INSIDE:

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RESEARCH UPDATES 2019 VOLUME 3

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IN THIS ISSUE: Inglis et al. conduct a literature review to examine how diet might decrease systemic inflammation to reduce cancer-related fatigue. Poirier and Volesky estimate the possible future reduction in cancer incidence with lifestyle modification. The effects of stress and stress reduction on the immune system are summarized by Antoni and Dhabhar. Sherman et al. design a study to see if an online writing exercise can help mitigate body-image distress in women with breast cancer. Lastly, Yang and colleagues review the literature to explore fear of cancer recurrence in adolescent and young adult cancer survivors.

NUTRITION AND CANCER-RELATED FATIGUE

Inglis J, Lin P, Kerns S, Kleckner I, Kleckner A, Castillo D, Mustian K, Peppone L.

Nutritional Interventions for Treating Cancer- Related Fatigue: A Qualitative Review

Nutrition and Cancer (2019), 71(1), 21-40

ABSTRACT: Cancer-related fatigue (CRF) is a debilitating syndrome that persists for many cancer survivors for years after treatment. Symptoms include early and persistent fatigue, functional decline, depression, and cognitive difficulties. Inflammation, assessed using pro-inflammatory biomarkers, is increased in cancer survivors with fatigue and treatments for fatigue are often aimed at reducing inflammation. Additionally, cancer and its treatment lead to nutritional complications, changes in body composition, and nutritional deficiencies that potentially weaken the cancer survivor and impact CRF. We conducted a qualitative review of clinical trials that assessed nutritional interventions for preventing and treating CRF. Further studies were examined that used nutritional interventions to address inflammation and fatigue, due to the dearth of nutrition research directly related to CRF. Dietary intake prior to, during, and after cancer treatment appears to affect fatigue levels. Increased protein intake may help preserve lean mass and body composition. Dietary patterns that reduce inflammation, such as the Mediterranean diet and other plant-based diets, appear tolerable to cancer survivors and may reduce fatigue. Supplementation with ginseng, ginger, or probiotics may improve cancer survivors' energy levels. Nutritional interventions, alone or in combination with other interventions should be considered as therapy for fatigue in cancer survivors

INSPIREHEALTH'S INTERPRETATION: Fatigue is one of the most common symptoms experienced by cancer patients both during and after treatment. Related to the fatigue, some patients may experience cognitive difficulties, hot flashes, depression, and insomnia. Collectively these symptoms may cause declines in one's daily functioning (e.g. reduced energy for tasks such as cooking, house work, employment, exercise) with consequent reduction in quality of life. Fatigue and its associated symptoms vary depending on the type of cancer, the treatments and one's pre-cancer health and nutrition status. Several biological mechanisms may contribute to cancer-related fatigue (CRF) but the one that is best understood is "dysregulation of the pro-inflammatory cytokine network". Practically speaking this dysregulation causes increased inflammation. Research has shown that common pro-inflammatory markers are increased in cancer survivors with fatigue.

The authors summarize current treatment options for CFR including pharmacological agents, psychological interventions such as cognitive behavioural therapy (CBT), and exercise. They caution that these treatment options may have untoward side effects (e.g. drug toxicity and interference with cancer medications), seem complicated and demanding (e.g. CBT), or be unmanageable and time-consuming (e.g. exercise). On the other hand, eating is a universal need so optimizing nutrition may be a more accessible way to mitigate CRF. This qualitative review includes 17 studies that examined the overall role of nutrition in cancer-related fatigue, as well as the roles of specific nutrients. The authors note the following dietary factors have good evidence for helping to reduce fatigue: adequate protein intake, soy consumption, and good intakes of fruits, vegetables, whole

grains, omega 3 fats, and vitamin D sufficiency. Studies with probiotics show some promising results but need to be replicated. Other dietary factors and supplements showing mixed results for CRF reduction include: ginseng, guarana, reishi mushroom, ginger, and herbs and foods from traditional Chinese medicine (eg. astragalus, schisandra). Although many cancer survivors are keenly interested in supplements, and while it is true that some nutrient deficiencies are related to fatigue (e.g. anemia secondary to iron or B12 deficiency, or to insufficient food intake or protein deficiency), it is important to know that research in this area is often of poor quality making robust conclusions and/or recommendations difficult. Understanding the underlying reason(s) for the fatigue helps to create an appropriate treatment plan. To this end, patients can consult with their Family Doctors, or book an appointment with one of our Dietitians or Medical Doctors at InspireHealth.

