

ABSTRACTS • 35th Annual Meeting • American Society of Preventive Oncology, Las Vegas, Nevada • March 5-8, 2011

The following are the 14 highest scoring abstracts of those submitted for presentation at the 35th Annual ASPO meeting held March 5-8, 2011 in Las Vegas, NV.

Oral Contraceptive Use and Parity Associations with Uncommon Breast Cancer Histologies in the Breast Cancer Family Registry: the Role of Family History

Work ME, John EM, Andrulis IL, Hopper JL, Liao Y, Hibshoosh H, Terry MB

Purpose: The effect of parity and oral contraceptive (OC) use on breast cancer risk differs by cancer subtype as defined by histology. Family history of breast cancer impacts decisions regarding both parity and oral contraceptive use; it is unknown whether reproductive risk factors are related to uncommon histologies in women with and without a strong family history.

Methods: Using population-based data from the Breast Cancer Family Registry, we conducted analyses using unordered polytomous regression to determine the role of family history in associations between parity, OC use, and breast cancer histologic subtype, among 3,260 cases and 2,997 controls. Histologic types examined included ductal and lobular as well as the uncommon histologies of mucinous, tubular, and medullary cancer.

Results: Twenty-eight percent of cases and 9% of controls had a family history (defined as at least 1 first-degree relative with breast cancer). Cases with and without family history were similar in regards to OC use (75% and 73%, respectively were ever-users) and parity (2.08 children in cases with family history, 2.10 in cases without). In a multivariable model, when compared with controls, OC use was inversely associated with tumors of mucinous histology (OR = 0.43, 95% CI 0.23–0.79 for use ≥ 5 years vs. never use). There was a stronger inverse association with OC use and the mucinous subtype among those without a family history (OR = 0.27, 95% CI 0.13–0.57), and a nonsignificant positive association in those with family history (OR = 2.19, 95% CI 0.40–11.84). High parity (≥ 3 children) was positively associated with medullary histology (OR = 2.62, 95% CI 1.16–5.91, compared with nulliparity); the association was stronger among women without a family history (OR = 4.31, 95% CI 1.67–11.12), and was not significantly associated among those with a family history (OR = 0.36, 95% CI 0.06–2.29). Parity was inversely associated with the mucinous type (OR = 0.45, 95% CI 0.21–0.96, compared

with nulliparity), and this effect remained stable in women with and without family history.

Conclusion: This study suggests that selected reproductive risk factors may only be related to uncommon breast cancer histologies among women without a family history of breast cancer.

Published online March 31, 2011.

doi: 10.1158/1055-9965.EPI-11-0084

©2011 American Association for Cancer Research.

Change in Colorectal Cancer Screening Decision Stage

Njoku A, Cocroft J, Daskalakis C, Sifri R, Bittner-Fagan H, Myers R

Introduction: Colorectal cancer screening (CRC) screening decision stage (SDS) is a measure of proximity to screening. Predictors of change in SDS have not been reported in the literature.

Objective: To assess SDS change and predictors of SDS among primary care patients 50 to 74 years of age who are enrolled in a randomized, controlled trial of behavioral interventions designed to increase CRC screening.

Methods: On a baseline survey, study participants reported on perceptions about CRC screening and SDS (i.e., decided to screen vs. had not decided to screen). Participants were randomized to one of three study groups: Control Group (usual care), Standard Intervention (SI) Group [mailed screening materials (i.e., informational booklet, a stool blood test kit, instructions for scheduling a screening colonoscopy, and a reminder)]; and a Tailored Navigation Intervention (TNI) Group (mailed screening materials tailored to baseline SDS and a navigation telephone call). TNI Group participants were asked to report current SDS, including current screening status, at navigation. We assessed change in SDS from baseline to navigation and performed multivariable analyses to identify predictors of SDS change.

