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RESEARCH UPDATES 2018 VOLUME 1

FOR THE LATEST IN WORLDWIDE SUPPORTIVE CANCER CARE

IN THIS ISSUE: Thomas and colleagues explore exercise-induced biochemical changes and their potential influences on cancer. Stefanopoulou and Grunfeld study mind-body interventions for vasomotor symptoms in menopausal women and women with breast cancer. Mustian's team compared pharmaceutical, psychological, and exercise-based interventions for the treatment of cancer-related fatigue. A qualitative study by Renzi's team explored patient empowerment processes among prostate cancer patients. And lastly, an exploratory article by Langevin and colleagues explored the role of connective tissue in cancer biology.

EXERCISE AND BIOCHEMISTRY

Thomas, R.J., Kenfield, S, A., & Jimenez, A.

Exercise-induced biochemical changes and their potential influence on cancer: a scientific review

British Journal of Sports Medicine, 2017;51:640-644

ABSTRACT | Aim: To review and discuss the available international literature regarding the indirect and direct biochemical mechanisms that occur after exercise, which could positively, or negatively, influence oncogenic pathways. **Methods:** The PubMed, MEDLINE, Embase and Cochrane libraries were searched for papers up to July 2016 addressing biochemical changes after exercise with a particular reference to cancer. The three authors independently assessed their appropriateness for inclusion in this review based on their scientific quality and relevance. **Results:** 168 papers were selected and categorised into indirect and direct biochemical pathways. The indirect effects included changes in vitamin D, weight reduction, sunlight exposure and improved mood. The direct effects included insulin-like growth factor, epigenetic effects on gene expression and DNA repair, vasoactive intestinal peptide, oxidative stress and antioxidant pathways, heat shock proteins, testosterone, irisin, immunity, chronic inflammation and prostaglandins, energy metabolism and insulin resistance. **Summary:** Exercise is one of several lifestyle factors known to lower the risk of developing cancer and is associated with lower relapse rates and better survival. This review highlights the numerous biochemical processes, which explain these potential anticancer benefits.

INSPIREHEALTH'S INTERPRETATION: These British and American researchers searched the literature to identify good quality studies examining the specific biological and chemical (biochemical) changes induced by exercise that may influence cancer development or treatment. They divided the effects into direct and indirect. For example, exercise may directly influence specific cell growth regulators to reduce the growth of cancer cells or it may improve mood and lessen anxiety which have been associated with improved survival – an indirect effect.

The authors list ten direct anti-cancer pathways. First, exercise may reduce levels of the hormone insulin-like growth factor (IGF-1), a hormone thought to promote cell growth and angiogenesis (new blood vessel growth) and inhibit apoptosis (programmed cell death). Exercise increases the protein that binds IGF-1, rendering it inactive. The second pathway relates to epigenetic effects on gene expression (the ability to turn genes off or on). Studies in men with prostate cancer have shown that regular exercise may turn off genes thought to foster prostate cancer cell growth, turn on those genes responsible for healthy DNA repair (alterations in DNA repair occur in tumour development), and protect the ends of chromosomes (telomeres) to help prevent errors when cells divide. Third, regular exercise lowers levels of the cancer-cell promoting hormone vasoactive intestinal peptide (VIP). Fourth, although exercise is known to transiently increase reactive oxygen species, compounds which could contribute to cancer, regular exercise also turns on a proportionately larger number of antioxidant genes. Trained individuals have higher levels of healthy antioxidant enzymes. It is also important to note that consumption of mostly plant-based foods

provides the necessary healthy polyphenols from which these antioxidant enzymes are synthesized. Production of heat shock proteins (HSPs) is the fifth biochemical benefit of exercise. HSPs are produced in tissues following a variety of stimuli including infection. It is believed that HSPs help to protect cells from damage and there is some evidence that they may help to protect vulnerable tissues and organs such as the heart and brain (re: cognition) during and after chemotherapy. Possible influence on testosterone is the sixth pathway discussed. Regular exercise may lower the androgen hormone testosterone which may benefit men with prostate cancer. Seventh, irisin is secreted from skeletal muscle during exercise and higher levels of this protein hormone may enhance the effectiveness of some chemotherapies. The related pathways of immunity, and chronic inflammation/prostaglandins are the eighth and ninth factors noted. Exercise recruits helpful white blood cells into the circulation, improves overall immune function, reduces chronic inflammation, and reduces prostaglandin levels (which may also help reduce inflammation and cancer progression). Finally, exercise helps to reduce insulin levels, the hormone responsible for blood sugar management, higher levels of which are associated with poorer cancer outcomes.

