Antioxidants

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Do Antioxidants Prevent Colorectal Cancer? A Meta-Analysis.


BACKGROUND: Oxidative stress is the first step involved in mutagenesis, carcinogenesis and aging. There has been great interest in recent years in potentially health benefits of dietary and antioxidant supplements in cancer prevention. OBJECTIVES: Our primary objectives were to estimate the global effect of antioxidants on colorectal cancer incidence, adenomatous polyposis recurrence, overall mortality and cancer related mortality. A secondary aim was to evaluate these effects across specific antioxidant compounds, dose and duration of antioxidant supplementation. METHODS: Using Cochrane Collaboration methodology we searched for all randomized controlled trials (RCTs) from 1966 till May 2009 (MEDLINE, Cochrane Controlled Clinical Trials Registry), comparing antioxidant supplements with placebo or no intervention on the occurrence of colorectal cancer or adenoma. The results expressed as relative risk (RR) and 95% confidence intervals (95% CI) were obtained using random and fixed effect meta-analysis. RESULTS: Twenty RCTs, including 26 8590 participants, were eligible: 12 analyzing the colorectal cancer incidence included 25 0676 participants and 8 analyzing colorectal adenoma recurrence included 17914 participants. Antioxidant supplements had no significant effect on colorectal cancer incidence or colorectal adenoma recurrence (RR = 0.94, 95% CI, 0.84-1.06, p = 0.32) in a random-effect meta-analysis. The antioxidant supplements had no significant effect on overall mortality (RR = 1.03, 95% CI, 0.99-1.07, p = 0.12) or cancer related mortality (RR = 1.05, 95% CI, 0.94-1.16, p = 0.38) in a random effect meta-analysis. Selenium supplementation was associated with a trend in reducing colorectal cancer incidence, (RR = 0.88, 95% CI, 0.55-1.40, p = 0.59), colorectal adenoma recurrence (RR = 0.70, 95% CI, 0.43-1.14, p = 0.16) and overall mortality (RR = 0.91, 95% CI, 0.82-1.02, p = 0.09). Beta carotene alone was associated with a slight increase in colorectal cancer incidence (RR = 1.09, 95% CI, 0.92-1.29, p = 0.34) and in combination with other antioxidants it was associated with an increase in mortality (RR = 1.05, 95% CI, 0.99-1.11, p = 0.10). For both selenium and beta carotene, the effect was not statistically significant. Vitamin C and Vitamin E combination slightly reduced colorectal cancer incidence with no effect on overall mortality. CONCLUSIONS: This meta-analysis found no evidence in favor of a protective effect of the studied antioxidant supplements in the prevention of colorectal cancer or cancer related mortality. Only selenium supplementation might have anticarcinogenic effects and requires further research.

INSPIREHEALTH’S INTERPRETATION: Reactive oxygen species (ROS) are chemically reactive molecules that fall into one of two categories depending on how they were generated. First, endogenous ROS are generated during the normal metabolism...
Cognitive training has been shown to improve or even restore cognitive function. In this small randomized controlled trial, 41 women who were on average 6 years post-breast-cancer-treatment were randomized to either a 12 week home-based online cognitive training program or a wait list group. The training program was associated with significant improvements in cognitive flexibility, verbal fluency and processing speed, with marginally significant downstream improvements in verbal memory as assessed via standardized measures. Self-ratings of EF skills, including planning, organizing, and task monitoring, also were improved in the active group compared with the wait list group. Our findings suggest that EF skills may be improved even in long-term survivors by using a computerized, home-based intervention program. These improvements may potentially include subjective EF skills, which suggest a transfer of the training program to real-world behaviors. INSPIREHEALTH’S INTERPRETATION: Chemobrain is the colloquial term – 2 –

Results indicated that antioxidant supplementation neither increased nor decreased CRC incidence, CRA recurrence, cancer-related mortality, or overall mortality. When the supplements were analyzed independently or in combination, only selenium supplementation taken alone or in combination was associated with a non-statistically significant trend to reduced CRC incidence, CRA recurrence, and mortality. Perhaps this is because dietary selenium is used to synthesize glutathione, the human body’s number one antioxidant peptide. There were insufficient data for vitamin A to perform the meta-analysis. The lack of efficacy for the antioxidants beta-carotene and vitamins C and E was present for various doses and combinations. Once the modest benefits of selenium were excluded from the analysis, the remaining anti-oxidants actually increased overall mortality by 5%. The findings of this well done meta-analysis underscore the complexity of using individual nutrients in supplement form as disease prevention and treatment. The authors conclude that it is possible that supplementation may only benefit those who are nutrient depleted and may be harmful to other groups. In the meantime, including a variety of healthy whole foods known to contain antioxidants such as vegetables and fruits is recommended.

