Cancer Epidemiology, Biomarkers & Prevention

ABSTRACTS • 37th Annual Meeting • American Society of Preventive Oncology Peabody Hotel, Memphis, TN, March 10–12, 2013

The following are the 18 highest scoring abstracts of those submitted for presentation at the 37th Annual ASPO meeting held March 10–12, 2013, in Memphis, TN.

An Efficient Resource to Accelerate Research into the Cause and Prevention of Breast Cancer: The Love/Avon Army of Women

Love, S

Background: It is well established that more research into the cause and prevention of breast cancer is needed. While studies are done in cell lines and lab animals, translation of findings to women is often delayed due to difficulty in recruitment. The Dr. Susan Love Research Foundation received a grant from the Avon Foundation for Women to form the Love/Avon Army of Women (AOW); an on-line recruitment resource designed to partner women with researchers in order to accelerate breast cancer research. Methods: Researchers submit a proposal to the AOW Scientific Advisory Committee. If a study is accepted, a mass e-mail describing the study procedures and inclusion/exclusion criteria is sent to the entire AOW database. Women sign up at www.armyofwomen.org to join and receive AOW e-mails about breast cancer research studies. Women self-select based on interest and study criteria, and undergo a secondary on-line screening before contact information is passed on to the researcher for the enrollment process. Results: Over 371,000 women have signed up, including survivors and women without a history of breast cancer, ranging from ages 18 to 100, representing all 50 US states and 49 countries. To date, the AOW has recruited for 70 studies. The diversity of the AOW members has proved beneficial for many studies, such as those needing to enroll racial/ethnic minorities, women of varying sexual orientations, or young survivors. A secondary goal of the AOW is to assist researchers new to research with human subjects. The AOW has successfully helped researchers cross the chasm, coaching them on what it takes to transition their research from animal models to human subjects. Conclusions: The AOW has proved to be a successful resource for scientists to accelerate accrual, expand the number and diversity of their subject population and to obtain exactly the type of specimens they need when they need it. This partnership between women and scientists has revolutionized research and accelerated efforts to eradicate breast cancer. The public is ready and willing to partner with the research community to find the answer to urgent clinical problems.

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Hormonal Risk Factors for Breast Cancer and DNA Methylation

Nichols H, Sandler D, DeRoo L, Xu Z, Taylor J

Epigenetic modifications influence gene expression and have been implicated in the development of breast cancer. Few studies have evaluated breast cancer risk factors in relation to DNA methylation. We examined known reproductive and hormonal risk factors for breast cancer and epigenome-wide methylation patterns. Participants included 612 women enrolled in the Sister Study prospective cohort who did not have breast cancer. DNA methylation profiling was performed using an Illumina array at the NIH Center for Inherited Disease (CIDR) on DNA extracted from whole blood. Methylation data was obtained at single CpG site resolution for 27,578 CpG sites covering >14,000 genes across 23 chromosomes. Statistical analyses were performed using normalized methylation residuals from a linear model adjusting for age and experimental variables. Controlling for a false discovery rate of 5% ($q < 0.05$), 1,452 methylation sites (1,220 in CpG islands) were differentially methylated in postmenopausal women compared to premenopausal women. Average methylation was increased at 1,040 sites and decreased at 412 sites. Gene ontology (GO) analysis suggested enrichment of several biological pathways including lobular involution. Among parous women, only 2 sites (1 CpG island) were differentially methylated among women with older versus younger ages at first birth. A single CpG site demonstrated lower average methylation values among long-term users of postmenopausal hormones compared to short-term users. No further statistically significant differences in methylation patterns ($q < 0.05$) were observed according to age at menarche, parity, breastfeeding history, or postmenopausal hormone use. These data support the menopausal transition as an influential period for epigenetic modifications; few associations between DNA methyl-

ation and other classical reproductive and hormonal breast cancer risk factors were observed.

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Lifestyle Factors and the Risk of a Second Breast Diagnosis after DCIS in the Wisconsin In Situ Cohort

