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RESEARCH UPDATES

FOR THE LATEST IN WORLDWIDE INTEGRATED CANCER CARE

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IN THIS ISSUE: In order to fight cancer, it is important to increase your vegetable and fruit intake (which decreases your risk of lung and gastric cancer according to studies by Buchner et al and Rossi et al.) and decrease your red meat intake (which increases your risk of chronic liver disease, hepatocellular carcinoma and colorectal cancer according to Freedman et al. and Squires et al.). Soy (according to Cho and associates) and vitamin D (according to Engel et al.) decrease the risk of breast cancer. Conversely, alcohol (according to Li and associates) and use of hormone replacement therapy (according to Saxena and colleagues) increase the risk.

In other areas, Yap and colleagues reported about OncoRx – a database that detects interactions between anticancer drugs and Complementary and Alternative Medicines (including Traditional Chinese Medicine), and in our study of the month Giovannucci found that vitamin D can have a protective effect against colorectal cancer.

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LUNG CANCER

Buchner, FL, H. B. Bueno-de-Mesquita, M. M. Ros, et al.

Variety in Fruit and Vegetable Consumption and the Risk of Lung Cancer in the European Prospective Investigation into Cancer and Nutrition.

Cancer Epidemiology Biomarkers and Prevention. 2010 September 2010; 199: 2278-2286.

BACKGROUND: We investigated whether a varied consumption of vegetables and fruits is associated with lower lung cancer risk in the European Prospective Investigation into Cancer and Nutrition study. **METHODS:** After a mean follow-up of 8.7 years, 1,613 of 452,187 participants with complete information were diagnosed with lung cancer. Diet diversity scores (DDS) were used to quantify the variety in fruit and vegetable consumption. Multivariable proportional hazards models were used to assess the associations between DDS and lung cancer risk. All models were adjusted for smoking behavior and the total consumption of fruit and vegetables.

RESULTS: With increasing variety in vegetable subgroups, risk of lung cancer decreases [hazard ratios (HR), 0.77; 95% confidence interval (CI), 0.64-0.94 highest versus lowest quartile; P trend = 0.02]. This inverse association is restricted to current smokers (HR, 0.73; 95% CI, 0.57-0.93 highest versus lowest quartile; P trend = 0.03). In continuous analyses, in current smokers, lower risks were observed for squamous cell carcinomas with more variety in fruit and vegetable products combined (HR/two products, 0.88; 95% CI, 0.82-0.95), vegetable subgroups (HR/subgroup, 0.88; 95% CI, 0.79-0.97), vegetable products (HR/two products, 0.87; 95% CI, 0.79-0.96), and fruit products (HR/two products, 0.84; 95% CI, 0.72-0.97).

CONCLUSION: Variety in vegetable consumption was inversely associated with lung cancer risk among current smokers. Risk of squamous cell carcinomas was reduced with increasing variety in fruit and/or vegetable consumption, which was mainly driven by the effect in current smokers.

IMPACT: Independent from quantity of consumption, variety in fruit and vegetable consumption may decrease lung cancer risk.

BREAST CANCER

Cho, YA, J. Kim, K. -S Park, et al.

Effect of Dietary Soy Intake on Breast Cancer Risk According to Menopause and Hormone Receptor Status.

Eur J Clin Nutr. 2010 September 2010; 649: 924-932.

BACKGROUND: Although high soy consumption may be associated with lower breast cancer risk in Asian populations, findings from epidemiological studies have been inconsistent. **OBJECTIVE:** We investigated the effects of soy intake on breast cancer risk among Korean women according to their menopausal and hormone receptor status. **METHODS:** We conducted a case-control study with 358 incident breast cancer patients and 360 age-matched controls with no history of malignant neoplasm. Dietary consumption of soy products was examined using a 103-item food frequency questionnaire.

