



## RESEARCH UPDATES WINTER 2017

### INSIDE:

Exercise and Fatigue .....	1
Lifestyle and Cancer Incidence .....	2
Psychoneuroimmunology .....	3
Antioxidants and Anti-Tumor Therapy ....	3
INTO THE VAULT .....	5

*Research Updates* is published quarterly to provide the latest supportive cancer care research to patients, health care providers, and the public.

To support this valuable educational service, please donate at:  
[www.inspirehealth.ca/donate](http://www.inspirehealth.ca/donate)

### FOR THE LATEST IN WORLDWIDE SUPPORTIVE CANCER CARE

**IN THIS ISSUE:** Lavoy and colleagues explore the relationship between exercise, inflammation, and fatigue among cancer survivors. A paper by Orenstein’s team looks at the role of lifestyle factors and cancer incidence across a 30 year study. Hulet and Armer explore spiritually- and mindfulness-based interventions and psychoneuroimmunological outcomes in breast cancer survivorship. Mut-Salud and colleagues explore the relationship between antioxidant intake and anti-tumor therapies. And lastly, an Into the Vault study by Fucic and colleagues examine environmental exposure to xenoestrogens and the effect on estrogen driven cancers.

## EXERCISE AND FATIGUE

LaVoy, E.C.P., Fagundes, C.P., Dantzer, R.

### Exercise, inflammation, and fatigue in cancer survivors

*Exercise Immunology Review*, (2016), 22: 82–93.

**ABSTRACT** | Cancer-related fatigue significantly disrupts normal functioning and quality of life for a substantial portion of cancer survivors, and may persist for years following cancer treatment. While the causes of persistent fatigue among cancer survivors are not yet fully understood, accumulating evidence suggests that several pathways, including chronic inflammation, autonomic imbalance, HPA-axis dysfunction, and/or mitochondrial damage, could contribute towards the disruption of normal neuronal function and result in the symptom of cancer-related fatigue. Exercise training interventions have been shown to be some of the more successful treatment options to address cancer-related fatigue. In this review, we discuss the literature regarding the causes of persistent fatigue in cancer survivors and the mechanisms by which exercise may relieve this symptom. There is still much work to be done until the prescription of exercise becomes standard practice for cancer survivors. With improvements in the quality of studies, evidenced-based exercise interventions will allow exercise scientists and oncologists to work together to treat cancer-related fatigue.

**INSPIREHEALTH’S INTERPRETATION:** Fatigue can be one of the most adverse and persistent side effects of cancer and its treatment. Up to one third of cancer patients report fatigue at six years post-diagnosis. The fatigue is often more than just physical tiredness and can include emotional and/or cognitive tiredness or exhaustion. Given the prevalence of this challenging side effect, efforts to develop strategies to reduce it are ongoing. Interestingly, cancer-related fatigue is unrelated to type of cancer, disease stage at diagnosis, tumour size, number of lymph nodes involved, length of cancer treatment or time since treatment. It is believed that cancer and its treatments including surgery, chemotherapy and radiation therapy all play roles in the development of cancer-related fatigue. In this thorough review, the authors summarize the underlying mechanisms thought to be related to persistent fatigue and the roles that exercise might play in alleviating it.

Much has been written about chronic inflammation as a potential mechanism leading to persistent fatigue. Levels of inflammatory molecules such as C-reactive protein (CRP) and messenger molecules called cytokines (often released from white blood cells) have been shown to be increased in fatigued versus non-fatigued cancer survivors. One reviewed study showed that the genes coding for inflammatory molecules of fatigued breast cancer survivors were upregulated. Inflammation outside the central nervous system (CNS i.e., brain and spinal cord) can communicate with the CNS causing the release of inflammatory molecules that can influence nerve cells (neurons) and decrease the availability of “feel-good” neurotransmitters such as serotonin and dopamine. It is also thought that an imbalance in the fight or flight (sympathetic) vs rest and digest (parasympathetic) nervous systems (together known as the “autonomic nervous system”) may be involved in fatigue. It seems that if the sympathetic nervous system is consistently more active than the parasympathetic nervous system, greater fatigue is

