



REsearch UPDATES

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IN THIS ISSUE: Soy isoflavones can serve a variety of purposes – Ahmad et al. found that soy isoflavones can reduce adverse side effects of radiation in patients with prostate cancer and Kang et al. found that higher intake of soy isoflavones was associated with a lower risk of recurrence in postmenopausal breast cancer patients.

Vitamin D is also very important – Bakhru et al. found that vitamin D deficiency is linked to the development of ovarian cancer in women living at certain latitudes, and Drake et al. found that lower levels of vitamin D were associated with poorer survival outcomes in patients with Non-Hodgkin's Lymphoma. Schmitz et al. found that exercise was beneficial for improving physical functioning and quality of life of cancer patients, but in our study of the month, Smith and Chagpar found that breast cancer survivors are no more likely to adhere to physical activity guidelines than the general public.

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PROSTATE CANCER



Ahmad, IU, J. D. Forman, F. H. Sarkar, et al.

Soy Isoflavones in Conjunction with Radiation Therapy in Patients with Prostate Cancer

Nutr Cancer. October 2010; 627: 996-1000.

BACKGROUND: Soy isoflavones sensitize prostate cancer cells to radiation therapy by inhibiting cell survival pathways activated by radiation. At the same time, soy isoflavones have significant antioxidant and anti-inflammatory activity, which may help prevent the side effects of radiation. Therefore, we hypothesized that soy isoflavones could be useful when given in conjunction with curative radiation therapy in patients with localized prostate cancer. In addition to enhancing the efficacy of radiation therapy, soy isoflavones could prevent the adverse effects of radiation. **METHODS:** We conducted a pilot study to investigate the effects of soy isoflavone supplementation on acute and subacute toxicity (6 mo) of external beam radiation therapy in patients with localized prostate cancer. Forty-two patients with prostate cancer were randomly assigned to receive 200 mg soy isoflavone (Group 1) or placebo (Group 2) daily for 6 mo beginning with the first day of radiation therapy, which was administered in 1.8 to 2.5 Gy fractions for a total of 73.8 to 77.5 Gy. Adverse effects of radiation therapy on bladder, bowel, and sexual function were assessed by a self-administered quality of life questionnaire at 3 and 6 mo.

RESULTS: Only 26 and 27 patients returned completed questionnaires at 3 and 6 mo, respectively. At each time point, urinary, bowel, and sexual adverse symptoms induced by radiation therapy were decreased in the soy isoflavone group compared to placebo group. At 3 mo, soy-treated patients had less urinary incontinence, less urgency, and better erectile function as compared to the placebo group. At 6 mo, the symptoms in soy-treated patients were further improved as compared to the placebo group. These patients had less dripping/leakage of urine (7.7% in Group 1 vs. 28.4% in Group 2), less rectal cramping/diarrhea (7.7% vs. 21.4%), and less pain with bowel movements (0% vs. 14.8%) than placebo-treated patients. There was also a higher overall ability to have erections (77% vs. 57.1%).

CONCLUSION: The results suggest that soy isoflavones taken in conjunction with radiation therapy could reduce the urinary, intestinal, and sexual adverse effects in patients with prostate cancer.



OVARIAN CANCER

Bakhru, A, J. B. Mallinger, R. J. Buckanovich and J. J. Griggs.

Casting Light on 25-Hydroxyvitamin D Deficiency in Ovarian Cancer: A Study from the NHANES

Gynecol Oncol. 2010; 1192:314-318.

OBJECTIVES: Ecological studies have long described a higher incidence of ovarian cancer in more extreme latitudes, where sun exposure, and presumably vitamin D exposure, is lower. Basic science studies have also noted polymorphisms of the vitamin D receptor in ovarian cancers. The aim of this study is to examine the relationship of serum vitamin D to ovarian cancer. **METHODS:** A case-control study of 7273 subjects from the National Health and Nutrition Examination Surveys (NHANES) was performed. Serum 25-hydroxyvitamin D (25[OH]D) levels were examined in both ovarian cancer patients and a control population. Logistic regression examined the odds of ovarian cancer for those with vitamin D levels below the median of the U.S. population.

RESULTS: Ovarian cancer cases were more than three times more likely to have low 25[OH]D levels (OR 3.68, 95% CI 1.03-13.21, $p = 0.04$). In the weighted multivariate model, the relationship persisted after adjusting for potential confounders, including age, body mass index, and diet. Adjusting for significant covariates, which included age and dietary calcium intake, ovarian cancer cases were nearly four times more likely to have low 25[OH]D levels (OR 3.92, 95% CI 1.11-13.85, $p = 0.03$).

