved eradication rates of conventional triple therapy for *H. pylori* infection.

SOURCE: Sezikli M, et al. Effects of alpha tocopherol and ascorbic acid on *Helicobacter pylori* colonization and severity of gastric inflammation. *Helicobacter* 2012;17:127-132.

Helicobacter pylori (*H. pylori*) creates a microenvironment through the formation of biofilms to protect itself from gastric acid and host defense systems, and increases oxidative stress in the area it colonizes.[1] It has been found that reactive oxygen species (ROS) are increased in patients infected with *H. pylori* and are decreased following *H. pylori* eradication.[2] Eradication rates using standard triple-therapy (clarithromycin, amoxicillin or metronidazole, and a proton pump inhibitor [metrionidazole is sometimes substituted for amoxicillin in allergic individuals]) typically do not exceed 80% and vary in degree between geographic locations.[3] Gastrointestinal (GI) side effects often reduce treatment tolerability and may cause treatment discontinuation and failure to eradicate *H. pylori*. Additionally, antibiotic resistance is becoming an important factor.

In the current trial, patients with *H. pylori*-positive non-ulcer dyspepsia were admitted to Haydarpasa Numune Education and Research Hospital's Gastroenterology Outpatient Clinic for potential participation in this open-label study. Patients who complained of dyspepsia and were infected with *H. pylori* as diagnosed by ^{14}C-urea breath test underwent upper GI endoscopy. Of those, 30 patients with a diagnosis of *H. pylori*-positive non-ulcer dyspepsia were included in the study. Twenty-two of the participants were women and the mean age was 35.4 $\pm$ 8.96 years.

The patients were given vitamin C 500 mg bid and vitamin E 200 IU (the form of vitamin E was not specified) bid orally for 4 weeks. Patients were not allowed to take any bismuth salts, non-steroidal anti-inflammatory drugs, proton-pump inhibitors, H_2-receptor blockers, antibiotics, or probiotics during the study.

In addition to the screening endoscopy, all participants underwent an additional upper endoscopy. Tissue samples were taken from the lesser and greater curvature in both the prepyloric antrum and corpus for histopathologic examination of the tissue and measurement of vitamins C and E concentration. Two independent pathologists carried out histopathologic examination of all tissue samples. Concentrations of gastric tissue vitamin C and E were measured with high-pressure liquid chromatography. Blood samples were also obtained prior to and following vitamin C and E intervention and were used to measure total antioxidant capacity (TAC).

Compared to baseline, *H. pylori* intensity (term representing the combination of gastritis, metaplasia, and the presence of the bacteria in the mucin layer) in the antrum decreased significantly by the end of therapy according to both pathologists (P = 0.007 and P = 0.039, respectively). Although *H. pylori* intensity in the corpus decreased following treatment, the change did not reach statistical significance. Neutrophilic activity in the antrum decreased significantly following therapy (P = 0.000* and P = 0.025, respectively) but not in the

corpus (the authors note that *H. pylori* colonizes predominately in the antrum). Compared to baseline, mean concentrations of vitamins C and E were significantly increased ($P = 0.000$* and $P = 0.006$, respectively). There were no significant changes in TAC following treatment.

**Editor's Note:* The authors use $P = 0.000$ twice in the paper to report statistical significance. Dr. Brown has been unable to obtain clarification from them.

COMMENTARY

The findings from this study provide information on how vitamins C and E affect *H. pylori* and possibly inflammation in patients with *H. pylori*-positive non-ulcer dyspepsia. More importantly, they provide support for an earlier clinical trial by the same investigators that found the addition of vitamins C and E to standard triple therapy significantly improved eradication of *H. pylori* in patients with *H. pylori*-positive non-ulcer dyspepsia.[4]

In that study, 160 patients infected with *H. pylori* were all treated with lansoprazole (30 mg bid), amoxicillin (1000 mg bid), clarithromycin (500 mg bid), and bismuth subcitrate (300 mg qid) for 14 days. Half the patients additionally received vitamin C (500 mg bid) and vitamin E (200 IU bid) during the 14-day treatment period. In persons receiving additional vitamin C and E therapy, *H. pylori* eradication was achieved in 73 (91.25%) of the 80 patients in the intention-to-treat (ITT) analysis and 73 (93.5%) of the 78 patients included in the per-protocol (PP) analysis. In the group receiving only standard therapy, the eradication rates were 48 (60%) of the 80 patients included in the ITT analysis and 48 (64%) of the 75 patients in the PP analysis. The difference in eradication rates between the two groups was significant for both those in the ITT analysis and PP analysis ($P < 0.05$).