experienced. This parasympathetic underactivity has also been associated with increased inflammation, as parasympathetic tone tends to provide more anti-inflammatory pathways. In addition to the autonomic nervous system, the hypothalamic-pituitary-adrenal axis (HPA-axis) is also involved in the stress response. Altered or flattened cortisol secretion (from the adrenal glands), which usually follows the sleep-wake circadian cycle (i.e., the levels rise and fall), may also contribute to fatigue. Flattened cortisol secretion has been associated with increased levels of fatigue.

The authors reviewed the literature regarding exercise as an effective tool for preventing and treating cancer-related fatigue. Exercises studied varied and included walking, cycling, yoga, resistance training, Qigong, and Tai Chi. Patients who participated in moderate to high intensity resistance exercise showed the most benefit. Interestingly, exercise is associated with increased levels of anti-inflammatory molecules, though fewer studies have specifically examined blood levels of such molecules. Exercise has also been shown to restore the balance between sympathetic and parasympathetic nervous system function, and increase the production of brain “feel-good” molecules. The authors summarize that although much more work needs to be done to better understand how exercise ameliorates cancer-related fatigue, current understanding is that exercise increases overall fitness, reduces chronic inflammation, increases parasympathetic nervous system activity and protects important neurotransmitters involved in feelings of overall wellbeing.

---

## LIFESTYLE AND CANCER INCIDENCE

Orenstein, L., Chetrit, A., & Dankner, R.

### Healthy lifestyle pattern is protective against 30-Yr cancer incidence in men and women: A cohort study

*Nutrition and Cancer* (2016) 68:3, 410-419, DOI: 10.1080/01635581.2016.1153673

**ABSTRACT | Objectives:** Investigate associations of healthier behaviors with 30-yr cancer incidence. **Subjects/Methods:** In 1982, 632 healthy men and women (ages 40–70) were interviewed for nutritional habits using a Food Frequency Questionnaire and a 24-h physical activity questionnaire. Blood pressure, weight, and height were measured, and blood was drawn for biochemical profiles. Thirteen and four subjects were excluded due to cancer diagnosis 1 yr from recruitment and extreme values of reported total daily calorie intake, respectively. **Results:** During a mean follow-up of 24.2 yr, 146 cancer incident patients (23.7%) were documented. Total cancer risk was 38% lower in the medium vegetable intake tertile [adjusted hazards ratio (HR) D 0.62, 95%confidence interval (CI): 0.40–0.95], and 66% higher in the medium fruit intake tertile (adjusted HR D 1.66, 95%CI: 1.08–2.55) compared to the lowest tertile. The risk of gastrointestinal cancers was 3 times greater for the highest, compared to the lowest, dairy consumption tertile (HR D 3.06, 95%CI: 1.01–9.23). “Healthy lifestyle” (normal BMI, never smoked, consuming high levels of dietary fiber and vegetables, and more physically active) reduced overall cancer risk (adjusted HR D 0.63, 95%CI: 0.44–0.91) as compared to the rest of the cohort. **Conclusions:** Our findings reinforce the importance of lifestyle-related factors, which are relatively low-cost and may contribute to reduction in the burden of malignant diseases.

**INSPIREHEALTH’S INTERPRETATION:** While there has been a great deal of research on the roles that individual lifestyle factors such as nutrition and physical activity play in cancer development, less is known about how these factors work in combination. In this study, over 600 Israeli adults (average age of 55) were sampled in 1982 and reassessed in 2013. The aim of this study was to investigate whether leading a healthy lifestyle at baseline (defined as never smoking, having a body mass index (BMI; a measure of body composition, where 20-25 is considered healthy) of 25 or less, being physically active more than five hours per week, and consuming more than 25 grams of fiber and at least 164 calories of vegetables each day) was related to lower cancer incidence rates at follow-up. At baseline, subjects completed very detailed diet and activity questionnaires and had their height, weight and blood pressure measured, as well as blood levels of lipids, glucose and insulin measured. At follow-up, 146 individuals (nearly one quarter of the sample) had been diagnosed with cancer. A higher proportion of those who developed cancer reported the highest levels alcohol and beef compared to those who did not develop cancer. Those individuals in the highest 1/3 intake of dairy products had higher gastrointestinal cancers compared to those in the lowest 1/3. Only about half of all subjects consumed the recommended 25 grams or more of fiber per day and there was a trend towards reduced cancer risk with increased fiber intake.