CONCLUSIONS: Prevalent ovarian cancer cases have lower serum 25-hydroxyvitamin D (25[OH]D) than the general population. Deficiency in vitamin D may provide an etiologic link between the long-known ecologic findings regarding latitude and the basic science noting polymorphisms in the vitamin D receptor.

NON-HODGKIN'S LYMPHOMA

Drake, MT, M. J. Maurer, B. K. Link, et al.

Vitamin D Insufficiency and Prognosis in Non-Hodgkin's Lymphoma

Journal of Clinical Oncology: official journal of the American Society of Clinical Oncology. Sep 2010; 2827:4191-4198.

PURPOSE: Vitamin D insufficiency is common in the United States, with low levels linked in some studies to higher cancer incidence, including non-Hodgkin's lymphoma (NHL). Recent data also suggest that vitamin D insufficiency is related to inferior prognosis in some cancers, although there are no data for NHL.

PATIENTS AND METHODS: We tested the hypothesis that circulating 25-hydroxyvitamin D [25(OH)D] levels are predictive of event-free survival (EFS) and overall survival (OS) in a prospective cohort of 983 newly diagnosed patients with NHL. 25(OH)D and 1,25-dihydroxyvitamin D [1,25(OH)(2)D] levels were measured by liquid chromatography-tandem mass spectrometry.

RESULTS: Mean age at diagnosis was 62 years (range, 19 to 94 years); 44% of patients had insufficient 25(OH)D levels (< 25 ng/mL) within 120 days of diagnosis. Median follow-up was 34.8 months; 404 events and 193 deaths (168 from lymphoma) occurred. After adjusting for known prognostic factors and treatment, 25(OH)D insufficient patients with diffuse large B-cell lymphoma (DLBCL) had inferior EFS (hazard ratio [HR], 1.41; 95% CI, 0.98 to 2.04) and OS (HR, 1.99; 95% CI, 1.27 to 3.13); 25(OH)D insufficient patients with T-cell lymphoma also had inferior EFS (HR, 1.94; 95% CI, 1.04 to 3.61) and OS (HR, 2.38; 95% CI, 1.04 to 5.41). There were no associations with EFS for the other NHL subtypes. Among patients with DLBCL and T-cell lymphoma, higher 1,25(OH)(2)D levels were associated with better EFS and OS, suggesting that any putative tumor 1-alpha-hydroxylase activity did not explain the 25(OH)D associations.

CONCLUSION: 25(OH)D insufficiency was associated with inferior EFS and OS in DLBCL and T-cell lymphoma. Whether normalizing vitamin D levels in these patients improves outcomes will require testing in future trials.



BREAST CANCER

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 Oct 18. [Epub ahead of print];

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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.

Rada, G, D. Capurro, T. Pantoja, et al.

Non-Hormonal Interventions for Hot Flashes in Women with a History of Breast Cancer

Cochrane Database of Systematic Reviews. 2010 9004923.

BACKGROUND: Hot flashes are common in women with a history of breast cancer. Hormonal therapies are known to reduce these symptoms but are not recommended in women with a history of breast cancer due to their potential adverse effects. The efficacy of non-hormonal therapies is still uncertain. **OBJECTIVES:** To assess the efficacy of non-hormonal therapies in reducing hot flashes in women with a history of breast cancer. **SEARCH STRATEGY:** We searched the Cochrane Breast Cancer Group Specialised Register, CENTRAL (The Cochrane Library), MEDLINE, EMBASE, LILACS, CINAHL, PsycINFO (August 2008) and WHO ICTRP Search Portal. We handsearched reference lists of reviews and included articles, reviewed conference proceedings and contacted experts. **SELECTION CRITERIA:** Randomized controlled trials (RCTs) comparing non-hormonal therapies with placebo or no therapy for reducing hot flashes in women with a history of breast cancer. **DATA COLLECTION AND ANALYSIS:** Two authors independently selected potentially relevant studies, decided upon their inclusion and extracted data on participant characteristics, interventions, outcomes and the risk of bias of included studies.

MAIN RESULTS: Sixteen RCTs met our inclusion criteria. We included six studies on selective serotonin (SSRI) and serotonin-norepinephrine (SNRI) reuptake inhibitors, two on clonidine, one on gabapentin, two each on relaxation therapy and homeopathy, and one each on vitamin E, magnetic devices and acupuncture. The risk of bias of most studies was rated as low or moderate. Data on continuous outcomes were presented inconsistently among studies, which precluded the possibility of pooling the results. Three pharmacological treatments (SSRIs and SNRIs, clonidine and gabapentin) reduced the number and severity of hot flashes. One study assessing vitamin E did not show any beneficial effect. One of two studies on



relaxation therapy showed a significant benefit. None of the other non-pharmacological therapies had a significant benefit. Side-effects were inconsistently reported.

