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INTEGRATIVE CANCER CARE

RESEARCH UPDATES MAY 2014

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FOR THE LATEST IN WORLDWIDE INTEGRATIVE CANCER CARE

IN THIS ISSUE: Courneya and colleagues examined the effectiveness of three exercise programs during chemotherapy in breast cancer patients and found that strength training and higher volumes of aerobic exercise were both safe and more effective at reducing chemotherapy-related symptoms than standard aerobic exercise. Gapstur et al. found that sleeping less than 5 hours per night was associated with increased risk of prostate cancer mortality. Applebaum and Breitbart commented on the importance of supportive care for the cancer caregiver and found that integrative interventions were successful in providing multiple benefits to caregivers. Rhondali and associates concluded that cancer patients with severe depression reported improvements following just one supportive/palliative care session. In a randomized double blind placebo controlled study, Bokmand and Flyger found that acupuncture treatment significantly reduced hot flashes and sleep disturbance in breast cancer patients. In a large prospective study, Brasky and colleagues found that the highest levels of dietary long chain omega-3 fatty acid intake were associated with increased endometrial cancer risk in overweight or obese women, and reduced risk in healthy weight women.

EXERCISE

Courneya, KS, D. C. McKenzie, J. R. Mackey, et al.

Effects of Exercise Dose and Type during Breast Cancer Chemotherapy: Multicenter Randomized Trial.

J Natl Cancer Inst. 2013 Dec 4; 10523: 1821-1832.

BACKGROUND: Exercise improves physical functioning and symptom management during breast cancer chemotherapy, but the effects of different doses and types of exercise are unknown. **METHODS:** A multicenter trial in Canada randomized 301 breast cancer patients to thrice-weekly supervised exercise during chemotherapy consisting of either a standard dose of 25 to 30 minutes of aerobic exercise (STAN; n = 96), a higher dose of 50 to 60 minutes of aerobic exercise (HIGH; n = 101), or a combined dose of 50 to 60 minutes of aerobic and resistance exercise (COMB; n = 104). The primary endpoint was physical functioning assessed by the Medical Outcomes Survey-Short Form (SF)-36. Secondary endpoints were other physical functioning scales, symptoms, fitness, and chemotherapy completion. All statistical tests were linear mixed model analyses, and the P values were two-sided. **RESULTS:** Follow-up assessment of patient-reported outcomes was 99.0%. Adjusted linear mixed-model analyses showed that neither HIGH (+0.8; 95% confidence interval [CI] = -0.8 to 2.4; P = .30) nor COMB (+0.5; 95% CI = -1.1 to 2.1; P = .52] were superior to STAN for the primary outcome. In secondary analyses not adjusted for multiple comparisons, HIGH was superior to STAN for the SF-36 physical component summary (P = .04), SF-36 bodily pain (P = .02), and endocrine symptoms (P = .02). COMB was superior to STAN for endocrine symptoms (P = .009) and superior to STAN (P < .001) and HIGH (P < .001) for muscular strength. HIGH was superior to COMB for the SF-36 bodily pain (P = .04) and aerobic fitness (P = .03). No differences emerged for body composition or chemotherapy completion. **CONCLUSIONS**: A higher volume of aerobic or combined exercise is achievable and safe during breast cancer chemotherapy and may manage declines in physical functioning and worsening symptoms better than standard volumes.

INSPIREHEALTH'S INTERPRETATION: While exercise is generally beneficial for breast cancer patients undergoing chemotherapy, the best combination of exercise type and duration to maximize health benefits is still unknown. This study investigated the difference in physical functioning and symptom management in women randomly assigned to three exercise programs: standard aerobic (cardiorespiratory) exercise (25-30 minutes, 3 times a week), high dose aerobic (50-60 minutes, 3 times a week), or combined, which included standard aerobic exercise and strength training (25-30 minutes of aerobic exercise, and 30-35 minutes of strength training, 3 times a week). The strength training program included 2 sets and 10-12 reps of 9 exercises that targeted major muscle groups of the body. The patients began their exercise program within 1 to 2 weeks of starting chemotherapy and finished 3 to 4 weeks after chemotherapy, exercising for an average of 16 weeks. The primary outcome was self-reported physical functioning as measured from the physical functioning subscale SF-36. No differences in physical functioning were found among the exercise programs.

