



RESEARCH UPDATES JUNE 2012

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FOR THE LATEST IN WORLDWIDE INTEGRATIVE CANCER CARE

IN THIS ISSUE: Mondul and colleagues reported that high cholesterol was associated with higher risk of advanced prostate cancer, and that statins might protect against this. Pettersson et al. found that dairy intake (with the exception of whole milk) after a prostate cancer diagnosis was associated with an increased risk of death. Kotsopoulos and associates found that breastfeeding protected against BRCA1-, (but not BRCA2-) associated breast cancer. Fedirko et al. reported that high prediagnostic levels of vitamin D were associated with improved survival in patients with colorectal cancer. Mekary et al. reported that men with high insulin sensitivity may be protected from colorectal cancer by eating more frequent, healthy meals. Ortiz and colleagues found that central obesity and insulin resistance were associated with the development of colorectal cancer. Jessri et al. found that a plant-based diet reduced the risk of esophageal cancer. O'Neill and associates found that exercise improved fitness and quality of life for patients with acute myeloid leukaemia. Shimazu and colleagues reported that limiting alcohol consumption reduced the risk of liver cancer. Bhandari and Rockett reported about the association between metabolic risk factors and cancer. Sharma et al. found that probiotic lozenges reduced the incidence of mucositis in patients with head and neck cancer who were receiving radiation or chemotherapy. In our study of the month, Ligibel et al. found that breast and colorectal cancer survivors experienced significant improvements in fitness and physical functioning as a result of a telephone-based physical activity intervention and lifestyle interventions are feasible in a group setting.

PROSTATE CANCER

Mondul, AM, S. J. Weinstein, J. Virtamo and D. Albanes.

Serum Total and HDL Cholesterol and Risk of Prostate Cancer.

Cancer Causes & Control. 2011 Nov; 2211: 1545-1552.

BACKGROUND: Studies suggest a decreased risk of high-grade prostate cancer in men with lower circulating total cholesterol and that statins may protect against aggressive disease. Confirmation in additional populations and examination of associations for lipoprotein subfractions are needed. **METHODS:** We examined prostate cancer risk and serum total and HDL cholesterol in the ATBC Study cohort (n = 29,093). Cox proportional hazards models were used to estimate the relative risk of total (n = 2,041), non-aggressive (n = 829), aggressive (n = 461), advanced (n = 412), and high-grade (n = 231) prostate cancer by categories of total and HDL cholesterol. **RESULTS:** After excluding the first 10 years of follow-up, men with higher serum total cholesterol were at increased risk of overall (≥ 240 vs. < 200 mg/dl: HR = 1.22, 95% CI 1.03-1.44, p-trend = 0.01) and advanced (≥ 240 vs. < 200 mg/dl: HR = 1.85, 95% CI 1.13-3.03, p-trend = 0.05) prostate cancer. Higher HDL cholesterol was suggestively associated with a decreased risk of prostate cancer regardless of stage or grade. **CONCLUSIONS:** In this population of smokers, high serum total cholesterol was associated with higher risk of advanced prostate cancer, and high HDL cholesterol suggestively reduced the risk of prostate cancer overall. These results support previous studies and, indirectly, support the hypothesis that statins may reduce the risk of advanced prostate cancer by lowering cholesterol.

Pettersson, A, J. L. Kasperzyk, S. A. Kenfield, et al.

Milk and Dairy Consumption among Men with Prostate Cancer and Risk of Metastases and Prostate Cancer Death.

Cancer Epidemiology Biomarkers and Prevention. 2012 March 2012; 213: 428-436.