The study also summarizes several dietary approaches. One, the palatable and accessible Mediterranean diet, is known to be anti-inflammatory and may help overall health and prevent several other diseases (e.g., diabetes, heart disease). Research into other dietary patterns such as the ketogenic diet, macrobiotic diet, and paleo diet has not shown consistent results with fatigue reduction. With limited science to support those diets as well as some concerns regarding accessibility, cost, and potential nutrient deficiencies, they are not recommended for most cancer survivors. At InspireHealth, our nutrition and medical teams can tailor nutrition suggestions to an individual's needs and preferences, based on sound research such as that summarized in this paper. We also offer other modalities which may help to mitigate CRF such as physical activity and exercise, meditation, relaxation, and acupuncture.

CANCER RISK FACTORS

Poirier, A.E., Ruan, Y., Volesky, K.D., et al.

The current and future burden of cancer attributable to modifiable risk factors in Canada: Summary of results

Preventive Medicine (2019), 122, 140–147

ABSTRACT | Nearly one in two Canadians are expected to be diagnosed with cancer in their lifetime. However, there are opportunities to reduce the impact of modifiable cancer risk factors through well-informed interventions and policies. Since no comprehensive Canadian estimates have been available previously, we estimated the proportion of cancer diagnosed in 2015 and the future burden in 2042 attributable to lifestyle and environmental factors, and infections. Population-based historical estimates of exposure prevalence and their associated risks for each exposure-cancer site pair were obtained to estimate population attributable risks, assuming the exposures were distributed independently and that the risk estimates were multiplicative. We estimated that between 33 and 37% (up to 70,000 cases) of incident cancer cases among adults aged 30 years and over in 2015 were attributable to preventable risk factors. Similar proportions of cancer cases in males (34%) and females (33%) were attributable to these risk factors. Tobacco smoking and a lack of physical activity were associated with the highest proportions of cancer cases. Cancers with the highest number of preventable cases were lung (20,100), colorectal (9800) and female breast (5300) cancer. If current trends in the prevalence of preventable risk factors continue into the future, we project that by 2042 approximately 102,000 incident cancer cases are expected to be attributable to these risk factors per year, which would account for roughly one-third of all incident cancers. Through various risk reduction interventions, policies and public health campaigns, an estimated 10,600 to 39,700 cancer cases per year could be prevented by 2042.

INSPIREHEALTH'S INTERPRETATION: Epidemiology is the study of the distribution (who, where, when, how) of disease in populations. The epidemiologists in this study examined the relationship between modifiable risk factors and cancer incidence in the Canadian population and estimated the number of cancers that could be prevented by 2042. In 2015, estimates indicate that 33.3% of new cancers in Canada could be attributed to lifestyle, environmental, and infectious agent risk factors. Not surprisingly, active tobacco smoking, physical inactivity, and excess body weight are the three greatest preventable contributors to cancer development and are associated with the development of many cancers including lung, oral, esophageal, stomach, liver, colorectal, kidney and bladder. Other important risk factors include excess alcohol consumption, low fruit and vegetable consumption, infections such as human papilloma virus (HPV, associated with oral, cervical and anal cancers), Helicobacteur pylori (H pylori, associated with stomach cancer), and hepatitis B/C (associated with liver cancer), and environmental exposure to UV radiation (associated with melanoma) and radon (associated with lung cancer).

The authors estimate that 79.7% of lung cancer, 46.6% of bladder cancer, 43.2% of colorectal cancer, 3.8% of prostate cancer and 21.4% of female breast cancer could be attributed to modifiable risk factors. The four most common adult cancers (lung, colorectal, breast and prostate) account for approximately 50% of all cancer diagnoses in Canada. The authors state that "…if the current trend in the prevalence of these risk factors continues unchanged into the future, 102,000 cancer cases attributed to preventable risk factors are expected to occur by 2042. However, we estimate that by 2042, between 11,000 and 40,000 cancer cases could be prevented per year based on modest and aspirational goals respectively". Modest goals include reducing excess weight by 5%, reducing average daily intake of processed and red meat by 0.2 and 0.5 servings per day, reducing residential radiation exposures above 200 Ba/m3 to 50 Ba/m3, maintaining HPV vaccination at 72.4%, reducing active/passive smoking, alcohol consumption, inadequate physical activity, low fruit and vegetable consumption, and UV radiation by 10%, and reducing the prevalence of Hepatitis B and C and H pylori infections by 10%. Aspiration goals include reducing excess weight by 25%, reducing processed and red meat intake by 1 and 2 servings per day respectively,

