



RESEARCH UPDATES FEBRUARY 2014

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DEAR READERS: After some careful thought, discussion, and planning, we have decided to update the format of our monthly Research Updates newsletter. Instead of presenting 10 – 12 abstracts per month with concise interpretations, we will be presenting 5-6 abstracts per month and delving deeper into the full text of each article. Our goal is to further educate our readers about the many facets of healthy living and provide a more thorough, informative, and hopefully educational analysis of each research paper presented.

IN THIS ISSUE: Di Maso and colleagues found that higher red meat consumption was associated with cancer of numerous sites, perhaps due to the carcinogens produced in the cooking process. Guest and associates found that a diet high in fat was associated with increased fatigue in breast cancer survivors. Zhang et al. found that energy intake in sisters was associated with higher breast cancer risk; however, this relationship was less pronounced in those with healthy BMI and exercise habits. Rundqvist and colleagues learned that even a single exercise bout has measurable, physiological cancer fighting benefits. Ahn and associates found that exercise in post-operative colon cancer patients quickened bowel recovery and resulted in sooner discharge from the hospital. Dieperink et al. discovered that while some men prefer spousal support during prostate cancer treatment, others prefer to receive treatment on their own.

NUTRITION

Di Maso, M, R. Talamini, C. Bosetti, et al.

Red Meat and Cancer Risk in a Network of Case-Control Studies Focusing on Cooking Practices.

Annals of Oncology. Dec 2013; 24(12): 3107-3112.

BACKGROUND: Consumption of red meat has been related to increased risk of several cancers. Cooking methods could modify the magnitude of this association, as production of chemicals depends on the temperature and duration of cooking.

METHODS: We analyzed data from a network of case-control studies conducted in Italy and Switzerland between 1991 and 2009. The studies included 1465 oral and pharyngeal, 198 nasopharyngeal, 851 laryngeal, 505 esophageal, 230 stomach, 1463 colon, 927 rectal, 326 pancreatic, 3034 breast, 454 endometrial, 1031 ovarian, 1294 prostate and 767 renal cancer cases. Controls included 11 656 patients admitted for acute, non-neoplastic conditions. Odds ratios (ORs) and confidence intervals (CIs) were estimated by multiple logistic regression models, adjusted for known confounding factors. **RESULTS:** Daily intake of red meat was significantly associated with the risk of cancer of the oral cavity and pharynx (OR for increase of 50 g/day = 1.38; 95% CI: 1.26-1.52), nasopharynx (OR = 1.29; 95% CI: 1.04-1.60), larynx (OR = 1.46; 95% CI: 1.30-1.64), esophagus (OR = 1.46; 95% CI: 1.23-1.72), colon (OR = 1.17; 95% CI: 1.08-1.26), rectum (OR = 1.22; 95% CI: 1.11-1.33), pancreas (OR = 1.51; 95% CI: 1.25-1.82), breast (OR = 1.12; 95% CI: 1.04-1.19), endometrium (OR = 1.30; 95% CI: 1.10-1.55) and ovary (OR = 1.29; 95% CI: 1.16-1.43). Fried meat was associated with a higher risk of cancer of oral cavity and pharynx (OR = 2.80; 95% CI: 2.02-3.89) and esophagus (OR = 4.52; 95% CI: 2.50-8.18). Risk of prostate cancer increased for meat cooked by roasting/grilling (OR = 1.31; 95% CI: 1.12-1.54). No heterogeneity according to cooking methods emerged for other cancers. Nonetheless, significant associations with boiled/stewed meat also emerged for cancer of the nasopharynx (OR = 1.97; 95% CI: 1.30-3.00) and stomach (OR = 1.86; 95% CI: 1.20-2.87). **CONCLUSIONS:** Our analysis confirmed red meat consumption as a risk factor for several cancer sites, with a limited impact of cooking methods. These findings, thus, call for a limitation of its consumption in populations of Western countries.

