



RESEARCH UPDATES SUMMER 2016

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FOR THE LATEST IN WORLDWIDE SUPPORTIVE CANCER CARE

IN THIS ISSUE: Reed and colleagues explore the relationship between emotional acceptance and sickness symptoms among a group of women with breast cancer. A paper by Cramer's team explores the effect of regular yoga and meditation practices on menopausal symptoms. Bjorkem-Bergman and Bergman look at the role of vitamin D on the immune system, in cancer, in depression, and in pain and palliative care. A study by Niravath reviews the literature around aromatase-inhibitor induced arthralgia and provides interventions to help to mitigate them. Ben-Arye and colleagues looked at the effect of a cuisine workshop on patients receiving chemotherapy. Lastly, an Into the Vault study by Oh and colleagues reports on an intervention using Medical Qigong and the effect on quality of life and inflammatory markers.

EMOTIONAL ACCEPTANCE

Reed, R.G., Weihs, K.L., Sbarra, D.A., et al.

Emotional acceptance, inflammation, and sickness symptoms across the first two years following breast cancer diagnosis.

Brain, Behavior, and Immunity (2016), 56: 165-74.

ABSTRACT | Purpose: Breast cancer diagnosis and treatment are associated with increased inflammatory activity, which can induce sickness symptoms. We examined whether emotional acceptance moderates the association between proinflammatory cytokines and self-reported sickness symptoms in women recently diagnosed with breast cancer. **Methods:** Women (N = 136) diagnosed with stage 0-III breast cancer within the previous 6 months provided plasma samples and completed the FACT: Physical Well-Being Scale, as well as the Acceptance of Emotion Scale every 3 months for 2 years. At each time point, we quantified interleukin (IL)-6, IL-8, IL-10, and tumor necrosis factor (TNF)-a using a high sensitivity multiplex assay. **Results:** Higher within-subject mean TNF-a across all time-points predicted higher mean sickness symptoms. At individual time-points, higher IL-6 and IL-8 levels were associated with higher sickness symptoms. Mean emotional acceptance across all time-points moderated the relationship between mean IL-8 and sickness symptoms, with sickness symptoms remaining persistently high in women with low emotional acceptance even when IL-8 levels were low. At individual time-points, emotional acceptance positively moderated the correlations of IL-8 and TNF-a with sickness symptoms, such that the associations between higher levels of these pro-inflammatory cytokines and higher sickness symptoms were attenuated when emotional acceptance was high. **Conclusion:** Emotional acceptance was shown for the first time to moderate the associations of cytokines with sickness symptoms in breast cancer patients over time following diagnosis and treatment. The association between emotional acceptance and sickness symptoms was significantly different from zero but relatively small in comparison to the range of sickness symptoms. Results suggest that targeting emotion regulation may help to break the cycle between inflammation and sickness symptoms in women with breast cancer.

INSPIREHEALTH'S INTERPRETATION: Many cells including both tumor cells and immune cells are known to secrete cytokines, chemical messenger molecules that can mediate inflammation in the body. This inflammatory environment can result in an array of symptoms known as "sickness symptoms". Sickness symptoms, such as nausea, fatigue and pain are thought to be adaptive when experienced acutely, providing an opportunity for the body to mount an attack. However, these symptoms can also heighten inflammation within the body, resulting in a cycle of inflammation and sickness. This study examined whether or not higher levels of emotional acceptance could mediate the relationship between cytokines and sickness symptoms to help reduce this inflammation/sickness cycle. It measured participants' emotional acceptance, sickness symptoms and blood concentrations of cytokines over a two year period. Emotional acceptance (EA) is defined as a willingness to feel both positive and negative emotions and allow emotions to develop and dissipate without attempts to control, change or reject them.