Results: Of 248 TNI Group participants, 205 (83%) received a navigation call. Background characteristics of these participants were as follows: white (76%), female (64%), aged 50–59 (67%), >high school education (52%), and married (62%). At baseline, 43 (21%) participants reported that they had not decided to screen, and 162 (79%) reported that they had decided to screen. At navigation, 55 (27%) participants reported a positive change in SDS (26 moved forward in SDS but did not screen and 29 screened). Participants who had not decided

to screen at baseline were more likely to exhibit positive change in SDS than those who had decided to screen at baseline (63% and 17%, respectively, $P < 0.0001$). Among participants who had not decided to screen at baseline, only one reported actual screening. Of those participants who had decided to screen, 28 actually screened.

Discussion: More than a quarter of participants reported a positive change in SDS in response to the mailed tailored intervention materials sent before the navigation call. Baseline SDS was a strong predictor of SDS change.

Published online March 31, 2011.

doi: 10.1158/1055-9965.EPI-11-0085

©2011 American Association for Cancer Research.

Sigmoidoscopy and Colonoscopy are Inversely Associated with Both Left- and Right-sided Advanced Adenomas

Burnett-Hartman A, Newcomb P, Phipps A, Passarelli M, Mandelson M, Zhu L, Upton M

Background: The U.S. Preventive Services Task Force recommends routine colorectal cancer screening starting at age 50; however, evidence is insufficient to recommend one screening method over the other methods. Common colorectal cancer screening methods include fecal occult blood tests (FOBT), sigmoidoscopy, and colonoscopy.

Objective: We examined the association between advanced adenomas, known precursors to colorectal cancer, and history of screening by FOBT, sigmoidoscopy, and colonoscopy.

Methods: We conducted a case-control study of advanced colorectal adenomatous polyps, which included 306 advanced adenoma cases and 2,287 controls without advanced adenomas, aged 24 to 79, who received an index colonoscopy from 1998 to 2007. All participants completed a questionnaire covering screening history and other colorectal cancer risk factors. Participants with polyps underwent a standard pathology review; adenomas ≥ 10 mm or at with at least 20% villous components were considered advanced adenomas. We used separate logistic regression models to estimate adjusted odds ratios (ORs) and 95% CIs for the associations between advanced adenomas and previous FOBT, sigmoidoscopy, and colonoscopy at least 2 years before the index colonoscopy.

Results: Each screening method was associated with decreased odds of advanced adenomas; however, only associations for sigmoidoscopy and colonoscopy were statistically significant. The OR for advanced adenomas, comparing participants with at least one previous FOBT to those who had never had FOBT, was 0.82 (95% CI: 0.63–1.06); for sigmoidoscopy, OR = 0.59 (95% CI: 0.46–0.77); and for colonoscopy, OR = 0.53 (95% CI: 0.39–0.72). These associations were similar with respect to left- and right-sided advanced adenomas.

Discussion: Our findings suggest colonoscopy and sigmoidoscopy have similar inverse associations with advanced adenomas in both left and right sides of the colon. This is in contrast to studies of colorectal cancer that suggest endoscopy is associated with a decreased risk for tumors of the left but not right side. The discrepancy between our findings and these studies may be explained if right-sided colorectal cancers are more likely to have nonadenoma precursors that are overlooked by screening.

Published online March 31, 2011.

doi: 10.1158/1055-9965.EPI-11-0086

©2011 American Association for Cancer Research.

Single Nucleotide Polymorphisms in Genes of One-Carbon Metabolism Pathway and Bladder Cancer Survival