McLaughlin V, Trentham-Dietz A, Hampton JM, Newcomb PA, Sprague BL

Purpose: Certain tumor factors have been associated with increased likelihood of a second breast diagnosis after treatment for ductal carcinoma in situ (DCIS) breast cancer. However, little information exists on modifiable lifestyle factors that affect prognosis after DCIS and may be useful for survivors in reducing their risk of a second breast cancer event. Methods: We examined the longitudinal association between body mass index (BMI), physical activity, and alcohol intake and risk of a second breast diagnosis among 1,925 DCIS survivors first diagnosed in 1997–2006 and enrolled in the Wisconsin In Situ Cohort. Data were collected during biennial patient interviews and diagnosis information was validated via pathology report. BMI, physical activity, and alcohol intake were examined over time using Chi-square and ANOVA methods. Cox proportional hazards regression was used to estimate the risk of a second diagnosis after adjustment for patient, tumor, and treatment factors. Repeated measures were incorporated to make use of exposure measurements taken at each post-diagnosis interview. Results: Over an average of 6.6 years of follow-up, 162 second breast cancer diagnoses were reported. Significant trends of increasing BMI and decreasing physical activity were observed over time since diagnosis ($p < 0.001$). For all women, a significant linear trend of increasing risk of a second diagnosis was found over increasing categories of post-diagnosis alcohol intake (p-trend 0.02). Among women treated with ipsilateral mastectomy, a reduction in risk was suggested with increasing post-diagnosis physical activity (HR 0.67, 95% CI 0.45, 1.02 for each additional hour/week). Among postmenopausal women, higher categories of post-diagnosis BMI were associated with increasing risk, although these results were of borderline significance (p-trend 0.09). Conclusion: This study is the first to examine the association of physical activity and alcohol intake with second breast diagnoses in an exclusively DCIS population. Our results suggest that DCIS survivors may reduce their risk of a second diagnosis by engaging in physical activity and reducing their alcohol consumption.

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A Prospective Study of Circulating Adipokine Levels and Risk of Multiple Myeloma

Hofmann J, Liao L, Pollak M, Wang Y, Pfeiffer R, Baris D, Andreotti G, Lan Q, Landgren O, Rothman N, Purdue M

Purpose: Obesity is associated with an increased risk of multiple myeloma (MM), although the biologic mechanisms underlying this association are unclear. We conducted a nested case-control study in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial to evaluate the hypothesis that altered circulating levels of adipokines, polypeptide hormones with pro- and anti-inflammatory properties secreted by adipose tissue, may partly explain the association between obesity and MM. Methods: We investigated whether circulating levels of leptin, total adiponectin, and high-molecular-weight (HMW) adiponectin are associated with MM among 174 cases and 348 controls in PLCO. Two controls were matched to each case on age at baseline, sex, race, date of phlebotomy, time of day of phlebotomy, and study year of specimen collection. Plasma adipokine concentrations were measured by enzyme-linked immunosorbent assay; overall coefficients of variation were $\leq$8.5%. Odds ratios (OR) and 95% confidence intervals (CI) were estimated using conditional logistic regression. Results: Inverse associations with MM were observed for total adiponectin (highest quartile vs. lowest: OR = 0.49, 95% CI = 0.26–0.93, P-trend = 0.03) and HMW adiponectin (OR = 0.44, 95% CI = 0.23–0.85, P-trend = 0.01). These associations remained after adjusting for body mass index (BMI), stratifying by sex, and restricting to cases diagnosed approximately eight years or more after blood collection. We observed a modest association between BMI and MM (OR per 5 kg/m^2 increase = 1.14, 95% CI = 0.94–1.39), which was attenuated by approximately 40% after adjusting for adiponectin. Leptin levels were not associated with MM. Conclusions: These results suggest that higher circulating levels of adiponectin are protective against MM, and that adiponectin may play an important role in obesity-related myelomagenesis. This study is, to our knowledge, the first prospective investigation of circulating adipokines and MM. Our findings are particularly intriguing in light of recent evidence that host-derived adiponectin is tumor-suppressive and a potential novel therapeutic target for MM and associated bone disease.

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Aspirin and Colorectal Cancer Incidence and Mortality by CTNNB1 Expression: A Molecular Pathological Epidemiology (MPE) Study

Sun R, Nishihara R, Qian ZR, Chan AT, and Ogino S

Purpose: Experimental studies showed that aspirin down-regulates the WNT/CTNNB1 (β-catenin) signaling

