

REsearch UPDATES

FOR THE LATEST IN WORLDWIDE INTEGRATIVE CANCER CARE

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IN THIS ISSUE: Now that spring is here, it's time to get active! Some studies that emphasize the importance of physical activity are the following: Liu et al. reported that physical activity can decrease the risk of prostate cancer, Beasley and colleagues found that physical activity reduced mortality in breast cancer survivors, and Gautam and associates found that a home-based exercise intervention led to improvements for postmastectomy patients with lymphedema. Sasuzuki and colleagues found that modifiable lifestyle behaviours such as exercising, having a healthy diet, and not smoking can collectively have a large impact on preventing cancer. In other news, Suhail et al. found that vitamins C and E were helpful in restoring antioxidant balance and provided protection against chemotherapy-related side-effects. Sun et al. found that dietary intake of calcium, vitamin D, vitamin C, riboflavin and folate were associated with a lower risk of colorectal cancer, whereas dietary intake of iron may be associated with a higher risk. Tretli and associates reported

that higher levels of Vitamin D were associated with greater survival from a variety of cancers. Andersen et al. found that involvement in decision-making about treatment options including CAM use and lifestyle changes is associated with a significantly better quality of life for cancer survivors. Kligler and colleagues reported that a "healing environment" intervention (similar to InspireHealth) was significantly beneficial for cancer patients. In our study of the month, McCulloch and associates reported that Pan-Asian medicine and vitamins improved survival of lung cancer patients when compared with conventional therapy alone.



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PROSTATE CANCER

Liu, Y, F. Hu, D. Li, et al.

Does Physical Activity Reduce the Risk of Prostate Cancer? A Systematic Review and Meta-Analysis.

Eur Urol. 2011 Nov; 605: 1029-1044.

CONTEXT: Numerous observational epidemiologic studies have evaluated the association between physical activity and prostate cancer (PCa); however, the existing results are inconsistent. **OBJECTIVE:** To determine the association between physical activity and risk of PCa. **EVIDENCE ACQUISITION:** A systematic search was performed using the Medline, Embase, and Web of Science databases through 15 May 2011 to identify all English-language articles that examined the effect of physical activity on the risk of PCa. This meta-analysis was conducted according to the guidelines for the meta-analysis of observational studies in epidemiology.

EVIDENCE SYNTHESIS: This meta-analysis consisted of 88,294 cases from 19 eligible cohort studies and 24 eligible case-control studies. When data from both types of studies were combined, total physical activity (TPA) was significantly associated with a decreased risk of PCa (pooled relative risk [RR]: 0.90; 95% confidence interval [CI], 0.84-0.95). The pooled RR for occupational physical activity (OPA) and recreational physical activity (RPA) were 0.81 (95% CI, 0.73-0.91) and 0.95 (95% CI, 0.89-1.00), respectively. Notably, for TPA, we observed a significant PCa risk reduction for individuals between 20 and 45 yr of age (RR: 0.93; 95% CI, 0.89-0.97) and between 45 and 65 yr of age (RR: 0.91; 95% CI, 0.86-0.97) who performed activities but not for individuals 65 yr of age.



CONCLUSIONS: There appears to be an inverse association between physical activity and PCa risk, albeit a small one. Given that increasing physical activity has numerous other health benefits, men should be encouraged to increase their physical activity in both occupational and recreational time to improve their overall health and potentially decrease their risk of PCa.

BREAST CANCER



Beasley, JM, M. L. Kwan, W. Y. Chen, et al.

Meeting the Physical Activity Guidelines and Survival After Breast Cancer: Findings from the After Breast Cancer Pooling Project.

Breast Cancer Res Treat. 2012 January; 1312: 637-643.

BACKGROUND: The 2008 Physical Activity (PA) Guidelines recommend engaging in at least 2.5 h (10 MET-hours/week) of moderate intensity PA per week (defined as 4 METs) to reduce risk of morbidity and mortality. This analysis was conducted to investigate whether this recommendation can be extended to breast cancer survivors. **METHODS:** Data from four studies of breast cancer survivors measuring recreational PA from semi-quantitative questionnaires a median of 23 months post-diagnosis (interquartile range 18-32 months) were pooled in the After Breast Cancer Pooling Project (n = 13,302). Delayed entry Cox proportional hazards models were applied in data analysis with adjustment for age, post-diagnosis body mass index, race/ethnicity, menopausal status, TNM stage, cancer treatment, and smoking history.