However, the researchers acknowledge that the SF-36 may not be the optimal scale for assessing physical functioning in breast cancer patients. Despite no differences detected by the questionnaire, important differences among exercise groups were observed in other areas. High dose aerobic exercise was superior to standard aerobic exercise for bodily pain and endocrine symptoms (e.g. hot flashes, night sweats, and vaginal dryness). Combined exercise improved muscular strength and reduced endocrine symptoms to a greater degree than standard aerobic exercise alone. Patients assigned to the combined exercise group attended only 66% (averaging 2 days per week) of their prescribed strength training sessions, however, they still improved upper and lower body muscular strength, and upper body endurance more than both the standard and high dose aerobic groups. Chemotherapy treatment usually results in reduced aerobic fitness. Compared to the standard aerobic and combined exercise groups, the high dose aerobic exercise group reduced the negative impact of chemotherapy on aerobic fitness, body pain, patient-reported physical functioning, fatigue, and endocrine symptoms. The authors conclude that strength training and higher dose aerobic exercise were well tolerated, safe, and in many areas measured, more beneficial than standard aerobic exercise during breast cancer chemotherapy treatment.

SLEEP

Gapstur, SM, W. R. Diver, V. L. Stevens, et al.

Work Schedule, Sleep Duration, Insomnia, and Risk of Fatal Prostate Cancer.

Am J Prev Med. 2014 2014; 463 SUPPL. 1: S26-S33.

BACKGROUND: Studies of breast cancer in women and laboratory studies provide evidence that shift work involving circadian rhythm disruption is a probable human carcinogen. However, evidence linking shift work and other circadian disruption factors to prostate cancer risk is limited. **PURPOSE:** To examine associations of work schedule (i.e., rotating shift work, fixed night and fixed afternoon/evening shift work); sleep duration; and insomnia frequency with prostate cancer mortality. **METHODS:** The Cancer Prevention Study-II is a large prospective cohort study of U.S. adults. Work schedule, sleep duration, insomnia frequency, and other information was self-reported in 1982. Among 305,057 employed men, aged ≥29 years who were cancer free at baseline, there were 4974 prostate cancer deaths during follow-up through 2010. In 2013, multivariable-adjusted relative risks (RRs) and 95% CIs were computed using Cox proportional hazards regression. **RESULTS:** Work schedule and insomnia frequency were not associated with risk of fatal prostate cancer. Short sleep duration was associated with higher risk of prostate cancer during the first 8 years of follow-up, compared to 7 hours/night, the RRs (95% CIs) for 3-5 and 6 hours/night were 1.64 (1.06, 2.54), and 1.28 (0.98, 1.67), respectively. There was no association between sleep duration and fatal prostate cancer during later follow-up. **CONCLUSIONS:** These results do not support associations of work schedule or insomnia frequency with prostate cancer mortality. The association between short sleep duration and higher risk of fatal prostate cancer only during the first 8 years of follow-up suggests that short sleep duration could affect later stages of prostate carcinogenesis.

INSPIREHEALTH'S INTERPRETATION: Lack of sleep, poor sleep, or irregular sleep patterns may increase one's risk of dying from certain cancers. This long prospective cohort study aimed to look at these variables with respect to prostate cancer. In 1982/1983, nearly 1.2 million adults filled out a questionnaire as part of the Cancer Prevention Study-II. Of these participants, 305,057 employed males became part of this current study on work, sleep, and risk of prostate cancer mortality (death). From the initial self-reported questionnaire, men were categorized based on variables that may affect sleeping patterns: work schedule (i.e. rotating shifts, fixed day shifts, fixed night shifts), average hours slept per night, and number of insomnia (sleeplessness) episodes per month. The researchers followed the men for 28 years following the single questionnaire and recorded those who died from prostate cancer (confirmed from death certificates or reported death codes).