In addition to the benefits to mood noted above, other indirect anti-cancer pathways of exercise include augmenting vitamin D levels via outdoor sunlight exposure, improving circadian rhythms (which may help sleep), and helping to maintain a healthy weight (reduced inflammation with immune benefit). These many benefits are clearly interrelated, especially the inflammation, immunity and insulin resistance pathways. Of all lifestyle measures one can take to improve wellbeing, and perhaps prognosis, after a cancer diagnosis, regular moderate exercise has the most robust evidence to support its uptake.

MIND-BODY PRACTICES

Stefanopoulou, E., & Grunfeld, E.A.

Mind-body interventions for vasomotor symptoms in healthy menopausal women and breast cancer survivors. A systematic review

Journal of Psychosomatic Obstetrics & Gynecology, 2017, 38:3, 210-225, DOI: 10.1080/0167482X.2016.1235147

ABSTRACT | Mind-body therapies are commonly recommended to treat vasomotor symptoms, such as hot flashes and night sweats (HFNS). The purpose of this systematic review was to evaluate the available evidence to date for the efficacy of different mind-body therapies to alleviate HFNS in healthy menopausal women and breast cancer survivors. Randomized controlled trials (RCTs) were identified using seven electronic search engines, direct searches of specific journals and backwards searches through reference lists of related publications. Outcome measures included HFNS frequency and/or severity or self-reported problem rating at post-treatment. The methodological quality of all studies was systematically assessed using predefined criteria. Twenty-six RCTs met the inclusion criteria. Interventions included yoga (n¼5), hypnosis (n¼3), mindfulness (n¼2), relaxation (n¼7), paced breathing (n¼4), reflexology (n¼1) and cognitive behavioural therapy (CBT) (n¼4). Findings were consistent for the effectiveness of CBT and relaxation therapies for alleviating troublesome vasomotor symptoms. For the remaining interventions, although some trials indicated beneficial effects (within groups) at post-treatment and/or follow up, between group findings were mixed and overall, methodological differences across studies failed to provide convincing supporting evidence. Collectively, findings suggest that interventions that include breathing and relaxation techniques, as well as CBT, can be beneficial for alleviating vasomotor symptoms. Additional large, methodologically rigorous trials are needed to establish the efficacy of interventions on vasomotor symptoms, examine long-term outcomes and understand how they work.

INSPIREHEALTH'S INTERPRETATION: Vasomotor symptoms (VMS) such as hot flashes and night sweats are very common in post-menopausal women due to reduced estrogen levels and are especially problematic in women with breast cancer. Treatments such as chemotherapy and hormone therapy (tamoxifen and aromatase inhibitors) can impair ovarian function resulting in rapid reductions in estrogen levels. In this systematic review the authors examined the evidence for the efficacy of several mind-body therapies in reducing the frequency and severity of vasomotor symptoms in women with and without breast cancer. Although many mind-body therapies such as yoga, relaxation, cognitive behavioural therapy, mindfulness, and mental imagery have been shown to improve overall mood, wellbeing, and sleep, evidence for their effectiveness for VMS is less clear. Unfortunately, well designed studies in this area are few. Of the initial 1829 studies obtained by searching electronic databases, only 26 (10 with women with, and 16 with women without, breast cancer) were thought to have appropriate quality for inclusion.

Results for all therapies examined were inconsistent with some studies showing benefit and others showing the same benefit as placebo. Importantly, however, no studies showed adverse effects of practicing these therapies. Evidence is more consistent for CBT and relaxation to reduce VMS, but again, overall these therapies have some evidence that they are certainly helpful for overall quality of life. Although there is insufficient evidence to consider mind-body therapies as evidence-based treatments for VMS, they can improve overall wellbeing, and even if some efficacy noted is due to placebo (which can be effective ~25-30% of the time), and there are no negative side effects, it seems reasonable for symptomatic women to try practicing mind-body therapies. The authors conclude that it would be helpful to have more rigorous research into these therapies to compare their efficacies and understand how they work.