RESULTS: The estimated mean intakes of total soy and isoflavones from this study population were 76.5 g per day and 15.0 mg per day, respectively. Using a multivariate logistic regression model, we found a significant inverse association between soy intake and breast cancer risk, with a dose-response relationship (odds ratios (OR) (95% confidence interval (CI)) for the highest vs the lowest intake quartile: 0.36 (0.20-0.64)). When the data were stratified by menopausal status, the protective effect was observed only among postmenopausal women (OR (95% CI) for the highest vs the lowest intake quartile: 0.08 (0.03-0.22)). The association between soy and breast cancer risk did not differ according to estrogen receptor (ER)/progesterone receptor (PR) status, but the estimated intake of soy isoflavones showed an inverse association only among postmenopausal women with ER/PR tumors.

CONCLUSIONS: Our findings suggest that high consumption of soy might be related to lower risk of breast cancer and that the effect of soy intake could vary depending on several factors.

Engel, P, G. Fagherazzi, A. Boutten, et al.

Serum 25(OH) Vitamin D and Risk of Breast Cancer: A Nested Case-Control Study from the French E3N Cohort.

Cancer Epidemiology Biomarkers and Prevention. 2010 September 2010; 199: 2341-2350.

BACKGROUND: High 25-hydroxyvitamin D [25(OH)D] serum concentrations have been found to be associated with reduced breast cancer risk. However, few studies have further investigated this relationship according to menopausal status, nor have they taken into account factors known to influence vitamin D status, such as dietary and serum calcium, parathyroid hormone, and estradiol serum levels. **METHODS:** We designed a nested case-control study within the French E3N cohort. Cases were women diagnosed with incident breast cancer (n = 636). Controls (n = 1,272) were matched with cases on age, menopausal status at blood collection, age at menopause, and center and year of blood collection. Multivariate logistic regression models were established.

RESULTS: We found a decreased risk of breast cancer with increasing 25(OH) vitamin D3 serum concentrations (odds ratio, 0.73; 95% confidence interval, 0.55-0.96; P trend = 0.02) among women in the highest tertile. We also observed a significant inverse association restricted to women under 53 years of age at blood sampling [odds ratio (T3 versus T1), 0.60; 95% confidence interval, 0.37-0.98; P trend = 0.04]. In premenopausal women, the risk was also decreased, although not significantly.

CONCLUSION: Our findings support a decreased risk of breast cancer associated with high 25(OH) vitamin D3 serum concentrations, especially in younger women, although we were unable to confirm a direct influence of age or menopausal status.

IMPACT: Randomized intervention trials with vitamin D supplementation are required to confirm its benefits on breast cancer risk, but the maintenance of adequate vitamin D levels should be encouraged by public health policy.

Li CI, Chlebowski RT, Freiberg M, Johnson KC, et al.

Alcohol Consumption and Risk of Postmenopausal Breast Cancer by Subtype: The Women's Health Initiative Observational Study.

J Natl Cancer Inst. 2010 Sep 22; 10218: 1422-1431.

BACKGROUND: Alcohol consumption is a well-established risk factor for breast cancer. This association is thought to be largely hormonally driven, so alcohol use may be more strongly associated with hormonally sensitive breast cancers. Few studies have evaluated how alcohol-related risk varies by breast cancer subtype. **METHODS:** We assessed the relationship between self-reported alcohol consumption and postmenopausal breast cancer risk among 87,724 women in the Women's Health Initiative Observational Study prospective cohort from 1993 through 1998. Multivariable adjusted Cox regression models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). All statistical tests were two-sided.