pathway in colon cancer cells. We investigated whether aspirin use was associated with lower incidence and superior survival in nuclear CTNNB1-positive colorectal cancer. Methods: In two large prospective studies (the Nurses' Health Study and the Health Professionals Follow-up Study), we collected the information on aspirin use every 2 years from 1980 through 2008. We used Cox proportional hazards regression to compute the multivariate hazard ratio for incidence and mortality according to tumor CTNNB1 expression patterns. Results: During 28 years and 3,166,091 person-years of follow-up, we documented 931 incident cases of colorectal cancer with available CTNNB1 expression data. Regular aspirin use was associated with a significantly lower risk of CTNNB1-positive cancer (multivariate HR = 0.65; 95% CI, 0.53–0.80), but not with the risk of CTNNB1-negative cancer (multivariate HR = 0.84; 95% CI, 0.70–1.01). A formal test of heterogeneity of the association according to CTNNB1 expression status did not reach statistical significance (P = 0.07). Regular aspirin use after diagnosis of colorectal cancer was associated with better colorectal cancer-specific survival among CTNNB1-positive tumor patients (multivariate HR = 0.53; 95% CI, 0.30–0.95). In contrast, among CTNNB1-negative tumor patients, post-diagnosis regular aspirin use was not associated with colorectal cancer-specific survival (multivariate HR = 1.06; 95% CI, 0.62–1.83) (P = 0.04 for interaction test between aspirin use and CTNNB1 status). Conclusions: Regular aspirin use was associated with lower incidence of nuclear CTNNB1-positive cancer, and better survival among patients with nuclear CTNNB1-positive cancer. Our molecular pathological epidemiology (MPE) study revealed the anti-tumor mechanism of aspirin, which might prevent cancer incidence and mortality by inhibiting tumor initiation and/or progression in the WNT/CTNNB1-related carcinogenesis pathway.

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Smoking and Colorectal Cancer Risk by Tumor Genetic and Epigenetic Subtypes: A Molecular Pathological Epidemiology (MPE) Study

Nishihara R, Chan AT, and Ogino S

Purpose: It remains to be investigated whether smoking is associated with colorectal carcinogenesis through specific epigenetic or genetic alterations, or abnormal protein expression. We comprehensively examined the influence of smoking on colorectal cancer risk by specific tumor molecular features, including epigenetic status (CpG island methylator phenotype [CIMP]), genomic instability (microsatellite instability [MSI]), oncogenic mutations (BRAF, KRAS, and PIK3CA), and tumor protein expressions (DNA methyltransferase-3B [DNMT3B], TP53, PTGS2 [cyclooxygenase-2], FASN, and CTNNB1 [b-catenin]). Methods: Follow-up of 134,204 individuals in two U.S. nationwide prospective cohorts (Nurses' Health Study [1980–2008] and Health Professionals Follow-up Study [1986–2008]) resulted in 1,292 incident rectal and colon cancers with available molecular data. Duplication method Cox proportional hazards model was used to calculate multivariate hazard ratio (HR) for developing a specific subtype of tumor according to smoking status. Results: Compared with never smokers, smoking of ≥40 cumulative pack-years was associated with increased risks for specific molecular types of colorectal cancer. Multivariate HRs are 2.12 for CIMP-high cancer (95% confidence interval [CI], 1.48- 3.03), 2.27 for MSI-high cancer (95% CI, 1.56–3.31), 2.00 for BRAF-mutated cancer (95% CI, 1.37–2.92), 1.37 for KRAS-wild-type cancer (95% CI, 1.12–1.68), 1.30 for PIK3CA-wild-type cancer (95% CI, 1.07–1.58), 1.33 for TP53-negative cancer (95% CI, 1.05–1.69), 1.37 for PTGS2-positive cancer (95% CI, 1.09–1.73), 1.36 for FASN-positive cancer (95% CI, 1.07–1.73), and 1.35 for CTNNB1-negative cancer (95% CI, 1.04–1.74). The influence of smoking significantly differed according to status of CIMP (P = 0.001 for heterogeneity test of CIMP-low vs. CIMP-high) and MSI (P = 0.0003 for heterogeneity test of MSS vs. MSI-high). There was no statistically significant differential association of smoking with other molecular subtypes. Conclusion: This molecular pathological epidemiology (MPE) study suggests that smoking might primarily cause epigenetic alterations, which lead to oncogenic mutations in colonic cells.

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Human Papillomavirus Vaccine Knowledge and Uptake among Adolescent Boys and Girls in an Appalachian Ohio County

Bhatta MP, Phillips L, Frew S, Burns J, Cascarelli N

Background: Population-based studies of human papillomavirus (HPV) vaccine uptake among both adolescent boys and girls are limited. The purpose of this study was to examine middle and high school student knowledge and behaviors surrounding the HPV vaccine in a rural Appalachian Ohio county. Methods: Five questions regarding the HPV vaccine were added to 2012 Youth Risk Behavior Survey (YRBS) administered in an Ohio Appalachian county. The participants were asked whether or not they had heard of the HPV vaccine; been given the vaccine and, if yes, the number of shots received; and whether their health care provider and/or their parents had discussed the vaccine with them. The voluntary and anonymous survey was completed by a total of 1,300 adolescent boys and girls. Results: Of the 596 and 704 high school students who completed the survey, 51.9% were male and 48.1% were female, and 95% were white.