In this study, EA was measured by the Acceptance of Emotion Scale (AES), which measures the degree to which the participants aligned with such statements as “I allow myself to be in touch with my feelings because it is good for me.”. Sickness symptoms were measured using the Functional Assessment of Cancer Therapy: Physical Well Being Scale (FACT-PWB) which asks participants to rate how strongly they identify with such statements as “I have a lack of energy”. Cytokines were measured through the collection and analysis of blood samples. The participants consisted of 136 women diagnosed with breast cancer. All patients continued their individual treatments throughout the course of the study. It was found that EA did indeed mediate the relationship between cytokine profile and sickness symptoms. That is, at higher levels of EA, higher levels of cytokines did not predict higher measures of sickness symptoms. In contrast, at low levels of EA, high inflammatory cytokine levels directly correlated with higher subjective sickness symptoms. This trend was found over time for both single individuals as well as between individuals when an average measure of EA was calculated.

This study suggests that holding an accepting and nurturing disposition towards one’s feelings, whether positive or negative, may provide a means of breaking the negative self-perpetuating cycle between sickness symptoms and inflammation, and in doing so provide a greater sense of wellbeing. Patients are encouraged to explore what it means to them to be emotionally accepting and seek out resources to support this process.

YOGA AND MEDITATION

Cramer, H., Rabsilber, S., Lauche, R., et al.

Yoga and Meditation for Menopausal Symptoms in Breast Cancer Survivors.

Cancer (2015), 121: 2175-84.

ABSTRACT | Breast cancer survivors have only very limited treatment options for menopausal symptoms. The objective of this trial was to evaluate the effects of a 12-week traditional Hatha yoga and meditation intervention on menopausal symptoms in breast cancer survivors. **Methods:** Patients were randomly assigned either to a 12-week yoga and meditation intervention or to usual care. The primary outcome measure was total menopausal symptoms (Menopause Rating Scale [MRS] total score). Secondary outcome measures included MRS subscales, quality of life (Functional Assessment of Cancer Therapy-Breast), fatigue (Functional Assessment of Chronic Illness Therapy-Fatigue), depression, and anxiety (Hospital Anxiety and Depression Scale). Outcomes were assessed at week 12 and week 24 after randomization. **Results:** In total, 40 women (mean age±standard deviation, 49.2±5.9 years) were randomized to yoga (n=19) or to usual care (n=21). Women in the yoga group reported significantly lower total menopausal symptoms compared with the usual care group at week 12 (mean difference, 25.6; 95% confidence interval, 29.2 to 21.9; P=.004) and at week 24 (mean difference, 24.5; 95% confidence interval, 28.3 to 20.7; P5.023). At week 12, the yoga group reported less somatovegetative, psychological, and urogenital menopausal symptoms; less fatigue; and improved quality of life (all P<.05). At week 24, all effects persisted except for psychological menopausal symptoms. Short-term effects on menopausal symptoms remained significant when only women who were receiving antiestrogen medication (n=36) were analyzed. Six minor adverse events occurred in each group. **Conclusions:** Yoga combined with meditation can be considered a safe and effective complementary intervention for menopausal symptoms in breast cancer survivors. The effects seem to persist for at least 3 months.

INSPIREHEALTH’S INTERPRETATION: Since yoga has been found to improve menopausal symptoms in, otherwise healthy women, this study investigated the effect of a 12 week, weekly yoga and meditation program on menopausal symptoms among breast cancer survivors. Many women with estrogen receptor positive breast cancer take anti-estrogen hormone therapy which can induce or exacerbate menopausal symptoms such as hot flashes, night sweats, vaginal dryness and emotional lability. In this randomized controlled trial, 40 women were randomized to either participate in a 90 minute weekly yoga and meditation class or to a control group (did not participate in the yoga program). The women had at least mild menopausal symptoms, had not participated in regular yoga practices within the last year, and had no surgeries, hormone-replacement therapy, or changes in medication during the course of the study. The groups were assessed via questionnaires that measured menopausal symptoms, quality of life, fatigue, and psychological distress at the end of the 12 week program as well as three months after the program.