Curiously, those in the middle third of fruit consumption had higher rates of cancer than those in either the lower or highest thirds, and those in the middle third of vegetable intake had lower rates of cancer than those in the lower or highest thirds. None of the dietary differences between those who developed cancer and those who did not were statistically significant, meaning the above associations could have been linked as much by chance as by actual cause and effect. Likewise, there were no differences in activity levels between those who developed cancer and those who did not. Interestingly, while individual lifestyle factors were not related to ultimate cancer risk, having an overall healthy lifestyle pattern was related to lower cancer risk. Individuals who never smoked, had a healthy weight, exercised for at least five hours per week, and consumed 25 grams or more of fiber per day and 164 or more calories of vegetables per day had a 37% reduction in cancer risk. Eating pulses such as lentils and beans a few times per week together with a variety of vegetables, fruits and whole grains on a daily basis will ensure meeting the fiber and vegetable guidelines for healthy eating. Although this study looked at cancer risk reduction with healthy lifestyle, this same advice applies to those who have already been diagnosed with cancer. Engaging in multiple healthy lifestyle habits seem to act synergistically and therefore supports the need to address healthy behaviours as an overall package.

## PSYCHONEUROIMMUNOLOGY

Hulett, J.M., & Armer, J.M.

### A systematic review of spiritually based interventions and psychoneuroimmunological outcomes in breast cancer survivorship

*Integrative Cancer Therapies* (2016). 15(4), 405-423, doi: 10.1177/1534735416636222.

**ABSTRACT | Objective:** This is a review of spiritually based interventions (eg, mindfulness-based stress reduction) that utilized psychoneuroimmunological (PNI) outcome measures in breast cancer survivors. Specifically, this review sought to examine the evidence regarding relationships between spiritually based interventions, psychosocial-spiritual outcomes, and biomarker outcomes in breast cancer survivors. **Methods:** A systematic search of 9 online databases was conducted for articles of original research, peer-reviewed, randomized and nonrandomized control trials from 2005-2015. Data were extracted in order to answer selected questions regarding relationships between psychosocial-spiritual and physiological measures utilized in spiritually based interventions. Implications for future spiritually based interventions in breast cancer survivorship are discussed. **Results:** Twenty-two articles were reviewed. Cortisol was the most common PNI biomarker outcome studied. Compared with control groups, intervention groups demonstrated positive mental health outcomes and improved or stable neuroendocrine-immune profiles, although limitations exist. Design methods have improved with regard to increased use of comparison groups compared with previous reviews. There are few spiritually based interventions that specifically measure religious or spiritual constructs. Similarly, there are few existing studies that utilize standardized religious or spiritual measures with PNI outcome measures. Findings suggest that a body of knowledge now exists in support of interventions with mindfulness-breathing-stretching components; furthermore, these interventions appear to offer potential improvement or stabilization of neuroendocrine-immune activity in breast cancer survivors compared to control groups. **Conclusion:** From a PNI perspective, future spiritually based interventions should include standardized measures of religiousness and spirituality in order to understand relationships between and among religiousness, spirituality, and neuroendocrine-immune outcomes. Future research should now focus on determining the minimum dose and duration needed to improve or stabilize neuroendocrine-immune function, as well as diverse setting needs, including home-based practice for survivors who are too ill to travel to group sessions or lack economic resources.