RESULTS: A total of 2944 invasive breast cancer patients were diagnosed during follow-up through September 15, 2005. In multivariable adjusted analyses, alcohol consumption was positively related to risk of invasive breast cancer overall, invasive lobular carcinoma, and hormone receptor-positive tumors (all P(trend) .022). However, alcohol consumption was more strongly related to risk of certain types of invasive breast cancer compared with others. Compared with never drinkers, women who consumed seven or more alcoholic beverages per week had an almost twofold increased risk of hormone receptor-positive invasive lobular carcinoma (HR = 1.82; 95% CI = 1.18 to 2.81) but not a statistically significant increased risk of hormone receptor-positive invasive ductal carcinoma (HR = 1.14; 95% CI = 0.87 to 1.50; difference in HRs per drink per day among current drinkers = 1.15; 95% CI = 1.01 to 1.32, P = .042). The absolute rates of hormone receptor-positive lobular cancer among never drinkers and current drinkers were, 5.2 and 8.5 per 10,000 person-years, respectively, whereas for hormone receptor-positive ductal cancer they were 15.2 and 17.9 per 10,000 person-years, respectively.

CONCLUSIONS: Alcohol use may be more strongly associated with risk of hormone-sensitive breast cancers than hormone-insensitive subtypes, suggesting distinct etiologic pathways for these two breast cancer subtypes.

Saxena, T, E. Lee, K. D. Henderson, et al.

Menopausal Hormone Therapy and Subsequent Risk of Specific Invasive Breast Cancer Subtypes in the California Teachers Study.

Cancer Epidemiology Biomarkers and Prevention. 2010 September 2010; 199: 2366-2378.

BACKGROUND: Although it is well established that combined estrogen-progestin therapy (EPT) increases breast cancer risk, questions remain regarding the effect of different formulations of hormones, whether certain women are at particularly high risk, and whether risk varies by tumor subtype. **METHODS:** We investigated hormone therapy (HT) use in relation to breast cancer risk in the California Teachers Study cohort; after a mean follow-up of 9.8 years, 2,857 invasive breast cancers were diagnosed.

RESULTS: Compared with women who had never used HT, women who reported 15 or more years of estrogen therapy (ET) use had a 19% greater risk of breast cancer (95% confidence interval, 1.03-1.37), whereas women using EPT for 15 or more years had an 83% greater risk (95% confidence interval, 1.48-2.26). Breast cancer risk was highest among women using continuous combined EPT regimens. Risks associated with EPT and ET use were increased with duration of HT use for women with a body mass index (BMI) of <29.9 kg/m2 but not for women with BMI of >=30 kg/m2. Elevated risks associated with EPT and ET use were confined to tumors that were positive for both estrogen and progesterone receptors and those that were HER2+ but were slightly diminished for HER2- tumors.

CONCLUSIONS: Breast cancer risks increased with longer duration of ET and EPT use, and risks were highest for continuous-combined EPT use. Furthermore, risks varied by BMI and tumor subtype.

IMPACT: These findings underscore the need for personalized risk-benefit discussions with women contemplating HT use.

HEPATOCELLULAR CARCINOMA

Freedman, ND, A. J. Cross, K. A. McGlynn, et al.

Association of Meat and Fat Intake with Liver Disease and Hepatocellular Carcinoma in the NIH-AARP Cohort.

J Natl Cancer Inst. 2010 08 Sep 2010; 10217: 1354-1365.

BACKGROUND: Several plausible mechanisms, including fat, iron, heterocyclic amines, and N-nitroso compounds, link meat intake with chronic liver disease (CLD) and hepatocellular carcinoma (HCC). Few studies have investigated these associations. **METHODS:** We prospectively examined the relationship between meat and associated exposures with CLD mortality (n = 551; not including HCC) and HCC incidence (n = 338) in 495006 men and women of the National Institutes of Health-AARP Diet and Health Study. Hazard ratios (HRs) and 95% confidence intervals (CIs) for the fifth (Q5) vs the first (Q1) quintile were estimated from multivariable adjusted Cox proportional hazards regression models. All tests of statistical significance were two-sided.