AUTHORS' CONCLUSIONS: Clonidine, SSRIs and SNRIs, gabapentin and relaxation therapy showed a mild to moderate effect on reducing hot flushes in women with a history of breast cancer.

LUNG CANCER

Lam, TK, I. Ruczinski, K. J. Helzlsouer, et al.

Cruciferous Vegetable Intake and Lung Cancer Risk: A Nested Case-Control Study Matched on Cigarette Smoking

Cancer Epidemiology Biomarkers and Prevention. October 2010; 19(10): 2534-2540.

BACKGROUND: Due predominantly to cigarette smoking, lung cancer is the leading cancer-related cause of death worldwide. Cruciferous vegetables may reduce lung cancer risk. The association between intake of cruciferous vegetables and lung cancer risk was investigated in the CLUE II study, a community-based cohort established in 1989. **METHODS:** We matched 274 incident cases of lung cancer diagnosed from 1990 to 2005 to 1,089 cancer-free controls on age, sex, and cigarette smoking. Dietary information was collected at baseline. Multivariable odds ratios (OR) and 95% confidence intervals (95% CI) were calculated using conditional logistic regression.

RESULTS: Intake of cruciferous vegetables was inversely associated with lung cancer risk (highest-versus lowest fourth: OR_{Q4vsQ1} , 0.57; 95% CI, 0.38-0.85; P-trend = 0.01). The inverse associations held true for former smokers (OR_{Q4vsQ1} , 0.49; 95% CI, 0.27-0.92; P-trend = 0.05) and current smokers (OR_{Q4vsQ1} , 0.52; 95% CI, 0.29-0.95; P-trend = 0.02).

CONCLUSIONS: After carefully controlling for cigarette smoking, higher intake of cruciferous vegetable was associated with lower risk of lung cancer.

IMPACT: The observed inverse association coupled with accumulating evidence suggests that intake of cruciferous vegetables is inversely associated with lung cancer risk, and this association seems to hold true beyond the confounding effects of cigarette smoking.

CERVICAL CANCER

Lee, C., S.-F Yang, C.-Y Peng, et al.

The Precancerous Effect of Emitted Cooking Oil Fumes on Precursor Lesions of Cervical Cancer

International Journal of Cancer. 15 Aug 2010; 127(4): 932-941.

BACKGROUND: Although cooking emission from high-temperature frying has been deemed a Group 2A carcinogen by the International Agency for Research on Cancer, little is known about its impact on cervical tumorigenesis. **METHODS:** To investigate the precancerous consequence of cooking oil fumes on cervical intraepithelial neoplasm (CIN), a community-based case-control study, which takes all known risk factors into consideration, was conducted in Taiwan. From 2003 to 2008, in a Pap smear screening and biopsy examination network, 206 pathology-verified women with inflammations/atypical squamous cells of undetermined significance or CIN grade-1 (CIN1) and 73 with CIN2-3 (defined as low-grade squamous intraepithelial lesions (LGSIL) and high-grade squamous intraepithelial lesions (HGSIL), respectively); and 1,200 area-and-age-matched controls with negative cytology were recruited. Multinomial logistic regression was applied in the multivariate analysis to determine the likelihood of contracting LGSIL or HGSIL.

RESULTS: The risks of the two lesions increased with the increase of carcinogenic high-risk human papillomavirus DNA load, with a clear dose-response relationship. Chefs were observed to experience a 7.9-fold elevated HGSIL risk. Kitchens with poor fume ventilation during the main cooking life-stage correlated to a 3.7-fold risk of HGSIL, but not for LGSIL. More than 1 hr of daily cooking in kitchens with poor fume conditions appeared to confer an 8.4-fold HGSIL risk, with an 8.3-fold heterogeneously higher odds ratio than that (aOR = 1.0) for LGSIL. Similar risk pattern has been reproduced among never-smoking women.

CONCLUSION: Our findings demonstrate the association between indoor exposure to cooking fumes from



heated oil and the late development of cervical precancerous lesions. This final conclusion needs to be verified by future research.

Muecke, R, L. Schomburg, M. Glatzel, et al.

Multicenter, Phase 3 Trial Comparing Selenium Supplementation with Observation in Gynecologic Radiation Oncology

Int J Radiat Oncol Biol Phys. 2010 Nov 1; 783: 828-835.