This study had two main conclusions. First, sleeping less than 5 hours per night was associated with a higher risk of prostate cancer mortality within 8 years of the questionnaire, but not after 28 years. Second, work schedule and insomnia were not associated with prostate cancer mortality. This study has a number of issues. The questionnaire did not collect data on total hours worked, and because it was only filled out once, did not take into account any change in career, job status (retirement), or work schedule that may have occurred in the 28 year follow-up period. Additionally, no objective data was collected to assess sleep cycles, quality of sleep, or number of sleep interruptions - all data was self-reported. It is very likely that the 1982/1983 classifications were incorrect in 2010. This study suggests that lack of sleep contributes to increased risk of prostate cancer mortality, however, to evaluate the relationship among prostate cancer mortality risk and hours slept, quality of sleep, and shift work, more rigorous study designs are required.

SUPPORTIVE CARE

Applebaum, AJ and W. Breitbart.

Care for the Cancer Caregiver: A Systematic Review.

Palliative & Supportive Care. 2013 Jun; 113: 231-252.

OBJECTIVE: Informal caregivers (ICs) are relatives, friends, and partners who have a significant relationship with and provide assistance (i.e., physical, emotional) to a patient with a life-threatening, incurable illness. The multidimensional burden that results from providing care to a patient with cancer is well documented, and as a result, a growing number of psychosocial interventions have been developed specifically to address this burden. The purpose of the present study was to characterize

the state of the science of psychosocial interventions for informal cancer caregivers. **METHOD:** A comprehensive systematic review of interventions for cancer caregivers was conducted via an electronic literature search of publications between 1980 and January 13, 2011. A final sample of 49 interventions was reviewed in detail. **RESULTS:** The interventions, which varied in terms of modality and patient population, fell into the following eight categories: psychoeducation, problem-solving/skills building interventions, supportive therapy, family/couples therapy, cognitive-behavioral therapy, interpersonal therapy, complementary and alternative medicine interventions, and existential therapy. Benefits and disadvantages of each of the categories are discussed, with special attention given to studies that produced null findings. **SIGNIFICANCE OF RESULTS:** Beyond specific techniques, structured, goal-oriented, and time-limited interventions that are integrative appear to be the most feasible and offer the greatest benefits for ICs of cancer patients. Future studies are needed to examine the specific benefits and challenges of delivering interventions in alternative modalities (Internet, Skype) so that the needs of a greater number of ICs may be addressed.

INSPIREHEALTH'S INTERPRETATION: Many people are affected by a cancer diagnosis. Friends, family members, and partners who provide support to a patient with cancer are termed informal caregivers. In the United States, roughly 4.6 million people supported a cancer patient as an informal caregiver in 2009. Previous researchers have commented that being an informal caregiver can be as demanding and time consuming as a full-time job. On average, an informal caregiver will spend 8.3 hours per day for almost 14 months providing care for a cancer patient. In addition to developing physical health problems, many caregivers feel unprepared and unsupported in this process. As a result, they can experience high levels of stress, depression, fear, and anxiety to levels that may surpass those felt by the patients they are supporting.