INSPIREHEALTH'S INTERPRETATION: This was a large case-control study (over 20 000 participants) that investigated cooked red meat consumption and the risk of developing a number of different cancers. This study examined the risk of increasing red meat intake by 50 g/day as measured by a food frequency questionnaire. When food is cooked, some of the substrates change their chemical make-up. For example, lycopene in tomatoes is more bioavailable (more easily absorbed) after being cooked. In some cases however, cooking creates compounds that negatively affect the human body. Cooking red meat at high temperatures creates heterocyclic amines (HCA) from protein substrates, and polycyclic aromatic hydrocarbons

(PAH) from fat substrates and smoke. As a general rule, the higher the temperature the meat is cooked at, the more HCA will be formed. Higher red meat consumption was associated with increased risk of cancer in the following areas: oral cavity, pharynx, nasopharynx, larynx, esophagus, colon, rectum, pancreas, breast, endometrium, and ovaries. Daily fried red meat consumption increased the risk of cancer in the esophagus by 352%. This study may have been improved by including data on processed red meat consumption. Processed meats are preserved with nitrate and nitrite compounds which are converted to carcinogenic nitrosamines (NA) in the human body. Limiting red meat consumption or choosing leaner, non-smoked meats and cooking them at low temperatures will help to reduce the amount of dietary carcinogens in your food.

NUTRITION

Guest, DD, E. M. Evans and L. Q. Rogers.

Diet Components Associated with Perceived Fatigue in Breast Cancer Survivors.

European J Cancer Care. Jan 2013; 221: 51-59.

Little is known about the contribution of diet components independent of body composition to persistent fatigue in breast cancer survivors. Therefore, our study aim was to determine the associations among dietary intake and fatigue in relation to and independent of adiposity and physical activity (PA) in breast cancer survivors. Baseline data from 42 breast cancer survivors enrolled in a randomised exercise trial were analysed: fatigue (Functional Assessment of Cancer Therapy for fatigue), diet components (3-day diet record), body mass index, per cent body fat (dual-energy X-ray absorptiometry) and PA (accelerometer). The mean age was 54 ± 9 years with an average body mass index of 30.5 ± 8.1 kg/m². Fatigue was positively associated with % of kcal/day fat intake ($r = 0.31$, $P < 0.05$) and inversely related to fibre g/day ($r = 0.38$, $P < 0.05$) and carbohydrate g/day intake ($r = 0.31$, $P < 0.05$). Mean fatigue was greater for participants eating <25 g/day of fibre compared with >25 g/day of fibre (15.7 ± 10.8 versus 6.4 ± 3.7 , $P < 0.005$). No significant associations were noted between fatigue and PA or body composition. Diets high in fibre and low in fat are associated with reduced fatigue in breast cancer survivors. The difference in fatigue for low- versus high-fibre diets exceeded the minimal clinically important difference of three units. Prospective studies evaluating the effect of changing diet on fatigue in breast cancer survivors are warranted.

INSPIREHEALTH'S INTERPRETATION: The authors of this American study analyzed baseline data from 42 women in remission following breast cancer treatment enrolled in a randomized exercise trial. This retrospective analysis of baseline data is termed "post-hoc" and is useful for exploring associations but not causation. All women had had surgery, 81% had chemotherapy, 83% had radiation and all were on adjuvant hormonal therapy. The aim of the analysis was to determine if there were any links between fatigue and specific dietary components (fat, fibre, carbohydrates (CHO)) in relation to and independent of body habitus and physical activity. Because healthy behaviours tend to cluster – those who exercise regularly tend to eat better, not smoke and maintain a healthy weight – teasing out the importance of a given factor or behaviour becomes difficult. On average this cohort of women exceeded both daily kilocalories and % dietary fat recommendation, ate less fibre and fewer fruits and vegetables than recommended, and were obese (BMI > 30 kg/m²). Findings revealed that increased intakes of carbohydrates and dietary fibre were associated with less fatigue (an inverse relationship) while increased % kcal from fat was associated with more fatigue (positive relationship). The authors wondered if the type rather than amount of CHO in the diet plays a greater role in fatigue. For example brown rice has more nutrient value and more stable effects on blood glucose and insulin than does white rice. They also postulate that higher dietary fibre intake may have beneficial effects on inflammation while a diet higher in saturated fats may add to chronic inflammation. Although significant associations were not found between fatigue and physical activity or body composition, the researchers comment that the small sample size and insufficient physical activity and BMI variability between participants (fairly homogenous participant characteristics) may explain this finding. This analysis supports the need for future prospective studies to examine effects that diet quality, even in the absence of weight loss, may have on cancer related fatigue. In the meantime, it is reasonable to recommend a nutrient rich whole food diet incorporating healthy carbohydrates and fats, and appropriate fibre intake together with regular moderate exercise for breast cancer and all cancer patients.