CANCER-RELATED FATIGUE

Mustian, K.M., Alfano, C.M., Heckler, C., et al.

Comparison of pharmaceutical, psychological, and exercise treatments for cancer-related fatigue: A meta-analysis

JAMA Oncology, 2017, 3(7):961-968. doi:10.1001/jamaoncol.2016.6914

ABSTRACT | Importance: Cancer-related fatigue (CRF) remains one of the most prevalent and troublesome adverse events experienced by patients with cancer during and after therapy. **Objective:** To perform a meta-analysis to establish and compare the mean weighted effect sizes (WESs) of the 4 most commonly recommended treatments for CRF—exercise, psychological, combined exercise and psychological, and pharmaceutical—and to identify independent variables associated with treatment effectiveness. **Data Sources:** PubMed, PsycINFO, CINAHL, EMBASE, and the Cochrane Library were searched from the inception of each database to May 31, 2016. **Study Selection:** Randomized clinical trials in adults with cancer were selected. Inclusion criteria consisted of CRF severity as an outcome and testing of exercise, psychological, exercise plus psychological, or pharmaceutical interventions. **Data Extraction and Synthesis:** Studies were independently reviewed by 12 raters in 3 groups using a systematic and blinded process for reconciling disagreement. Effect sizes (Cohen *d*) were calculated and inversely weighted by SE. **Main Outcomes and Measures:** Severity of CRF was the primary outcome. Study quality was assessed using a modified 12-item version of the Physiotherapy Evidence-Based Database scale (range, 0-12, with 12 indicating best quality). **Results:** From 17,033 references, 113 unique studies articles (11,525 unique participants; 78% female; mean age, 54 [range, 35-72] years) published from January 1, 1999, through May 31, 2016, had sufficient data. Studies were of good quality (mean Physiotherapy Evidence-Based Database scale score, 8.2; range, 5-12) with no evidence of publication bias. Exercise (WES, 0.30; 95%CI, 0.25-0.36; $P < .001$), psychological (WES, 0.27; 95%CI, 0.21-0.33; $P < .001$), and exercise plus psychological interventions (WES, 0.26; 95%CI, 0.13-0.38; $P < .001$) improved CRF during and after primary treatment, whereas pharmaceutical interventions did not (WES, 0.09; 95%CI, 0.00-0.19; $P = .05$). Results also suggest that CRF treatment effectiveness was associated with cancer stage, baseline treatment status, experimental treatment format, experimental treatment delivery mode, psychological mode, type of control condition, use of intention-to-treat analysis, and fatigue measures (WES range, -0.91 to 0.99). Results suggest that the effectiveness of behavioral interventions, specifically exercise and psychological interventions, is not attributable to time, attention, and education, and specific intervention modes may be more effective for treating CRF at different points in the cancer treatment trajectory (WES range, 0.09-0.22). **Conclusions and Relevance:** Exercise and psychological interventions are effective for reducing CRF during and after cancer treatment, and they are significantly better than the available pharmaceutical options. Clinicians should prescribe exercise or psychological interventions as first-line treatments for CRF.

INSPIREHEALTH'S INTERPRETATION: Cancer-related fatigue is one of the most common and disabling adverse effects for those with cancer. It is different than fatigue from everyday life, which can occur from working hard or staying up late. Cancer-related fatigue can significantly reduce quality of life and impair the ability to complete treatment. Despite its severity and the fact that is quite common, there is no consensus as to the most effective way to treat it. The four most common treatments are exercise, psychological, exercise plus psychological, and pharmaceutical. This article is the first to examine all studies that investigated the effectiveness of these four methods on cancer-related fatigue. Of all peer-review English-written studies, 113 provided sufficient data to be included in this meta-analysis. The authors found significant improvements among all four intervention types. However, exercise, psychological, and exercise plus psychological interventions produced greater improvements in cancer-related fatigue than pharmaceutical interventions. No significant differences were found between exercise, psychological, or exercise and psychological. However, the optimal type of intervention may depend on where a patient is along the cancer treatment trajectory.