RESULTS: We found inverse associations between white meat and risk of CLD (HR = 0.52, 95% CI = 0.39 to 0.70, 7.5 vs 18.2 cases per 100000 person-years) and HCC (HR = 0.52, 95% CI = 0.36 to 0.77, 5.8 vs 14.3 cases per 100000 person-years). Red meat was associated with higher risk of CLD (HR = 2.59, 95% CI = 1.86 to 3.61, 22.3 vs 6.2 cases per 100000 person-years) and HCC (HR = 1.74, 95% CI = 1.16 to 2.61, 14.9 vs 5.7 cases per 100000 person-years). Among fat types, results were strongest for saturated fat (for CLD, HR = 3.50, 95% CI = 2.48 to 4.96, 23.0 vs 6.5 cases per 100000 person-years; for HCC, HR = 1.87, 95% CI = 1.23 to 2.85, 14.5 vs 6.3 cases per 100000 person-years). After mutual adjustment, risk estimates persisted for saturated fat, red meat, and white meat. Heme iron, processed meat, nitrate, and nitrite were positively associated with CLD but not with HCC. Individual heterocyclic amines, 2-amino-3,4,8-trimethylimidazo[4,5,- f]quinoxaline (DiMeIQx), 2-amino-3,8-dimethylimidazo[4,5-f] quinoxaline (MeIQx), and 2-amino-1-methyl-6-phenyl-imidazo[4,5-b] pyridine (PhIP), were not associated with either outcome.

CONCLUSION: Our results suggest that red meat and saturated fat may be associated with increased CLD and HCC risk, whereas white meat may be associated with reduced risk.

COLORECTAL CANCER

Squires, J, B. Roebothan, S. Buehler, et al.

Pickled Meat Consumption and Colorectal Cancer (CRC): A Case-Control Study in Newfoundland and Labrador, Canada.

Cancer Causes and Control. 2010 September 2010; 219: 1513-1521.

OBJECTIVE: Although a large body of epidemiological research suggests that red meat intake increases the risk of colorectal cancer, little is known regarding how such an association varies across populations and types of red meat. The objective of this study was to assess whether an association exists between the intakes of total red meat and pickled red meat and the risk of colorectal cancer in study subjects residing in Newfoundland and Labrador. **METHODS:** This case-control study of 1,204 residents of Newfoundland and Labrador was part of a larger study on colorectal cancer. Personal history food frequency questionnaires were used to collect retrospective data from 518 individuals diagnosed with colorectal cancer and 686 controls. Intakes were ranked and divided into tertiles. Logistic regression was used to examine the possible association between meat intakes and colorectal cancer diagnosis while controlling for possible confounding factors.

RESULTS: A positive, but non-statistically significant, association between total red meat intake and CRC was observed in this study. Pickled red meat consumption was found to be significantly associated with an

increased risk of CRC (men, OR = 2.07, 95% CI 1.37-3.15; women, OR = 2.51, 95% CI 1.45-4.32), the odds ratios increasing with each tertile of consumption, suggesting a dose-response effect.

CONCLUSION: Intake of pickled red meat appears to increase the risk of colorectal cancer in Newfoundland and Labrador.

ANTICANCER DRUGS AND COMPLEMENTARY AND ALTERNATIVE MEDICINES

Yap, KY, E. Y. Kuo, J. J. Lee, et al.

An Onco-Informatics Database for Anticancer Drug Interactions with Complementary and Alternative Medicines used in Cancer Treat-ment and Supportive Care: An Overview of the OncoRx Project.

Supportive Care in Cancer. 2010 Jul; 187: 883-891.

PURPOSE: Cancer patients are at high risk of manifesting interactions from use of anticancer drugs (ACDs) and complementary and alternative medicines (CAMs). These interactions can result in sub-therapeutic effects or increased toxicities which may compromise the outcome of chemotherapy. It is important for practitioners to gain convenient access to ACD-CAM interaction information so as to make better-informed decisions in daily practice. This paper describes the creation of an oncology database (OncoRx) that documents ACD-CAM interactions, including traditional Chinese medicines (TCMs) that are commonly used for cancer treatment, prevention, and supportive care therapy. **METHODS:** Information regarding ACDs, CAMs, and drug interactions were collated from 14 sources, inclusive of hardcopy and online resources, and input into a modified web server with a database engine and a programming interface using a combination of software and programming scripts.

