



REsearch UPDATES

FOR THE LATEST IN WORLDWIDE INTEGRATIVE CANCER CARE

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IN THIS ISSUE: Aronson et al. reported that fish oil supplements and a low fat diet can have a beneficial effect on prostate cancer. Kovacic and Kovacic reported that relaxation training can be helpful for patients with breast cancer. Boyle and colleagues found that exercise is helpful to reduce colorectal cancer. In a similar vein, Lynch and colleagues reported that colorectal cancer survivors who watched a lot of TV and had sedentary lifestyles had a lower quality of life. Psaltopoulou et al. found that people who consumed more olive oil had lower odds of developing cancer – both in general and more specifically with respect to breast and digestive system cancer. Enblom and associates found that acupuncture was effective for radiotherapy-induced vomiting. Brinkman and colleagues reported that alpha-linolenic acid may protect against bladder cancer. Davies and associates

reported that sun exposure increased vitamin D levels, but supplementation was necessary to achieve optimal levels, particularly in melanoma patients and people living in temperate climates. Hayes et al. reported that weight lifting is safe for women with lymphedema. Je and colleagues reported that women who drank four or more cups of coffee per day had a lower risk of endometrial cancer. In our study of the month, Lambe et al. reported that blood glucose levels below the threshold for diabetes may reduce the risk of postmenopausal breast cancer and endometrial cancer.

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PROSTATE CANCER

Aronson, WJ, N. Kobayashi, R. J. Barnard, et al.

Phase II Prospective Randomized Trial of a Low-Fat Diet with Fish Oil Supplementation in Men Undergoing Radical Prostatectomy.

Cancer Prevention Research. 2011 December 2011; 412: 2062-2071.

BACKGROUND: Preclinical studies suggest lowering dietary fat and decreasing the ratio of omega-6 to omega-3 polyunsaturated fatty acids decreases the risk of prostate cancer development and progression. **METHODS:** We conducted a phase II randomized trial to test the effect of decreasing dietary fat combined with decreasing the dietary omega-6:omega-3 ratio on biomarkers related to prostate cancer development and progression. Patients undergoing radical prostatectomy were randomly assigned to receive a low-fat diet with 5 grams of fish oil daily (dietary omega-6:omega-3 ratio of 2:1) or a control Western diet (omega-6:omega-3 ratio of 15:1) for four to six weeks prior to surgery. The primary endpoint was change in serum insulin-like growth factor I (IGF-1) between arms. Secondary endpoints were serum IGFBP-1, prostate prostaglandin E2 levels, omega-6:omega-3 fatty acid ratios, COX-2, and markers of proliferation and apoptosis.

RESULTS: Fifty-five patients were randomized and 48 completed the trial. There was no treatment difference in the primary outcome. Positive secondary outcomes in the low-fat fish oil versus Western group were reduced benign and malignant prostate tissue omega-6:omega-3 ratios, reduced proliferation (Ki-67 index), and reduced proliferation in an ex vivo bioassay when patient sera was applied to prostate cancer cells in vitro. In summary, four to six weeks of a low-fat diet and fish oil capsules to achieve an omega-6:omega-3 fatty acid ratio of 2:1 had no effect on serum IGF-1 levels, though in secondary analyses,



the intervention resulted in decreased prostate cancer proliferation and decreased prostate tissue omega-6:omega-3 ratios.

CONCLUSION: These results support further studies evaluating reduction of dietary fat with fish oil supplementation on modulating prostate cancer biology.

BREAST CANCER

Kovacic, T and M. Kovacic.

Impact of Relaxation Training According to Yoga in Daily Life System on Self-Esteem After Breast Cancer Surgery.

Journal of Alternative and Complementary Medicine. 2011 01 Dec 2011; 1712: 1157-1164.

