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INTEGRATIVE CANCER CARE

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FOR THE LATEST IN WORLDWIDE INTEGRATIVE CANCER CARE

IN THIS ISSUE: Kampshoff and colleagues review the literature pertaining to exercise adherence among cancer survivors. A study by Yang and colleagues illustrated a decreased risk of hepatocellular carcinoma with increased vegetable intake. Davis and Goforth explore both the effects, and recommendations for short- and long-term insomnia among cancer survivors. A study by Chan and colleagues review the influence that body mass index may have on breast cancer survival. Ferreira and colleagues look at BPA as a possible carcinogen. The Into the Vault study by Block and colleagues review the literature surrounding antioxidant supplementation during chemotherapy.

EXERCISE ADHERENCE

Kampshoff, C.S., Jansen, F., van Mechelen, W., et al.

Determinants of exercise adherence and maintenance among cancer survivors: A systematic review.

International Journal of Behavioral Nutrition and Physical Activity. 2014; 11(80): 44-64.

For an exercise intervention to be successful, it is important that cancer survivors adhere to the prescribed program. To be able to improve adherence and to preserve achieved beneficial effects, insights into the relevant and modifiable determinants is important. Therefore, we aimed to systematically review determinants of exercise adherence and maintenance in cancer survivors using a socio-ecological approach. Studies were identified in PubMed, Embase, PsycINFO and SPORTDiscus up to July 2013. We included full-text articles that: 1) were conducted among adult cancer survivors; 2) quantitatively assessed factors associated with intervention adherence and maintenance, and 3) were published in English. The methodological quality of the selected studies was examined. A best evidence synthesis was applied. Eighteen studies were included. Median methodological quality was 53% and ranged from 21-78% of maximum score. Twelve studies focused on determinants of exercise adherence and evaluated 71 potential determinants: 29 demographic and clinical, 27 psychological, ten physical, four social factors, and one environmental factor. Six studies focused on determinants of exercise maintenance after completion of an intervention, and investigated 63 factors: 22 demographic and clinical, 28 psychosocial, nine physical, three social and one environmental factor. We found moderate evidence for a positive association between exercise history and exercise adherence. Inconsistent findings were found for age, gender and education as well as for psychological factors such as stage of change, perceived behavioral control, self-efficacy, extraversion, attitude, intention, fatigue, and quality of life, and physical factors including cardiovascular fitness, body mass index, and baseline physical activity. Exercise history is positively associated with exercise adherence. Future trials should further study the influence of social and environmental determinants on exercise adherence and maintenance in addition to demographic, psychological and physical determinants.

INSPIREHEALTH'S INTERPRETATION: The benefits of exercise through all stages of a cancer diagnosis have been well-established. Exercise has been shown to help mitigate side effects from treatments, decrease fatigue, improve physiological and psychological outcomes, decrease incidences of recurrence, and improve longevity. Despite these known benefits, rates of activity among cancer survivors are less than optimal. Even though individuals may adopt an exercise regime, for benefit to be sustained over the long term, the regime must be adhered to. This research paper examined the factors contributing to exercise adherence and maintenance among cancer survivors. Eighteen studies employing an exercise intervention measuring adherence among adult cancer survivors were included in this review. Determinants of adherence were classified into demographic and clinical (e.g. age, gender, stage of disease), psychological (e.g. intention to exercise, quality of life), physical (e.g. past exercise behaviour, strength, body composition), social (e.g. family support), and environmental (e.g. neighbourhood walkability, distance

to fitness centre) factors. Of all of the factors examined, past exercise behaviour was a significant indicator of exercise adherence. No other factors were statistically significant. A few limitations to this study should be discussed in order to put the findings into perspective. First, the studies reviewed had inconsistent findings, partially due to sample size and methodology. This made it difficult to review determinants across different studies. Second, one requirement to be included in this review was that the study was an exercise intervention. A common limitation of intervention trials is that the people enrolling in the trial tend to already be active. Because of this, it would make sense that the only variable showing a significant effect on adherence was past exercise behaviour given that the majority of participants enrolling in the interventions likely had a previous interest in exercise, prompting them to enroll in the studies.