Previous studies adding either vitamin C alone or vitamins C and E have had mixed results. One study added 500 mg/day of vitamin C to standard triple therapy for 1 week and found that eradication rates were 78% in those taking vitamin C compared to 48.8% for those receiving only standard therapy.[5] However, another study using the same dose of vitamin C found no improvement in eradication rates when taken with triple therapy.[6] Finally, a study looking at the effects of vitamin C (250 mg/day) and vitamin E (200 IU/day) found no additional eradication effect when taken with amoxicillin, metronidazole, and lansoprazole.[7] The authors of the current study suggest that the amount of vitamins C and E may have been too low in this trial.

Summary Points

- Reactive oxygen species are increased in patients infected with *H. pylori* and are decreased following *H. pylori* eradication.
- Through their antioxidant actions, vitamins C and E appear to disrupt the microenvironment created by *H. pylori* and have been found to improve eradication rates in patients treated with standard triple therapy.
- Other promising adjunctive therapies include probiotics, N-acetylcysteine, and cranberry.

Considering other adjunctive therapies for the treatment of *H. pylori*, the largest body of clinical data to date is for probiotics. Three meta-analyses have looked at the use of probiotics to both reduce side effects associated with standard therapy and also improve eradication rates and have slightly different conclusions. A 2007 meta-analysis (14 studies)[8] and a 2009 meta-analysis (eight studies limited to just those using *Lactobacilli* strains)[9] concluded that probiotics were effective in reducing side effects such as diarrhea, bloating, and taste disturbances and also improved eradication rates. A more recent 2011 meta-analysis (four studies) agreed with the reduction of side effects of triple therapy with adjunctive use of probiotics but did not find evidence that they improved eradication rates.[10] Recently, Spanish researchers have isolated a *Bifodobacterium bifidum* strain (CECT 7366) that has shown potent anti-*H. pylori* activity in vitro and in mice.[11]

Preliminary research has also pointed to N-acetylcysteine (NAC) and cranberry as potentially promising adjunctive therapies to improve standard *H. pylori* eradication therapy. Increasing attention has been paid in the past several years to the role that biofilm formation plays in increasing the resistance to antibiotic therapy for pathogenic bacteria such as *Escherichia coli* and *H. pylori*. Following an in vitro study that found NAC disrupted biofilm formation by *H. pylori*, a small study looked at the ability of NAC to improve eradication therapy in patients who had previously failed to eradicate *H. pylori*.[12] In an open-label study, 40 patients with a history of four failed attempts to eradicate *H. pylori* received either NAC (600 mg/day) or no additional treatment for 1 week prior to 1 week of triple therapy. At baseline, evidence of biofilms was found in all patients. Two

months after the end of eradication therapy, *H. pylori* was eradicated in 13 (65%) patients who received NAC compared to four (20%) of 20 patients who did not receive NAC ($P < 0.01$). In all patients who had successful eradication, biofilms had disappeared.

In addition to activity against uropathogenic *E. coli*, cranberry also has been shown to inhibit adhesion of *H. pylori*.[13,14] A double-blind, randomized trial in Israel studied the adjunctive effect of cranberry juice on eradication of *H. pylori* in subjects being treated with omeprazole, amoxicillin, and clarithromycin. One hundred seventy-seven patients with *H. pylori* infection were included in the study. The addition of 500 mL/day of cranberry juice during triple therapy and for 2 weeks following significantly improved eradication rates in female patients but not male patients.[15]

The ability of relatively inexpensive and safe adjunctive therapies to disrupt the microenvironment created by *H. pylori* appears to hold promise for improving treatment outcomes for patients receiving standard triple therapy. Of greater concern clinically would be the ability of these combinations to affect outcomes in patients with peptic ulcer disease. It will be interesting to see if ongoing use of the combination of vitamins C and E, probiotics, and cranberry may also prevent recurrence of *H. pylori* infection. Could this be a natural triple therapy? ■

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CARDIOVASCULAR DISEASE

ABSTRACT & COMMENTARY

We're Out of Milk: Dietary Calcium and CVD

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

SYNOPSIS: A large observational study conducted in Germany has found little evidence that higher levels of dietary calcium are associated with a reduced risk of cardiovascular disease events. The additional finding of an elevation in risk with the use of calcium supplements suggests that caution is warranted when recommending them.