COGNITIVE TRAINING


Difficulties with thinking and problem solving are very common among breast cancer survivors. We tested a computerized cognitive training program for 41 breast cancer survivors. The training program was associated with significant improvements in thinking and problem-solving skills. Our findings demonstrate potential for our online, home-based cognitive training program to improve cognitive difficulties among breast cancer survivors. BACKGROUND: A majority of breast cancer (BC) survivors, particularly those treated with chemotherapy, experience long-term cognitive deficits that significantly reduce quality of life. Among the cognitive domains most commonly affected include executive functions (EF), such as working memory, cognitive flexibility, multitasking, planning, and attention. Previous studies in other populations have shown that cognitive training, a behavioral method for treating cognitive deficits, can result in significant improvements in a number of cognitive skills, including EF. MATERIALS AND METHODS: In this study, we conducted a randomized controlled trial to investigate the feasibility and preliminary effectiveness of a novel, online EF training program in long-term BC survivors. A total of 41 BC survivors (21 active, 20 wait list) completed the 48 session training program over 12 weeks. The participants were, on average, 6 years after therapy. RESULTS: Cognitive training led to significant improvements in cognitive flexibility, verbal fluency and processing speed, with marginally significant downstream improvements in verbal memory as assessed via standardized measures. Self-ratings of EF skills, including planning, organizing, and task monitoring, also were improved in the active group compared with the wait list group. CONCLUSIONS: Our findings suggest that EF skills may be improved even in long-term survivors by using a computerized, home-based intervention program. These improvements may potentially include subjective EF skills, which suggest a transfer of the training program to real-world behaviors. These changes following cancer treatment are akin to those observed in mild traumatic (eg. concussive) brain injury or mild cognitive impairment.

Cognitive training has been shown to improve or even restore cognitive function. In this small randomized controlled trial, 41 women who were on average 6 years post-breast-cancer-treatment were randomized to either a 12 week home-based online
cognitive training program (commercially available at www.luminosity.com) or a wait list control group. Forty-eight (5 exercises, 4 times/week) sessions were designed to improve executive function (EF). It was also hoped that EF training could improve other "real world" skills such as fluid reasoning, attention, language and social skills. Standardized neuropsychological tests designed to assess cognitive flexibility (the ability to generate alternate solutions to problems), language skills, working short-term memory, and processing speed were administered at baseline after 12 weeks of training. The wait list control group completed the cognitive training program following the research study. Although study participants were enrolled irrespective of baseline cognitive status, analyses showed that their baseline scores were significantly lower than those obtained from 49 age-matched female controls. Following the training program, results showed significant improvements in several aspects of EF including cognitive flexibility and processing speed. Even verbal fluency which wasn’t formally trained (indicating a positive downstream effect) improved. Although this is a small study, the findings are very encouraging and illustrate that EF can be improved even many years after treatment.

RESISTANCE TRAINING AND BONE METASTASES

Safety and Efficacy of Resistance Exercise in Prostate Cancer Patients with Bone Metastases.

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**BACKGROUND:** Due to concerns of fragility fracture, exercise is a perceived contraindication for prostate cancer patients with bone metastases. These patients experience significant functional impairment and muscle atrophy, which may lead to an increased likelihood of skeletal complications (i.e., pathological fracture, bone pain) and/or falls. Safe resistance exercise prescription may counteract this effect. The aim of this feasibility trial was to determine the safety and efficacy of resistance exercise by prostate cancer survivors with bone metastatic disease. **METHODS:** Twenty men with established bone metastases secondary to prostate cancer were randomly assigned to a 12-week resistance exercise program in which exercise prescription was based on the location of bone lesions (n=10) or usual care (n=10). Outcomes included safety and tolerance of the exercise program, physical function, physical activity level, body composition, fatigue, quality of life and psychological distress. Outcomes were compared between groups using analysis of covariance adjusted for baseline values. **RESULTS:** Participants had significant disease load with 65% of participants presenting with two or more regions affected by bone metastases and an average Gleason score of 8.2 ± 0.9. Five participants (exercise=2; usual care=3) did not complete the intervention, three of which were due to advancing disease (exercise=2; usual care=1). No adverse events or skeletal complications occurred during the supervised exercise sessions. The exercise program was well tolerated as evidenced by high attendance (83%) and compliance rates (93%), and the ability of the participants to exercise at an intensity within the target range for cancer survivors (rating of perceived exertion =13.8±1.5). The change in physical function (muscle strength ∼11%); submaximal aerobic exercise capacity ∼5% and ambulation ∼12%), physical activity level (∼24%) and lean mass (∼3%) differed significantly between groups following the intervention, with favorable changes in the exercise group compared with the usual care group. No significant between-group differences were observed for fatigue, quality of life or psychological distress. **CONCLUSIONS:** This initial evidence involving a small sample size suggests that appropriately designed and supervised resistance exercise may be safe and well tolerated by prostate cancer patients with bone metastatic disease and can lead to improvements in physical function, physical activity levels and lean mass. Future trials involving larger sample sizes are required to expand these preliminary findings.