At the end of the program, as well as three months afterwards, women in the yoga and meditation group improved in somato-vegetative (e.g., hot flashes, palpitations, sleep problems, joint and muscle problems), urogenital, and overall menopausal symptoms compared to those in the control group. The yoga and meditation group also improved in social, emotional, and functional quality of life after the program when compared to the control group. Quality of life overall and fatigue were significantly improved both at the end of the program and three months thereafter. Anxiety and depression yielded no statistical difference between the groups. Although the small study size may limit the power and generalizability of the results, the authors conclude that yoga and meditation practices are generally safe and effective in improving menopausal symptoms, quality of life, and fatigue in women with breast cancer.

VITAMIN D

Bjorkem-Bergman, L., & Bergman, P.

Vitamin D and patients with palliative cancer.

BMJ Supportive & Palliative Care (2016), 0: 1–5, doi:10.1136/bmjspcare-2015-000921.

ABSTRACT | Vitamin D is a hormone that is synthesised in the skin in the presence of sunlight. Sufficient vitamin D levels are important—not only for a healthy skeleton—but also for a healthy immune system. Many patients with cancer have insufficient vitamin D levels, and low vitamin D levels are associated with increased ‘all-cause mortality’ and especially mortality due to cancer. Low vitamin D levels have also been associated with increased risk of infections, increased pain, depressive disorders and impaired quality of life. We review the role of vitamin D in the immune system, in relation to cancer disease, pain and depression. We have recently performed an observational study in 100 patients with palliative cancer in Sweden. The main result was that low vitamin D levels were associated with higher opioid dose, that is, more pain. We also describe a case report where vitamin D supplementation resulted in radically decreased opioid dose, less pain and better well-being. Vitamin D supplementation is not connected with any adverse side effects and is easy to administrate. Thus, we hypothesise that vitamin D supplementation to patients with palliative cancer might be beneficial and could improve their well-being, decrease pain and reduce susceptibility to infections. However, more clinical studies in this field are needed before firm conclusions can be drawn.

INSPIREHEALTH’S INTERPRETATION: It has long been known that vitamin D plays an important role in calcium balance and hence bone health. More recently, it has also been shown that vitamin D is important for our immune systems, nervous systems and cardiovascular systems. Vitamin D is synthesized in the skin when it is exposed to ultraviolet (UV) B sunlight. Smaller amounts of vitamin D are provided through foods such as meat and fish. Many also augment vitamin D intake with supplements. Low vitamin D levels are often found in cancer patients and are associated with increased mortality rates in some cancers. Increased risk of infection, increased pain, depressed mood and reduced quality of life have also been associated with insufficient vitamin D levels. Interestingly, vitamin D is involved in regulating the ways in which many genes express themselves which may explain its many varied physiological roles.

The authors of this paper review vitamin D’s roles in the immune system, in cancer, in depression, and in pain and palliative care. They also describe the results of an observational study examining the vitamin D levels in 100 palliative care patients in Sweden. Vitamin D can induce antibodies at mucosal surfaces to defend against invading viruses and bacteria, and may activate white blood cells called macrophages to behave in an anti-tumor way in order to help eradicate malignant cells. Low vitamin D levels are also associated with increased pain and poorer pain control. Interestingly, low vitamin D in the pain setting may simply be a marker for low UVB exposure as UVB light can provide analgesia via the production of endorphins. Because cancer, depression, and pain are often associated, and because low vitamin D levels are associated with all of these illnesses, and because vitamin D supplementation is very well tolerated, it is reasonable to consider the use of vitamin D supplementation in this population. The authors also review a case report of one patient with metastatic gastrointestinal cancer who was experiencing severe pain and whose vitamin D levels were virtually undetectable. Following vitamin D supplementation his pain was reduced to such an extent that he was able to discontinue his opioid medication. Of course, no cause and effect can be attributed to this one example, but it is an interesting anecdote about a possible vitamin D/cancer-related pain link. InspireHealth physicians are able to discuss vitamin D and whether or not supplementation may be of benefit.