OBJECTIVES: The purpose of this pilot study was to gather information on the immediate and short-term effects of relaxation training according to the Yoga In Daily Life system on the self-esteem of patients with breast cancer. **DESIGN:** This is a parallel-groups design. **SETTINGS/LOCATION:** Baseline interventions took place at the Institute for Oncology of Ljubljana (Slovenia). At discharge, the experimental group was issued with audio-cassette recordings containing the instructions for relaxation training to be practiced individually at home for an additional 3 weeks. **SUBJECTS:** The convenience sample of 32 patients with breast cancer was recruited from an accessible population of hospitalized women. Patients were randomized to the experimental (n=16) and to the control group (n=16). **INTERVENTIONS:** Both groups received the same standard physiotherapy for 1 week, while the experimental group additionally received a group relaxation training sessions according to the Yoga in Daily Life system. At discharge, the experimental group was issued with audiocassette recordings containing similar instructions for relaxation training to be practiced individually at home for an additional 3 weeks. **OUTCOME MEASURES:** Outcome measures were obtained by blinded investigators (physiotherapists) using standardized questionnaires (Rosenberg Self-Esteem Scale) at baseline (after the surgery); at 1 week (1 week postattendance; at discharge); and at 4 weeks (4 weeks postattendance); prior the commencement of radiation.

RESULTS: Analysis of variance showed that there were statistically significant differences between the experimental and control group in all measuring self-esteem scores over the study period (p<0.05).

CONCLUSIONS: The results indicate that relaxation training according to the Yoga in Daily Life system could be a useful clinical physiotherapy intervention for patients who have breast cancer and who are experiencing low self-esteem. Although this kind of relaxation training can be applied to clinical oncology in Slovenia, more studies need to be done.

COLORECTAL CANCER

Boyle, T, J. Heyworth, F. Bull, et al.

Timing and Intensity of Recreational Physical Activity and the Risk of Subsite-Specific Colorectal Cancer.

Cancer Causes and Control. 2011 December 2011; 2212: 1647-1658.

PURPOSE: Although there is convincing evidence that physical activity reduces colon cancer risk, there are important questions that remain unanswered about the association. These include the timing and intensity of activity required to optimally reduce risk, and whether physical activity has a different effect on cancers at different sites within the colon. We conducted a case-control study to investigate these issues. **METHODS:** A case-control study of colorectal cancer was conducted in Western Australia in 2005-2007. Data were collected on various risk factors. The estimated effects of recreational physical activity on the risk of cancers of the distal colon, proximal colon, and rectum were analyzed using multinomial logistic regression. This analysis included 870 cases and 996 controls.

RESULTS: The risk of distal colon cancer was reduced by performing a high level of vigorous-intensity activity between the ages 19 and 34 years (women), 35 and 50 years (men), after the age of 51 years (men and women), and consistently over the adult lifetime (men and women). The risk of rectal cancer was reduced by performing a high level of vigorous activity between the ages 35 and 50 years (men), and consistently over the adult lifetime (men). Proximal colon cancer risk was not associated with physical activity in any of the age periods or over the adult lifetime. Moderate intensity activity did not reduce the risk of colorectal cancer.

CONCLUSION: Physical activity may have a greater effect on the risk of distal colon cancer than proximal colon cancer. Vigorous physical activity is required to reduce colorectal cancer risk.



Lynch, BM, E. Cerin, N. Owen, et al.

E-VERSION EXTRA

Television Viewing Time of Colorectal Cancer Survivors is Associated Prospectively with Quality of Life.

Cancer Causes and Control. 2011 August 2011; 228: 1111-1120.

OBJECTIVE: To examine prospective associations of television viewing time with quality of life, following a colorectal cancer diagnosis. **METHODS:** One thousand, nine hundred and sixty-six colorectal cancer survivors were recruited through the Queensland Cancer Registry. Interviews were conducted at 5, 12, 24, and 36 months post-diagnosis. Generalized linear mixed models estimated the effects of television viewing time on quality of life.

RESULTS: Participants who watched >5 h of television per day had a 16% lower total quality of life score than did participants reporting <2 h per day. Deleterious associations of television viewing time were found with all quality of life subscales: functional well-being showed the strongest association (23% difference in quality of life scores between highest and lowest television viewing categories), and social well-being the weakest association (6% difference). Participants who increased their television viewing by one category (e.g., <2 h, increasing to 3-4 h per day) had a proportional decrease of some 6% in their quality of life score (intra-individual effect).

CONCLUSIONS: The deleterious associations of television viewing time with quality of life were clinically significant and consistent over time. Decreasing sedentary behavior may be an important behavioral strategy to enhance the quality of life of cancer survivors.

OLIVE OIL

Psaltopoulou, T, R. I. Kostis, D. Haidopoulos, et al.