**INSPIREHEALTH’S INTERPRETATION:** Bone metastases can affect up to 75% of men who develop prostate cancer and are associated with a higher fracture risk due to sclerotic lesions on bone sites. In many of these patients, physical activity is avoided to reduce fracture risk and prevent exacerbation of the condition. Reduced physical activity levels can lead to wasting of muscle and skeletal tissue, deteriorating fitness levels, and poor quality of life. Research has shown that resistance training can build muscle, strengthen bone, protect against cancer metastases, and improve cancer recovery and the effectiveness of treatment. This study looked at how patients undergoing (prostate and bone) metastatic cancer treatment benefited from a tailored exercise program which did not stress afflicted bone sites further. Twenty male prostate cancer patients aged 57-83 years were randomly split into the ‘exercise prescription’ group or the usual care group. In the exercise group, supervised exercise sessions were conducted twice weekly for 12 weeks and consisted of approximately 60 minutes of "moderately intense" activity with 8 different (patient specific) resistance exercises. The resistance programs designed for each patient avoided loading of bone sites with confirmed sclerotic lesions. Patients were encouraged to supplement the supervised exercise with 150 minutes of moderate intensity aerobic walking or cycling per week.
Outcome measures were: safety and tolerability of exercise, fitness levels and physical abilities, body composition, cancer related fatigue, quality of life, and psychological distress before and after the intervention. Compliance to the program was 93% with no reported increase in pain. Two exercise group subjects dropped out of the study (compared to 3 in the control group), one due to further chemotherapy treatment, and one due to bone pain during the two week study break over winter holidays. Average perceived level of exertion – reported immediately after each class on a scale from 6 (easiest) to 20 (hardest) – was 13.8, or, “somewhat hard”. The main findings of this study were that appropriate resistance exercise prescription was well tolerated, did not increase skeletal complications (measured as pain at lesion sites and skeletal fractures), improved physical function, physical activity levels and lean mass percentage. The authors commented further that this short intervention (24 hours of total exercise time) significantly improved muscular strength, aerobic capacity, ability to move, and quality of life. These benefits have been associated with fewer falls and other skeletal complications which often result in morbidity, mortality and potentially costly treatments. Although 20 subjects is a relatively small sample size, this study shows that even in patients with serious structural conditions, resistance exercise can be of significant benefit. The current American College of Sports Medicine recommended guidelines for exercise of 150 minutes moderate intensity exercise weekly has been shown to be beneficial in a number of studies. Treatment via supervised patient specific resistance exercise may further optimize one’s ability to improve muscle and bone strength (improve bone density), and increase quality of life in a relatively short time. It is also worth noting that though the supervised exercise was moderately intense, it was well tolerated by the patients with little to no adverse effects.

**OMEGA-3 FATTY ACIDS**


**Intake of Long-Chain Omega-3 Fatty Acids from Diet and Supplements in Relation to Mortality.**


Evidence from experimental studies suggests that the long-chain ω-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid have beneficial effects that may lead to reduced mortality from chronic diseases, but epidemiologic evidence is mixed. Our objective was to evaluate whether intake of long-chain ω-3 fatty acids from diet and supplements is associated with cause-specific and total mortality. Study participants (n = 70,495) were members of a cohort study (the Vitamins and Lifestyle Study) who were residents of Washington State aged 50-76 years at the start of the study (2000-2002). Participants were followed for mortality through 2006 (n = 3,051 deaths). Higher combined intake of eicosapentaenoic acid and docosahexaenoic acid from diet and supplements was associated with a decreased risk of total mortality (hazard ratio (HR) = 0.82, 95% confidence interval (CI): 0.73, 0.93) and mortality from cancer (HR = 0.77, 95% CI: 0.64, 0.92) but only a small reduction in risk of death from cardiovascular disease (HR = 0.87, 95% CI: 0.68, 1.10). These results suggest that intake of long-chain ω-3 fatty acids may reduce risk of total and cancer-specific mortality.