SOURCE: Li K, et al. Associations of dietary calcium intake and calcium supplementation with myocardial infarction and stroke risk and overall cardiovascular mortality in the Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition study (EPIC-Heidelberg). *Heart* 2012;98:920-925.

Between 1994 and 1998, a German research group assembled a cohort of 23,980 people between the ages of 35 and 64 who were free of existing cardiovascular disease and very low- or high-calorie dietary patterns. Study participants completed a food frequency questionnaire (FFQ) to assess dietary sources of calcium, and an interview and follow-up questionnaires to measure use of calcium supplements. Total calcium intake was divided into quartiles — 0-603, 604-748, 749-924, and > 924 mg/day for men, and 0-610, 611-738, 739-898, and > 898 mg/day for women. Supplement use was categorized as no use, calcium only, calcium plus other supplements, and other supplements only. Cardiovascular events (myocardial infarction [MI], stroke, and cardiovascular disease-related death) were recorded over an average follow-up time of 11 years. Relative hazards (relative risks taking into account survival time) were calculated using Cox Proportional Hazards regression. The regression models adjusted for a number of potential confounding factors, including age, sex, education level, physical activity level, vitamin D intake, total caloric intake, self-reported diabetes at baseline, and calcium supplement use (when modeling total calcium intake). Separate models considered all cardiovascular events, and only those occurring more than 2 years after the study period began.

There were few statistically significant associations, positive or negative, between total calcium intake in any amount and cardiovascular events. Those reported were as follows. As compared with those in the lowest quartile of calcium intake (Quartile 1), those in Quartile 3 had a **lower** relative risk of MI (hazard ratio [HR] = 0.69, 95% confidence interval [CI] 0.50 to 0.94). This association persisted when events in the first 2 years were excluded (HR = 0.67, 95% CI 0.48 to 0.94). When compared with those in Quartile 1, those in Quartile 2 had a **higher** relative risk of stroke (HR = 1.50, 95% CI 1.06 to 2.11), but this association did not remain significant when the first 2 years of events were excluded. Finally, in a model that excluded the first 2 years of events, those in Quartile 2 had a **higher** relative risk of death from cardiovascular causes as compared with those in Quartile 1 (HR = 1.51, 95% CI 1.05 to 2.17). There was no statistical evidence of a dose-response relationship for any outcome. In models assessing the effect of supplement use, those who reported taking only calcium supplements had a **higher** risk of MI as compared with those reporting no use of any supplements (HR = 2.39, 95% CI 1.12 to 5.12 when considering all events, and HR = 2.70, 95% CI 1.26 to 5.79 when excluding the first 2 years). There was no similar association with the other outcomes or for those taking other supplements as well as calcium.

Summary Points

- Calcium from dietary sources does not appear to provide much cardiovascular benefit.
- Calcium from supplements may elevate cardiovascular risk when combined with other characteristics that are not yet fully understood.

COMMENTARY

Simply because of its size and design, this study carries considerable weight. Findings from small, tightly controlled experiments (such as clinical feeding studies) must be interpreted with caution until they are validated in larger samples and under more natural conditions. This study's size builds confidence in the precision of its estimates. Its prospective design helps to minimize numerous kinds of potential bias in its results. At the same time, its observational nature (dietary elements were not "prescribed," simply recorded) adds greatly to its generalizability. The dietary patterns of the participants are likely to reflect those of a much larger population. Finally, the use of hard endpoints, events that are unlikely to go unnoticed, rather than markers that require active efforts to identify, increases the probability of complete ascertainment. However, there are also a few issues in the design of this study that should affect how we evaluate its conclusions.

First, diet data were collected only once, at baseline. This ignores any changes in diet over the course of the study. It could be argued that any such changes would have been too proximal to have much effect on the outcomes, but there is evidence that even short-term changes can have measurable effects on some relevant parameters, such as markers of inflammation. Such changes may also have been motivated by health states related directly or indirectly to the outcomes of interest. Information on supplements was collected at each follow-up interval as well as at baseline. This permitted a richer analysis, including a separate set of models for each participant's most recent reported supplement use. Balancing this is the fact that these separate analyses did not produce results that were materially different from those obtained with baseline data.