BACKGROUND: Whether milk and dairy intake after a prostate cancer diagnosis is associated with a poorer prognosis is unknown. We investigated postdiagnostic milk and dairy intake in relation to risk of lethal prostate cancer (metastases and prostate cancer death) among participants in the Health Professionals Follow-Up Study. **METHODS:** The cohort consisted of 3,918 men diagnosed with apparently localized prostate cancer between 1986 and 2006, and followed to 2008. Data on milk and dairy intake were available from repeated questionnaires. We used Cox proportional hazards models to calculate HRs and 95% CIs of the association between postdiagnostic milk and dairy intake and prostate cancer outcomes. **RESULTS:** We ascertained 229 prostate cancer deaths and an additional 69 metastases during follow-up. In multivariate analysis, total milk and dairy intakes after diagnosis were not associated with a greater risk of lethal prostate cancer. Men with the highest versus lowest intake of whole milk were at an

increased risk of progression (HR = 2.15, 95% CI: 1.28-3.60; P trend = 0.07). CONCLUSIONS: With the exception of whole milk, our results suggest that milk and dairy intake after a prostate cancer diagnosis is not associated with an increased risk of lethal prostate cancer. IMPACT: This is the first larger prospective study investigating the relation between postdiagnostic milk and dairy intake and risk of lethal prostate cancer.

BREAST CANCER

Kotsopoulos, J, Lubinski, J, L. Salmena, et al.

Breastfeeding and the Risk of Breast Cancer in BRCA1 and BRCA2 Mutation Carriers.

Breast Cancer Res. 2012 March 2012; 14: R42.

INTRODUCTION: Breastfeeding has been inversely related to breast cancer risk in the general population. Clarifying the role of breastfeeding among women with a BRCA1 or BRCA2 mutation may be helpful for risk assessment and for recommendations regarding prevention. We present an updated analysis of breastfeeding and risk of breast cancer using a large matched sample of BRCA mutation carriers. METHODS: We conducted a case-control study of 1,665 pairs of women with a deleterious mutation in either BRCA1 (n = 1,243 pairs) or BRCA2 (n = 422 pairs). Breast cancer cases and unaffected controls were matched on year of birth, mutation status, country of residence and parity. Information about reproductive factors, including breastfeeding for each live birth, was collected from a routinely administered questionnaire. Conditional logistic regression was used to estimate the association between ever having breastfed, as well as total duration of breastfeeding, and the risk of breast cancer. RESULTS: Among BRCA1 mutation carriers, breastfeeding for at least one year was associated with a 32% reduction in risk (OR = 0.68; 95% CI 0.52 to 0.91; P = 0.008); breastfeeding for two or more years conferred a greater reduction in risk (OR = 0.51; 95% CI 0.35 to 0.74). Among BRCA2 mutation carriers, there was no significant association between breastfeeding for at least one year and breast cancer risk (OR = 0.83; 95% CI 0.53 to 1.31; P = 0.43). CONCLUSIONS: These data extend our previous findings that breastfeeding protects against BRCA1-, but not BRCA2-associated breast cancer. BRCA mutation carriers should be advised of the benefit of breastfeeding in terms of reducing breast cancer risk.

COLORECTAL CANCER

Fedirko, V, E. Riboli, A. Tjonneland, et al.

Prediagnostic 25-Hydroxyvitamin D, VDR and CASR Polymorphisms, and Survival in Patients with Colorectal Cancer in Western European Populations.

Cancer Epidemiology Biomarkers and Prevention. 2012 April 2012; 214: 582-593.

BACKGROUND: Individuals with higher blood 25-hydroxyvitamin D [25(OH)D] levels have a lower risk of developing colorectal cancer (CRC), but the influence of 25(OH)D on mortality after CRC diagnosis is unknown. METHODS: The association between prediagnostic 25(OH)D levels and CRC-specific (N = 444) and overall mortality (N = 541) was prospectively examined among 1,202 participants diagnosed with CRC between 1992 and 2003 in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. Multivariable Cox proportional hazards models were used to calculate HRs and corresponding 95% CIs according to 25(OH)D quintiles and genetic variation within the VDR and CASR genes. Potential dietary, lifestyle, and metabolic effect modifiers were also investigated. RESULTS: There were 541 deaths, 444 (82%) due to CRC. Mean follow-up was 73 months. In multivariable analysis, higher 25(OH)D levels were associated with a statistically significant reduction in CRC-specific (P trend = 0.04) and overall mortality (P trend = 0.01). Participants with 25(OH)D levels in the highest quintile had an adjusted HR of 0.69 (95% CI: 0.50-0.93) for CRC-specific mortality and 0.67 (95% CI: 0.50-0.88) for overall mortality, compared with the lowest quintile. Except for a possible interaction by prediagnostic dietary calcium intake (P interaction = 0.01), no other potential modifying factors related to CRC survival were noted. The VDR (FokI and BsmI) and CASR (rs1801725) genotypes were not associated with survival. CONCLUSIONS: High prediagnostic 25(OH)D levels are associated with improved survival of patients with CRC. IMPACT: Our findings may stimulate further research directed at investigating the effects of blood vitamin D levels before, at, and after CRC diagnosis on outcomes in CRC patients.