Olive Oil Intake is Inversely Related to Cancer Prevalence: A Systematic Review and a Meta-Analysis of 13,800 Patients and 23,340 Controls in 19 Observational Studies.

Lipids in Health & Disease. 2011 10127.

BACKGROUND AND AIMS: Dietary fat, both in terms of quantity and quality, has been implicated to cancer development, either positively or negatively. The aim of this work was to evaluate whether olive oil or monounsaturated fat intake was associated with the development of cancer. **METHODS:** A systematic search of relevant studies, published in English, between 1990 and March 1, 2011, was performed through a computer-assisted literature tool (i.e., Pubmed). In total 38 studies were initially allocated; of them 19 case-control studies were finally studied (13800 cancer patients and 23340 controls were included). Random effects meta-analysis was applied in order to evaluate the research hypothesis.

RESULTS: It was found that compared with the lowest, the highest category of olive oil consumption was associated with lower odds of having any type of cancer (log odds ratio = -0.41, 95%CI -0.53, -0.29, Cochran's Q = 47.52, p = 0.0002, I-sq = 62%); the latter was irrespective of the country of origin (Mediterranean or non-Mediterranean). Moreover, olive oil consumption was associated with lower odds of developing breast cancer (logOR = -0.45 95%CI -0.78 to -0.12), and a cancer of the digestive system (logOR = -0.36 95%CI -0.50 to -0.21), compared with the lowest intake.

CONCLUSION: The strength and consistency of the findings states a hypothesis about the protective role of olive oil intake on cancer risk. However, it is still unclear whether olive oil's monounsaturated fatty acid content or its antioxidant components are responsible for its beneficial effects.

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ACUPUNCTURE

Enblom, A, A. Tomasson, M. Hammar, et al.

Pilot Testing of Methods for Evaluation of Acupuncture for Emesis during Radiotherapy: A Randomised Single Subject Experimental Design.

Acupuncture in Medicine. 2011 Jun; 292: 94-102.

BACKGROUND: Many acupuncture studies are of weak methodological quality, possibly due to lack of pilot testing. This pilot study tested design features, including test of feasibility, compliance to treatment and





data collection, level of blinding success and the patients' potential perceived effects of the treatment, in preparation for an efficacy study. **METHOD:** A modified single subject experimental design was conducted. 10 cancer patients were randomised to verum penetrating acupuncture or non-penetrating sham needles for 30 min 2-3 times/week during radiotherapy over abdomen/pelvis. They answered test-retested emesis questions ($r=0.527-1.0$) covering nausea, vomiting, use of antiemetics, wellbeing and activities of daily living.

RESULTS: Overall, the patients completed 98% of the 345 emesis-questionnaire days and 101 of the 115 offered treatments. All patients believed they received verum acupuncture. 10 patients experienced antiemetic effects, seven relaxation, five pain-reduction and five experienced sleep improvement. Two types of nausea questions showed absolute concordance ($r=1.0$) (n of observations=456). Nausea was experienced by one of five verum acupuncture treated patients (duration median 0% of the radiotherapy-days) and four of five sham acupuncture treated patients (duration median 24% of the radiotherapy-days). Patients experiencing nausea rated decreased wellbeing and performance of daily activities compared to patients free from nausea.

CONCLUSIONS: All patients were blinded, complied with verum/sham treatments and data-collection, and believed they had effects of the received treatment. The methods for verum/sham treatment and data collection may thus be used in an adequately powered randomised controlled study of the effect of acupuncture for radiotherapy-induced emesis.

BLADDER CANCER

Brinkman, MT, M. R. Karagas, M. S. Zens, et al.

Intake of Alpha-Linolenic Acid and Other Fatty Acids in Relation to the Risk of Bladder Cancer: Results from the New Hampshire Case-Control Study.

Br J Nutr. 2011 Oct; 1067: 1070-1077.

BACKGROUND AND AIMS: The role of dietary fat in bladder cancer aetiology is currently unclear due to few studies, equivocal findings and a lack of information on important dietary fatty acids. The aim of the present study was to investigate the association between the intake of major dietary fats and fatty acids and the risk of bladder cancer. **METHODS:** A case-control study was conducted in New Hampshire, USA. Dietary data were collected from 322 cases and 239 controls, and OR and 95 % CI were calculated using unconditional logistic regression. Adjustment was made for potential confounders: sex, age, smoking status, pack-years smoked, cholesterol and energy intake.