AROMATASE-INHIBITOR ARTHRALGIA

Niravath, P.

Aromatase inhibitor-induced arthralgia: a review.

Annals of Oncology (2013), 00: 1–7, doi:10.1093/annonc/mdt037.

ABSTRACT | Though aromatase inhibitors (AIs) are an essential part of estrogen receptor-positive (ER+) breast cancer therapy, many patients discontinue the medicine before their adjuvant therapy is completed because of the arthralgia which often accompanies the medicine. Up to half of women on AI therapy experience joint pain, and up to 20% will become noncompliant with the medicine because of the joint pain. Yet, very little is known about what causes AI-induced arthralgia (AIA), and there is no established, effective treatment for this difficult problem. It compromises survivors’ quality of life and leads to non-compliance. This paper will discuss AIA in depth, including potential etiologies, clinical significance, risk factors, and possible management solutions. Of note, this article presents one of the first proposed algorithms which clearly lays out a treatment plan for AIA, incorporating a variety of interventions which have been proven by the available literature.

INSPIREHEALTH’S INTERPRETATION: Women with estrogen receptor positive (ER positive) breast cancer are typically offered anti-estrogen hormone therapy as part of their long-term treatment regime. Medications such as tamoxifen and the aromatase inhibitors (AIs) anastrozole, exemestane, and letrozole all act to counter the effects of estrogen on breast tissue. Although AIs are the most effective hormonal therapy for post-menopausal women, with improved disease-free survival and reduced recurrence risk, they can also cause arthralgia (joint pain/stiffness). Many women discontinue their AIs due to significant arthralgia. For any given woman, one AI may be better tolerated than another, but studies have shown no significant differences in the overall incidence of aromatase inhibitor-induced arthralgia (AIA). Although incidence rates of AIA vary, the true incidence

is thought to be as high as 50%. The most commonly affected joints are wrists, hands and knees. Onset of symptoms can occur anywhere from a couple of weeks to more than 10 months (average 1.6 months) after AI initiation and typically peak at about 6 months. Women who develop AIA may have a lower risk of recurrence, perhaps indicating that symptoms reflect greater estrogen depletion. There is some evidence that estrogen may have analgesic properties and it is postulated that this analgesic effect may be related to an evolutionary adaptation to better tolerate the pain of childbirth. Additionally, higher levels of estrogen may suppress the production of inflammatory molecules.

Interestingly, exercise has been shown to release anti-inflammatory molecules and is the most effective tool for managing AIA. The other modality shown in a randomized controlled trial to be effective is acupuncture (i.e. true acupuncture is more effective than sham acupuncture). Unfortunately, there haven't been many robust trials performed to investigate AIA management. Women troubled by AIA can switch from one AI to another or even to the older hormone therapy tamoxifen (which seems to have lower risk of arthralgia) if AIA is an issue. There may also be a role for vitamin D supplementation (see also Bjorkhem-Bergman study in this issue) and a large multi-centre trial is currently underway to investigate this hypothesis. Yoga may also be an effective intervention. Curiously, the use of anti-inflammatory medications has not been shown to be beneficial and the use of these medications is associated with significant side effects such as gastrointestinal bleeding and kidney problems. The use of the newer COX-2 anti-inflammatories such as celebrex should probably be avoided because they are thought to increase the risk of heart attack and stroke. Maintenance of healthy body weight is also an important part of AIA management. Both regular exercise and healthy weight are known to reduce the risk of recurrence of breast cancer, so even in the absence of AIA, it is prudent to consider optimizing these two cornerstones of healthy lifestyle.

INTEGRATIVE CUISINE

Ben-Arye, E., Keshet, Y., Miller Shahbar, I., et al.

The kitchen as therapy: qualitative assessment of an integrative cuisine workshop for patients undergoing chemotherapy.

Supportive Care in Cancer (2016), 24: 1487–1495.

