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IN THIS ISSUE: A paper by Nguyen's team reviews the side effects of androgen deprivation therapy and techniques to help mitigate them. Pan and colleagues explore the effect of yoga on treatment-related side effects and quality of life among women with breast cancer. Mols and colleagues examine chemotherapy-induced peripheral neuropathy among colorectal cancer patients. An Into the Vault Study by Kang et al. looks at the effects of soy isoflavones on breast cancer recurrence and death. A final Into the Vault Study by Wood's team explores the impact that gratitude can have on sleep.

PROSTATE CANCER

Nguyen, P.L., Alibhai, S., Basaria, S., et al.

Adverse Effects of Androgen Deprivation Therapy and Strategies to Mitigate Them

European Urology (2015), 67(10), 825-836

ABSTRACT | Context: Androgen-deprivation therapy (ADT) is a key component of treatment for aggressive and advanced prostate cancer, but it has also been associated with adverse effects on bone, metabolic, cardiovascular, sexual, and cognitive health as well as body composition. **Objective:** To review the current literature on the adverse effects of ADT and strategies for ameliorating harm from ADT. **Evidence acquisition:** The Medline database (through PubMed) was searched from inception to August 1, 2013, for studies documenting the side effects of ADT and for randomized and prospective trials of interventions to mitigate those side effects. **Evidence synthesis:** Adverse effects of ADT include decreases in bone mineral density; metabolic changes such as weight gain, decreased muscle mass, and increased insulin resistance; decreased libido and sexual dysfunction; hot flashes; gynecomastia; reduced testicle size; anemia; and fatigue. Several observational studies suggest an increased risk of diabetes and cardiovascular events, although most published studies report that ADT is not linked to greater cardiovascular mortality. Randomized trials have found value in treatments for some adverse effects including bone loss (bisphosphonates, denosumab, selective estrogen receptor modulators), markers of metabolic syndrome (exercise, diet, metformin), gynecomastia (tamoxifen, prophylactic radiation), muscle loss (resistance and aerobic exercise), and hot flashes (venlafaxine, medroxyprogesterone, cyproterone acetate, gabapentin). **Conclusions:** ADT is often a necessary component of the treatment of aggressive prostate cancer, yet it has known harms that can impair health and quality of life. Clinicians should be aware of interventions that can help mitigate these adverse effects. **Patient summary:** Androgen deprivation therapy is a critical component of the management of aggressive and advanced prostate cancer, but it causes adverse effects including bone loss, metabolic changes, gynecomastia, muscle loss, hot flashes, and possibly increased cardiovascular events. Clinicians should be aware of interventions that can help mitigate these adverse effects.

INSPIREHEALTH'S INTERPRETATION: Androgens such as testosterone are sex hormones that promote male characteristics. They are critical for male sexual and reproductive function and are responsible for the development of secondary sexual characteristics such as face and body hair, and increased muscle and bone mass. Because prostate cancer cells require androgens to proliferate, men with prostate cancer are sometimes treated with androgen deprivation therapy (ADT) to block the production and/or effects of androgens. ADT is used as the single first-line treatment to treat cancer that has spread outside the prostate (metastases), when prostate cancer recurs after previous non-hormone-based treatment, and in men who are at high risk of cancer recurrence after surgery or radiation therapy. Although ADT can improve survival, its side effects can negatively affect quality of life (QOL). Adverse effects include: anemia, loss of bone density, gynecomastia (breast growth in men), metabolic consequences (e.g., increased risk of insulin resistance (risk factor for diabetes and heart disease), weight

gain, loss of muscle mass), decreased libido, erectile dysfunction and hot flashes. These symptoms are often accompanied by irritability and emotional disturbances including depression. Several strategies have been studied to mitigate these common and troubling adverse effects and promote treatment adherence. Patients may be prescribed medications to prevent/treat gynecomastia, hot flashes, bone loss and insulin resistance. Exercise shows promise for helping to reduce some of the side effects; preliminary evidence suggests that performing resistance and aerobic exercise for 12 weeks may help to reduce bone loss, muscle loss, weight gain, fatigue, hot flashes, changes to cognition and decreased libido. In addition, a balanced diet may also reduce side effects. The authors suggest a calcium intake of at least 1200mg/day (from diet and/or supplements) and supplemental vitamin D of 800–1000IU/day for all men on ADT to help prevent bone loss.