Second, the FFQ method of collecting diet information is good, but not perfect. In this study, the FFQ results were validated using twelve 24-hour food recall exercises. The correlation between the

FFQ and what was reported for the 24-hour recall periods for the two most important categories for calcium intake — dairy foods and non-alcoholic beverages — were 0.58 and 0.70, respectively. This suggests that information about general eating habits and information about specific consumption in multiple intervals did not match up ideally. Balancing this to some degree is the large sample size, which would tend to minimize the impact on precision of individual mismeasurements. However, it is difficult to assess the likely impact on the results of any systematic bias in the assessment of dietary exposures.

Third, the authors note that there may have been underreporting of calcium supplement use. They point out that their reported rate (3.6%) is lower than that of another study of older Germans (8% for men and 27% for women) and lower than the rate reported in U.S. National Health Interview Survey data (11% overall). This may imply that supplement use was actually higher in the EPIC study than it appeared. If so, a critical finding — increased risk with supplement use — might have been understated.

These issues notwithstanding, this paper should dampen enthusiasm for the use of calcium in the prevention of cardiovascular disease. There was limited earlier support for such a relationship, but this paper is generally in line with the finding of no association reported in most studies.[1-4] Although adequate calcium intake remains important for bone health, calcium from dietary sources appears to have little or no impact on cardiovascular events, and calcium supplementation may add some risk without any concomitant benefit. ■

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CANCER

ABSTRACT & COMMENTARY

No 'Go' with CoQ10 for Treatment-Related Fatigue

By Russell H. Greenfield, MD

SUMMARY: **Results of this well-done trial strongly suggest that CoQ10 administration over 24 weeks' time does not help relieve the treatment-related fatigue experienced by a significant proportion of women with newly diagnosed breast cancer.**

SOURCE: Lesser GJ, et al. A randomized, double-blind, placebo-controlled study of oral coenzyme Q10 to relieve self-reported treatment-related fatigue in newly diagnosed patients with breast cancer. *J Support Oncol* doi.org/10.1016/j.suponc.2012.03.003.

The majority of people receiving treatment for cancer experience a degree of fatigue that severely impairs their quality of life, and very few generally effective treatments exist to address the condition. The authors designed this randomized, double-blind, placebo-controlled study of coenzyme Q10 (CoQ10) in women with newly diagnosed breast cancer beginning adjuvant chemotherapy to evaluate CoQ10 supplementation's effect on treatment-induced fatigue, overall quality of life (QOL), and depression. Together with other eligibility criteria, subjects had to have an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 (at least able to walk and manage self-care) and not have lost more than 5% of their total body weight in the prior 3 months. Participants were stratified by chemotherapy type (anthracycline vs no anthracycline) and whether they received radiation therapy, and were then randomized to receive either 300 mg CoQ10 (Soft Gel Technologies, Los Angeles, California) or placebo daily, each combined with 300 IU vitamin E (to facilitate absorption, also from Soft Gel Technologies, Los Angeles, California), in divided doses three times a day with food for 24 weeks. Interventions were begun no later than 4 days after treatment with chemotherapy had started. Adherence to study protocol was assessed through serial determinations of serum CoQ10 and vitamin E levels at baseline and following 8, 16, and 24 weeks of treatment. Various QOL tools were employed to capture information on the primary outcome of fatigue, as well as the secondary endpoints of

Summary Points

- CoQ10 assists with cellular energy production within mitochondria and may support improved exercise tolerance in people with mild-to-moderate heart failure.
- Fatigue is a common adverse effect of cancer treatment.
- This study strongly suggests CoQ10 does not relieve treatment-related fatigue in women newly diagnosed with breast cancer across a variety of treatment regimens.

overall QOL, depression, and social support, and included the POMS-F, the FACIT-F, a self-reported LASA-Fatigue score, the FACT-B, CES-D, and the Medical Outcomes Study Social Support Survey (all of which are well-described by the study authors). Assessments were made at baseline and then after 8, 16, and 24 weeks of therapy.