PURPOSE: We assessed whether adjuvant supplementation with selenium improves the selenium status and reduces side effects of patients treated by radiotherapy (RT) for cervical and uterine cancer. **METHODS AND MATERIALS:** Whole-blood selenium concentrations were measured in patients with cervical cancer (n = 11) and uterine cancer (n = 70) after surgical treatment, during RT, at the end of RT, and 6 weeks after RT. Patients with initial selenium concentrations of less than 84µg/L were randomized before RT either to receive 500µg of selenium (in the form of sodium selenite [selenase, biosyn Arzneimittel GmbH, Fellbach, Germany]) by mouth on the days of RT and 300µg of selenium on the days without RT or to receive no supplement during RT. The primary endpoint of this multicenter Phase 3 study was to assess the efficiency of selenium supplementation during RT; the secondary endpoint was to decrease radiation-induced diarrhea and other RT-dependent side effects.

RESULTS: A total of 81 patients were randomized. We enrolled 39 in the selenium group (SG) and 42 in the control group (CG). Selenium levels did not differ between the SG and CG upon study initiation but were significantly higher in the SG at the end of RT. The actuarial incidence of diarrhea of Grade 2 or higher according to Common Toxicity Criteria (version 2) in the SG was 20.5% compared with 44.5% in the CG (p = 0.04). Other blood parameters, Eastern Cooperative Oncology Group performance status, and self-reported quality of life were not different between the groups.

CONCLUSIONS: Selenium supplementation during RT is effective in improving blood selenium status in selenium-deficient cervical and uterine cancer patients and reduces the number of episodes and severity of RT-induced diarrhea.

EXERCISE

Schmitz KH. Courneya KS. Matthews C. et al.

American College of Sports Medicine Roundtable on Exercise Guidelines for Cancer Survivors

Medicine & Science in Sports & Exercise. 2010 Jul; 427: 1409-1426.

BACKGROUND: Early detection and improved treatments for cancer have resulted in roughly 12 million survivors alive in the United States today. This growing population faces unique challenges from their disease and treatments, including risk for recurrent cancer, other chronic diseases, and persistent adverse effects on physical functioning and quality of life. Historically, clinicians advised cancer patients to rest and to avoid activity; however, emerging research on exercise has challenged this recommendation. **METHODS:** To this end, a roundtable was convened by American College of Sports Medicine to distill the literature on the safety and efficacy of exercise training during and after adjuvant cancer therapy and to provide guidelines.

RESULTS: The roundtable concluded that exercise training is safe during and after cancer treatments and results in improvements in physical functioning, quality of life, and cancer-related fatigue in several cancer survivor groups.

CONCLUSION: Implications for disease outcomes and survival are still unknown. Nevertheless, the benefits to physical functioning and quality of life are sufficient for the recommendation that cancer survivors follow the 2008 Physical Activity Guidelines for Americans, with specific exercise programming adaptations based on disease and treatment-related adverse effects. The advice to "avoid inactivity," even in cancer patients with existing disease or undergoing difficult treatments, is likely helpful.



STUDY OF THE MONTH

Smith, SG and A. B. Chagpar.

Adherence to Physical Activity Guidelines in Breast Cancer Survivors

Am Surg. 2010 Sep; 769:962-965.

BACKGROUND: Physical activity in breast cancer survivors has been shown to improve outcomes. **METHODS:** This study evaluated breast cancer patients' adherence to physical activity guidelines in a population-based study. Data from the 2007 National Health Interview Survey were used to compare adherence to physical activity guidelines in patients with breast cancer with the general population. Statistical analyses were performed using SUDAAN software.

RESULTS: In 2007, 327 breast cancer survivors and 23,030 others from the general population were surveyed. Breast cancer survivors were significantly older than the general population (mean age 64.9 vs. 45.6 years, $P < 0.001$) and tended to be female (99.4 vs. 51.2%, $P < 0.001$). Despite being significantly more likely to have interacted with a healthcare professional within the past year (96.7 vs. 82.1%, $P < 0.001$), fewer breast cancer survivors reported following physical activity guidelines than nonbreast cancer survivors (4.64 vs. 12.0%, $P < 0.001$). Controlling for age, gender, and interaction with healthcare providers, breast cancer survivors were no more likely to follow physical activity guidelines than the general population (OR: 0.73; 95% CI: 0.41-1.30, $P = 0.282$).

CONCLUSION: Despite more interaction with healthcare providers, breast cancer survivors are no more likely to adhere to activity guidelines than the general population.



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