This research would suggest that those individuals who have a history of participating in physical activity have greater adherence to exercise programs following their cancer diagnosis. Despite these findings, it is always important to remain cognisant of the benefits of regular activity, despite your previous behaviour. Findings from other research have indicated a greater health benefit to those engaging in activity following a diagnosis in comparison to engaging in the same amount of activity prior to a diagnosis, suggesting that it is never too late to start. There are a number of tips to help with exercise motivation and adherence, and the InspireHealth Exercise Team would be happy to meet with you about them.

HEPATOCELLULAR CARCINOMA

Yang, Y., Zhang, D., Feng, N., Chen, N., Liu, J., Chen, G., & Zhu, Y.

Increased intake of vegetables, but not fruit, reduces risk for hepatocellular carcinoma: A meta-analysis.

Gastroenterology. 2014; 147: 1031-1042.

BACKGROUND & AIMS: The anti-cancer effects of vegetables and fruit have been investigated extensively, but the association between vegetable and fruit consumption and risk of hepatocellular carcinoma (HCC) has not been quantified. We performed a meta-analysis of observational studies to clarify the association. **METHODS:** We identified eligible studies, published from 1956 through May 31, 2014, by searching PubMed, Web of Science, and EMBASE. Random-effects models were used to calculate summary relative risks (RRs) and dose–response analyses were conducted to quantify associations. Heterogeneity among studies was evaluated using Cochran's Q and I2 statistics. **RESULTS:** A total of 19 studies involving 1,290,045 participants and 3912 cases of HCC were included in the meta-analysis. The summary RR for HCC was 0.72 for individuals with high intake vs low intake of vegetables (95% confidence interval [CI]: 0.63–0.83) and 0.92 with a daily increase in vegetable intake (100 g/d) (95% CI: 0.88–0.95). Subgroup analyses showed that this inverse association did not change regardless of history of hepatitis, alcohol drinking, smoking, or energy intake. The summary RR for HCC among individuals with high vs low intake of fruit was 0.93 (95% CI: 0.80–1.09), and 0.99 with a daily increase in fruit intake (100 g/d) (95% CI: 0.94–1.05). Conclusions: Based on a meta-analysis, increased intake of vegetables, but not fruit, is associated with lower risk for HCC. The risk of HCC decreases by 8% for every 100 g/d increase in vegetable intake. The findings should be confirmed by future studies with validated questionnaires and strict control of confounders.

INSPIREHEALTH'S INTERPRETATION: Fruits and vegetables are nutrient-dense, and their consumption (in conjunction with other modifiable lifestyle factors such as diet, exercise, and not smoking) may help to reduce the risk of developing a number of chronic diseases. This study reviewed papers published between 1956 and 2014 that examined relationships between fruit and vegetable intake and risk of hepatocellular carcinoma (HCC). The studies reviewed looked at 1,290,045 participants. Researchers analyzed the data by grouping and comparing total vegetable and total fruit intake in relation to HCC risk, and by examining the extent to which incremental increases in daily total vegetable and fruit intake related to HCC risk. Seventeen studies examined the relationship between vegetable intake and HCC risk. Those who consumed higher vegetable intake compared to lower, had a 30% reduced risk of HCC. However, because this research is a meta-analysis, definitions of "high" and "low" intake vary across studies which can limit the weight of this particular finding. One of the main findings of this study related to increasing daily vegetable intake and showed that for every 100 gram increase of vegetable intake per day an 8% lower risk of HCC was observed. No such observation was found when the analyses were repeated for fruit intake. From a whole foods perspective, there are many reasons why increasing one's vegetable intake is beneficial for overall health. For example, vegetables are good sources of phytonutrients and fiber.