reducing radon exposures about 100 Ba/m3 to 50 Bq/m3, increasing HPV vaccination to 80% among girls and boys, and reducing all other above-mentioned risk factors by 50%. It is also important to note that as much as cancer incidence could be reduced with risk factor modification, many cancers do not have identifiable lifestyle or environmental associations. Also, many Canadians develop risk-factor-associated cancers without having any of the associated risks. However, understanding the magnitude of potentially modifiable risk factors helps to inform public health policy and individuals about optimal lifestyle for health.

STRESS AND THE IMMUNE SYSTEM

Antoni, M.H., & Dhabhar, F.S.

The impact of psychosocial stress and stress management on immune responses in patients with cancer

Cancer (2019), 125, 1417-1431

ABSTRACT | The range of psychosocial stress factors/processes (eg, chronic stress, distress states, coping, social adversity) were reviewed as they relate to immune variables in cancer along with studies of psychosocial interventions on these stress processes and immune measures in cancer populations. The review includes molecular, cellular, and clinical research specifically examining the effects of stress processes and stress-management interventions on immune variables (eg, cellular immune function, inflammation), which may or may not be changing directly in response to the cancer or its treatment. Basic psychoneuroimmunologic research on stress processes (using animal or cellular/tumor models) provides leads for investigating biobehavioral processes that may underlie the associations reported to date. The development of theoretically driven and empirically supported stress-management interventions may provide important adjuncts to clinical cancer care going forward.

INSPIREHEALTH'S INTERPRETATION: The authors of this review article synthesized research examining the effects of stress on immune processes that may affect cancer growth and spread. They also reviewed if and how various stress reduction techniques might mitigate stress' potential negative consequences. They define stress as a "…constellation of events that involves a stimulus (stressor), which precipitates a reaction in the brain (stress perception) and in turn, actives physiologic fight-or-flight [stress] responses in the body." Stressors cause the release of hormones that orchestrate the stress response. The adrenal gland releases the three main "stress hormones": norepinephrine (noradrenaline), epinephrine (adrenaline) and cortisol. Importantly, short-term stress (lasting minutes to hours – e.g. job interview, public speaking, exercise) can have adaptive and protective effects. However, chronic stress (lasting weeks to years – e.g. caregiving, interpersonal struggles, financial hardship, social isolation) may lead to immune dysfunction and adverse health effects.

The authors list three mechanisms by which stress is thought to interfere with immune function: 1) suppression of protective immunity, 2) induction/exacerbation of chronic inflammation, and 3) enhancement of immunosuppressive mechanisms. The first mechanism relates to protective immunity which enables efficient wound healing and elimination of infections and cancer, and drives vaccine effectiveness and cancer immunotherapy. Chronic stress is thought to reduce protective immune responses (via the three stress hormones above) responsible for tumour surveillance, and inhibit tumour progression/invasion/spread (metastasis) by suppressing various immunologically important white blood cells. Second, chronic stress may increase pro-inflammatory molecules which also shifts the balance away from tumour-protective immunity. Additionally, chronic stress has been associated with glucocorticoid (e.g. cortisol) receptor resistance with resultant failure to reduce the inflammatory response. Chronic inflammation is an important factor in tumour initiation, progression and metastasis and also contributes to cancer-related fatigue, depression and sleep disturbance further exacerbating the stress/immune dysfunction cycle. Third, chronic stress increases certain unhelpful white blood cells (including specific B and T lymphocytes) to suppress protective anti-tumour activity. Harnessing the beneficial effects of short-term stress has been an area of research interest. For example, exercise may enhance anti-tumour immunity and the immune system in general. Stress management techniques including physical therapies (e.g. yoga, muscle relaxation training, massage, acupuncture), mindfulness training, cognitive behavioural therapy (CBT), and improving interpersonal/communication skills are often employed in the cancer setting.