Although additional research is needed, acupuncture also appears to reduce hot flashes; studies have shown significant improvements in hot flashes for men receiving weekly auricular acupuncture treatments. In conclusion, the side effects of ADT can negatively impact QOL and it is important to explore options to mitigate these effects. Although additional research is needed, select medications, exercise, diet and, perhaps acupuncture may ameliorate ADT's negative effects. Feel free to talk to your health care provider about how to best manage any adverse treatment effects.

BREAST CANCER

Pan, Y., Yang, K., Wang, Y., et al.

Could yoga practice improve treatment-related side effects and quality of life for women with breast cancer? A systematic review and meta-analysis

Asia-Pacific Journal of Clinical Oncology (2015). doi: 10.1111/ajco.12329.

ABSTRACT | Aim: To determine if yoga as a complementary and alternative therapy was associated with enhanced health and treatment-related side effects in patients with breast cancer. This systematic review examines whether yoga practice provides any measurable benefit, both physically and psychologically, for women with breast cancer. **Methods:** PubMed, EMBASE and the Cochrane Library for randomized controlled trials (RCTs) throughout June 2013. We evaluated the quality of the included studies by the Cochrane Handbook 5.2 standards and analyzed the data using the Stata software, version 10.0. Meta-regression and subgroup analysis were also performed to identify additional predictors of outcome and to assess heterogeneity. **Results:** Sixteen RCTs with a total of 930 participants were included. Comparing yoga groups to control groups, there was a statistically significant difference in overall health-related quality of life, depression, anxiety and gastrointestinal symptoms. Meta-regression analyses revealed that the duration of yoga practice and type of control group partly explained the heterogeneity. Subgroup analyses revealed that yoga had a positive effect on anxiety only when it had been practiced for longer than 3 months. Only the wait-list control group showed an effect of yoga on physical well-being. **Conclusion:** The current evidence demonstrates that yoga practice could be effective in enhancing health and managing some treatment-related side effects for patients recovering from breast cancer. In future clinical studies, clinicians should consider the patient's wishes along with the current best evidence of the effects of yoga practice in their clinical decision-making.

INSPIREHEALTH'S INTERPRETATION: Yoga is a mind-body practice which is commonly used as a complementary therapy for women with breast cancer. Yoga typically involves various body postures, focused breathing and meditation. It is widely practiced for overall relaxation and well-being and has been associated with a reduction in menopausal symptoms such as hot flashes, improvements in cancer treatment side effects, and better cortisol (a stress hormone) regulation. In order to further explore the effects of a yoga practice for individuals with breast cancer, these researchers conducted a meta-analysis of randomized control trials (RCTs) that examined the physical and psychological effects of yoga in women who had had breast cancer treatment. The results of 930 participants from 16 RCTs were reviewed; 538 women participated in yoga programs, and 493 women served as controls (not participating in yoga). Nine of the studies were from Western cultures (Europe and North America), and seven were conducted in India. In general, the yoga sessions lasted from three to six months, one to three times per week (60 to 90 classes per session), and included various types of yoga practice (e.g., lyengar, restorative, Hatha).

Overall, results found significant reductions in depression (reported in ten studies) and anxiety (reported in ten studies), and significant improvements in health-related quality of life (reported in four studies), and gastrointestinal symptoms (reported in four studies) for individuals who practiced yoga compared to those who did not. Additionally, anxiety symptoms decreased when the duration of the yoga practice increased beyond three months. No improvements were found for physical well-being (reported in eight studies), fatigue (reported in nine studies), sleep quality (reported in six studies), or pain (reported in four studies).

To explain the positive results, the authors proposed that the psychological benefits of yoga may be due to a relaxation response from the yoga itself. Overall, this paper indicated that yoga may lead to positive outcomes for breast cancer patients, but more research should be conducted to confirm these findings. InspireHealth members are welcome to join the many yoga classes offered at all InspireHealth locations.