Regarding whether they had ever heard of the HPV vaccine, 49.1%, 29.6%, 21.2% respectively reported 'yes', 'no', and 'don't know/not sure'. Girls were more likely to report having heard of the HPV vaccine than boys (56.7% vs. 42.19%; $p < 0.001$). In all, 19.5% and 24.5% of the participants indicated having their parents and a health care provider respectively having discussed the HPV vaccine with them. Girls were two times as likely to report having a parent discuss the HPV vaccine with them than boys ($P < 0.01$). They were also almost three times as likely than boys to report a health care provider having discussed the vaccine with them ($p < 0.01$). Overall, 11.4% boys and 21.3% girls reported having received at least one dose of the vaccine ($p < 0.001$). The HPV uptake rates among middle and high school boys and girls respectively were 9.2%, 13.2%, 14.4%, and 27.4%. Conclusion: The HPV vaccine knowledge, as well as parental and health care provider communication regarding the HPV vaccine, particularly with the boys, remains low among these rural Appalachian adolescents. The role of these two factors on the HPV vaccine uptake among this adolescent population needs to be further explored.

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Physical Activity, Tumor PTGS2 Expression, and Colorectal Cancer Survival: A Molecular Pathological Epidemiology (MPE) Approach

Yamauchi M, Nishihara R, Chan AT, and Ogino S

Purpose: Evidence suggests that energy balance in tumor microenvironment may influence systemic inflammatory status and cancer progression through its effect on prostaglandin biosynthesis. We examined whether the physical activity after diagnosis of colorectal cancer was associated with improved survival in PTGS2-positive colorectal cancer. Methods: Utilizing 605 stage I–III colon and rectal cancers in two prospective cohort studies, we assessed patient survival according to physical activity and tumor PTGS2 status. Cox proportional hazards regression was used to calculate multivariate hazard ratio (HR), adjusting for clinical and other tumor features (including microsatellite instability and BRAF and KRAS mutations). Results: Among patients with PTGS2-positive cancer, compared with the least active first quartile, the multivariate HRs were 0.30 (95% confidence interval [CI], 0.14–0.62) for the second quartile, 0.38 (95% CI, 0.20–0.71) for the third quartile, and 0.18 (95% CI, 0.08–0.41) for the fourth quartile of increasing physical activity ($P = 0.0002$ for trend). In contrast, among patients with PTGS2-negative cancer, physical activity level was not significantly associated with colorectal cancer-specific survival ($P = 0.84$ for trend). We observed significant interaction between physical activity and tumor PTGS2 status ($P = 0.024$ for interaction). Conclusion: Post-diagnosis physical activity was associated with better survival among patients with PTGS2-positive colorectal cancer. This finding from molecular pathological epidemiology (MPE) suggests that PTGS2 may be a tumor biomarker that may predict stronger benefit from exercise in colorectal cancer patients.

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Contribution of Health Behaviors to the Association between Area-Level Socioeconomic Status and Cancer Mortality

Hastert T, Beresford A, White E

Background: Area-level socioeconomic status (SES) is increasingly recognized as an important predictor of health outcomes; however, its association with cancer mortality is not established. Moreover, mediators of the association between area-level factors and health outcomes are not well understood. The purpose of this study is to quantify the association between area-level SES and cancer mortality and to identify whether and to what extent behaviors mediate the association. Methods: We identified the census block groups of participants in the VITamins And Lifestyle (VITAL) Study cohort and constructed an SES index using data from the 2000 U.S. Census. Participants included 54,736 men and women ages 50–76 years with no history of cancer at baseline (2000–2002). Cancer deaths ($n = 1,488$) were tracked through the Washington State death file over 7.7 years of follow-up. We tested whether eight modifiable risk factors (e.g. body mass index (BMI), physical activity, diet, alcohol, smoking, screening) mediated the association between area-level SES and cancer mortality. Results: Living in the lowest-SES areas was associated with 77% higher cancer mortality than living in the highest-SES areas (hazard ratio (HR): 1.77, 95% confidence interval (CI): 1.50, 2.11). Adding modifiable risk factors into the models explained 45% (95% CI: −68%, −11%) of the association. In models controlling for individual education and income, area-level SES remained associated with cancer mortality (HR highest- vs. lowest-SES areas: 1.37, 95% CI: 1.14, 1.65) and adding modifiable risk factors reduced the association by 37% (95% CI: −99%, 22%). Smoking, physical activity and screening mediated the largest proportion of the association, while diet, alcohol use and BMI had little explanatory effect for the health disparities. Conclusions: Low area-level SES is associated with increased cancer mortality. This association persists after accounting for individual education and income and is partially mediated by smoking, physical activity, and screening.