Although research has shown effectiveness for stress reduction, less is known about whether or not these psychological benefits are associated with physiological and immune system improvements and overall better outcomes for those with cancer. Small studies have shown some improvement in the responses of immunologically important/helpful white blood cells, reduction in evening cortisol (higher evening cortisol levels are associated with stress and immune dysfunction), and reduction in pro-inflammatory molecules. Other interesting rodent-based research has shown that pharmacological use of beta-blockers (to dampen the fight-or-flight response and commonly used for hypertension) and COX inhibitors (anti-inflammatories) may reduce the risk of cancer metastasis. These medications given pre-operatively to a small group of women with breast cancer resulted in an increase in beneficial immune cell activity. It is necessary to say that much more research needs to be done to know if the benefits of such medications outweigh their known risks. Also in breast cancer patients, similar benefits were found with post-op CBT-based stress management. Further research will be needed to determine when, how and for whom stress management interventions should/could be offered and whether or not immune benefit (as measured with immune cells in the blood) translates to morbidity reduction and/or survival benefit.

BODY IMAGE AND BREAST CANCER

Sherman, K.A., Przezdziecki, A., Alcorso, J., et al.

Reducing body image–related distress in women with breast cancer using a structured online writing exercise: Results from the My Changed Body randomized controlled trial

Journal of Clinical Oncology (2018), 36, 1930-1940. Doi: 10.1200/JCO.2017.76.3318

ABSTRACT | Purpose: Breast cancer treatment adverse effects result in one in three survivors experiencing body image–related distress (BID) that negatively impacts on a woman's ability to recover after cancer and into survivorship. My Changed Body (MyCB) is a Web-based psychological intervention to alleviate BID and improve body appreciation in survivors of breast cancer (BCSs) through a single-session, self-compassion focused writing activity. This randomized controlled trial evaluated the impact of MyCB on BID and body appreciation in BCSs. The moderating effect of lymphedema status (affected or unaffected) and appearance investment (self-importance placed on personal appearance) and the mediating effect of self-compassion were evaluated. **Patients and Methods:** Women (disease-free stage I to III BCSs who had experienced at least one negative event related to bodily changes after breast cancer) were randomly assigned to MyCB (n = 149) or an expressive writing control arm (n = 155). Primary outcomes were reduction in BID and improvement in body appreciation 1 week after intervention. Secondary outcomes included psychological distress (depression and anxiety) and self-compassion. Follow-up assessments occurred 1 week, 1 month, and 3 months after writing. **Results:** Compliance with the MyCB intervention was 88%, and attrition was 9.2%. Intent-to-treat linear mixed models indicated that participants who received MyCB reported significantly less BID (P = .035) and greater body appreciation (P = .004) and self-compassion (P , .001) than expressive writing participants. Intervention effects on BID were moderated by lymphedema status (P = .007) and appearance investment (P = .042). Self-compassion mediated effects on both primary outcomes. Therapeutic effects were maintained at 1 month (BID and body appreciation) and 3 months (body appreciation) after intervention. Significant reductions in psychological distress (1-month depression, P=.001; 1-week and 1-month anxiety, P = .007) were evident for MyCB participants with lymphedema. **Conclusion:** This study supports the efficacy of MyCB for reducing BID and enhancing body appreciation among BCSs.

INSPIREHEALTH'S INTERPRETATION: Approximately half of breast cancer survivors (BCSs) experience concerns about their appearance or bodily changes. Body image–related distress (BID) is associated with increased depression, anxiety, and impairments in daily functioning. Adjusting to these changes is a complex challenge since treatment is physically and emotionally demanding. Quality of life for a breast cancer patient is associated with how she perceives herself and her relationship with her body. Some women experience fear and shame concerning their altered bodies and the chronic distress related to these changes can hamper resumption of normal life after cancer. This randomized controlled trial (RCT) examined whether or not a therapeutic self-compassion focused writing approach could mitigate BID in BCSs.

The researchers evaluated the impact of a self-compassion–based online writing program (My Changed Body or MyCB) on BID and body appreciation in BCSs. 149 women were assigned to the MyCB group and 155 to an online unstructured expressive writing (EW) control arm. Compliance with the MyCB intervention was an impressive 88%, and drop-out was only 9.2%. Findings indicated that the MyCB writing intervention demonstrated statistically and clinically meaningful benefits compared with unstructured, self-directed EW for improving BID. Participants who received the MyCB therapeutic writing program reported significantly lower BID and greater body appreciation and self-compassion. For BID, the beneficial effect, which included improvements in depression, anxiety, and self-compassion was particularly strong for BCSs who placed high importance on their appearance and for those women with secondary lymphedema, (two subgroups of BCSs known to experience the greatest body image concerns after treatment). Therapeutic effects were maintained at one month (BID and body appreciation) and three months (body appreciation) after intervention. Significant reductions in psychological distress were noted for MyCB participants with lymphedema. The authors conclude that the MyCB program reduces BID and enhances emerging evidence that self-compassion interventions may be beneficial for addressing body image concerns in BCSs. Future research is needed to replicate these findings beyond three months and to ascertain the impact of MyCB on other aspects of psychosocial functioning impacted by BID such as overall quality of life, and social, work, and relationship functioning.