RESULTS: Engaging in at least 10 MET-hours/week of PA was associated with a 27% reduction in all-cause mortality (n = 1,468 events, Hazard Ratio (HR) = 0.73, 95% CI, 0.66-0.82) and a 25% reduction in breast cancer mortality (n = 971 events, HR = 0.75, 95% CI 0.65-0.85) compared with women who did not meet the PA Guidelines (<10 MET-hours/week). Risk of breast cancer recurrence (n = 1,421 events) was not associated with meeting the PA Guidelines (HR = 0.96, 95% CI, 0.86-1.06). **CONCLUSION:** These data suggest that adhering to the PA guidelines may be an important intervention target for reducing mortality among breast cancer survivors.

Gautam, AP, A. G. Maiya and M. S. Vidyasagar.

Effect of Home-Based Exercise Program on Lymphedema and Quality of Life in Female Postmastectomy Patients: Pre-Post Intervention Study.

Journal of Rehabilitation Research and Development. 2011 48(10) (pp 1261-1268):

BACKGROUND: Lymphedema is a debilitating complication following mastectomy, affecting the arm functions and quality of life (QOL) of breast cancer patients. Studies have shown the beneficial effects of upper-limb exercises on lymphedema in clinical settings. However, there is a dearth of evidence regarding the effect of home-based exercises on lymphedema; therefore, we examined the effect of a home-based exercise program on lymphedema and QOL in postmastectomy patients. **METHODS:** Thirty-two female postmastectomy lymphedema patients participated in an individualized home-based exercise program for 8 weeks. Arm circumference, arm volume, and QOL (36-Item Short Form Health Survey) were measured before and after the program. Data were analyzed with the use of paired t-tests for circumferential and volumetric measures and Wilcoxon signed ranks tests for QOL. Significance level was set at $p < 0.01$ with Bonferroni correction ($\alpha/n = 0.05/5 = 0.01$).

RESULTS: Analysis showed a statistically significant improvement in the affected upper-limb circumference and volume (~122 mL reduction, $p < 0.001$) and in the QOL scores ($p < 0.001$) at the end of the home-based exercise program.

CONCLUSION: The individualized home-based exercise program led to improvement in affected upper-limb volume and circumference and QOL of postmastectomy lymphedema patients.





Suhail, N, N. Bilal, H. Y. Khan, et al.

Effect of Vitamins C and E on Antioxidant Status of Breast-Cancer Patients Undergoing Chemotherapy.

J Clin Pharm Ther. 2012 February 2012; 371: 22-26.

WHAT IS KNOWN AND OBJECTIVE: Reactive oxygen/nitrogen species generated by antineoplastic agents are prime suspects for the toxic side-effects of acute or chronic chemotherapy. The present study was undertaken to test whether vitamins C and E (VCE) supplementation protect against some of the harmful effects of commonly used anticancer drugs in breast-cancer patients. **METHODS:** In a randomized 5-month study, the activity of various antioxidant enzymes (superoxide dismutase, catalase, glutathione-S-transferase and glutathione reductase) and the levels of malondialdehyde and reduced glutathione were measured in forty untreated breast-cancer patients (stage II) and compared with those of healthy controls. The degree of DNA damage was also assessed in the peripheral lymphocytes of the patients by alkaline single cell gel electrophoresis. The untreated patients were then randomly assigned to either treatment with chemotherapy alone (5-fluorouracil 500 mg/m² i.v. day 1, doxorubicin 50 mg/m² i.v. day 1 and cyclophosphamide 500 mg/m² i.v. day 1, every 3 weeks for six cycles) or to the same chemotherapy regimen supplemented with VCE (vitamin C 500 mg tablet and vitamin E 400 mg gelatin capsule). On completion of the treatments, both the groups were studied again for the levels of the markers measured prior to treatment.

RESULTS AND DISCUSSION: The untreated group showed significantly lower levels of antioxidant enzymes ($P < 0001$) and reduced glutathione ($P < 0001$), and more extensive lipid peroxidation ($P < 0001$) and DNA damage than healthy controls. Similar but less pronounced patterns were observed in the patients receiving chemotherapy alone. The group of patients receiving VCE supplementation had all the marker levels moving towards normal values. Activities of superoxide dismutase, catalase, glutathione-S-transferase and glutathione reductase, and the levels of reduced glutathione were significantly increased ($P < 001$) while, the levels of malondialdehyde and DNA damage were significantly ($P < 001$) reduced in the VCE supplemented group relative to those of patients receiving chemotherapy alone as well as relative to the pretreatment levels.

WHAT IS NEW AND CONCLUSION: Co-administration of VCE restored antioxidant status, lowered by the presence of breast-cancer and chemotherapy. DNA damage was also reduced by VCE. The results suggest that VCE should be useful in protecting against chemotherapy-related side-effects and a randomized control trial to evaluate the effectiveness of VCE in breast-cancer patients using clinical outcomes would be appropriate.