This review focused on 49 research studies that provided support-related interventions for informal caregivers. Each of the interventions studied fell into one of the following categories: psychoeducation, supportive therapy, problem solving / skill building, family / couples therapy, cognitive behavioural therapy, interpersonal therapy, complementary and alternative medicine, and existential therapy. In 65% of the interventions studied, both the informal caregivers and the cancer patients they cared for experienced significant improvements in overall functioning. Interventions which included more than one of the above categories were successful in providing multiple benefits to informal caregivers. In the studies that did not show significant benefit, the authors of this review noted some methodological reasons to help explain why (e.g. shorter follow-up periods, and inclusion of subjects who were already receiving enough support or had only low to moderate baseline levels of distress). The authors note that while most informal caregivers and patients preferred face-to-face interaction, telephone communication worked well in some cases. Here at InspireHealth, we see firsthand the importance of support and offer the same programs and classes to our support members that we do for our patient members, both online at the InspireHealth Virtual Centre, and in person at our centres in Vancouver, Victoria, and Kelowna.

SUPPORTIVE CARE

Rhondali, W, S. Yennurajalingam, J. Ferrer, et al.

Association between Supportive Care Interventions and Patient Self-Reported Depression among Advanced Cancer Outpatients.

Supportive Care in Cancer. 2014 April 2014; 224: 871-879.

PURPOSE: Advanced cancer patients often experience moderate to severe physical and emotional distress. One of the main components of emotional distress is depression. The objective of this study was to examine the association between supportive care interventions and patient self-reported depression (PSRD) among advanced cancer outpatients. **METHODS:** We included consecutive patients seen in the outpatient Supportive Care Center between February 2008 and February 2010 with at least one follow-up visit. We used the Edmonton Symptom Assessment Scale (ESAS) to assess their symptom intensity. Clinical improvement of PSRD was defined as an improvement of at least 30% between the initial visit and the first follow-up. We used logistic regression models to assess possible predictors of improvement in PSRD. **RESULTS:** We included 444 patients with a median age of 59 years (Q1-Q3; 51-65). The most common type of cancer was gastrointestinal (98, 22%). Out of the 444 patients, 160 (36%) reported moderate/severe depression at baseline (ESAS item score $\geq$ 4/10). Higher baseline depression intensity was significantly associated to anxiety ($r = 0.568$, $p = 0.046$), total symptom distress score (TSDS; $r = 0.550$, $p < 0.001$) and personal history of depression ($r = 0.242$, $p = 0.001$). Of the 160 patients, 90 (56%) with moderate/severe PSRD at baseline showed a significant improvement at the follow-up visit ($p = 0.038$). Improvement in anxiety, sedation, and feeling of well-being were associated with higher depression improvement (OR 7.93, CI 3.74-16.80 and OR 2.44, CI 1.09-5.46, respectively). **CONCLUSIONS:** More than 50% patients with moderate/severe PSRD significantly improved after one single supportive/palliative care consultation. Improvements of anxiety and sedation were independently associated with PSRD improvement.

INSPIREHEALTH'S INTERPRETATION: Patients with advanced cancer can experience significant physical and emotional symptoms, with depression occurring about 25% of the time. The authors of this University of Texas study reviewed the medical records of 444 patients with advanced cancer to determine if a consultation with their interdisciplinary palliative care team could reduce depressive symptoms. They also examined the relationships between various physical and emotional symptoms as related to depression. Participants completed the Edmonton Symptom Assessment Scale (ESAS) at the initial and follow-up clinic visits. The ESAS measures symptoms such as pain, fatigue, nausea, anxiety, sedation, well-being and depression. Clinical improvement was defined as a 30% improvement on the ESAS depression score for those whose depression was initially rated as moderate to severe. Of the 160 patients with moderate to severe depression, 56% showed clinical improvement though

this result was not statistically significant. Improvements in fatigue, anxiety, sedation and well-being were all associated with improvements in mood. Overall, those reporting higher levels of depression also reported a higher intensity of all physical and emotional symptoms. Because physical and emotional symptoms can exacerbate depression and vice versa, it is important to discuss and manage all symptoms together. The advantage of a supportive care palliative approach is that multiple physical and psychosocial symptoms can be addressed at one consultation. Although the presence or absence of moderate to severe depression did not seem to be associated with survival, for those with clinical mood improvement a trend to increased survival was noted. It is important for those living with cancer and their care providers to always address physical, emotional, and social symptoms and issues.