EXERCISE

Zhang, FF, E. M. John, J. A. Knight, et al.

Total Energy Intake and Breast Cancer Risk in Sisters: The Breast Cancer Family Registry.

Breast Cancer Res Treat. Jan 2013; 1372: 541-551.

Energy restriction inhibits mammary tumor development in animal models. Epidemiologic studies in humans generally do not support an association between dietary energy intake and breast cancer risk, although some studies suggest a more complex interplay between measures of energy intake, physical activity, and body size. We examined the association between total energy intake jointly with physical activity and body mass index (BMI) and the risk of breast cancer among 1,775 women diagnosed with breast cancer between 1995 and 2006 and 2,529 of their unaffected sisters, enrolled in the Breast Cancer Family Registry. We collected dietary data using the Hawaii-Los Angeles Multiethnic Cohort food frequency questionnaire. Using

conditional logistic regression to estimate the odds ratios (OR) and 95 % confidence intervals (CI) associated with total energy intake, we observed an overall 60 – 70 % increased risk of breast cancer among women in the highest quartile of total energy intake compared to those in the lowest quartile (Q4 vs. Q1: OR = 1.6, 95 % CI: 1.3-2.0; P (trend) < 0.0001); these associations were limited to pre-menopausal women or women with hormone receptor-positive cancers. Although the associations were slightly stronger among women with a higher BMI or lower level of average lifetime physical activity, we observed a positive association between total energy intake and breast cancer risk across different strata of physical activity and BMI. Our results suggest that within sisters, high energy intake may increase the risk of breast cancer independent of physical activity and body size. If replicated in prospective studies, then these findings suggest that reductions in total energy intake may help in modifying breast cancer risk.

INSPIREHEALTH'S INTERPRETATION: This was a very interesting study on the effect of total energy intake on breast cancer risk in sisters. By comparing sisters instead of standard control subjects, some confounding variables are removed from the equation: genetic influence on breast cancer is much less of a factor, and parental and environmental influences during childhood are also likely shared by sisters. More than just energy intake, these investigators looked at the influence of moderate and strenuous physical activity, and BMI on the relationship between energy intake and breast cancer risk. Overall, higher energy intake was linearly associated with increased risk of breast cancer. However, in women with a BMI < 25 kg/m² (ie. healthy weight), the association was weaker. The association was again weaker in women who were more physically active. This intuitively makes sense; a more active body requires more energy as fuel for the body during activity, and as building blocks for muscle and tissue repair. Based on a well-designed, retrospective, case-control study, the take home message here is that maintaining a healthy body weight through both physical activity and adequate energy consumption is associated with reduced risk of breast cancer.



EXERCISE

Rundqvist, H, M. Augsten, A. Stromberg, et al.

Effect of Acute Exercise on Prostate Cancer Cell Growth.

PLoS One. July 2013; 8(7): e67579.

Physical activity is associated with reduced risk of several cancers, including aggressive prostate cancer. The mechanisms mediating the effects are not yet understood; among the candidates are modifications of endogenous hormone levels. Long-term exercise is known to reduce serum levels of growth stimulating hormones. In contrast, the endocrine effects of acute endurance exercise include increased levels of mitogenic factors such as GH and IGF-1. It can be speculated that the elevation of serum growth factors may be detrimental to prostate cancer progression into malignancy. The incentive of the current study is to evaluate the effect of acute exercise serum on prostate cancer cell growth. We designed an exercise intervention where 10 male individuals performed 60 minutes of bicycle exercise at increasing intensity. Serum samples were obtained before (rest serum) and after completed exercise (exercise serum). The established prostate cancer cell line LNCaP was exposed to exercise or rest serum. Exercise serum from 9 out of 10 individuals had a growth inhibitory effect on LNCaP cells. Incubation with pooled exercise serum resulted in a 31% inhibition of LNCaP growth and pre-incubation before subcutaneous injection into SCID mice caused a delay in tumor formation. Serum analyses indicated two possible candidates for the effect; increased levels of IGFBP-1 and reduced levels of EGF. In conclusion, despite the fear of possible detrimental effects of acute exercise serum on tumor cell growth, we show that even the short-term effects seem to add to the overall beneficial influence of exercise on neoplasia.