LIFESTYLE

Sasazuki, S, M. Inoue, M. Iwasaki, et al.

Combined Impact of Five Lifestyle Factors and Subsequent Risk of Cancer: The Japan Public Health Center Study.

Prev Med. 2012 01 Feb 2012; 542: 112-116.

OBJECTIVE: To evaluate whether 5 combined healthy lifestyle factors (not smoking, moderate drinking, eating minimum salt-preserved foods, being physically active, and having appropriate body mass index) are associated with reduced risk of cancer. **METHODS:** Participants were enrolled in the Japan Public Health Center Study and responded to the 5-year follow-up questionnaire covering lifestyle factors in 1995-1999 at ages 45-74 years. During follow up through December 31, 2006, 3451 and 2125 cases of cancer were newly identified in men and women, respectively.

RESULTS: For men and women, a factor-dependent risk reduction was observed for healthy lifestyles and cancer development. Compared to 0-1 healthy lifestyle factors, the adjusted RRs and 95% CIs for adherence to 2, 3, 4, and 5 healthy factors were 0.86 (0.78-0.95), 0.72 (0.65-0.80), 0.61 (0.54-0.69), and 0.57 (0.45-0.72), respectively, for men (P for trend < 0.0001) and 0.86 (0.53-1.40), 0.73 (0.46-1.16), 0.68 (0.42-1.08), and 0.63 (0.39-1.01), respectively, for women (P for trend = 0.0003). Risk was reduced 14% and 9% by each one healthy lifestyle for men and women, respectively. Risk reduction was more pronounced among elderly women.

CONCLUSION: These combined lifestyle factors have a considerable impact on preventing cancer.



Ehlers, S, C. Patten, J. Cerhan, et al.

E-VERSION EXTRA

Modifiable Unhealthy Lifestyle Behaviors among Pre-Transplant Hematologic Cancer Survivors: Change since Diagnosis and Receipt of Provider Advice to Change.

Psycho-Oncology. Conference: 9th Annual Conference of the American Psychosocial Oncology Society, APOS Miami, FL United States. Conference Start: 20120223 Conference End: 20120225. Conference Publication: (var.pagings). 2012 February 2012; 213.

PURPOSE: Modifiable unhealthy lifestyle behaviors are leading preventable causes of death, disability, and disease in the general population. Evidence is building to link these behaviors to cancer survivor outcomes. **METHODS:** Using baseline data from a prospective study, we examined change since diagnosis across lifestyle behaviors, including tobacco use, alcohol use, physical activity, and fruit and vegetable intake among a sample of 303 adult survivors preparing for Hematopoietic Stem Cell Transplantation (HSCT). Participants were predominantly married, Caucasian, and seeking HSCT for the treatment of multiple myeloma, non-Hodgkin lymphoma, acute leukemias, and also amyloidosis, representing approximately 90% of a large HSCT program.

RESULTS: Since their transplant related diagnosis, survivors recalled that fruit and vegetable consumption stayed the same or increased for nearly 90% of survivors, while physical activity decreased or stayed the same for 90% of survivors. BMI decreased or stayed the same for nearly 80% of survivors. In regard to tobacco and alcohol use within the year before transplant evaluation, only 17% reported tobacco use and 58% reported alcohol use. The majority of these sub-samples decreased use of both tobacco and alcohol. A minority of survivors reported receipt of provider advice to change behaviors or lose weight, ranging from 21% to 29% of non-substance use guidelines, and 6.0-20% of substance use guidelines. Among the sub-sample of survivors not meeting all four behavioral guidelines (physical activity, fruit and vegetable, tobacco, alcohol), 42.8% reported receipt of advice to change at least one behavior. This proportion did not differ by age, gender, marital status, performance status, or disease type.

CONCLUSIONS: Over 95% of survivors preparing for transplant do not meet all American Cancer Society guidelines for physical activity, fruit and vegetable consumption, tobacco use, and alcohol use. Less than half reported receipt of advice to change these behaviors, but significant improvements were documented for change in nutrition and substance use behaviors. Physical activity significantly decreased.

RESEARCH IMPLICATIONS: These results support preparation for transplant (and other medical events) as a largely untapped teachable moment for positive lifestyle change. Results highlight the need for behavioral intervention development and routine assessment of health behaviors. Future studies should examine survivor health outcomes in relation to guideline adherence, survivor intervention preferences, multiple versus single behavior interventions, and Survivor Care Plans as intervention platforms.