RESULTS: OncoRx currently contains a total of 117 ACDs and 166 CAMs. Users are able to search for interactions based on various CAM uses: cancer treatment or prevention, immune-system-related, alopecia, nausea, and vomiting, peripheral neuropathy and pain, inflammation, fatigue, and non-cancer related. Pharmacokinetic data on ACDs and CAMs, characteristics of CAMs based on TCM principles, and drug interaction parameters such as effects, mechanisms, evidences, and proposed management plans, are shown in the search results.

CONCLUSION: OncoRx is an oncology database which detects ACD interactions. It is currently able to detect interactions with CAMs. It is hoped that OncoRx will serve as a useful resource to clinicians, educators, trainers, and students working in the oncology setting.

GASTRIC CANCER

Rossi, M, V. Rosato, C. Bosetti, et al.

Flavonoids, Proanthocyanidins, and the Risk of Stomach Cancer.

Cancer Causes and Control. 2010 October 2010; 2110: 1597-1604.

BACKGROUND: Flavonoids have been suggested to be responsible for the potential beneficial properties of fruit and vegetables on stomach cancer risk. **METHODS:** To provide further information on flavonoids, proanthocyanidins, and gastric cancer risk, we analyzed data from a case-control study conducted in Italy. Subjects were 230 cases with incident, histologically confirmed gastric cancer and 547 frequency-matched controls, admitted to the same hospitals of cases for acute, non-neoplastic conditions. Subjects were interviewed using a reproducible and valid food frequency questionnaire. We estimated the odds ratios (ORs) of gastric cancer and their corresponding 95% confidence intervals (CIs) using unconditional logistic regression models including terms for major recognized gastric cancer risk factors.

RESULTS: The ORs of the highest quintile of intake compared to the lowest were below unity for all classes of flavonoids, in the absence, however, of significant associations. Strong inverse relations were found for proanthocyanidins. The OR was 0.44 (95% CI, 0.25-0.76) for monomers and dimers combined and 0.36 (95%

CI, 0.21-0.63) for polymers with three or more mers. Further adjustment for fruit and vegetables, or vitamin C, did not materially change these associations.

CONCLUSION: This is the first epidemiological study to suggest that dietary proanthocyanidins have a favorable role on gastric cancer risk.

STUDY OF THE MONTH

Giovannucci, E.

Epidemiology of Vitamin D and Colorectal Cancer: Casual Or Causal Link?

Journal of Steroid Biochemistry & Molecular Biology. 2010 Jul; 1211-2: 349-354.

INTRODUCTION: Since Garland and Garland hypothesized that better vitamin D status lowered risk of colorectal cancer in 1980, the relation between vitamin D status and colorectal cancer risk has been investigated in epidemiologic studies. These studies are reviewed. **MATERIALS AND METHODS:** Various approaches have been used to estimate vitamin D status, including direct measures of circulating 25(OH)vitamin D levels, surrogates or determinants of vitamin D (including region of residence, intake, and sun exposure estimates, or a combination of these). These measures of vitamin D status have been studied in relation to colorectal adenoma, cancer incidence and mortality.

RESULTS: In general, all lines of inquiry from observational studies indicate that an association between better vitamin D status and lower colorectal cancer risk exists. While most of the studies have examined vitamin D status in relation to risk of cancer, some evidence suggests that vitamin D may be additionally important for colorectal cancer progression and mortality.

DISCUSSION: Although confounding factors cannot be entirely excluded, the consistency of the association using various approaches to measure vitamin D, for diverse endpoints and in diverse populations shows high consistency and is suggestive of a causal association. Thus, improving vitamin D status could be potentially beneficial against colorectal cancer incidence and mortality.