**INSPIREHEALTH'S INTERPRETATION:** The authors of this study reviewed the research pertaining to the psychoneuroimmunological outcomes of spiritually-based interventions (primarily mindfulness-based stress reduction (MBSR)) among breast cancer survivors. The authors described spiritually-based interventions as mindfulness, meditation, yoga, Tai Chi, Qi Gong, guided imagery and affirmations. In this review, psychoneuroimmunology (PNI) can be defined as the relationship between stress and other psychological processes with both the nervous and immune systems. The concepts of PNI are rooted in the mind-body connection, such that stress, psychological processes and behavior affect the body's immune system through the nervous system's signals to release hormones or compounds such as cortisol, immunoglobulins and/or compounds related to telomeres. The authors of this paper identified several gaps in the current literature of spiritually-based interventions and PNI outcomes, primarily related to the types of interventions, PNI outcome measures, and psychosocial outcomes. They reviewed all published studies between 2005 and 2015 on this area of study and identified 22 studies. The primary interventions used were MBSR, followed by yoga, cognitive-based stress management, guided imagery, relaxation and visualization, mindfulness-based cancer recovery, Qi Gong, and Tai Chi. The primary PNI biomarker measured was cortisol (the body's primary stress hormone). Psychosocial outcomes included quality of life, depression, stress, anxiety, fatigue, mindfulness, and mood.

When reviewing the studies' findings, the researchers identified positive outcomes of spiritually-based interventions on mental health outcomes, primarily quality of life, depression, stress, anxiety, mood, and fatigue. Of the 12 studies measuring the biomarker cortisol, eight reported positive changes in cortisol activity (either decreased cortisol levels or healthier release pattern throughout the day), and four indicated no change or stable levels of cortisol when compared to a control group. Two studies examined PNI markers related to telomere length and activity. Telomeres are protective caps on DNA strands that may be shortened with age, stress and/or illness. Although this is not enough data to draw conclusions from without further research, these studies found that MBSR practices preserved telomere length among breast cancer survivors, whereas telomere length was shortened among controls. Overall, this paper would suggest that spiritually-based practices such as meditation, yoga, relaxation and visualization, Tai Chi and Qi Gong may have positive influences on psychosocial outcomes such as quality of life and stress, as well as overall immune function. Further studies are needed among cancer patients currently undergoing active treatments. InspireHealth offers a number of programs in yoga, meditation, and relaxation.

---

## ANTIOXIDANTS AND ANTI-TUMOR THERAPY

Mut-Salud, n., Álvarez, P.J., Garrido, J.M., et al.

### Antioxidant intake and antitumor therapy: Toward nutritional recommendations for optimal results

*Oxidative Medicine and Cellular Longevity* (2016), Article ID 6719534

**ABSTRACT |** The role of the induction of oxidative stress as the mechanism of action of many antitumor drugs is acquiring an increasing interest. In such cases, the antitumor therapy success may be conditioned by the antioxidants present in our own body, which can be synthesized de novo (endogenous) or incorporated through the diet and nutritional supplements

(exogenous). In this paper, we have reviewed different aspects of antioxidants, including their classification, natural sources, importance in diet, consumption of nutritional supplements, and the impact of antioxidants on health. Moreover, we have focused especially on the study of the interaction between antioxidants and antitumor therapy, considering both radiotherapy and chemotherapy. In this regard, we found that the convenience of administration of antioxidants during cancer treatment still remains a very controversial issue. In general terms, antioxidants could promote or suppress the effectiveness of antitumor treatment and even protect healthy tissues against damage induced by oxidative stress. The effects may depend on many factors discussed in the paper. These factors should be taken into consideration in order to achieve precise nutritional recommendations for patients. The evidence at the moment suggests that the supplementation or restriction of exogenous antioxidants during cancer treatment, as appropriate, could contribute to improving its efficiency.