Mekary, RA, F. B. Hu, W. C. Willett, et al.

The Joint Association of Eating Frequency and Diet Quality with Colorectal Cancer Risk in the Health Professionals Follow-Up Study.

Am J Epidemiol. 2012 01 Apr 2012; 1757: 664-672.

BACKGROUND: The results of most case-control studies have suggested a positive association between eating frequency and colorectal cancer risk. Because no prospective cohort studies have done so to date, the authors prospectively examined this association. METHODS: In 1992, eating frequency was assessed in a cohort of 34,968 US men in the Health Professionals Follow-up Study. Cox proportional hazards regression models were used to estimate relative risks and 95% confidence intervals for various levels of eating frequency. Effect modifications by overall dietary quality (assessed using the Diet Approaches to Stop Hypertension score) and by factors that influence insulin resistance were further assessed. RESULTS: Between 1992 and 2006, a total of 583 cases of colorectal cancer were diagnosed. When comparing the highest eating frequency category (5-8 times/day) with the reference category (3 times/day), the authors found no evidence of an increased risk of colorectal cancer (multivariate relative risk

= 0.88, 95% confidence interval: 0.62, 1.26) or colon cancer (multivariate relative risk = 0.78, 95% confidence interval: 0.49, 1.25). There was an implied inverse association with eating frequency among participants who had healthier diets (high Diet Approaches to Stop Hypertension score; P for interaction = 0.01), especially among men in the high-insulin-sensitivity group (body mass index (weight (kg)/height (m)²) <25, >=2 cups of coffee/day, and more physical activity; P for interaction < 0.01, P for trend = 0.01). CONCLUSION: There was an implied protective association between increased eating frequency of healthy meals and colorectal cancer risk and in men with factors associated with higher insulin sensitivity.

Ortiz, AP, C. L. Thompson, A. Chak, et al.

Insulin Resistance, Central Obesity, and Risk of Colorectal Adenomas.

Cancer. 2012 01 Apr 2012; 1187: 1774-1781.

BACKGROUND: Increasing evidence supports insulin resistance (IR) as the underpinning of the obesity-colorectal neoplasia link. The homeostasis model assessment-IR (HOMA-IR) is a widely accepted index of evolving hyperinsulinemia and early IR. Studies of the relation between HOMA-IR and colorectal adenomas are limited. Therefore, the authors sought to determine the associations of HOMA-IR and central obesity (waist to hip ratio [WHR]) with risk of colorectal adenomas in a screening colonoscopy-based study. METHODS: The authors collected lifestyle information and fasting blood samples from 1222 participants (320 incident adenoma cases and 902 without adenomas) before their screening colonoscopies. Unconditional logistic regression models were used to assess risk associations. RESULTS: In multivariate analysis of participants (n = 1093) reporting no antidiabetic medication use, those in the top quartile of WHR were twice as likely (odds ratio [OR], 2.18; 95% confidence interval [CI], 1.33-3.57; P-trend = .003) and those in the top quartile of HOMA-IR were 63% more likely (OR, 1.63; 95% CI, 1.09-2.44; P-trend = .01) to have adenomas compared with those in the bottom quartiles. Stratified analysis revealed a statistically significant interaction between HOMA-IR and sex (P-interaction = .04), with the association largely limited to men; compared with those in the bottom tertile, men in the top tertile of HOMA-IR were twice more likely to have adenomas (OR, 2.11; 95% CI, 1.18-3.78; P-trend = .01). CONCLUSIONS: The results support central obesity and insulin resistance, particularly in men, as important risk factors for the development of early colorectal neoplasia.