COLORECTAL CANCER

Mols, F., Beijers, A.J.M., Vreugdenhil, G., et al.

Chemotherapy-induced peripheral neuropathy, physical activity and health-related quality of life among colorectal cancer survivors from the PROFILES registry

Journal of Cancer Survivorship (2015). DOI 10.1007/s11764-015-0427-1.

ABSTRACT | Purpose: To gain insight into the association of physical activity (PA), chemotherapy-induced peripheral neuropathy (CIPN) and health-related quality of life among colorectal cancer survivors, up to 11 years after diagnosis. **Methods:** Data of the second data wave of a Dutch prospective population-based survey among colorectal cancer survivors diagnosed between 2000 and 2009 as registered by the Eindhoven Cancer Registry was used. 83% (n=1648) of patients filled out the EORTC QLQ-C30 and the EORTC QLQ-CIPN20 of which 506 patients (31%) were treated with chemotherapy. **Results:** Treatment with chemotherapy was associated with a higher percentage of patients reporting CIPN symptoms regardless of PA. Furthermore, not meeting the Dutch PA guideline of 150 min of moderate to vigorous PA a week was associated with more CIPN among patients treated with chemotherapy. Also patients not treated with chemotherapy reported CIPN-like symptoms, especially when not meeting the PA guideline. Statistically significant and clinically relevant worse scores on almost all EORTC QLQ-C30 subscales were reported by those not meeting the PA guideline compared to those who did meet the guideline, regardless of CIPN symptoms. However, these differences were more pronounced in the group with many CIPN symptoms (e.g. upper 30%). **Implications for Cancer Survivors:** Alertness among health care professionals and patients for the importance of PA is warranted, as meeting the PA guideline was associated with less CIPN-like symptoms and a higher health-related quality of life regardless of treatment with chemotherapy.

INSPIREHEALTH'S INTERPRETATION: Some chemotherapy agents used to treat colorectal (and other) cancers can cause chemotherapy-induced peripheral neuropathy (CIPN). CIPN results when chemotherapy damages the peripheral nerves (nerves outside the brain and spinal cord). Symptoms of CIPN can be quite disabling and include pain, numbness and tingling, muscle weakness, balance problems and bowel and bladder dysfunction. Some studies have shown that physical activity can reduce the incidence and severity of CIPN for cancer patients. To further assess this relationship, researchers investigated the link between CIPN, physical activity, and health-related quality of life among colorectal cancer survivors in a cross-sectional study. Study participants were individuals enlisted in a Dutch cancer registry who had been diagnosed with colorectal cancer up to 11 years prior to the study.

Surprisingly (by North American standards), over 80% of the participants met physical activity guidelines (150 minutes of weekly moderate-vigorous physical activity). Not surprisingly, participants who received chemotherapy were more likely to report CIPN symptoms than those colorectal cancer survivors who did not receive chemotherapy. Of those who received chemotherapy, a significantly greater number of underactive individuals (i.e., those who did not meet physical activity guidelines) reported CIPN symptoms compared to individuals who were sufficiently active. Interestingly, this pattern was also found for participants that did not receive chemotherapy, with a greater number of underactive participants reporting CIPN symptoms than active individuals. Furthermore, not meeting physical activity guidelines was associated with lower health-related quality of life, regardless of CIPN symptoms.

Although there were limitations to this study (e.g., the data was self-reported and the sample was highly active to begin with), the results indicate that regardless of treatment (i.e., receiving chemotherapy or not), lack of physical activity is associated with increased CIPN symptoms and reduced health-related quality of life, even after controlling for health-related factors such as osteoarthritis, rheumatoid arthritis, and diabetes. These results can be added to the growing body of research supporting the many health benefits of exercising at a moderate to vigorous intensity for at least 150 minutes per week. Working with a trained exercise therapist will help you to ensure that you are exercising in a safe and progressive manner to obtain the greatest health benefits.

INTO THE VAULT

Kang, X., Zhang, Q., Wang, S., et al.

Effect of soy isoflavones on breast cancer recurrence and death for patients receiving adjuvant endocrine therapy

CMAJ (2010). 182(17): 1857-1862.