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Immune Reconstitution and Risk of Hodgkin's Lymphoma among a Sample of HIV-Infected Male Veterans

Kowalkowski M, Chiao E

Purpose: In contrast to certain AIDS-defining cancers, the incidence of Hodgkin's lymphoma (HL) has increased since the introduction of combined antiretroviral therapy (cART). Although HIV-associated HL has been strongly linked to the Epstein-Barr virus, the causes for the increased incidence of HL in the cART era remain unclear. The aim of this study was to evaluate the effect of cART utilization and possible immune reconstitution inflammatory syndrome (IRIS), through monitoring the activity of immunologic measures (e.g., nadir CD4 prior to cART, recent CD4, percent of time with undetectable HIV viral load), on the incidence of HL among a sample of HIV-infected male veterans. Methods: We performed a retrospective cohort study utilizing data from the Veterans Affairs HIV Clinical Case Registry (VA-CCR) from 1985–2010. HL cases were identified using ICD-9 codes. Women were excluded due to low numbers. We also excluded individuals without identifiable CD4 or viral load measurement, no cART use, <90 days of follow-up, and prevalent HL cases occurring prior to or within 90 days of HIV diagnosis. We analyzed the relationship between immunologic measures associated with cART utilization and the incidence of HL, calculated in multivariable Poisson regression models adjusted for demographic and time-varying immunologic covariates. Results: The final sample included 31,596 cART users, contributing 288,968 person-years and 219 HL cases (IR = 76 per 100,000 person-years). In multivariable regression models, the risk of HL was higher among veterans with recent CD4 <200 copies/cell (IRR = 1.57, 95%CI = 1.05–2.34) and between 200–350 copies/cell (IRR = 1.68, 95%CI = 1.17–2.40), compared to individuals with >350 copies/cell. Also, HL risk was increased among veterans within 1 year (IRR = 2.38, 95%CI = 1.60–3.53) and 1–2 years (IRR = 1.89, 95%CI = 1.27–2.82) after cART initiation, compared to >2 years. Conclusion: Recent CD4 counts <350 copies/cell were associated with an increased risk of HL among cART users. Additionally, risk of HL was increased in the 2 years directly following cART initiation. Findings indicate an EBV-associated IRIS may function in HL development in HIV-infected individuals.

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Overuse of Pap Testing Among Older Women and Women with a Hysterectomy

Kepka D, Breen N, King J, Meissner H, Benard V, Roland K, & Saraiya M

Background: As of 2012, leading national organizations have agreed on evidence-based recommendations for Pap testing. They recommended against Pap testing for women over age 65 years who have had adequate prior screening and are not at high risk and for women without a cervix following a hysterectomy who do not have a history of high-grade precancerous lesion or cervical cancer. Few studies have investigated overuse of Pap testing among US women. Methods A cross-sectional study was conducted using data from the 2010 National Health Interview Survey (NHIS). NHIS is a nationally-representative survey of the civilian non-institutionalized population of the United States that employs a random, stratified, multi-stage cluster sampling design. The survey is conducted annually using computer-assisted in-person interviewing. It includes sections on self-reported participant demographic characteristics, health status, and use of healthcare services. In 2010, the NHIS administered a Cancer Control Supplement with questions on cervical cancer screening, hysterectomy status, and timing of hysterectomy (n = 12,320). All analyses account for the complex survey design of NHIS. Results Approximately 3/5 of women over age 65 years reported a Pap test in the past three years and nearly 2/3 of women reporting a hysterectomy also reported a recent Pap test since their hysterectomy. Adjusted proportions calculated using multivariate logistic regression models showed that among women over age 70 years, higher level of education ($p < .05$) and no hysterectomy ($p < .001$) were associated with receipt of a recent Pap test (received within past 3 years after age 65 years). Among women who have undergone a hysterectomy, younger age ($p < .001$), Hispanic and Black race/ethnicity ($p < .001$), higher income ($p < .001$), and private healthcare coverage ($p < .01$) were associated with receipt of a recent Pap test since hysterectomy. Conclusion: Pap testing in average-risk women over age 65 years and in women who have undergone a hysterectomy is high despite past recommendations. Now that all leading national organizations have released new guidelines in 2012, improved efforts are needed to significantly reduce overuse of Pap testing in the future.