ESOPHAGEAL CANCER

Jessri, M, B. Rashidkhani, B. Hajizadeh, et al.

Macronutrients, Vitamins and Minerals Intake and Risk of Esophageal Squamous Cell Carcinoma: A Case-Control Study in Iran.

Nutrition Journal. 2011 10137.

BACKGROUND: Although Iran is a high-risk region for esophageal squamous cell carcinoma (ESCC), dietary factors that may contribute to this high incidence have not been thoroughly studied. The aim of this study was to evaluate the effect of macronutrients, vitamins and minerals on the risk of ESCC. METHODS: In this hospital-based case-control study, 47 cases with incident ESCC and 96 controls were interviewed and usual dietary intakes were collected using a validated food frequency questionnaire. Data were modeled through unconditional multiple logistic regression to estimate odds ratios (OR) and 95% confidence intervals (CI), controlling for age, sex, gastrointestinal reflux, body mass index, smoking history (status, intensity and duration), physical activity, and education. RESULTS: ESCC cases consumed significantly more hot foods and beverages and fried and barbecued meals, compared to the controls (p < 0.05). After adjusting for potential confounders, the risk of ESCC increased significantly in the highest tertiles of saturated fat [OR:2.88,95%CI:1.15-3.08], cholesterol [OR:1.53, 95%CI: 1.41-4.13], discretionary calorie [OR:1.51, 95%CI: 1.06-3.84], sodium [OR:1.49,95%CI:1.12-2.89] and total fat intakes [OR:1.48, 95%CI:1.09-3.04]. In contrast, being in the highest tertile of carbohydrate, dietary fiber and (n-3) fatty acid intake reduced the ESCC risk by 78%, 71% and 68%, respectively. The most cancer-protective effect was observed for the combination of high folate and vitamin E intakes (OR: 0.02, 95%CI: 0.00-0.87; p < 0.001). Controls consumed 623.5 times higher selenium, 5.48 times as much beta-carotene and 1.98 times as much alpha-tocopherol as the amount ESCC cases consumed. CONCLUSION: This study suggests that high intake of nutrients primarily found in plant-based foods is associated with a reduced esophageal cancer risk. Some nutrients such as folate, vitamin E and selenium might play major roles in the etiology of ESCC and their status may eventually be used as an epidemiological marker for esophageal cancer in Iran, and perhaps other high-risk regions.

EXERCISE

O'Neill, S, K. Fisher-Schlombs, H. Breunis, et al.

A Pilot Study of an Exercise Intervention for AML Patients Undergoing Induction Chemotherapy.

Journal of Clinical Oncology. 2011 Annual Meeting; ConferenceASO.

BACKGROUND: Induction chemotherapy (IC) to treat acute myeloid leukaemia (AML) requires 4-5 weeks of hospitalization, leading to deconditioning, declines in quality of life (QOL) and significant fatigue. Four exercise studies have demonstrated improved fitness, strength, QOL, and fatigue in AML patients undergoing IC, but were limited by small sample sizes, recruitment of mostly younger

adults and lack of safety data. OBJECTIVES: 1) To determine recruitment, retention and participation of AML patients in an exercise intervention during hospitalization for IC; 2) to provide efficacy estimates on physical fitness and QOL outcomes; 3) to examine safety of the exercise program. METHODS: Patients presenting with newly diagnosed or relapsed AML scheduled to undergo IC at Princess Margaret Hospital were recruited. Subjects were approached 4-5 days per week to perform 30 minutes of individualized, supervised aerobic and resistance exercises. QOL was measured with the EORTC QLQ-C30 and fatigue with the FACT-F subscale. Fitness measures included VO2max, grip and leg strength, and 6-minute walk test. Outcomes were assessed at baseline and post-induction with descriptive statistics and paired t-tests. RESULTS: Over 6 months, 35 of 47 eligible subjects were enrolled (mean age 56.4 y, SD 12.9). Recruitment was high (74%), retention was excellent (1 drop-out), adherence was very good (80%) and the intervention was safe (1 possible grade II toxicity in 600+ patient-days of follow-up). Preliminary efficacy estimates suggest benefits in QOL and physical fitness outcomes (Table). CONCLUSIONS: Exercise is a safe, promising intervention for improving fitness and QOL in AML patients undergoing curative treatment. Next steps are to conduct a randomized phase II trial and to examine impact of exercise on treatment tolerability. (Table presented).