Chang SC, Yang YC, Zhang ZF

One-carbon metabolism pathway plays an important role in carcinogenesis through its involvement in DNA methylation and biosynthesis. Epidemiologic studies have indicated the associations between genetic polymorphisms in this pathway and the susceptibility of various cancers, including bladder cancer. However, few studies have focused on their associations with bladder cancer prognosis. Using follow-up data from 249 bladder cancer patients who have been treated at the Memorial Sloan-Kettering Cancer Center from 1993 to 1997, we investigated the associations between survival time of bladder cancer patients and single nucleotide polymorphisms (SNPs) involved in the one-carbon metabolism pathway. Epidemiologic data were collected by trained interviewers. Genotyping of seven SNPs in methylenetetrahydrofolate reductase (MTHFR), methionine synthase (MTR), methionine synthase reductase (MTRR), DNA methyltransferase 1 (DNMT1), and aldehyde dehydrogenase 2 (ALDH2) genes was performed using SNPlex and Taqman assays (Applied Biosystems) with DNA isolated from blood samples collected at time-of-interview. Survival curves were estimated using the Kaplan-Meier method, and differences in distributions were evaluated by log-rank tests and Cox proportional hazards models. Overall, no obvious associations were observed between the studied SNPs and all-cause mortality among bladder cancer patients after adjustment on age, gender, race/ethnicity, smoking status, and tumor stage. However, after stratification on smoking status, increased survival time was found among ever-smoked carriers of MTRR rs1532268 and rs1801394 variant allele, with adjusted HRs of 0.65 (95% CI = 0.45–0.95) and 0.65 (95% CI = 0.43–0.98), respectively. Increased survival time was also observed among never smokers with ALDH2 rs2238151 C/T or T/T

genotypes, compared to those with the C/C genotype (HR = 0.23, 95% CI = 0.06–0.90). Our findings suggest that smoking may interact with one-carbon metabolism pathway related genetic polymorphisms on survival among bladder cancer patients. Future studies with larger sample sizes are needed to confirm the associations.

Published online March 31, 2011.

doi: 10.1158/1055-9965.EPI-11-0087

©2011 American Association for Cancer Research.

The Cancer Stroop Task as an Implicit Measure of Cognitive Interference in Head and Neck Cancer Patients

Milbury K, Badr H

Given the stigmatizing and debilitating nature of head and neck cancer (HNC) and its treatment, patients are at risk of developing trauma symptoms such as cognitive interference (unwanted, disturbing thoughts) that can increase their risk for distress. Most measures of cognitive interference employ a self-report format making them susceptible to self-presentation and defensive biases. To address these limitations, we developed and implemented an implicit measure, a cancer Stroop task (CST), with the goal to establish a link between implicit intrusive cognitions and distress (BSI) and self-reported intrusive cognitions (Impact of Events Scale, IES). As part of an observational spousal support study, 70 patients (87% male) completed self-report measures and then engaged in problem-solving discussions with their spouses about cancer-related concerns in the lab. Afterward, the computerized CST was administered. Participants were instructed to color-name each stimulus word while ignoring word meaning. Slower responses to emotionally salient (cancer) versus neutral words reflect their power to automatically capture attention and become intrusive. Results revealed a significant inverse association between response time to cancer words and distress ($P < 0.001$) and self-reported cognitive intrusion ($P < 0.01$) so that individuals who responded more slowly revealed greater distress and cognitive intrusion compared to individuals with faster responses. These findings suggest that the CST is a promising measure of cognitive interference as it is associated with self-report measures of distress and cognitive intrusion. Unlike self-report measures assessing intrusive cognitions over the past 7 days, this implicit measure allows to examine the effects of immediate environmental antecedents on cognitive interference. Thus, our next step in this ongoing study will be to behaviorally code the cancer discussion for supportiveness on the spouse as a predictor of cognitive interference as measured by the CST.

Published online March 31, 2011.

doi: 10.1158/1055-9965.EPI-11-0088

©2011 American Association for Cancer Research.

The Association between Prognostic Demographic and Tumor Characteristics of Breast Carcinomas with Serum 25-OH Vitamin D Levels

Peppone L, Rickles A, Huston A, Sprod L, Hicks D, Mustian K, Skinner K

Objective: Epidemiologic studies show that women with low 25-OH vitamin D levels have an increased risk of breast cancer incidence and mortality. However, there is a lack of research examining vitamin D levels and prognostic variables in breast cancer patients. The aim of this study is to identify the associations between 25-OH vitamin D levels, demographic variables, and prognostic pathological and genetic characteristics of breast cancers.