CLINICAL IMPLICATIONS: Health behaviors such as tobacco use, alcohol use, physical activity, and nutrition represent intervention targets that promote optimal cancer treatment outcomes. Most survivors report they have not received advice to change their lifestyle behaviors, and thus may benefit from educational and behavioral interventions to promote health.

COLORECTAL CANCER

Sun, Z, Y. Zhu, P. P. Wang, et al.

Reported Intake of Selected Micronutrients and Risk of Colorectal Cancer: Results from a Large Population-Based Case-Control Study in Newfoundland, Labrador and Ontario, Canada.

Anticancer Res. 2012 February 2012; 322: 687-696.

AIM: The impact of micronutrient intake and colorectal cancer (CRC) risk is poorly understood. The objective of this study was to evaluate the associations of selected micronutrients with risk of incident CRC in study participants from Newfoundland, Labrador (NL) and Ontario (ON), Canada. **MATERIALS AND METHODS:** We conducted a population-based study among 1760 case participants and 2481 age- and sex-matched control participants. Information on diet and other lifestyle factors were measured using a food frequency questionnaire and a personal history questionnaire. Odds ratios (OR) and 95% confidence intervals (CI) were calculated using unconditional logistic regression, controlling for covariables.

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RESULTS: Highest compared to lowest quartile intakes of certain micronutrients were associated with lower risk of CRC, including: calcium (from food and supplements (FS), OR=0.59; 95% CI=0.45-0.77, and from food only (FO): OR=0.76, 95% CI=0.59-0.97), vitamin C (FS:OR=0.67; 95%CI:0.51-0.88), vitamin D (FS: OR=0.73; 95% CI: 0.57-0.94, FO: OR=0.79, 95% CI=0.62-1.00), riboflavin (FS: OR=0.61; 95% CI=0.47-0.78, and folate (FS: OR=0.72; 95% CI=0.56-0.92). Higher risk of CRC was observed for iron intake (highest versus lowest quintiles: OR=0.34, 95% CI=1.01-1.78).

CONCLUSION: This study presents evidence that dietary intake of calcium, vitamin D, vitamin C, riboflavin and folate are associated with a lower risk of incident CRC and that dietary intake of iron may be associated with a higher risk of the disease.

VITAMIN D

Tretli, S, G. G. Schwartz, P. A. Torjesen and T. E. Røsbjerg.

Serum Levels of 25-Hydroxyvitamin D and Survival in Norwegian Patients with Cancer of Breast, Colon, Lung, and Lymphoma: A Population-Based Study.

Cancer Causes and Control. 2012 February 2012; 232: 363-370.

PURPOSE: We investigated the association between serum levels of 25-hydroxyvitamin D (25-OHD) and risk of death in Norwegian cancer patients. **METHODS:** The study population was 658 patients with cancers of the breast (n = 251), colon (n = 52), lung (n = 210), and lymphoma (n = 145), obtained from JANUS, a population-based serum bank in Norway. Serum samples were collected within 90 days of cancer diagnosis and were analyzed for 25-OHD. Patients were diagnosed during 1984-2004 and were followed for death throughout 2008. We used Cox regression models to assess the relationship between serum 25-OHD and risk of death.

RESULTS: Three hundred and ninety-nine patients died during follow-up, of whom 343 (86%) died from cancer. Adjusted for sex, age at diagnosis, and season of blood sampling, patients with 25-OHD levels below 46 nmol/L at diagnosis experienced shorter survival. Compared to patients in the lowest quartile of serum 25-OHD, the risk of cancer death among patients in the highest quartile was significantly reduced (HR 0.36 95% CI 0.27, 0.51). The estimated change in risk of cancer death was most pronounced between the first and the second quartile. The associations between 25-OHD levels and survival were observed for all four cancers.

CONCLUSIONS: Higher circulating serum levels of 25-OHD were positively associated with the survival for cancers of the breast, colon, lung, and lymphoma.

OVARIAN CANCER

Andersen, MR, E. Sweet, K. A. Lowe, et al.

Involvement in Decision-Making about Treatment and Ovarian Cancer Survivor Quality of Life.

Gynecol Oncol. 2012 March 2012; 1243: 465-470.

PURPOSE: This study sought to better understand the long-term effects on women's health related quality of life (HRQOL) of involvement in decision-making about their surgical and chemotherapeutic treatments for ovarian cancer treatment and about follow-up care after treatment. **METHODS:** Using a cross-sectional survey design, a sample of 219 ovarian cancer patient/survivors from Western Washington who were between 3 months and ten years post-diagnosis were recruited via a mailed survey sent by their gynecological oncologist and interviewed about their ovarian cancer treatment, use of Complementary and Alternative Medicine (CAM), Health related quality of life, and their involvement in decision-making about their cancer treatment and follow-up care.