INSPIREHEALTH'S INTERPRETATION: There is evidence that long-term exercise is beneficial for both prevention and progression of prostate cancer. The goal of this study was to evaluate the effects of a single bout of aerobic exercise on the growth of prostate cancer cells. To examine prostate cancer cell growth, an established prostate cancer cell line (LNCaP) was cultured with either 5% resting serum, or 5% post-exercise serum. Though the sample size was small, the results were statistically significant. Exercise serum inhibited growth of LNCaP cells in 9 of 10 subjects, with an average inhibition of 31%. Additionally, these investigators measured the response of 23 different serum cytokines (small proteins that are important in cell to cell communication, especially in the immune system) and growth factors to the same bout of exercise. From the arterial blood samples compared at rest and post-exercise, there were two differences that may help explain the growth inhibition

associated with the exercise serum. First, insulin like growth factor binding protein (IGFBP-1) levels were 35% higher in the exercise serum. IGFBP-1 reduces the amount of active circulating IGF, which regulates cell proliferation and programmed cell death. High levels of circulating IGF have been associated with increased risk of prostate cancer, whereas higher levels of IGFBP-1 are associated with reduced risk. Second, Epidermal growth factor (EGF) levels were 18% lower in the exercise serum. EGF stimulates the growth and proliferation of many cell types, including LNCaP prostate cancer cells. To summarize, arterial serum taken after an acute bout of aerobic exercise reduced the growth of cultured LNCaP prostate cancer cells by 31%. This inhibition may be due to increases in circulating levels of IGFBP-1 and decreases in EGF. These data suggest that even a short, single bout of aerobic exercise may help to reduce the risk of prostate cancer.

EXERCISE

Ahn, KY, H. Hur, D. H. Kim, et al.

The Effects of Inpatient Exercise Therapy on the Length of Hospital Stay in Stages I-III Colon Cancer Patients: Randomized Controlled Trial.

Int J Colorectal Dis. May 2013; 285: 643-651.

PURPOSE: This study aimed to examine the effects of a postsurgical, inpatient exercise program on postoperative recovery in operable colon cancer patients. **METHODS:** We conducted the randomized controlled trial with two arms: postoperative exercise vs. usual care. Patients with stages I-III colon cancer who underwent colectomy between January and December 2011 from the Colorectal Cancer Clinic, were recruited for the study. Subjects in the intervention group participated in the postoperative inpatient exercise program consisted of twice daily exercise, including stretching, core, balance, and low-intensity resistance exercises. The usual care group was not prescribed a structured exercise program. The primary endpoint was the length of hospital stay. Secondary endpoints were time to flatus, time to first liquid diet, anthropometric measurements, and physical function measurements. **RESULTS:** A total of 31 (86.1 %) patients completed the trial, with adherence to exercise interventions at 84.5 %. The mean length of hospital stay was 7.82 ± 1.07 days in the exercise group compared with 9.86 ± 2.66 days in usual care (mean difference, 2.03 days; 95 % confidence interval (CI), -3.47 to -0.60 days; $p=0.005$) in per-protocol analysis. The mean time to flatus was 52.18 ± 21.55 h in the exercise group compared with 71.86 ± 29.2 h in the usual care group (mean difference, 19.69 h; 95 % CI, -38.33 to -1.04 h; $p=0.036$). **CONCLUSIONS:** Low-to-moderate-intensity postsurgical exercise reduces length of hospital stay and improves bowel motility after colectomy procedure in patients with stages I-III colon cancer.