Method: This study cohort consists of 155 women who underwent breast cancer surgery at the University of Rochester between 1/2009 and 9/2010. Vitamin D levels were obtained in the 1-year period before and after surgery (74% of vitamin D levels within 6 months). Prognostic variables included age, race, menopausal status, Oncotype DX score, TNM staging, ER/PR status, and HER2 expression. ANCOVA, linear regression, and logistic regression were used to determine the association between prognostic variables and 25-OH vitamin D levels, while controlling for relevant covariates (age, race, and month of blood draw).

Results: Non-Caucasian (OR = 3.8; $P < 0.01$) and premenopausal (OR = 3.5; $P < 0.01$) breast cancer patients were significantly more likely to have suboptimal 25-OH vitamin D levels than Caucasian and postmenopausal patients, respectively. Women with invasive breast tumors were more likely to have suboptimal vitamin D levels (invasive OR = 2.4; $P = 0.10$) and lower mean 25-OH vitamin D levels (invasive: 30.5 ng/mL vs. *in situ*: 36.9 ng/mL; $P = 0.04$). A significant correlation ($r = -0.42$; $P = 0.04$) between decreasing vitamin D levels and increasing Oncotype score was noted. Breast cancer patients who had ER- and triple-negative breast tumors were more likely to have suboptimal levels of 25-OH vitamin D (ER-OR = 2.4; $P = 0.07$; triple-negative OR = 2.6; $P = 0.09$).

Conclusions: Breast cancer patients with suboptimal vitamin D levels were more likely to have tumors with more aggressive tumor profiles, worse prognostic markers (ER- and triple-negative tumors), and higher recurrence risk (Oncotype scores), lending support to previous research that found decreased breast cancer survival among vitamin D deficient individuals. Further research is needed to elucidate the biological relationship between vitamin D and prognostic breast cancer markers.

Published online March 31, 2011.

doi: 10.1158/1055-9965.EPI-11-0089

©2011 American Association for Cancer Research.

Methylation of Retinoic Acid Receptor, Beta (RARβ) Gene Increases Risk for Prostate Cancer in African-American Men

Rybicki B, Mitache N, Do K, Jankowski M, Tang D, Rundle A, Bock C, Beebe-Dimmer J, Belinsky S

DNA methylation is an indicator of the initiation of prostate carcinogenesis and as such has utility as a marker of risk in pathologically negative prostate tissue samples. We conducted a matched case-control study nested in a historical cohort of over 6,000 men with pathologically benign prostate specimens identified between January 1991 and November 2002 with no previous history of prostate cancer. Eligible cases were diagnosed with prostate cancer at least one year after cohort entry. Controls were selected through incidence density sampling and matched to cases on date and age at cohort entry, race, and type of specimen. In 310 matched prostate cancer case-control pairs (65% white; 35% African American), we assayed the DNA of the benign prostate specimen for presence of methylation in a five-gene panel (APC, RARβ, CCND2, RASSF1, MGMT) and then estimated the risk of developing prostate cancer associated with methylation at each gene for the whole sample and stratified by race. Overall, methylation of RARβ had the strongest association with prostate cancer risk (HR = 1.94; 95% CI = 1.30–2.91). In race-stratified analyses, the majority of the increased risk associated with RARβ was found in the African-American sample (HR = 3.40; 95% CI = 1.68–6.88). In addition, APC was also associated with increased risk for prostate cancer in the African-American sample (HR = 2.17; 95% CI = 1.09–4.29). In a model that included both genes, only RARβ remained statistically significantly associated with prostate cancer (HR = 3.14; 95% CI = 1.54–6.44). In whites, methylation was not associated with prostate cancer for any of the five genes assayed. In summary, positive methylation status at RARβ and APC in pathologically benign prostate is associated with significant increased risk for subsequent prostate cancer, but primarily in African-American men. Whether this race-specific risk is due to racial differences in environmental stimuli and/or biology is unclear, but further study of DNA methylation in the earliest stages of prostate carcinogenesis may help explain the disproportionate burden of this disease among African-American men.

Published online March 31, 2011.

doi: 10.1158/1055-9965.EPI-11-0091

©2011 American Association for Cancer Research.