**INSPIREHEALTH’S INTERPRETATION:** Many research studies in the past few years have touted the health benefits of long-chain omega-3 fatty acids (eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)). One way that EPA and DHA positively influence health is by reducing inflammation. Long-chain omega-3 fatty acids have been shown previously to inhibit the activity of pro-inflammatory transcription factors, and antagonize pro-inflammatory omega-6 fatty acids. This is important because chronic inflammation has been associated with increased chronic disease risk. However, recent research looking at EPA and DHA consumption and human mortality risk has produced mixed results. The authors of this study aimed to determine the effect of EPA and DHA consumption from both dietary and supplemental sources on mortality from cardiovascular disease, mortality from cancer, and mortality overall. The subjects in this study were part of the VITAL (Vitamins and Lifestyle Study) cohort. This large prospective study followed over 70 000 men and women (50-77 years of age) for up to 6 years. Long-chain omega-3 fatty acid intake was measured through a specifically designed food frequency questionnaire. Potentially confounding variables (i.e. physical activity, alcohol consumption, smoking, fruit and vegetable intake) were statistically controlled for. Long-chain fatty acid intake was then compared to deaths from all causes, cardiovascular disease, and cancer.

Compared to subjects in the lowest quartile of consumption, subjects who reported consuming the most EPA and DHA had an 18% reduced risk of death overall, and a 23% reduced risk of death from cancer. Interestingly, subjects who reported consuming the highest amounts of EPA and DHA were also more likely to be male, more physically active, more highly educated, eat more fruits and vegetables, and drink more alcohol. This study included a large number of participants, a well-designed food frequency questionnaire, and follow-up period of up to 6 years. However, the questionnaire was only filled out once during the study period and therefore did not take into account any dietary changes that may have occurred afterwards. The authors noted this limitation and reminded the reader that the questionnaire used included dietary data for the previous 10 years.
years. Overall this study was well done and the results from it suggest that higher levels of EPA and DHA intake reduce the risk of both all-cause, and cancer mortality. Consuming 2 to 3 servings of cold water fatty fish per week will provide the amount of EPA and DHA shown in this study to reduce mortality risk.

CURCUMIN
Li, Y and T. Zhang.
Targeting Cancer Stem Cells by Curcumin and Clinical Applications.
Cancer Lett. 2014 May 1; 3462: 197-205.
Curcumin is a well-known dietary polyphenol derived from the rhizomes of turmeric, an Indian spice. The anticancer effect of curcumin has been demonstrated in many cell and animal studies, and recent research has shown that curcumin can target cancer stem cells (CSCs). CSCs are proposed to be responsible for initiating and maintaining cancer, and contribute to recurrence and drug resistance. A number of studies have suggested that curcumin has the potential to target CSCs through regulation of CSC self-renewal pathways (Wnt/beta-catenin, Notch, sonic hedgehog) and specific microRNAs involved in acquisition of epithelial-mesenchymal transition (EMT). The potential impact of curcumin, alone or in combination with other anticancer agents, on CSCs was evaluated as well. Furthermore, the safety and tolerability of curcumin have been well-established by numerous clinical studies. Importantly, the low bioavailability of curcumin has been dramatically improved through the use of structural analogues or special formulations. More clinical trials are underway to investigate the efficacy of this promising agent in cancer chemoprevention and therapy. In this article, we review the effects of curcumin on CSC self-renewal pathways and specific microRNAs, as well as its safety and efficacy in recent human studies. In conclusion, curcumin could be a very promising adjunct to traditional cancer treatments.

INSPIREHEALTH’S INTERPRETATION: This paper investigates the effectiveness of curcumin, a phytonutrient compound in turmeric (an Indian spice), as a cancer chemopreventative agent. Interestingly, curcumin may target cancer stem cells (CSC). There is evidence that tumor growth is driven by a minority number of stem cells. Chemotherapeutic drugs and radiotherapy may reduce tumor size but most do not target CSC. As a result, tumor resistance and recurrence may occur. This article highlighted studies that provide evidence on how curcumin reduces CSC growth through multiple signaling pathways. Reduced CSC growth has been shown in the following cancers: glioma, breast, colorectal, pancreatic, brain, and esophageal. Curcumin ingestion resulted in no significant toxicity observed in clinical trials up to 8000 mg/day but the major drawback was its low bioavailability. Curcumin on its own is not well absorbed; up to 75% consumed may be excreted in feces. Researchers have been working on curcumin analogs with the hopes of increasing bioavailability while maintaining its cancer chemopreventative properties. As well, nanoparticles, liposomes (a sphere with a ‘fat-like’ shell and curcumin trapped in the middle), and phospholipids (fats), may increase the uptake of curcumin.