INSPIREHEALTH'S INTERPRETATION: This small Korean randomized controlled trial (RCT) examined the effects of implementing an early post-operative exercise program had on patients' recovery. A total of 31 patients with stages I-III colon cancer who underwent either laparoscopic or open (larger abdominal incision) colectomy (excision of the part of the colon containing cancer) were randomized to either the exercise or usual care group. One surgeon performed all surgeries eliminating any possible confounding factors related to surgical protocol or technique. Those in the exercise group began with stretching and very low intensity resistance exercises while still bed bound. They progressed to more involved resistance and balance exercises as their mobility and walking tolerance improved. The usual care group started walking as soon as they were able, but didn't perform any other specific exercises. Results showed that patients in the usual care group stayed in hospital an average of 2.03 days longer than those in the exercise group. Furthermore, the median time to flatus (passage of gas) in the exercise group was 23 hours shorter compared with the control group. Both these results were statistically significant. All subjects were monitored for 30 days post-operatively and no major complications occurred in either group ensuring the safety of the exercise protocol. Overall, this small but well-designed RCT showed that a simple post-colectomy exercise routine promoted quicker bowel recovery (earlier flatus) and earlier hospital discharge. Because this was an RCT, these factors suggest causation rather than simple association. One day earlier for passage of flatus and two days earlier to discharge may not seem like significant time frames, but many patients will say that these two milestones are very meaningful for their overall recovery and well-being. The recommended exercises could easily be implemented by those undergoing colectomy for colon cancer.

PSYCHOSOCIAL SUPPORT

Dieperink, KB, L. Wagner, S. Hansen, et al.

Embracing Life After Prostate Cancer. A Male Perspective on Treatment and Rehabilitation.

European J Cancer Care. Jul 2013; 224: 549-558.

This study explores prostate cancer patients' experiences of rehabilitation after radiotherapy with androgen deprivation therapy (ADT). Patients who had completed a multidisciplinary rehabilitation programme with psychosocial support and physiotherapy were interviewed in two focus groups: Group 1 consisted of six men who came to the rehabilitation with their spouses, and Group 2 of seven men who came alone. Meaning condensation was used to analyse the interviews. Radiotherapy was described as full-time work. Adverse effects due to ADT influencing masculinity and identity were emphasised. The men embraced life

with a particular sense of humour. Whether rehabilitation was experienced as useful depended on the health professionals' approach, and on the patients' motivation and effort to contribute to health promotion, and to convert experiences into coping strategies. The supportive role of the spouse was emphasised by several, but some men preferred to handle the process alone. In conclusion, men undergoing ADT should be carefully informed of the consequences. Spousal involvement in rehabilitation must be decided by the patient. The focus group interviews themselves had a positive impact on the men's understanding of their rehabilitation processes. The specific male approach and differences between the needs of female and male cancer patients are important to understand when planning rehabilitation.

INSPIREHEALTH'S INTERPRETATION: In this qualitative Danish study 13 men with stages I-III (ie. no distant metastatic spread) prostate cancer were divided into two focus groups. This study was part of a larger overall investigation examining a more comprehensive rehabilitation program for men with prostate cancer who were treated with radiation and androgen deprivation therapy (ADT). The rehabilitation program included two counseling sessions with a nurse, and two sessions with a physiotherapist. Group assignment for the focus groups was based on whether or not the men had involved (FG1) or not involved (FG2) a spouse in the larger rehabilitation program. Each focus group met once with an experienced nurse and a senior researcher. In general, side effects from radiation related to bladder and bowel dysfunction and were minor and improved with time. In contrast, adverse effects from ADT including weight gain/body image changes (increased fatty tissue to abdomen, breasts, buttocks), hot flashes and sexual function declines were particularly significant and were complicated by inconsistent and even incomplete information given by health care professionals. Despite these adverse effects, participants expressed gratitude for life. The authors found that humour and the ability to embrace life one day at a time were effective coping strategies. Earlier spousal involvement was seen to enhance the rehabilitation process for men in FG1, while men in FG2 were more used to handling things themselves. These differences may reflect the general relationship between the couple. Overall the men enjoyed the focus groups sessions and the ability to discuss their treatment experiences. In summary, this small qualitative study found that androgen deprivation therapy more than radiation therapy had significant adverse effects; especially on masculinity and male sexuality and identity. The ability to meet in a small, facilitated focus group was beneficial and the man should decide whether or not to involve his spouse in the rehabilitation process. In addition, health care professionals need to fully explain potential adverse effects of proposed treatments and invite patients to discuss their questions and concerns.

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