This study shows that there is a benefit in reducing HCC risk with increased vegetable intake. As fruits and vegetables often get lumped into the same category, attempts to increase one's intake often means increasing fruits at the expense of vegetables. Though fruit is a fantastic food group, in excess it can provide a surplus of simple carbohydrates. The nutritionists at InspireHealth recommend aiming for two to four times as many servings of vegetables as fruit daily. In consideration of seasonal eating, consuming less fruit in the winter and more fruit in the summer and fall also seems prudent. Importantly, however, these findings support the fact that there are no negative consequences to eating more fruit. Eating more produce, whether vegetables or fruits, will do no harm, and are always better choices than processed or 'junk' food.

INSOMNIA

Davis, M.P. & Goforth, H.W.

Long-term and Short-term Effects of Insomnia in Cancer and Effective Interventions.

The Cancer Journal. 2014; 20(5): 330-344.

Sleep disorders and insomnia are more prevalent in patients with cancer than in the normal population. Sleep disorders consist of delayed sleep latency, waking episodes after sleep onset, unrefreshing sleep, reduced quality of sleep, and reduced sleep efficiency. Sleep disorders cluster with pain, fatigue, depression, anxiety, and vasomotor symptoms, depending on stage of disease, treatment, and comorbidities. Premorbid sleep problems and shift work have been associated with a higher prevalence of cancer; in fact, shift work has been labeled a carcinogen. Treatment for insomnia includes cognitive behavioral therapy with sleep hygiene, bright-light therapy, exercise, yoga, melatonin, and hypnotic medications. Unfortunately, there are few randomized trials in cancer-related sleep disorders such that most recommendations particularly for hypnotics are based on treatment for primary insomnia. In this article, insomnia is reviewed as a predisposing factor to cancer, prior to and during treatment, in cancer survivorship and in advanced cancer. Recommendations for treatment are based on low-quality evidence but are also reviewed.

INSPIREHEALTH'S INTERPRETATION: Insomnia and sleep disorders can affect up to 70% of cancer patients yet only about a third of patients mention this issue to their physician. Sleep disorders may include delayed sleep onset, frequent awakening at night with periods of alertness (greater than 30 minutes), reduced sleep efficiency (time spent sleeping versus total time in bed with lights off), and non-refreshing sleep or poor sleep quality. Insomnia is defined as a sleep disturbance that occurs at least three times a week for at least one month and is associated with daytime impairment. Insomnia may result in mood disturbances, tension headaches, memory impairment, fatigue, reduced mental functioning, and other daytime impairments. The authors emphasized that sleep disorders and insomnia tend to cluster with pain, fatigue or illnesses such as depression or heart disease. They mention that cancer patients frequently experience depression, pain, and fatigue along with insomnia and that it may be difficult to tease out cause and effect. Lethargy, fatigue, and sleepiness due to insomnia and sleep disorders may be mistaken for cancer-related fatigue. Medication may also be associated with insomnia. Approximately 30-50% of cancer survivors experience sleep disorders and impairment, which often cluster with fatigue, anxiety, and depression. Insomnia during cancer is typically not an isolated issue. Such clustering of symptoms may be linked through hormonal, immune, and neurological processes (although a mechanism has not been proven). As well, cancer may induce negative feedback on melatonin production and release, thereby disrupting circadian rhythm (i.e., our biological clock) and reducing the ability to sleep. Impairments in circadian rhythm have been associated with cellular stress and cancer development. Sleep duration has been linked to cancer risk. The authors emphasize that the International Agency for Research on Cancer (IARC) labels shift work as a human carcinogen. Sleep duration and risk of developing cancer has been documented as following a 'U'-like pattern, in that there is an increased risk of developing cancer with too little or too much sleep. Risk of lung cancer is 117% greater for sleep durations of less than 6.5 hours and 88% greater for sleep durations longer than 8 hours.