ACUPUNCTURE

Bokmand, S and H. Flyger.

Acupuncture Relieves Menopausal Discomfort in Breast Cancer Patients: A Prospective, Double Blinded, Randomized Study.

Breast. 2013 Jun; 223: 320-323.

BACKGROUND: This study evaluates the effect of acupuncture on hot flashes and disturbed night sleep in patients treated for breast cancer. The effect of acupuncture was tested against a sham-acupuncture group and a no-treatment control group. Plasma estradiol was measured to rule out this as cause of effect. Side effects of the treatment were registered. **METHODS:** We randomized 94 women into the study: 31 had acupuncture, 29 had sham acupuncture and 34 had no treatment. **FINDINGS:** In the acupuncture group, 16 patients (52%) experienced a significant effect on hot flashes compared with seven patients (24%) in the sham group ($p < 0.05$). The effect came after the second acupuncture session and lasted for at least 12 weeks after last treatment. A statistically significant positive effect was seen on sleep in the acupuncture group compared with the sham-acupuncture and no-treatment groups. The effect was not correlated with increased levels of plasma estradiol. No side effects of acupuncture were registered. **INTERPRETATION**: We find that acupuncture significantly relieves hot flashes and sleep disturbances and is a good and safe treatment in women treated for breast cancer.

INSPIREHEALTH'S INTERPRETATION: In this very well designed Danish study, 94 women aged 45-74 years old with a history of surgically treated breast cancer who were experiencing troublesome hot flashes and disturbed sleep were randomized to receive acupuncture, sham acupuncture, or no treatment. In a "double blind" study, the experimenters examining the data do not know which of the 3 groups each individual participant was assigned to, and the patients do not know whether they are receiving the "real" treatment or the "sham" treatment. This is a very strong experimental design that reduces experimenter bias and the placebo effect. Acupuncture and sham acupuncture treatments were weekly for 5 consecutive weeks and patients were followed for a further 12 weeks to observe lasting effects of the treatments. Most women were taking anti-estrogen hormone therapy (tamoxifen, letrazole, or exemestane) and only 2 had received chemotherapy. This type of hormone therapy is known to exacerbate vasomotor symptoms such as hot flashes and night sweats. Results indicated that acupuncture significantly reduced hot flashes and improved sleep, and that these treatment effects lasted for up to 12 weeks. Furthermore, no specific adverse effects were noted.

Although the mechanisms of acupuncture's therapeutic effects are unknown, it has been hypothesized that a release of endorphins may modulate the thermoregulatory zone in the brain, such that a neutral sensation of temperature is felt over a larger temperature range. Other researchers have suggested that acupuncture's benefit might be due to increased hormone (e.g. estrogen) levels: an undesirable effect in women with breast cancer. The authors of this study carefully measured plasma estradiol (blood estrogen) and didn't find any such increases. In summary, vasomotor symptoms are common in post-menopausal women and can be significantly exacerbated by anti-estrogen hormone therapy used in breast cancer treatment. In this double blind randomized controlled trial, acupuncture was beneficial in the absence of raising estrogen with no adverse clinical effects. Rarely does a treatment offer benefit with little or no risk. Acupuncture is a safe and effective option for treating difficult vasomotor symptoms in women taking hormone therapy for breast cancer treatment.

OMEGA-3 FATTY ACIDS

Brasky, TM, M. L. Neuhouser, D. E. Cohn, et al.

Associations of Long-Chain -3 Fatty Acids and Fish Intake with Endometrial Cancer Risk in the VITamins and Lifestyle Cohort.

Am J Clin Nutr. 2014 01 Mar 2014; 993: 599-608.