**INSPIREHEALTH'S INTERPRETATION:** There is great interest in the potential roles of antioxidants in our overall health, and in cancer development and treatment. But what are antioxidants? To answer this question it is important to review some basic chemistry concepts. When substances are oxidized they gain electrons or become more negatively charged. Oxidation reactions are often balanced by reduction reactions which occur when substances lose electrons or become more positively charged. Together, these reactions are called redox (reduction/oxidation) reactions. Oxidation is so called because it is often (though not always) oxygen which gains electrons (is reduced) as other substances lose electrons (become oxidized). Usually these reactions are balanced so there is no net gain or loss of electrons. However, in our bodies some metabolic processes do not result in a completely balanced transfer of electrons, and when this happens in the presence of oxygen, free-radical (i.e., contain an unpaired electron) substances called reactive oxygen species (ROS) can form. These oxygen-based molecules are highly reactive because they possess unpaired electrons, and electrons want to be paired. Though ROS can have both helpful and harmful qualities (helpful when they are used by certain cells of our immune system to kill viruses, bacteria or tumours, and harmful when they grab electrons from and damage otherwise healthy lipids (e.g. cell membranes), proteins, and DNA), on balance, their harm tends to outweigh their benefit. When the body contains more ROS than antioxidants, oxidative stress is said to occur. Oxidative stress has been associated with the development of many chronic and degenerative illnesses such as cardiovascular disease, neurodegenerative diseases, cancer and aging. In fact, oxidative DNA damage is responsible for cancer development. ROS are produced during normal cell metabolism or from exposure to external factors such as pollution, cigarette smoke, microbes, and radiation.

With this background, it is easier to understand that antioxidants are molecules which become oxidized themselves to prevent, delay or eliminate oxidative damage to other healthy molecules. Antioxidants occur naturally in our bodies (endogenous) and we can also consume them through diet or supplements (exogenous). Exogenous antioxidants can be divided into three main categories: polyphenols, vitamins, and minerals. Polyphenols are the most abundant group of exogenous antioxidants and are found in all plants. They include the isoflavones geistein and daidzein found in soy, catechins such as EGCG in green tea, quercetin found in apples, citrus, and onions, and resveratrol found in red grapes, peanuts and berries. Antioxidant vitamins include vitamins C, E, K, and the vitamin A precursors carotenoids (e.g. beta-carotene and lycopene). Selenium and zinc are examples of antioxidant minerals. Plants contain all three categories of antioxidants to help protect them against heat, bacteria, insects etc. Eating a variety of vegetables, fruits, herbs, spices, nuts, seeds and whole grains is an excellent way to ensure an optimal intake of healthy antioxidants. In fact, because they work synergistically, it is generally agreed that it is best to obtain antioxidants through a mostly plant-based diet rather than with supplements which might negatively affect our bodies redox balance.

Research around the use of antioxidant supplements, both for cancer prevention as well as treatment has yielded mixed and often conflicting results. Because radiation therapy and many chemotherapies use oxidative damage to kill cancer cells, there is concern that taking supplement antioxidants during treatment may lessen treatment effects. Indeed, some research had confirmed these concerns. On the other hand, some believe that the use of antioxidant supplements may help to protect healthy cells from damage and thus reduce treatment's negative effects (e.g. to the heart and nervous systems), and there is some research to support this assertion too. Oncologists currently recommend avoiding any antioxidant supplements during treatment with radiation and chemotherapy and the bulk of the current literature certainly supports this recommendation. Unfortunately, many of the studies examining antioxidant use after a diagnosis of cancer are poor quality, limiting any interpretations of results.

Until such time as better quality studies are done to see whether or not supplemental antioxidants during cancer treatment provide overall net benefit or risk, it remains prudent to avoid them. However, continuing to eat a variety of healthy, whole-food, plant-based foods, especially after a cancer diagnosis, is widely recommended for overall dietary antioxidant intake.

## INTO THE VAULT:

Fucic, A., Gamulin, M., Ferencic, Z., et al.