These associations remained significant after controlling for smoking status. The risk of developing breast cancer is 43% higher among women who sleep less than 7 hours per night compared to those who sleep more than 7 hours per night. The risk of developing colorectal cancer increased 35% with sleep duration above 9 hours. Increased risk of developing colorectal cancer from sleep less than 5 and greater than 7 hours of sleep has been found in some but not all studies. Chemotherapy and radiation may worsen sleep disturbances but further trials are needed to understand how treating insomnia during cancer treatment influences outcomes. It is not clear that successful treatment of a symptom or illness that clusters with insomnia will improve sleep. The authors recommend a comprehensive plan including cognitive behavioural therapy, physical exercise, sleep hygiene, yoga, and pharmacotherapy to treat cancer-related insomnia. Insomnia tends to exacerbate pain and fatigue. Therefore, treatment of insomnia may not only improve sleep but also pain tolerance and daily fatigue. Light therapy and hypnotics may be effective in treating insomnia but the supporting evidence in sparse.

BREAST CANCER

Chan, D.S.M., Vieira, A.R., Aune, D., Bandera, E.V., et al.

Body mass index and survival in women with breast cancer – systemic literature review and meta-analysis of 82 follow-up studies.

Annals of Oncology. 2014; 25: 1901-1914

BACKGROUND: Positive association between obesity and survival after breast cancer was demonstrated in previous meta-analyses of published data, but only the results for the comparison of obese versus non-obese was summarised. **METHODS:** We systematically searched in MEDLINE and EMBASE for follow-up studies of breast cancer survivors with body mass index (BMI) before and after diagnosis, and total and cause-specific mortality until June 2013, as part of the World Cancer Research Fund Continuous Update Project. Random-effects meta-analyses were conducted to explore the magnitude and the shape of the associations. **RESULTS:** Eighty-two studies, including 213 075 breast cancer survivors with 41 477 deaths (23 182 from breast cancer) were identified. For BMI before diagnosis, compared with normal weight women, the summary relative risks (RRs)

of total mortality were 1.41 [95% confidence interval (CI) 1.29–1.53] for obese (BMI >30.0), 1.07 (95 CI 1.02–1.12) for overweight (BMI 25.0–<30.0) and 1.10 (95% CI 0.92–1.31) for underweight (BMI <18.5) women. For obese women, the summary RRs were 1.75 (95% CI 1.26–2.41) for pre-menopausal and 1.34 (95% CI 1.18–1.53) for post-menopausal breast cancer. For each 5 kg/m2 increment of BMI before, <12 months after, and ≥12 months after diagnosis, increased risks of 17%, 11%, and 8% for total mortality, and 18%, 14%, and 29% for breast cancer mortality were observed, respectively. **CONCLUSIONS:** Obesity is associated with poorer overall and breast cancer survival in pre- and post-menopausal breast cancer, regardless of when BMI is ascertained. Being overweight is also related to a higher risk of mortality. Randomised clinical trials are needed to test interventions for weight loss and maintenance on survival in women with breast cancer.

INSPIREHEALTH'S INTERPRETATION: This comprehensive review and meta-analysis investigated relationships between body mass index (BMI) and risk of death among women with breast cancer from 82 studies. A meta-analysis combines data from a collection of studies to determine consistent patterns. This is important because results from a single study are typically not as meaningful as a pooled effect across many studies. BMI is associated with body fatness and is calculated by dividing a person's mass (in kilograms) by their height (in meters) squared. The main take home point from this article is that woman are at an increased risk of death due to breast cancer and for total mortality (death by any cause) as BMI increases above the normal range (associations range from 7% to 41%). These associations remain largely significant regardless of whether BMI is assessed before or 12 months prior to breast cancer diagnosis. Women with BMIs less than the normal range trended towards an increased risk of death due to breast cancer or for total mortality, but only some associations were statistically significant (except when BMI was assessed beyond 12 months after diagnosis). Obese women with breast cancer have a greater risk of dying, both from their disease and by all causes combined, than overweight or normal weight women. The authors found that woman with breast cancer increase their risk of dying by 11-18% for every increase in five BMI points. A limitation to the present study is that cause-and-effect cannot be determined. That is, while BMI is associated with mortality, this study does not assess whether BMI *causes* the increased risk or not. Also, BMI does not directly measure body fat and does not distinguish between fat, muscle, bone, or connective tissue mass. For example, older adults tend to have more body fat than younger adults for a given BMI. However, on a population level, BMI is typically a fair estimator of body fat. The authors support current guidelines which state that woman with breast cancer should remain as lean as possible within the normal range of body weight, before and after diagnosis.