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Cross-Sectional & Longitudinal Associations between Light-Intensity Physical Activity & Physical Function Among Cancer Survivors

Blair C, Morey M, Desmond R, Sloane R, Snyder D, Cohen H, Demark-Wahnefried W

Purpose: While moderate-vigorous intensity physical activities (MVPA) confer the greatest health benefits, evidence suggests that light-intensity activities are also beneficial, particularly for older adults and individuals with moderate-severe comorbidities. Cross-sectional and longitudinal associations between light-intensity

physical activity and physical function were examined in elderly cancer survivors, who are at increased risk for age- and treatment related comorbidities, including accelerated functional decline. Methods: The analysis included 641 breast, prostate, and colorectal cancer survivors (54% female) aged 65 and older who participated in a 1-year, home-based diet and exercise intervention designed to reduce the rate of physical function decline. Pre- and post-intervention physical activity and function were assessed via the CHAMPS questionnaire, the SF-36 physical function subscale (PFS) and the Late Life Function and Disability Index basic and advanced lower-extremity function (LEF) subscales. ANCOVA was used to compare means of physical function across levels of PA intensity (low-light (LLPA): 1.0-2.0 METs; high-light (HLPA): 2.1-2.9 METs; MVPA: ≥3.0 METs). Results: After adjustment for age, sex, BMI, comorbidities, symptoms, and MVPA, increasing tertiles of baseline light-intensity activity were associated with higher scores for all 3 measures of baseline physical function (all p-values <0.005). Associations were stronger for HLPA than for LLPA. Compared with survivors who decreased or remained stable in MVPA and HLPA at the post-intervention follow-up, those who increased in HLPA, but not MVPA, reported higher physical function scores (LSMeans (95% CI): SF-36 PFS: −5.58 (−7.96, −3.20) vs. −2.54 (−5.83, 0.75), p = 0.14; basic LEF: -2.00 (−3.45, −0.55) vs. 0.28 (−1.72, 2.28), p = 0.07; advanced LEF: −2.58 (−4.00, −1.15) vs. 0.44 (-1.52, 2.40), p = 0.01). Conclusions: Our findings suggest that increasing light-intensity activities, especially HLPA, may be a viable approach to reducing the rate of physical function decline in individuals who are unable or reluctant to initiate or maintain adequate levels of moderate-intensity activities.

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Differences in Mammographic Density Decline over Time in Breast Cancer Cases and Women at High Risk for Breast Cancer

Work ME, Reimers LL, Quante AS, Crew KD, Whiffen A, Terry MB

Introduction: High absolute breast density and increased breast density over time are strongly associated with breast cancer risk, and breast density generally decreases with increasing age. We examined mammographic density data from members of the Women At Risk High-Risk Registry at Columbia University Medical Center (WAR), a cohort defined as at high risk for breast cancer due to family history of breast cancer, history of lobular carcinoma in situ, and/or benign breast disease, to determine changes in their breast density over time. Methods: Within the WAR cohort of 1598 women, we conducted a nested case-control study of 66 incident cases of invasive breast cancer and 70 women without cancer, matched on age and time between first and second mammogram. For each participant, we collected two mammograms (for the cases, both mammograms occurred before cancer diagnosis), to examine differences in absolute density, percent density, and change in density between cases and controls. The average time between first and second mammogram was 4.6 years for both cases and controls, with a range of between 1 and 15 years. Results: Using linear regression with change in percent density as the outcome, and time between first and second mammogram as the independent variable, we found that among women without breast cancer, density decreased as time between first and second mammogram increased (β = −2.15, p = 0.005). In contrast, there was no overall change in density among the cases associated with time between first and second mammogram (β = 0.69, p = 0.39). In an ANCOVA comparing the slopes of the regression lines, the slopes were significantly different for cases versus controls (p = 0.009). Conclusion: In a cohort of women at high risk for breast cancer, breast density does not decrease as time between mammograms increases, for women who go on to develop breast cancer. For women who do not develop breast cancer, breast density decreases significantly over time.

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The Role of Geography in Low Mammography Screening Rates and Late-Stage Breast Cancer Diagnosis in Utah