### Environmental exposure to xenoestrogens and oestrogen related cancers: reproductive system, breast, lung, kidney, pancreas, and brain

*Environmental Health* (2012), 11(Suppl 1):S8

**ABSTRACT** | The role of steroids in carcinogenesis has become a major concern in environmental protection, biomonitoring, and clinical research. Although historically oestrogen has been related to development of reproductive system, research over the last decade has confirmed its crucial role in the development and homeostasis of other organ systems. As a number of anthropogenic agents are xenoestrogens, environmental health research has focused on oestrogen receptor level disturbances and of aromatase polymorphisms. Oestrogen and xenoestrogens mediate critical points in carcinogenesis by binding to oestrogen receptors, whose distribution is age-, gender-, and tissue specific. This review brings data about cancer types whose aetiology may be found in environmental exposure to xenoestrogens. Cancer types that have been well documented in literature to be related with environmental exposure include the reproductive system, breast, lung, kidney, pancreas, and brain. The results of our data mining show (a) a significant correlation between exposure to xenoestrogens and increased, gender-related, cancer risk and (b) a need to re-evaluate agents so far defined as endocrine disruptors, as they are also key molecules in carcinogenesis. This revision may be used to further research of cancer aetiology and to improvement of related legislation. Investigation of cancers caused by xenoestrogens may elucidate yet unknown mechanisms also valuable for oncology and the development of new therapies.

**INSPIREHEALTH INTERPRETATION:** Naturally occurring and human-made chemicals which can interfere with our hormone systems are called endocrine (i.e. hormone) disruptors. Xenoestrogens (“foreign” estrogens) are endocrine disrupting steroid compounds that can mimic estrogen’s effects by blocking or activating estrogen receptors. Naturally occurring xenoestrogens include plant-derived estrogen-like compounds called phytoestrogens while human-made xenoestrogens include chemicals found in plastics, pesticides, detergents, and cosmetics/fragrances. Petroleum-based chemicals such as polyethylene terephthalate (PET) and Bisphenol-A (BPA) are two examples of xenoestrogens used in the plastics industry. Because these estrogen-like compounds can mimic naturally occurring estrogen, the delicate balance of our hormone system can be detrimentally altered. Although estrogen (aka oestrogen in Britain) has important roles in bone health and reproduction, estrogen receptors are found throughout the body implying that estrogens may have significant roles in the biological pathways of many tissues. Both women and men produce estrogen, but levels in women are much higher.

These authors highlight some of the possible associations between xenoestrogens and cancers of the breast, lung, kidney, pancreas, brain, and reproductive system (e.g. testicular and ovarian). For example, approximately 160 xenoestrogens have been studied with respect to breast cancer development. Possible associations between dairy products, well-cooked meat, plastics, air pollution, and heavy metals such as cadmium and the cancers listed above are all thought to be related to the estrogen-disrupting activities of these products and/or chemicals. For breast cancer and lung cancer there may even be synergistic effects between alcohol and estrogen and cigarette smoke and estrogen respectively. Given the ubiquitous nature of possible endocrine-disrupting chemicals (EDC’s), exposure to them can occur via skin, air, water and diet. Wanting to minimize exposure to potentially harmful xenoestrogens and other EDC’s may seem like a daunting task. Fortunately resources such as the Environmental Working Group ([www.ewg.org](http://www.ewg.org)), the Canadian Cancer Society ([www.cancer.ca](http://www.cancer.ca)), and the American Cancer Society ([www.cancer.org](http://www.cancer.org)) can help you minimize your exposure to these potentially harmful substances.

**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](mailto:library@inspirehealth.ca)

#### Lower Mainland Vancouver Centre

#200-1330 West 8th Ave.  
Vancouver, BC, V6H 4A6  
604.734.7125

#### Vancouver Island Victoria Centre

#212-2187 Oak Bay Ave.  
Victoria, BC V8R 1G1  
250.595.7125

#### Southern Interior Kelowna Centre

#123-565 Bernard Ave.  
Kelowna, BC V8R 1G1  
250.861.7125

[inspirehealth.ca](http://inspirehealth.ca)