LIVER CANCER

Shimazu, T, S. Sasazuki, K. Wakai, et al.

Alcohol Drinking and Primary Liver Cancer: A Pooled Analysis of Four Japanese Cohort Studies.

International Journal of Cancer. 2012 01 Jun 2012; 13011: 2645-2653.

BACKGROUND: Because studies of the association between alcohol intake and the risk of primary liver cancer use varying cut-off points to classify alcohol intake, it is difficult to precisely quantify this association by meta-analysis of published data. Furthermore, there are limited data for women in prospective studies of the dose-specific relation of alcohol intake and the risk of primary liver cancer. METHODS: We analyzed original data from 4 population-based prospective cohort studies encompassing 174,719 participants (89,863 men and 84,856 women). After adjustment for a common set of variables, we used Cox proportional hazards regression to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) of primary liver cancer incidence according to alcohol intake. We conducted a meta-analysis of the HRs derived from each study. RESULTS: During 1,964,136 person-years of follow-up, 804 primary liver cancer cases (605 men and 199 women) were identified. In male drinkers, the multivariate-adjusted HRs (95% CI) for alcohol intakes of 0.1-22.9, 23.0-45.9, 46.0-68.9, 69.0-91.9 and ≥ 92.0 g/day, as compared to occasional drinkers, were 0.88 (0.57-1.36), 1.06 (0.70-1.62), 1.07 (0.69-1.66), 1.76 (1.08-2.87) and 1.66 (0.98-2.82), respectively (p for trend = 0.015). In women, we observed a significantly increased risk among those who drank ≥ 23.0 g/day, as compared to occasional drinkers (HR: 3.60; 95% CI: 1.22-10.66). CONCLUSION: This pooled analysis of data from large prospective studies in Japan indicates that avoidance of (1) heavy alcohol drinking (≥ 69.0 g alcohol/day) in men and (2) moderate drinking (≥ 23.0 g alcohol/day) in women may reduce the risk of primary liver cancer.

METABOLIC SYNDROME

Bhandari, R and I. R. H. Rockett.

Cancer Incidence Linked with Two Or More Metabolic Risk Factors.

American Journal of Epidemiology. Conference: 3rd North American Congress of Epidemiology Montreal, QC Canada. Conference Start: 20110621 Conference End: 20110624. Conference Publication: (var.pagings). 2011 01 Jun 2011; 173S322.

BACKGROUND: Obesity, hypertension, diabetes, and hyperlipidemia have been separately implicated as metabolic risk factors for cancer. While metabolic syndrome is defined as having three or more metabolic risk factors, this study evaluated the hypothesis that two or more such factors elevate cancer risk. METHODS: Data were derived from the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study, a cohort study which followed 14,407 non-institutionalized civilian adults from 1971-75 until 1992. This current study was confined to 8,338 female and 5,703 male participants aged 25-74 years who were cancer-free at baseline. Multivariable logistic regression analysis was used to examine the research hypothesis. RESULTS: An unadjusted odds ratio of 1.59 (95% Confidence Interval: 1.30-1.95) provided preliminary evidence that participants with two or more metabolic risk factors had an excess likelihood for developing cancer relative to those with one or none. Hypertension, overweight/obesity, and hyperlipidemia (even at 170 mg/dL), were each associated with excess cancer risk. Controlling for race, age, sex, family income, education, physical activity, smoking, and blood-relatives with a cancer diagnosis, participants with two or more metabolic risk factors were 26% more likely to develop cancer than the referent (adjusted odds ratio: 1.26; 95% Confidence Interval: 1.01-1.57). CONCLUSION: Augmenting the evidence base, this research indicates combinations of metabolic risk factors are cancer determinants. Interventions which control these factors can significantly reduce the burden of healthcare cost and suffering from multiple diseases that include cancer.