BISPHENOL A (BPA) EXPOSURE

Ferreira, L.L., Couto, R., & Oliveira, P.J.

Bisphenol A as epigenetic modulator: Setting the stage for carcinogenesis?

European Journal of Clinical Investigation. 2015; 45 (S1): 32–36

BACKGROUND: Bisphenol A (BPA) is one of the most widely produced chemicals worldwide and is often used in the production of food and beverage containers. As a result of BPA contact with food, drink and toiletries, its ingestion and absorption by humans has been growing. The industrialization and modern lifestyles brought a constant exposure to several health-disturbing compounds and ushered a new era of chronic diseases. The endocrine disruptor potential of BPA is well known, but the research around its epigenotoxic effects raised further concerns whether chronic exposure to BPA can contribute to chronic human illness, including cancer in hormone-sensitive organs. **MATERIALS AND METHODS:** Focusing on computerized databases, we reviewed original and review articles which elucidate and link some of the information already available about BPA and related epigenetic alterations. **RESULTS:** A number of studies indicate that short-term administration of low or high-doses of BPA may be associated with an increased risk of epigenetic modifications, increasing the risk for carcinogenesis. However, it is clear that more studies considering real daily exposures are essential to define a real tolerable daily intake and to tighten up manufactory regulations. **CONCLUSION:** In this review, we highlight some evidences suggesting a relationship between BPA exposure, genotoxic activity and epigenetic modifications, which may prime for carcinogenesis.

INSPIREHEALTH'S INTERPRETATION: Bisphenol A (BPA) is a synthetic chemical compound used to make plastics and epoxy resins. BPA is found in water bottles and sports equipment as well as in thermal paper (eg. receipts) and in the linings of food and beverage cans. Because of its ubiquitous nature, humans are exposed to BPA through ingestion, skin absorption, and air. Though typical exposure levels are well below recommended tolerable daily intakes (TDI), concerns have arisen because BPA mimics the hormone estrogen and is therefore considered an endocrine (or hormone) disrupting chemical (EDC). The authors of this paper note that as an EDC, BPA may cause deleterious effects via genetic modifications, hormone disruption, or epigenetic processes and they sought to examine the latter. Epigenetics refers to changes in the expression of genes, rather than to alterations in the genetic code itself. Genes code for the synthesis of products (usually proteins) and the extent to which these products are synthesized is modulated by gene expression. For example, a gene coding for an enzyme can be turned on (allowing for its expression) or turned off (not expressed) by a particular drug. Because BPA has a weak estrogenic effect, it can bind to estrogen receptors and potentially alter cellular processes either by its role as an endocrine disruptor or through epigenetic processes. These authors reviewed the many biochemical pathways by which these epigenetic effects might occur, including those which could potentially accelerate cancer initiation. Large population studies have shown associations between

high blood levels of BPA and increased risk of a variety of illnesses including diabetes, cardiovascular disease, polycystic ovarian disease, low sperm count, and cancer. Though research has shown current exposure levels to be safe, Canada and the EU have banned BPA in baby bottles (particularly as the vulnerability to BPA exposure in infants is unknown) and many companies are making BPA-free plastics. While awaiting new data, it is reasonable to adopt the precautionary principle and limit exposure to BPA. Switching from plastic containers to glass or stainless steel and limiting the use of canned foods by cooking from scratch are potential ways to reduce BPA exposure. Interestingly, other studies have shown a 50-70% reduction in urine BPA levels after eating fresh foods for only three days.