RESULTS: Multivariate regression analyses revealed age, but not stage of cancer to be a significant predictor of perceived involvement in decision-making about ovarian cancer treatment and follow-up. Age also predicted CAM use with older patients using herbal CAM, and younger patients using CAM activities and CAM providers (p < 0.5). Controlling for demographic, disease, and treatment characteristics involvement in decision-making about surgery and follow-up care were associated with better mental



health in survivorship ($p < 0.05$). Involvement in decision-making about use of CAM and about lifestyle health changes was associated with greater vitality and better role-emotional health in survivorship (respectively; both; $p < 0.05$).

CONCLUSIONS: As has been found in studies of breast cancer survivors, perceived involvement in decision-making about ovarian cancer treatment including surgery and follow-up care after treatment is associated with better quality of life for cancer survivors. Involvement in decision-making about the use of CAM and about changes in lifestyle health practices also appear to help survivor's emotional health related quality of life. Prospective studies are needed to determine the mechanisms by which perceived involvement in decision-making about treatment might influence survivor quality of life.

OPTIMAL HEALING ENVIRONMENT

Kligler, B, P. Homel, L. B. Harrison, et al.

Impact of the Urban Zen Initiative on Patients' Experience of Admission to an Inpatient Oncology Floor: A Mixed-Methods Analysis.

Journal of Alternative & Complementary Medicine. 2011 Aug; 178: 729-734.

PURPOSE: The purpose of this study was to evaluate the impact of the Urban Zen Initiative, an "optimal healing environment" intervention, at Beth Israel Medical Center on both quantitative and qualitative measures of the experience of patients admitted for inpatient oncology care. **MATERIALS AND METHODS:** A quasi-experimental design was used comparing a baseline sample of patients admitted to the oncology floor before the intervention to a similar group admitted during the intervention. Data collected included the Profile of Mood States, the EuroQol-5D (EQ-5D), and, on a subset of patients, a semistructured qualitative interview.

RESULTS: Patients in the intervention group experienced significantly less emotional distress during their stay when compared to patients in the baseline group. There were also significantly greater improvements in pain and discomfort during the stay in the treatment group as compared to controls. The qualitative analysis described a number of possible explanations for this change including increased sense of connection and control as well as specific techniques for symptom relief.

CONCLUSIONS: It is possible to improve the experience of patients admitted for inpatient cancer care with a "healing environment" intervention. Further studies are needed that incorporate randomized design and the ability to examine specific components of the intervention independently as well as the impact of the intervention as a whole.

STUDY OF THE MONTH

McCulloch, M, M. Broffman, M. Van Der Laan, et al.

Lung Cancer Survival with Herbal Medicine and Vitamins in a Whole-Systems Approach: Ten-Year Follow-Up Data Analyzed with Marginal Structural Models and Propensity Score Methods.

Integrative Cancer Therapies. 2011 September 2011; 103: 260-279.

BACKGROUND: Complementary and alternative medicines are used by up to 48% of lung cancer patients but have seen little formal assessment of survival efficacy. **METHODS:** In this 10-year retrospective survival study, the authors investigated Pan-Asian medicine + vitamins (PAM+V) therapy in a consecutive case series of all non-small-cell lung cancer patients ($n = 239$) presenting at a San Francisco Bay Area Chinese medicine center (Pine Street Clinic). They compared short-term treatment lasting the duration of chemotherapy/radiotherapy with long-term therapy continuing beyond conventional therapy. They also compared PAM+V plus conventional therapy with conventional therapy alone, using concurrent controls from the Kaiser Permanente Northern California and California Cancer Registries. They adjusted for confounding with Kaplan-Meier, Cox regression, and newer methods-propensity score and marginal structural models (MSMs), which when analyzing data from observational studies or clinical practice records can provide results comparable with randomized trials.



RESULTS: Long-term use of PAM+V beyond completion of chemotherapy reduced stage IIIB deaths by 83% and stage IV by 72% compared with short-term use only for the duration of chemotherapy. Long-term PAM+V combined with conventional therapy reduced stage IIIA deaths by 46%, stage IIIB by 62%, and stage IV by 69% compared with conventional therapy alone. Survival rates for stage IV patients treated with PAM+V were 82% at 1 year, 68% at 2 years, and 14% at 5 years.

CONCLUSIONS: PAM+V combined with conventional therapy improved survival in stages IIIA, IIIB, and IV, compared with conventional therapy alone. Prospective trials using PAM+V with conventional therapy for lung cancer patients are justified.



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