ABSTRACT | Objective: Patients undergoing chemotherapy frequently suffer from gastrointestinal (GI) symptoms and functional difficulties in preparing and eating meals. We conducted a qualitative assessment of an integrative cuisine workshop program designed for patients receiving chemotherapy, examining the effects of the program on patient-reported GI symptoms and nutritional challenges. **Patients and methods:** Patients were referred to a complementary/integrative medicine (CIM)-trained physician for consultation, followed by a patient-tailored treatment program. Patients with GI-related symptoms and nutritional concerns were offered a two-session integrative cuisine workshop program. The effects of the workshops were examined using inductive and deductive qualitative research methodologies. Patient narratives, as recorded in the Measure Yourself Concerns and Wellbeing (MYCAW) study tool, and electronic medical files were analyzed. **Results:** Of 125 patients referred to the integrative cuisine program, 86 participated in at least one workshop. Participants and non-participants had similar demographic and disease related characteristics, as well as quality-of-life (QOL)-related concerns. Inductive analysis suggested that participation in the workshops was helpful in developing social relationships, providing emotional support, and enhancing spirituality and nutritional awareness. Implementing the recommended changes at home led to improved QOL-related outcomes. The predominant themes derived from deductive analysis were the implementation of dietary changes and improved gastrointestinal and emotional issues. **Conclusions:** Chemotherapy-treated patients participating in an integrative cuisine workshop program showed improved QOL outcomes, specifically GI and emotional-related symptoms, and a reduction in nutritional and functional concerns. Increased knowledge and awareness of nutrition and supplement use ultimately resulted in implementation of the CIM recommendations by patients at home.

INSPIREHEALTH'S INTERPRETATION: This exploratory research study investigated the effects of a cooking workshop among cancer patients actively receiving chemotherapy. The cuisine workshops took place at an Oncology Health Centre in Israel between 2009 and 2010 and consisted of one or two 3-hour sessions in groups of three to six. Those who participated in at least one cuisine workshop received a questionnaire to assess fatigue, gastrointestinal concerns, emotional distress, and other quality of life factors. The cuisine workshops were led by a dietician, an occupational therapist, and a social worker or spiritual care provider. During the workshop, patients prepared a variety of meals made from mostly plant-based foods including nuts, vegetables, spices, and herbs. Participants received recipes and were educated about foods that may improve gastrointestinal-related symptoms and fatigue. Facilitators also discussed food safety, potential for side effects, and food interactions with conventional anti-cancer treatments. At the end of meal preparation, participants ate their meal together and were asked to contemplate what they prepared. Approximately 6-12 weeks later, participants filled out a questionnaire. In this qualitative study, researchers investigated themes based on answers from the questionnaire. Common themes identified included improved social relationships, emotional support, spirituality, enhanced awareness and nutritional knowledge. An increased sense of strength as well as improved movement and function were also identified. The main conclusions of the study were that patients who participated in the cuisine workshop improved in a number of quality of life related benefits, some of which included gastrointestinal concerns, fatigue, emotional distress, and attitude and changes about diets and herbs. It is important to note that this study is exploratory in nature, and as such, there was no control group. As well, participants

actively chose to attend the workshop, so it's possible that they were already interested in health- and food-related topics. Since participants received literature stating that the foods may improve gastrointestinal symptoms and fatigue, it is not clear if their subsequent improvement was due to the food itself, education, social aspect of the workshop, or due to participation in a research study. This pilot (preliminary) study indicates that cuisine workshops may be beneficial for those undergoing chemotherapy. InspireHealth offers an array of cooking classes, offering recipes and information on a variety of food types.

INTO THE VAULT: MEDICAL QIGONG

Oh, B., Butow, P., Mullan, B., et al.

Impact of medical Qigong on quality of life, fatigue, mood and inflammation in cancer patients: A randomized controlled trial.

Annals of Oncology (2010), 21; 608-614.