The authors found that exercise may be the most effective method during primary treatment and exercise and psychological interventions may be the most effective post-primary treatment. Also, cancer-related fatigue is associated with other variables such as cancer stage, and treatment status and type. Interestingly, age, sex, cancer type, or exercise mode are not associated with cancer-related fatigue intervention effectiveness. Cancer-related fatigue interventions are most effective when in-person or group-based formats are used. Aerobic and anaerobic exercises were both effective at reducing cancer-related fatigue. Strengths of this meta-analysis include the large number of studies examined and the use of standard and valid measures of cancer-related fatigue. Some limitations were that participants were predominantly female (78%) with breast cancer (47% of all cancers) and that only a few published studies examined exercise plus psychological interventions or pharmaceutical interventions.

In conclusion, this research strongly supports exercise, psychological interventions, or a combination thereof, to improve cancer-related fatigue. Pharmaceutical interventions alone may not be effective. The authors recommend that clinicians should prescribe exercise and psychological interventions to manage and improve cancer-related fatigue. InspireHealth offers patients one-on-one consultations with an exercise therapist as well as a variety of exercise programs and classes.

PATIENT EMPOWERMENT

Renzi, C., Fioretti, C., Oliveri, S., et al.

A qualitative investigation on patient empowerment in prostate cancer

Frontiers in Psychology (2017), 8, 1-12

ABSTRACT | Purpose: Men with prostate cancer often describe low levels of empowerment. eHealth interventions may represent useful tools to deliver care and education and to meet patients' needs within an empowerment framework. In order to design a platform for cancer patients' empowerment within the H2020 iManageCancer project, the perspective of the target population for the platform was assessed. The present study aims to assess the qualitative experience of prostate cancer patients during treatment in order to provide insights for clinical practice with a particular focus on the design of a web platform to promote cancer patients' empowerment. **Methods:** Ten patients undergoing radiation therapy treatment took part in a semi-structured interview to explore different aspects of patient empowerment. Four main thematic areas were addressed: patient-healthcare providers' communication, decision-making, needs, and resources. A qualitative approach using thematic analysis was followed. **Results:** Half of the patients reported little to no possibility to share information and questions with healthcare providers. With regards to decision-making, the role of healthcare providers was perceived as directive/informative, but half of the patients perceived to assume an active role in at least one interaction. Difficulties and needs included the choice of the specialist or of the structure after diagnosis, clinicians' support in self-management, surgical consequences, and side effects, preparation for radiation therapy. Resources included family and social support both from a practical and from an emotional perspective, coping style, and work schedule management. **Conclusions:** These results suggest that relations with healthcare providers should be supported, especially immediately after diagnosis and after surgery. Support to self-management after surgery and at the beginning of radiation therapy treatment also constitutes a priority. The adoption of a personalized approach from the beginning of prostate cancer care flow may promote patient empowerment, overcoming the aforementioned needs and mobilizing resources. The social network represents an important resource that could be integrated in interventions. These considerations will be taken into account in the design of a cancer self-management platform aiming to increase patients' empowerment.

INSPIREHEALTH'S INTERPRETATION: This study was conducted to gain a better understanding of patients' perspectives about treatment decision making after a diagnosis of cancer. The goal was to use the information gathered to create an online platform with tools to support patient empowerment. Patients are empowered when they feel a sense of control over their health and related decisions. The researchers conducted this study to examine the conditions in which patients feel active in their health decisions as well as difficulties they face and needs they may have. Interviews were conducted with ten men with prostate cancer, aged 40-75 years old, undergoing radiation therapy. This qualitative method of collecting data allows researchers to gain a deeper understanding of an individual's experience. The interviews focused on the themes of patient-physician quality of communication, quality of decision making, patient difficulties and needs, and patient resources. These themes were considered along a timeline or "careflow", from diagnosis, and throughout treatment (surgery to radiation). Only half of the patients felt they had good communication with their physician. A directive physician communication style was associated with a more passive patient role in decision making, while a shared style of communication was associated with an active patient role in decision making.

This study demonstrated that the current model of care is mostly non-collaborative; patients reported unmet needs related to communication and decision making and an overall lack of information. Patient difficulties, needs, and resources were categorized as organizational (surgical complications), emotional (choice of specialist), or both (family and social support network). While resources were important from diagnosis onwards, difficulties and needs appeared more frequently following surgery. It is important to note that the interviews were conducted while men were in the radiation phase of careflow, which could have an impact on patient priorities.