Henry KA, Stroup NM, Kinney AY

Purpose: Mammography screening rates in Utah have been lower than other states for nearly 20 years. We examine the role of geographic factors on mammography screening rates and late-stage breast cancer diagnosis in Utah. Methods: Mammography screening data from the 2008 and 2010 Utah Behavioral Risk Factor Surveillance System included Utah women aged 40–74 (weighted N = 417,064). Utah Cancer Registry data included women 40+ years, who were diagnosed with breast cancer from 2004–2008 (N = 6,500). Multilevel logistic regression was used to examine the association between measures of geographic access to mammography (travel time, geo access scores, rural/urban residence) and individual factors (age, race/ethnicity, insurance) and the odds of (a) not having a mammogram within the last two years and (b) being diagnosed with late stage breast cancer. Geo access scores are composite values based on the number of mammography facilities and the distribution of drive times. Results: Overall 32.7% (95%CI 31.1%–34.5%) of Utah women 40–74 reported not having a mammogram

within the last 2 years and 31.3% of women aged 40+ were diagnosed with late-stage breast cancer. A disproportionate number 43.1% (95%CI 39.9%–46.3%) of women 40–49 did not have a mammogram within the last 2 years compared to women 50–74 (26.8% 95%CI 24.9%–28.7%). Geographic access measures were not associated with mammography screening and late-stage breast cancer diagnosis among women 40–74. Travel time was moderately significant for women living >20 minutes from a mammography facility compared to women living <5 min (OR = 1.23 95%CI 1.01–1.50), even after controlling for age, race/ethnicity, and insurance status. Women aged 50+ with low geo access scores had higher odds (OR = 1.20 95%CI 1.04 1.37) of late-stage breast cancer diagnosis compared to women with high geo access scores. Conclusion: Geographic access may be a risk factor for late-stage breast cancer for specific segments of the population, who may benefit from targeted interventions to improve early detection. Future work should consider alternate geographic access measures and other potential sociodemographic or cultural barriers to screening in Utah.

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Elevated Serum Calcium as a Biological Marker For Ovarian Cancer

Skinner HG, Schwartz GG

Background: Biological markers useful for detecting ovarian cancer at early stages are urgently needed. Because a subset of ovarian cancers is associated with hypercalcemia (serum calcium greater than the normal reference range), we hypothesized that high-normal serum calcium levels might be associated with ovarian cancer in general. Methods: We examined associations between total and ionized serum calcium and ovarian cancer mortality in the Third National Health and Nutrition Survey (NHANES III) using Cox proportional hazard models. We then examined associations of serum calcium with incident ovarian cancer in a second prospective cohort, the NHANES Epidemiological Follow-up Study (NHEFS). Results: In NHANES III, eleven deaths from ovarian cancer occurred over 95,556 person-years of follow-up. After adjustment for age, height, body mass index, and cigarette smoking, the risk for fatal ovarian cancer increased 52% for each 0.1 mmol/L increase in total serum calcium (RH = 1.52, 95% CI 1.06–2.19) and 144% per each 0.1 mmol/L increase in ionized serum calcium (RH = 2.44, 95% CI = 1.45–4.09). Significant associations persisted after adjustment for established ovarian cancer risk factors including nulliparity and the never use of oral contraceptives. In the NHEFS, 8 incident ovarian cancers occurred over 31,089 person-years of follow-up. After adjusting for covariates, there was a 63% increase in the risk for ovarian cancer for each 0.1 mmol/L increase in total serum calcium (95% CI 1.14–2.34). Similar results were observed for albumin-adjusted serum calcium. Conclusions: These findings suggest that higher serum calcium may be a biomarker of ovarian cancer. This is the first report of prospective positive associations between indices of calcium in serum and ovarian cancer. These findings require confirmation in other cohorts.

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The Impact of Colonoscopy Screening Guidelines that Incorporate Precursors in the Serrated Pathway: A Cost-Effectiveness Analysis

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Background: In 2012, the U.S. Multi-Society Task Force on CRC published guidelines that include sessile serrated polyps (SSPs) as important new precursors to target during a screening colonoscopy. Previously, adenomas were the only polyp precursor targets of colonoscopy. Objective: The purpose of this study is to estimate the incremental cost-effectiveness ratio for colonoscopy comparing the new guidelines to the former guidelines. Methods: We developed a Markov model for CRC that included three pathways: 1) de novo from colonic epithelium without a polyp precursor, 2) through the adenoma-carcinoma sequence, and 3) through an SSP precursor. Then, we simulated the effect of screening colonoscopy on CRC incidence and mortality applying the new guidelines vs. the old guidelines in a hypothetical US cohort of 100,000 adults who began screening at age 50 and ended screening at age 75. Adults progressed through the model for 50 one-year cycles until death or age 100. Costs for CRC detection and treatment were estimated from a limited societal perspective using Medicare reimbursement data. We calculated the cost per life-year (LY) gained for the new CRC screening guidelines and the old guidelines compared to no intervention. Then we compared the two sets of guidelines to one another. Preliminary Results: CRC screening via colonoscopy in this hypothetical cohort of 100,000 adults using the old guidelines prevented 4,161 new CRC cases and 1,901 deaths. Implementing the new guidelines avoided an additional 452 CRC cases and 178 deaths. The old guidelines resulted in 0.064 LY-gained and an $800 increase in costs per person compared to the natural history of CRC with no intervention, with a cost-effectiveness ratio of $12,500/LY. The new guidelines resulted in 0.068 LY-gained and a $405 increase in costs per person compared to no intervention, with a cost-effectiveness ratio of $5,956/LY. Comparing the new guidelines to the old guidelines, the difference in LY-gained was 0.004, and

the difference in costs was -$395 per person. Conclusion: CRC screening that includes evaluation of SSPs may be cost-effective, and potentially cost-saving, compared to prior guidelines.