INTO THE VAULT: ANTIOXIDANT SUPPLEMENTATION

Block, K.I., Koch, A.C., Mead, M.N., et al.

Impact of antioxidant supplementation on chemotherapeutic efficacy: A systematic review of the evidence from randomized controlled trials.

Cancer Treatment Reviews. (2007) 33, 407– 418.

PURPOSE: Much debate has arisen about whether antioxidant supplementation alters the efficacy of cancer chemotherapy. Some have argued that antioxidants scavenge the reactive oxygen species integral to the activity of certain chemotherapy drugs, thereby diminishing treatment efficacy. Others suggest antioxidants may mitigate toxicity and thus allow for uninterrupted treatment schedules and a reduced need for lowering chemotherapy doses. The objective of this study is to systematically review the literature in order to compile results from randomized trials that evaluate concurrent use of antioxidants with chemotherapy. **DESIGN:** MEDLINE, Cochrane, CinAhl, AMED, AltHealthWatch and EMBASE databases were searched. Only randomized, controlled clinical trials that reported survival and/or tumor response were included in the final tally. The literature searches were performed in duplicate following a standardized protocol. No meta-analysis was performed due to heterogeneity of tumor types and treatment protocols used in trials that met the inclusion criteria. **RESULTS:** Of 845 articles considered, 19 trials met the inclusion criteria. Antioxidants evaluated were: glutathione (7), melatonin (4), vitamin A (2), an antioxidant mixture (2), vitamin C (1), N-acetylcysteine (1), vitamin E (1) and ellagic acid (1). Subjects of most studies had advanced or relapsed disease. **CONCLUSION:** None of the trials reported evidence of significant decreases in efficacy from antioxidant supplementation during chemotherapy. Many of the studies indicated that antioxidant supplementation resulted in either increased survival times, increased tumor responses, or both, as well as fewer toxicities than controls; however, lack of adequate statistical power was a consistent limitation. Large, well-designed studies of antioxidant supplementation concurrent with chemotherapy are warranted.

INSPIREHEALTH'S INTERPRETATION: Whether adding antioxidant (AO) supplements such as melatonin, vitamin C or glutathione to chemotherapy is beneficial or harmful is a matter of some controversy. In simplified terms, chemotherapy is thought to exert its effect in part by causing oxidative damage to cancer cells. Theoretically, adding an antioxidant may diminish chemotherapy's effectiveness. However, if AO's reduce the toxicity to healthy cells (eg. heart, nerves, kidneys), they may allow for more complete chemotherapy treatment schedules and doses, and reduce concerning side-effects. These authors reviewed the following AO's that had been examined in good quality randomized controlled trials: glutathione, melatonin, N-acetylcysteine, vitamins A,C,E, and ellagic acid. Of 845 screened references only 19 met the inclusion criteria. A total of 1554 patients were evaluated in the 19 studies and most had advanced or relapsed cancers. Results showed no evidence to support concerns that AO's reduced chemotherapy efficacy. In fact, most studies reported survival and/or treatment response advantages in those who took antioxidants during chemotherapy, in addition to reduced toxicity rates (with the exception of high dose Vitamin A which has documented toxicities of its own). Although the results of this review are encouraging, the authors noted several study limitations which restrict clear conclusions about AO supplementation during chemotherapy. The trials used a variety of outcome measures and studied different cancers so the question of tumor protection by AO's remains unanswered. Also, many studies were too small to detect meaningful results, and although the authors examined the best quality research available, many studies still didn't use the best methodology. Though reassuring, these findings need to be replicated in larger, better designed trials before concluding that the concurrent use of AO's and chemotherapy is not only not harmful, but may in fact be beneficial.

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