Currently, these methods are promising but further research is necessary as the number of published scientific studies in this area is low. Consuming curcumin alone is not recommended as an effective chemopreventative method. A number of studies have shown beneficial effects of curcumin on a variety of cancers, but delivering curcumin to CSC remains a challenge. InspireHealth nutritionists recommend consuming curcumin in combination with oil and freshly-ground black pepper to improve its absorption.

INTO THE VAULT
Lappe, JM, D. Travers-Gustafson, K.M. Davies, et al.
Vitamin D and Calcium Supplementation Reduces Cancer Risk: Results of a Randomized Trial.
BACKGROUND: Numerous observational studies have found supplemental calcium and vitamin D to be associated with reduced risk of common cancers. However, interventional studies to test this effect are lacking. OBJECTIVE: The purpose of this analysis was to determine the efficacy of calcium alone and calcium plus vitamin D in reducing incident cancer risk of all types. DESIGN: This was a 4-y, population-based, double-blind, randomized placebo-controlled trial. The primary outcome was fracture incidence, and the principal secondary outcome was cancer incidence. The subjects were 1179 community-dwelling women randomly selected from the population of healthy postmenopausal women aged >55 y in a 9-county rural area of Nebraska centered at latitude 41.4 degrees N. Subjects were randomly assigned to receive 1400-1500 mg supplemental calcium/d alone
(Ca-only), supplemental calcium plus 1100 IU vitamin D3/d (Ca + D), or placebo. **RESULTS:** When analyzed by intention to treat, cancer incidence was lower in the Ca + D women than in the placebo control subjects (P < 0.03). With the use of logistic regression, the unadjusted relative risks (RR) of incident cancer in the Ca + D and Ca-only groups were 0.402 (P = 0.01) and 0.532 (P = 0.06), respectively. When analysis was confined to cancers diagnosed after the first 12 mo, RR for the Ca + D group fell to 0.232 (CI: 0.09, 0.60; P < 0.005) but did not change significantly for the Ca-only group. In multiple logistic regression models, both treatment and serum 25-hydroxyvitamin D concentrations were significant, independent predictors of cancer risk. **CONCLUSIONS:** Improving calcium and vitamin D nutritional status substantially reduces all-cancer risk in postmenopausal women.

**INSPIREHEALTH’S INTERPRETATION:** Accumulating evidence demonstrates a link between exposure to solar radiation and reduced cancer incidence. This association is thought to be mediated by vitamin D which is synthesized in the skin when exposed to sunlight. The mechanisms by which vitamin D may reduce cancer incidence are not completely understood, but it is known that approximately 200 human genes can respond to vitamin D, many of which encode for proteins important in regulating cell proliferation, differentiation and death – three very important factors in cancer development. Although this association has been investigated for many cancer types, data supporting a protective role of calcium (Ca)+vitamin D has been the most robust in colorectal cancers. However, most of this evidence comes from observational studies which are only able to show association and not causation. The authors of this study designed a double-blind randomized placebo-controlled trial to examine the relationships between supplementing with 1400-1500 mg/day Ca, 1000 IU/d vitamin D, or both compared to placebo and the incidence of fractures and cancer in 1179 healthy post-menopausal women.

Women who took Ca+vitamin D were 60% less likely to develop cancer and those in the Ca-only group were 47% less likely to develop cancer when compared to the placebo group. When the authors excluded cancers diagnosed in the first year of the study (hypothesizing that these early cancers may have been present but undiagnosed on study entry), the Ca+vitamin D group were 77% less likely to develop cancer, while risk reduction in the Ca-only group was essentially unchanged at 42%. Blood levels of vitamin D were also measured at baseline and 1 year and higher levels at both times were themselves strong predictors of cancer risk. Vitamin D levels in the Ca+vitamin D group rose from an average of 71.8 nmol/L (low normal) to 96 nmol/L (mid normal), indicating a meaningful increase. Although controversial, it is generally thought that protective vitamin D levels lie between 75-150 nmol/L. Serum vitamin D levels are not covered in BC and cost $61.32. Despite these impressive findings, others have criticized the authors’ failure to comment on treatment-specific compliance and the unexpectedly high cancer rates in the placebo group (both of which could potentially overestimate the obtained risk-reduction), as well as the study’s statistical analysis methodology. Research has shown that vitamin D plays a role in cancer prevention, however, there has not been as much research on its effect as a therapeutic agent. InspireHealth is currently conducting a research project on the effects of vitamin D supplementation as a therapeutic agent in patients with stage IV colon cancer. InspireHealth medical practitioners can help you decide if vitamin D testing and/or supplementation is right for you.