ABSTRACT | Background: Substantial numbers of cancer patients use complementary medicine therapies, even without a supportive evidence base. This study aimed to evaluate in a randomized controlled trial, the use of Medical Qigong (MQ) compared with usual care to improve the quality of life (QOL) of cancer patients. **Patients and methods:** One hundred and sixty-two patients with a range of cancers were recruited. QOL and fatigue were measured by Functional Assessment of Cancer Therapy—General and Functional Assessment of Cancer Therapy—Fatigue, respectively, and mood status by Profile of Mood State. The inflammatory marker serum C-reactive protein (CRP) was monitored serially. **Results:** Regression analysis indicated that the MQ group significantly improved overall QOL ($t_{144} = 25.761$, $P < 0.001$), fatigue ($t_{153} = 25.621$, $P < 0.001$), mood disturbance ($t_{122} = 2.346$, $P = 0.021$) and inflammation (CRP) ($t_{99} = 2.042$, $P < 0.044$) compared with usual care after controlling for baseline variables. **Conclusions:** This study indicates that MQ can improve cancer patients' overall QOL and mood status and reduce specific side-effects of treatment. It may also produce physical benefits in the long term through reduced inflammation.

INSPIREHEALTH'S INTERPRETATION: Medical Qigong is a mind-body practice taken from Traditional Chinese Medicine. It, along with other Chinese Medicine exercise modalities such as Tai Chi, have increased in popularity due to noted effects such as improving balance, coordination, and muscular endurance, as well as decreasing stress, anxiety, and inflammation. Physiologically, it is believed that these modalities help to harmonize the two divisions of the autonomic nervous system: the sympathetic system ("fight or flight") and the parasympathetic system ("rest and digest"). Few larger-scale research studies have been performed examining the effect of Medical Qigong on the side effects and symptoms of cancer patients, therefore, the authors of this study sought to study this relationship. One hundred and sixty two cancer patients between the ages of 31 and 86 (mean age was 60 years old) were randomized to either a Medical Qigong group or a control group. All participants took part in baseline measurements of quality of life, mood, fatigue, and inflammatory biomarkers (C-reactive protein). Participants in the Medical Qigong group then took part in a ten week program, consisting of two 90 minute sessions per week. Those in the control group continued with their usual medical care. The 90 minute session consisted of a discussion of health issues, breathing exercises, gentle stretching and movements while both standing and sitting. Participants in the intervention group were encouraged to practice at home and keep a diary. Following the ten week study, the same measurements as baseline were taken. The researchers found that those in the Medical Qigong group had reported significantly greater improvements in quality of life, fatigue, and mood disturbances (including depression, anxiety, tension, lack of vigor, and fatigue) than the control group. The Medical Qigong group also had significantly lower levels of inflammatory markers than the control group following the intervention.

Overall, the results from this study indicate that the practice of mindfulness-based movement activities such as Medical Qigong may have significant effects on psychosocial factors as well as systemic inflammation. The authors suggest that the link to decreased inflammation may be through improved immune function, as previous studies have suggested that Medical Qigong can support proper immune function, which in turn could lower levels of inflammation. Overall, practices such as Qigong and/or Tai Chi may be a beneficial addition to a regular routine as a low-intensity form of exercise beneficial for both mind and body.

InspireHealth provides patients with the knowledge, tools, and services to support their overall health during and after cancer treatment. Our medical doctors value conventional cancer treatments such as chemotherapy, radiation, and surgery. At the same time, they recognize the importance of supporting health, immune function, body, mind, and spirit.

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

InspireHealth's *Research Updates* are compiled by Rachel Mark, M.A. (kin)—with guidance from the editorial board—using InspireHealth's Research Information System, a unique supportive cancer care knowledge management database. The editorial board includes: Dr. Janice Wright, MD, CEO, Dr. Hannah Nette, MD, Dr. Lori McFarlane, MD, and Terry Heidt, M.Sc. For more information, email library@inspirehealth.ca

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