The Association of Serum Phthalates and Parabens with Mammographic Breast Density

Sprague B, Trentham-Dietz A, Hedman C, Hemming J, Hampton J, Buist D, Aiello Bowles E, Burnside E, Sisney G

Humans are exposed to a large number of environmental chemicals which have estrogenic activity, raising

concern regarding potential effects on breast tissue and breast cancer risk. Phthalates are commonly found in personal care products, such as shampoos, lotions, and shaving products, and are present in many consumer plastics, adhesives, detergents, and pharmaceuticals. Parabens are also found in personal care products, and are additionally used as antimicrobials in foods. *In vitro* studies have demonstrated that many phthalates and parabens can bind to the estrogen receptor and initiate estrogenic cellular pathways, and a recent case-control study found that urinary concentrations of mono-ethyl-phthalate were positively associated with breast cancer risk. We examined the cross-sectional association of circulating serum levels of phthalates and parabens with mammographic breast density (a marker for breast cancer risk). A total of 261 postmenopausal women (ages 55–70, with no history of postmenopausal hormone use) were recruited from mammography clinics in Madison, Wisconsin. Patients completed a questionnaire regarding known breast cancer risk factors and provided a blood sample that was analyzed for mono-ethyl-phthalate, mono-butyl-phthalate, mono-benzyl-phthalate, butyl paraben, and propyl paraben. Percent breast density was measured from patients' mammograms as a continuous variable using a computer-assisted thresholding method (Cumulus software). After adjusting for age and body mass index, mono-ethyl-phthalate was positively associated with percent breast density. Women with detectable mono-ethyl-phthalate levels (>0.4 ng/mL; $N = 36$) had higher percent breast density than women with no detectable mono-ethyl-phthalate ($N = 225$) in their serum (16.8% vs. 12.8%; $P = 0.03$). Serum levels of mono-butyl-phthalate and mono-benzyl-phthalate were generally below the limits of detection. Serum levels of butyl-paraben and propyl-paraben were higher (detectable in 55% and 67% of patients, respectively), but neither was associated with breast density ($P > 0.20$). These results suggest that further investigation into the potential influence of mono-ethyl-phthalate (and its parent compound diethyl-phthalate) on breast tissue is warranted.

Published online March 31, 2011.

doi: 10.1158/1055-9965.EPI-11-0092

©2011 American Association for Cancer Research.

Cervical Cancer Screening Efficacy in Older Women

Kamineni A, Weinmann S, Shy KK, Mandelson MT, Glass AG, Weiss NS

Although the effectiveness of cervical cancer screening, by means of the Pap smear, has been firmly established in reproductive-age women, the usefulness of cytologic screening in older women is unclear. We sought to assess the degree to which such screening in older women can reduce the incidence of cervical cancer. We conducted a case-control study to evaluate

the efficacy of cervical cancer screening in older women enrolled in one of two large health maintenance organizations in the northwestern United States. Cases ($n = 69$) consisted of those women, 55 to 79 years of age, who were diagnosed with invasive cervical cancer during 1980 to 1999 as enumerated by regional cancer registries. Controls ($n = 208$) were women sampled from among enrollees who had not previously had a hysterectomy and were similar to cases in terms of age and length of enrollment in the health plan. We reviewed medical records to ascertain demographic, reproductive, and cervical screening history information during the 7 years before the reference date. Only tests which occurred during the presumed detectable preinvasive phase (DPP) of the disease, when screening could be beneficial, were considered and we evaluated results for a series of plausible estimates of this interval. Compared to cases, controls were more likely to have had a Pap test during the DPP, regardless of the estimate used. After adjustment for age and current smoking status, screening was associated with a substantial reduction in the risk of invasive cervical cancer (DPP = 72 months: OR, 0.23; 95% CI, 0.11–0.44). We observed only small differences in the odds ratio across the various estimates of the DPP that were employed. Analysis of the relative incidence of invasive cervical cancer in relation to the time following a negative screening test suggested a large reduction during the first year (OR, 0.09; 95% CI, 0.03–0.24). The incidence remained low for several years thereafter, returning to the incidence among unscreened women after 5 to 7 years. Cervical cancer screening is highly efficacious in older women. This needs to be explicitly considered in weighing the benefits and costs of such screening beyond the reproductive years.