MUCOSITIS IN HEAD AND NECK CANCER

Sharma, A, G. K. Rath, S. P. Chaudhary, et al.

Lactobacillus Brevis CD2 Lozenges Reduce Radiation- and Chemotherapy-Induced Mucositis in Patients with Head and Neck Cancer: A Randomized Double-Blind Placebo-Controlled Study.

Eur J Cancer. 2012 April 2012; 486: 875-881.

BACKGROUND: Oral mucositis is a frequent and serious complication in patients receiving chemo-radiotherapy for head and neck squamous cell carcinoma. This study evaluated the effects of administering *Lactobacillus brevis* CD2 lozenges on the incidence and severity of mucositis and tolerance to chemo-radiotherapy. **METHODS:** Two hundred patients suitable for chemo-radiotherapy were enrolled in a randomised, double-blind study to receive daily treatment with lozenges containing either *L. brevis* CD2 or placebo. Anticancer therapy was RT 70 Grays/35 fractions over 7 weeks with weekly Inj. Cisplatin 40 mg/m². The study treatment was given during, and for 1 week after completion of anticancer therapy. Primary end-points were the incidence of grade III and IV oral mucositis and the percentage of patients able to complete anticancer treatment. **FINDINGS:** The efficacy analysis included the 188 patients who received ≥ 1 week of study treatment. Grade III and IV mucositis developed in 52% of patients in the *L. brevis* CD2 arm and 77% in the placebo arm ($P < 0.001$). Anticancer treatment completion rates were 92% in the *L. brevis* CD2 arm and 70% in the placebo arm ($P = 0.001$). A larger proportion of patients remained free of mucositis when treated with *L. brevis* CD2 (28%) compared to the placebo (7%). **INTERPRETATION:** *L. brevis* CD2 lozenges reduced the incidence of grade III and IV anticancer therapy-induced oral mucositis and were associated with a lower overall rate of mucositis and a higher rate of anticancer treatment completion.

STUDY OF THE MONTH

Ligibel, JA, J. Meyerhardt, J. P. Pierce, et al.

Impact of a Telephone-Based Physical Activity Intervention upon Exercise Behaviors and Fitness in Cancer Survivors Enrolled in a Cooperative Group Setting.

Breast Cancer Res Treat. 2012 February 2012; 1321: 205-213.

BACKGROUND: Observational studies demonstrate an association between physical activity and improved outcomes in breast and colon cancer survivors. To test these observations with a large, randomized clinical trial, an intervention that significantly impacts physical activity in these patients is needed. **METHODS:** The Active After Cancer Trial (AACT) was a multicenter pilot study evaluating the feasibility of a telephone-based exercise intervention in a cooperative group setting. Sedentary (engaging in < 60 min of recreational activity/week) breast and colorectal cancer survivors were randomized to a telephone-based exercise intervention or usual care control group. The intervention was delivered through the University of California at San Diego; participants received ten phone calls over the course of the 16-week intervention. All participants underwent assessment of physical activity, fitness, physical functioning, fatigue and exercise self-efficacy at baseline and after the 16-week intervention. One hundred and twenty-one patients were enrolled through ten Cancer and Leukemia Group B (CALGB) institutions; 100 patients had breast cancer and 21 had colorectal cancer. **RESULTS:** Participants randomized to the exercise group increased physical activity by more than 100 versus 22% in controls (54.5 vs. 14.6 min, $P = 0.13$), and experienced significant increases in fitness (increased 6-min walk test distance by 186.9 vs. 81.9 feet, $P = 0.006$) and physical functioning (7.1 vs. 2.6, $P = 0.04$) as compared to the control group. **CONCLUSIONS:** Breast and colorectal cancer survivors enrolled in a multicenter, telephone-based physical activity intervention increased physical activity and experienced significant improvements in fitness and physical functioning. Lifestyle intervention research is feasible in a cooperative group setting.

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