A total of 236 women participated in the study (age range 28-85 years, median = 51 years; 87% non-Hispanic whites). The vast majority (84%) were receiving anthracycline chemotherapy, and more than half (61%) also received radiation therapy. Subjects generally reported low levels of fatigue at baseline, while 44% had serum CoQ10 levels deemed lower than normal (< 0.64 µg/ mL). By 8 weeks' time, CoQ10 levels had tripled in the intervention group from a mean (SD) of 0.7 (0.4) µg/mL at baseline to 2.2 (1.2) µg/mL; however, average post-treatment CoQ10 levels were lower than baseline in 12% of participants in the CoQ10 arm. Vitamin E levels almost doubled from 13.8 (8.7) µg/mL at baseline to 24.1 (15.1) µg/mL at 8 weeks, but again average post-treatment vitamin E levels were lower than baseline for 11% of subjects. Fatigue increased significantly in both groups once chemotherapy was initiated ($P < 0.001$) and gradually lessened thereafter, never returning to pretreatment levels. Models of treatment effect failed to show any benefit from CoQ10 supplementation compared with placebo for the relief of treatment-related fatigue regardless of baseline and subsequent serum CoQ10 concentration at any time during the study, including at trial's end (24 weeks). Subjects in both treatment groups experienced an overall decrease in QOL ($P < 0.001$); this was not significantly ameliorated by CoQ10 administration. Likewise, the non-significant increase in depressive symptoms detected following the start of adjuvant chemotherapy was not impacted by the use of CoQ10 when compared with placebo. Adverse effects experienced by participants were not significantly different between the two groups. The researchers conclude that their results show there is no benefit to supplementation with "standard-dose" CoQ10 for the management of treatment-related fatigue in women newly diagnosed to have breast cancer.

COMMENTARY

A review of the therapeutic approach to cancer-related fatigue published last year reported that 50-90% of people being treated for cancer, especially those receiving different modalities, experience distressing fatigue that dramatically impairs QOL and often impacts their ability to complete their course of treatment.[1] The National Comprehensive Cancer Network defines cancer-related fatigue as "a persistent subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and that significantly interferes with usual functioning."[2] Notably, it is not usually relieved with rest alone.

Regular screening for fatigue throughout treatment is now recommended; however, available treatment options remain largely ineffective. Such was the genesis of the current study, especially in light of the fact that CoQ10 is known to play an important role in energy production within mitochondria and has been shown to benefit exercise capacity in some people with mild-to-moderate left heart failure at doses as low as 100 mg per day. How disappointing then that, even with significant increases in CoQ10 levels in the majority of subjects receiving active therapy at a dose of 300 mg daily, no meaningful benefit was experienced with respect to perceived energy levels and activity. The finding that slightly more than 10% of participants did not achieve significant increases in serum levels of CoQ10 and vitamin E is interesting, but is little more than a footnote in relation to the central findings, and does not weaken the argument against CoQ10's use for the management of treatment-related fatigue.

The authors rightly point out that attrition was very high (97 subjects withdrew prior to their final assessments), but this is not uncommon with the study population at hand. Reasons for withdrawal were in line with those common to almost all studies addressing cancer patients and were heavy on treatment toxicity, including inability to tolerate oral medications.

The search for interventions that offer meaningful relief from treatment-related fatigue for people

with cancer is far from over. Non-pharmacological means that show promise include regular exercise and cognitive behavioral therapy, but there is little or no reason to further pursue the potential benefit of CoQ10 in this setting — it is not indicated. ■

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CME QUESTIONS

1. The beneficial outcomes from exercise have primarily been identified with which type of cancer?

a. Breast
b. Colon
c. Gynecologic
d. Prostate

2. The general safety of exercise for cancer survivors is supported by:

a. a few randomized controlled trials with conflicting results.
b. an overwhelming amount of data from randomized controlled trials.
c. evidence from observational studies only.

3. Which of the following patients does the American Cancer Society recommend be particularly cautious with physical exercise?

a. Those at risk of lymphedema
b. Those with cancer
c. Those with severe fatigue from chemotherapy
d. All of the above

4. The primary mechanism whereby vitamins C and E appear to disrupt *H. pylori* infection and possibly improve eradication rates include:

a. disruption of biofilms.
b. anti-adherence activity.
c. antioxidant activity.

5. Other supplements that may hold promise for improving *H. pylori* eradication rates include:

a. N-acetylcysteine.
b. probiotics.
c. cranberry.
d. All of the above

6. Rising levels of calcium intake are associated with a lower risk of cardiovascular events.

a. Yes
b. No

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[IN FUTURE ISSUES]

Omega-3 fatty acids and dementia

Chocolate and cardiovascular disease

Acupuncture and depression

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