ABSTRACT | Background: The intake of soy isoflavones among women with breast cancer has become a public health concern, because these compounds have weak estrogenic effects. There is little clinical evidence about their safety for patients with breast cancer who are receiving adjuvant endocrine therapy. **Methods:** For patients who underwent surgery for breast cancer between August 2002 and July 2003 and who were receiving adjuvant endocrine therapy, we examined associations between dietary intake of soy isoflavones and recurrence of breast cancer and death. We measured dietary intake of soy isoflavones at baseline using a validated food frequency questionnaire. We estimated hazard ratios (HRs) and 95% confidence intervals (CIs) by means of multivariable Cox proportional hazards regression models. We further stratified the analyses by

hormonal receptor status and endocrine therapy. **Results:** The median follow-up period for the 524 patients in this study was 5.1 years. Among premenopausal patients, the overall death rate (30.6%) was not related to intake of soy isoflavones (HR = 1.05, 95% CI 0.78–1.71 for the highest quartile [> 42.3 mg/day] v. the lowest quartile [< 15.2 mg/day], p for trend = 0.87). Relative to postmenopausal patients in the lowest quartile of soy isoflavone intake, the risk of recurrence for postmenopausal patients in the highest quartile was significantly lower (HR = 0.67, 95% CI 0.54–0.85, p for trend = 0.02). Inverse associations were observed in patients with estrogen and progesterone receptor positive disease and those receiving anastrozole therapy. **Interpretation:** High dietary intake of soy isoflavones was associated with lower risk of recurrence among postmenopausal patients with breast cancer positive for estrogen and progesterone receptor and those who were receiving anastrozole as endocrine therapy.

INSPIREHEALTH'S INTERPRETATION: In the August/September 2015 issue of *Research Updates*, we reviewed a paper by Hwang and Choi examining the mechanisms by which dietary phytoestrogens (plant-based estrogen-like compounds) might exert anti-cancer effects. In this issue we will explore in detail one of the papers cited in Hwang and Choi's review. This Chinese study was published in the Canadian Medical Association Journal in 2010 and its results help to shed light on a common dilemma facing women with breast cancer.

Whether or not to consume isoflavone-rich soy products is a question many women with breast cancer ask. Isoflavones are one of the four main classes of phytoestrogens and soybeans are the richest source of isoflavones. Because soy isoflavones have weak estrogenic activity there is concern that soy food consumption by women with breast cancer, especially those with estrogen-positive breast cancer who are taking adjuvant “anti-estrogen” hormone therapy, may not be safe. In 2002-2003, 524 women with estrogen- and/or progesterone-receptor (ER and PR) positive breast cancer (stages 1-3) participated in the study. All women had undergone surgery and were taking hormone therapy. All 248 premenopausal women and 190/276 postmenopausal women were taking tamoxifen and 86/276 postmenopausal women were taking the aromatase inhibitor anastrozole. Eighty-five percent of the participants received chemotherapy and 55% received radiation therapy. The women completed a comprehensive questionnaire covering demographics, physical activity and usual diet, and were interviewed to obtain very detailed information about soy intake from five years pre-diagnosis to time of study. Patients were followed-up in 2008. There was no association between soy intake and breast cancer recurrence or death among premenopausal women (i.e., neither benefit nor risk). However, among postmenopausal women with both estrogen- and progesterone-receptor positive breast cancer, and for those receiving anastrozole therapy, an inverse relationship between soy intake and recurrence was observed; those with the highest intake of soy foods had the lowest risk of breast cancer recurrence.

Importantly, there were no differences in physical activity, cancer stage or other dietary factors for women who consumed the highest amounts of soy to account for this finding. Like premenopausal women, there was no association between soy intake and death for postmenopausal women. The authors concluded that their findings are consistent with two other large scale studies examining soy intake and risk of breast cancer recurrence and “suggest that the beneficial effects of soy isoflavones may be achieved through the estrogen and progesterone receptors”. They caution, however, that more large multicenter trials are needed before soy foods can be confidently recommended after a diagnosis of breast cancer. While soy foods may be safe and even protective, it is generally agreed that soy supplements should be avoided.

INTO THE VAULT

Wood, A.M., Joseph, S., Lloyd, J., et al.