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Predictors of Colorectal Cancer Surveillance among Radiation-treated Survivors of Childhood Cancer

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Purpose: To identify predictors of adherence to colorectal cancer (CRC) surveillance guidelines among survivors of childhood cancer who received ≥30 Gy radiotherapy to the abdomen, pelvis, or spine, and were 36 years or older at the time of last contact. Methods: We sought to identify predictors of self-reported CRC surveillance participation among 5-year survivors who completed the Childhood Cancer Survivor Study (CCSS) 2007 Follow-Up Questionnaire and met the criteria above. Univariate and multivariable generalized linear models with a log link and Poisson distribution were used to calculate relative risks (RR) with 95% confidence intervals (95% CI) for adherence to CRC surveillance guidelines (i.e., home stool blood testing and/or colonoscopy/sigmoidoscopy). Results: The mean age of 711 childhood cancer survivors eligible for the study was 44 years (SD = 5.2 years). Among them, 231 (32.5%) reported ever performing home stool blood testing and 276 (38.8%) reported ever having colonoscopy or sigmoidoscopy. Of the 711 participants, 60 (8.4%) reported home stool blood testing in the past year (meeting screening guidelines for the general adult population) and 207 (29.1%) reported having a colonoscopy or sigmoidoscopy in the past 5 years (meeting surveillance recommendations for survivors of childhood cancer treated with radiation). In the multivariable analyses, factors associated with CRC surveillance were age 50 years or older (RR = 2.4, 95% CI = 1.9–2.9); having routine cancer follow-up visit within one year prior to questionnaire completion (RR = 1.7, 95% CI = 1.2–2.5); having a physical impairment requiring the assistance of others for routine activities of daily living (RR = 1.7, 95% CI = 1.2–2.2); and having discussed future cancer risk with a physician at their most recent follow-up visit (RR = 1.3, 95% CI = 1.1–1.6). Conclusions: More than 70% of survivors at risk for CRC were not screened as recommended. Indeed, unless a physician discussed their future cancer risk, most survivors were not screened until they reached age 50, the time at which CRC screening is recommended for individuals at average CRC risk. These findings underscore the need for education of survivors and their physicians regarding the heightened CRC risk following radiation.

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Breast cancer susceptibility loci in association with age at menarche, age at natural menopause and the reproductive lifespan

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Purpose: Genome wide association studies have identified common single nucleotide polymorphisms (SNPs) associated with breast cancer risk. Many of these SNPs have an unknown biologic significance. Hormonal risk factors may mediate the relationships between these loci and breast cancer risk. We explored the relation between breast cancer susceptibility loci and menstrual factors using data from two population-based studies. Methods: In the first dataset, composed of 1328 women ages 20–74 years without a breast cancer diagnosis who participated in an established population-based study conducted in three U.S. states, we used linear regression to assess the associations between 13 previously-identified breast cancer loci with age at menarche, age at natural menopause and the reproductive lifespan. The reproductive lifespan is defined as the time between age at menarche and age at natural menopause, excluding time for pregnancy, oral contraceptive use and lactation. A polygenic risk score created as the sum of the number of risk allele copies in the SNPs was also evaluated for an association with menstrual traits. Significant results were then evaluated in the second dataset comprised of 1353 women ages 43–86 years recruited as part of a cohort study based in Beaver Dam, WI. Results: Polygenic score and 13 loci were not associated with either age at menarche or reproductive lifespan. Two SNPs were associated with age at natural menopause; each increase in the number of copies of the minor allele (A) of rs17468277 (CASP8) was associated with a 1.12 year decrease in age at natural menopause (p = 0.02). The minor allele (G) of SNP rs10941679 (5p12) (p = 0.01) was associated with a 1.01 year increase in age at natural menopause, although these results were not replicated in the follow-up study (p = 0.14 and 0.98, respectively). Conclusions: We did not find evidence to support the hypothesis that breast cancer susceptibility loci are related to menstrual factors.

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