To improve patient empowerment, the researchers proposed the development of a "therapeutic alliance" between the patient and the health professional supported by an eHealth platform. A website or application could provide tools that address patient needs (information tailored to a patient) and support physician-patient communication. For example, reference figures (individuals acting as a decision-making resource) could aid decision making or provide feedback on patient priorities. Information provided may vary depending on where along the treatment trajectory the patient is.

InspireHealth supports patients to develop tools and resources to help them with challenges they may be facing. Consultations with our multi-disciplinary team provide the opportunity to explore various strategies for appropriate decision making as well as for stress and symptom management. Our programs and workshops explore options to help individuals develop skills in communication, self-care, exercise, and nutrition.

CONNECTIVE TISSUE BIOLOGY

Langevin, H.M., Keely, P., Mao, J., et al.

Connecting (T)issues: How research in fascia biology can impact integrative oncology

Cancer research (2017), 76(21), 6159-6162

ABSTRACT | Complementary and integrative treatments, such as massage, acupuncture, and yoga, are used by increasing numbers of cancer patients to manage symptoms and improve their quality of life. In addition, such treatments may have other important and currently overlooked benefits by reducing tissue stiffness and improving mobility. Recent advances in cancer biology are underscoring the importance of connective tissue in the local tumor environment. Inflammation and fibrosis are well-recognized contributors to cancer, and connective tissue stiffness is emerging as a driving factor in tumor growth. Physical-based therapies have been shown to reduce connective tissue inflammation and fibrosis and thus may have direct beneficial effects on cancer spreading and metastasis. Meanwhile, there is currently little knowledge on potential risks of applying mechanical forces in the vicinity of tumors. Thus, both basic and clinical research are needed to understand the full impact of integrative oncology on cancer biology as well as whole person health.

INSPIREHEALTH'S INTERPRETATION: Although physical therapies such as yoga, massage, acupressure and acupuncture can benefit cancer patients, little is known about how their mechanical forces act on the body. There is growing interest in the “possibility that mechanical forces produced within tissues during exercise could directly impact tumour growth or recurrence”. Forces from physical treatments can be active (e.g. stretching) or passive (e.g. massage) depending on the therapy. For example, certain yoga poses create a stretch in the muscle, while massage creates pressure in the muscle. The application of these forces can influence cell function by inducing particular biochemical cell signals. This process, called mechanotransduction, is moderated by connective tissue. There are many different types of connective tissue, including tendons (attaching muscle to bone), ligaments (connecting bones to other bones), cartilage (which act as shock absorbers in joints and between bones), fascia (encasing groupings of muscles), and blood.

The authors reviewed the research examining the links between pathologies (diseases), connective tissue, and cellular changes arising from mechanotransduction. While still a new area of research, they report that pathological (unhealthy) connective tissue is characterized by inflammation and/or fibrosis (stiffer tissue). Imaging technologies show that in comparison to healthy tissue, malignant tumours have a “stiffer” cellular environment. Whether cancer cells cause a stiffer environment and/or whether a stiffer cancer environment could promote the development of cancer cells remains unclear. Also, cancer treatments can increase connective tissue stiffness. Through mechanotransduction, it is possible that physical therapies could change the cell environment by impacting cell signaling; this could ultimately influence processes related to cancer cell growth such as angiogenesis (new blood vessel growth). Future research should consider the impact of these forces on both the specific cancer environment (non-cancer cells living with/near cancer cells) as well as on the cancer cells themselves. Caution, however, should be practiced when applying pressures and forces to the actual site of a tumour as the safety of these techniques is currently unknown.

Though patients can benefit from physical manipulation of connective tissue, it still isn't clear what happens at the cellular and molecular levels during and after these manipulations. This is an exciting area of research and the ultimate hope is to be able to develop specific physical treatments that could promote the natural healing response of the body. InspireHealth offers exercise therapy consultations to develop an individualized exercise plan. Yoga and strength based classes, acupuncture, and self-acupressure massage workshop, are also available.

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, Emily Medd, M.Sc., and Terry Heidt, M.Sc. For more information, email info@inspirehealth.ca

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