Gratitude influences sleep through the mechanism of pre-sleep cognitions

Journal of Psychosomatic Research (2009). 66(1), 43-48.

ABSTRACT | Objectives: To test whether individual differences in gratitude are related to sleep after controlling for neuroticism and other traits. To test whether pre-sleep cognitions are the mechanism underlying this relationship. **Method:** A cross-sectional questionnaire study was conducted with a large (186 males, 215 females) community sample (ages=18–68 years, mean=24.89, S.D.=9.02), including 161 people (40%) scoring above 5 on the Pittsburgh Sleep Quality Index, indicating clinically impaired sleep. Measures included gratitude, the Pittsburgh Sleep Quality Index (PSQI), self-statement test of pre-sleep cognitions, the Mini-IPIP scales of Big Five personality traits, and the Social Desirability Scale. **Results:** Gratitude predicted greater subjective sleep quality and sleep duration, and less sleep latency and daytime dysfunction. The relationship between gratitude and each of the sleep variables was mediated by more positive pre-sleep cognitions and less negative pre-sleep cognitions. All of the results were independent of the effect of the Big Five personality traits (including neuroticism) and social desirability. **Conclusion:** This is the first study to show that a positive trait is related to good sleep quality above the effect of other personality traits, and to test whether pre-sleep cognitions are the mechanism underlying the relationship between any personality trait and sleep. The study is also the first to show that trait gratitude is related to sleep and to explain why this occurs, suggesting future directions for research, and novel clinical implications.

INSPIREHEALTH'S INTERPRETATION: Insomnia is a very common condition characterized by problems falling or staying asleep. Those with insomnia often report having non-restorative sleep. About 30% of Canadian adults report insomnia and

about 30% of them (10% of the population) report persistent or chronic insomnia that impairs daytime functioning. Those with a diagnosis of cancer are at risk of developing or worsening insomnia due to the illness itself, the treatments given, and the psychological stressors associated with having a potentially life-threatening illness.

In general, the two main treatments for insomnia are medications (often with undesirable side effects) and behavioural therapy (i.e., sleep hygiene (e.g., regular exercise, evening relaxation, reducing/avoiding caffeine and alcohol) and cognitive behavioural therapy). The authors of this British study examined whether or not the positive psychological trait of gratitude was associated with sleep quality and quantity. Increasing evidence shows that positive psychological well-being is linked to improved sleep, and gratitude is often considered the quintessential positive psychological trait. Grateful people tend to focus on the positive in their environment and social relationships. Because positive psychological traits such as gratitude are often associated with underlying personality traits, these authors used questionnaires and statistical analysis to control for personality traits. In the psychological literature five broad categories of personality, called the Big Five personality traits, have been described: openness to experience/intellect/imagination, extraversion, agreeableness, conscientiousness, and neuroticism/emotional stability.

Four hundred and one healthy participants (186 male, 215 female), average age 25 years old, were recruited from London and East Midlands, UK. A high seventy-five percent of those approached agreed to study participation. They completed five questionnaires to measure sleep quality and quantity, gratitude, the Big Five personality traits, pre-sleep cognitions, and social desirability. All questionnaires are frequently used and well validated in the literature. Five sleep variables were examined with respect to gratitude: total sleep quality, subjective sleep quality, sleep latency (time it takes to fall asleep), sleep duration, and daytime function/dysfunction. Results indicated that 40% of the participants were classified as poor sleepers. After controlling for the effects of the Big Five and social desirability, gratitude still significantly predicted better overall sleep and positive pre-sleep cognitions were found to mediate the relationship between gratitude and sleep. In other words, it is not just those who have personality characteristics typically associated with positive thinking who sleep better; even those with more emotionally labile personalities who are able to focus on positive thoughts (e.g. “enjoyable things I did in the last few days”) and gratitude at sleep time, sleep better.

However, because this was a cross-sectional study, causal relationships cannot be assessed. In addition, study subjects were young healthy people, so the results may not be as relevant for those with cancer. Future research examining whether purposefully exploring thoughts of gratitude at sleep time helps those with insomnia would be most interesting.

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

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

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

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