BACKGROUND: Inflammation plays an important role in endometrial cancer etiology. Long-chain ω-3 (n-3) polyunsaturated fatty acids (PUFAs), derived from marine sources, are thought to be antiinflammatory; however, several studies of fish consumption suggest an increase in risk. **OBJECTIVE:** This study examined whether intakes of long-chain ω-3 PUFAs, including eicosapentaenoic acid (EPA; 20:5ω-3) and docosahexaenoic acid (DHA; 22:6ω-3), from diet and supplements and intake of fish are associated with endometrial cancer risk. **DESIGN:** Between 2000 and 2002, 22,494 women aged 50-76 y, living in western Washington State, were recruited to the VITamins And Lifestyle cohort study. Incident endometrial cancers (n = 263) were

identified through the Surveillance, Epidemiology, and End Results cancer registry after 9 y of follow-up. Multivariable-adjusted HRs and 95% CIs for the association of intakes of individual long-chain ω-3 PUFAs and fish with endometrial cancer risk were estimated by using Cox proportional hazards. **RESULTS:** Women in the highest compared with the lowest quintile of dietary EPA + DHA intake had a 79% increased risk of endometrial cancer (95% CI: 16%, 175%; P-trend = 0.026). Results were similar for EPA and DHA measured individually and for fish intake. When data were stratified by body mass index (in kg/m(2); <25 or ≥25), increases in risk of long-chain ω-3 PUFAs were restricted to overweight and obese women, and statistically significant reductions in risk were observed for normal-weight women. **CONCLUSIONS:** The overall increased risk reported here confirms the findings of several prior observational studies of fish intake, which observed similar increases in risk. Randomized trials are needed to confirm these findings.

INSPIREHEALTH'S INTERPRETATION: Endometrial cancer is the fourth most common cancer in women. Previous studies have shown that high levels of systemic inflammation are associated with increased risk of endometrial cancer development. Long chain omega-3 fatty acids (EPA and DHA) are anti-inflammatory in nature, but research studies investigating their effect on endometrial cancer risk have been conflicting. In a case-control study by Arem et al. (2013), increasing dietary levels of EPA and DHA were associated with a linear reduction in endometrial cancer risk. In contrast, the Iowa Women's Health Study showed an increased risk of endometrial cancer when comparing the highest levels of seafood intake with the lowest. The current study included 22,494 women, and 263 developed endometrial cancer during the study period. This study found that overall, women who consumed the most EPA and DHA from marine sources had a 79% higher incidence of endometrial cancer than women who consumed the least. However, this association changed when body mass index (BMI) was taken into account. In healthy weight women (BMI < 25), those who consumed the highest amount of EPA and DHA had a 61% lower risk of endometrial cancer. Whereas in overweight or obese women (BMI ≥ 25), the highest amount of EPA and DHA consumption compared to the lowest was associated with a 175% higher risk of endometrial cancer. The authors propose an interesting explanation. Previous studies have shown that consumption of EPA and DHA may increase production of female sex hormones. Adipose tissue (made of fat cells) also produces estrogen. In overweight or obese women, the increased estrogen production from excess adipose tissue coupled with production from high levels of EPA and DHA consumption may result in a greater risk of endometrial cancer.

Additionally, this study's results were consistent across consumption of many different fish types. The authors postulate that because omega-3 content in fish varies substantially across fish types, perhaps other fat soluble components (environmental pollutants such as mercury, polychlorinated biphenyls, or dioxins) may be responsible for the observed increased risk. This strong study was supported by its prospective design and large sample size. However, food frequency questionnaires, no matter how well designed can be inaccurate. Though this study was well done, this level of evidence is not enough to determine a cause and effect relationship. To determine cause and effect, the next step would be a randomized controlled trial. This study suggests that healthy weight women may benefit more from fish consumption than overweight or obese women. InspireHealth continues to support moderate consumption of wild fish.

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InspireHealth's programs are supported by current research and can be safely integrated with patient's conventional treatments.

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