RESULTS: Statistically significant reduced odds of bladder cancer were observed for high intakes (highest quartile v. lowest quartile) of α -linolenic acid (ALA) (OR 0.26, 95 % CI 0.10, 0.65; P for trend = 0.01) and vegetable fat (OR 0.39, 95 % CI 0.18, 0.86; P for trend = 0.03). Borderline statistically significant reduced odds were detected for polyunsaturated fat (OR 0.43, 95 % CI 0.19, 0.98; P for trend = 0.07) and linoleic acid (OR 0.43, 95 % CI 0.19, 0.96; P for trend = 0.06). These fats and fatty acids were highly correlated and following adjustment for each other, the only potential inverse association to remain was for ALA.

CONCLUSION: The present findings suggest that ALA may have a protective role against developing bladder cancer; however, further investigation and replication in other epidemiological studies are required. Future research should focus on the type, source and quantities of different dietary fatty acids consumed.

VITAMIN D

Davies, JR, Y.-M Chang, H. Snowden, et al.

The Determinants of Serum Vitamin D Levels in Participants in a Melanoma Case-Control Study Living in a Temperate Climate.

Cancer Causes and Control. 2011 October 2011; 2210: 1471-1482.

BACKGROUND: We report the determinants of serum levels of vitamin D in a U.K. melanoma case-control study benefitting from detailed exposure and genotyping data. **METHODS:** Sun exposure, supplemental vitamin D, and SNPs reported to be associated with serum levels were assessed as predictors of a single serum 25-hydroxyvitamin D3 measurement adjusted for season, age, sex, and body mass index.



RESULTS: Adjusted analyses showed that vitamin D levels were sub-optimal especially in the sun-sensitive individuals (-2.61 nmol/L, $p = 0.03$) and for inheritance of a genetic variant in the GC gene coding for the vitamin D-binding protein (-5.79 for heterozygotes versus wild type, $p = <0.0001$). Higher levels were associated with sun exposure at the weekend in summer (+4.71 nmol/L per tertile, $p = <0.0001$), and on hot holidays (+4.17 nmol/L per tertile, $p = <0.0001$). In smoothed scatter plots, vitamin D levels of 60 nmol/L in the non-sun-sensitive individuals were achieved after an average 6 h/day summer weekend sun exposure but not in the sun-sensitive individuals. Users of supplements had levels on average 11.0 nmol/L higher, $p = <0.0001$, and achieved optimal levels irrespective of sun exposure.

CONCLUSIONS: Sun exposure was associated with increased vitamin D levels, but levels more than 60 nmol/L were reached on average only in individuals reporting lengthy exposure (>12 h/weekend). The sun-sensitive individuals did not achieve optimal levels without supplementation, which therefore should be considered for the majority of populations living in a temperate climate and melanoma patients in particular. Inherited variation in genes such as GC is a strong factor, and carriers of variant alleles may therefore require higher levels of supplementation.

EXERCISE



Hayes, SC, R. M. Speck, E. Reimet, et al.

Does the Effect of Weight Lifting on Lymphedema Following Breast Cancer Differ by Diagnostic Method: Results from a Randomized Controlled Trial.

Breast Cancer Res Treat. 2011 November 2011; 1301: 227-234.

BACKGROUND AND AIMS: The lymphedema diagnostic method used in descriptive or intervention studies may influence results found. The purposes of this work were to compare baseline lymphedema prevalence in the physical activity and lymphedema (PAL) trial cohort and to subsequently compare the effect of the weight-lifting intervention on lymphedema, according to four standard diagnostic methods. The PAL trial was a randomized controlled intervention study, involving 295 women who had previously been treated for breast cancer, and evaluated the effect of 12 months of weight lifting on lymphedema status. **METHODS:** Four diagnostic methods were used to evaluate lymphedema outcomes: (i) interlimb volume difference through water displacement, (ii) interlimb size difference through sum of arm circumferences, (iii) interlimb impedance ratio using bioimpedance spectroscopy, and (iv) a validated self-report survey.