FEAR OF RECURRENCE

Yang, Y., Li, W., Wen, Y., Wang, H., Sun, H., Liang, W, Zhang, B., & Humphris, G.

Fear of cancer recurrence in adolescent and young adult cancer survivors; a systematic review of the literature

Psycho-Oncology (2018), 28, 675 - 686. doi: 10.1002/pon.5013

ABSTRACT | Objective: The current systematic review aims to provide an overview of fear of cancer recurrence (FCR) in adolescent and young adult cancer survivors (15-39 years at cancer diagnosis, AYAs). **Methods:** MEDLINE, PubMed, PsycINFO, and Embase databases were independently searched to identify relevant quantitative articles. PRISMA systematic review procedures were followed with quality assessment. **Results:** Seventeen studies were included in the current review. All were quantitative studies that utilized a cross-sectional study design. Seven articles reported results of FCR prevalence, six studied determinants related to FCR, and 11 articles provided information about consequences of FCR. Prevalence of FCR ranged from 31% to 85.2% among AYA survivors. Associations between sociodemographic/clinical variables and FCR

were inconsistent. Psychological distress and higher treatment intensity were positively associated with higher FCR levels. Lower scores on levels of physical, psychological functioning, and overall health-related quality of life (QoL) were identified as consequences of increased FCR. **Conclusion:** FCR appears to be a prevalent concern among adolescent and young adult cancer populations. Adequate assessment to determine need for support and intervention is still required. Longitudinal studies in AYAs are warranted to understand the development and potential influence of FCR. Age-appropriate and flexible psychological care would be more successful potentially with this crucial background information.

INSPIREHEALTH'S INTERPRETATION: Fear of cancer recurrence (FCR) is defined as "fear, worry, or concern relating to the possibility that cancer will come back or progress". FCR can be a long-term issue, continuing to affect quality of life many years after treatment is complete. In adults, FCR is more likely experienced by people who were diagnosed at a younger age, women, and in those who experience more physical symptoms (e.g. pain, neuropathy, fatigue). The authors of this paper summarized the research on FCR in adolescent and young adults (AYAs, defined as 15 and 39 years old at diagnosis), based on certain criteria (type of study, what was measured). Seventeen studies were included in the review with sample sizes ranging from 20 to 1395 people. Three studies focused on survivors of breast cancer, one of gynecological cancer, one of leukemia, and eleven of mixed diagnoses. To measure FCR most studies used questionnaires but only eight studies used validated questionnaires (approved to measure what they are trying to measure).

The authors note that it was challenging to determine the prevalence of FCR (how many cases in a given population) since the studies used different questionnaires with different scales. The prevalence of FCR in AYA cancer survivors ranged from 29-85%. Six of the seventeen studies examined factors that influence FCR. Results were mixed; some studies had opposite findings, but the authors concluded that there is some evidence that being female, and having higher treatment intensity and more psychological distress are linked to greater FCR. Consequences of FCR include impaired psychological function and lower overall health related quality of life. The authors highlight the importance of the need for more research on this topic to better identify AYA specific needs related to FCR. Unfortunately, no clear cut-off measure for clinically significant FCR exists making its study challenging. More research is needed to understand which interventions best address FCR in AYA for improved overall quality of life.

InspireHealth's counselling services and Young Adult programs can help support those with FCR. InspireHealth Victoria's Young Adult programs include yoga, cooking classes, and outdoor activities such as kayaking and paddle boarding. These programs are open to adults 16-39 years and their support people.

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, CMO; Dr. Hannah Nette, MD; Dr. Lori McFarlane, MD; Emily Medd, MSc; Lynda Soberanes, MSc, RD; and Zahra Tromsness, MHSc, RD. For more information, email info@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

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