RESULTS: Of the 295 women who participated in the PAL trial, between 22 and 52% were considered to have lymphedema at baseline according to the four diagnostic criteria used. No between-group differences were noted in the proportion of women who had a change in interlimb volume, interlimb size, interlimb ratio, or survey score of ≥ 5 , ≥ 5 , $\geq 10\%$, and 1 unit, respectively (cumulative incidence ratio at study end for each measure ranged between 0.6 and 0.8, with confidence intervals spanning 1.0).

CONCLUSIONS: The variation in proportions of women within the PAL trial considered to have lymphoedema at baseline highlights the potential impact of the diagnostic criteria on population surveillance regarding prevalence of this common morbidity of treatment. Importantly though, progressive weight lifting was shown to be safe for women following breast cancer, even for those at risk or with lymphedema, irrespective of the diagnostic criteria used.

COFFEE

Je, Y, S. E. Hankinson, S. S. Tworoger, et al.

A Prospective Cohort Study of Coffee Consumption and Risk of Endometrial Cancer Over a 26-Year Follow-Up.

Cancer Epidemiology Biomarkers and Prevention. 2011 December 2011; 2012: 2487-2495.

BACKGROUND: Coffee has been reported to lower levels of estrogen and insulin, two hormones implicated in endometrial carcinogenesis, but prospective data on the relation between coffee consumption and risk of endometrial cancer are limited. **METHODS:** We prospectively assessed coffee consumption in relation to endometrial cancer risk in the Nurses' Health Study (NHS) with 67,470 female participants aged 34 to 59 in 1980. Cumulative average coffee intake was calculated with all available questionnaires to assess long-term effects. Cox regression models were used to calculate incidence rate ratios (RR), controlling for other risk factors.





RESULTS: Fewer than 4 cups of coffee per day were not associated with endometrial cancer risk. However, women who consumed 4 or more cups of coffee had 25% lower risk of endometrial cancer than those who consumed less than 1 cup per day (multivariable RR = 0.75; 95% CI = 0.57-0.97; P trend = 0.02). We found the similar association with caffeinated coffee consumption (RR for ≥ 4 vs. < 1 cup/d = 0.70; 95% CI = 0.51-0.95). For decaffeinated coffee consumption, a suggestive inverse association was found among women who consumed 2 or more cups per day versus < 1 cup/mo. Tea consumption was not associated with endometrial cancer risk.

CONCLUSIONS: These prospective data suggest that four or more cups of coffee per day are associated with a lower risk of endometrial cancer.

IMPACT: Drinking of coffee, given its widespread consumption, might be an additional strategy to reduce endometrial cancer risk. However, addition of substantial sugar and cream to coffee could offset any potential benefits.

STUDY OF THE MONTH

Lambe, M, A. Wigertz, H. Garmo, et al.

Impaired Glucose Metabolism and Diabetes and the Risk of Breast, Endometrial, and Ovarian Cancer.

Cancer Causes & Control. 2011 Aug; 228: 1163-1171.

BACKGROUND: Epidemiological evidence indicates that individuals with type 2 diabetes are at an increased risk of cancer. Elevated glucose levels, below the diagnostic threshold for diabetes, have also been suggested to be associated with increased cancer risks. **METHODS:** We investigated possible associations between glucose levels and the risk of breast, endometrial, and ovarian cancer in a cohort of more than 230,000 women, for which information on outcome and potential confounders was obtained by record linkage to population-based registers.

RESULTS: Diabetes was associated with an increased risk of postmenopausal breast cancer (HR = 1.22, 95% CI 1.04-1.43). An indication of a slightly elevated breast cancer risk was also found in postmenopausal women with impaired glucose metabolism (HR = 1.11, 95% CI 0.96-1.28). Diabetes (HR = 1.46, 95% CI 1.09-1.96) and impaired glucose metabolism (HR = 1.41, 95% CI 1.08-1.85) were associated with an increased risk of endometrial cancer. No associations were found between glucose levels and ovarian cancer risk. Following adjustment for BMI, estimates were attenuated for endometrial cancer, while point estimates for breast and ovarian cancer remained essentially unchanged.

CONCLUSIONS: Our results indicate that glucose levels below the diagnostic threshold for diabetes modify the risk not only of endometrial cancer but possibly also of postmenopausal breast cancer.

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