Published online March 31, 2011.

doi: 10.1158/1055-9965.EPI-11-0093

©2011 American Association for Cancer Research.

Predictors and Health Consequences of Epigenetic Changes Associated with Excess Body Weight in Women of Child-bearing Age

Piyathilake C, Badiga S, Johanning G, Alvarez R, Partridge E

Background: Epigenetic alterations occurring during pregnancy have recently emerged as important factors for developmental programming of the fetus leading to obesity-related diseases in children. However, the role of excess body weight (EBW) in the modification of epigenetic patterns or its health consequences during child-bearing age is largely unknown. Because a lower degree of DNA methylation of long interspersed nucleotide element-1 (LINE-1) in PBMCs was shown to be associated with a higher risk of developing obesity-related diseases, for example cancer, the purpose of this study was to (1) evaluate the influence of indicators of obesity (BMI, WC,

and % body fat) on PBMC LINE-1 methylation, (2) determine the predictors of PBMC LINE-1 methylation, and (3) determine the influence of PBMC LINE-1 methylation on biomarkers of obesity-related diseases.

Methods: The study population consisted of 470 child-bearing age women. We quantified the degree of PBMC LINE-1 methylation by pyrosequencing. Folate concentrations were measured using a microbiological assay. The degree of LINE-1 methylation ($>$ median vs. \leq median) was the dependent variable in logistic models that specified BMI (>25 vs. ≤ 25), WC (>88 cm vs. ≤ 88 cm), or % body fat ($>33\%$ vs. $\leq 33\%$) separately as the independent predictors of primary interest, adjusting for other relevant variables. The predictors and determinants of lower LINE-1 methylation were evaluated among women with EBW.

Results: Women with higher BMI, WC, or % body fat were 2.0, 1.9, and 1.8 times more likely to have lower LINE-1 methylation, respectively ($P = 0.003, 0.005, \text{ and } 0.01$). The predictors and determinants of lower LINE-1 methylation yielded similar patterns with all three indicators of obesity. The following results are based on models run with BMI as the indicator for EBW. Women with higher plasma folate concentrations were less likely to have lower LINE-1 methylation (OR = 0.54, $P = 0.0009$). Higher LINE-1 methylation was associated with lower insulin resistance as indicated by HOMA (OR = 0.50, $P = 0.02$).

Conclusions: EBW-associated lower LINE-1 methylation in women of child-bearing age appears to have significant, and potentially transgenerational, health consequences. Higher folate status may exert beneficial effects on obesity-related health outcomes.

Published online March 31, 2011.

doi: 10.1158/1055-9965.EPI-11-0094

©2011 American Association for Cancer Research.

MicroRNA-Related Genetic Variants as Predictors of Early Stage Non-Small Cell Lung Cancer Clinical Outcomes

Pu X, Lu C, Stewart DJ, Gu J, Hildebrandt MAT, Lin J, Lippman SM, Xifeng W

Purpose: MicroRNAs (miRNA) can function as oncogenes or tumor suppressors. In this study, we test the hypothesis that genetic variation within miRNA processing genes or miRNA binding sites in cancer-related genes may alter clinical outcomes for non-small cell cancer (NSCLC) patients.

Methods: We genotyped 72 single nucleotide polymorphisms (SNPs) from eight miRNA processing genes and 168 SNPs from 133 predicted miRNA binding sites in 535 patients with early stage (stages I, IIA, and IIB) NSCLC to determine the effect of these variations on progression risk and overall survival. We further conducted a subset analysis to exclude potential bias due to different treatment regimens.

Results: In the analysis of overall survival, an *FAS* SNP remained significant for decreased risk after multiple comparisons in all early patients (HR: 0.59, 95% CI: 0.44–0.77; GG: MST = 58 mos, GA + AA: MST = 118 mos) and surgery plus chemotherapy subgroup (HR: 0.19, 95% CI: 0.07–0.46, $P = 1.84 \times 10^{-5}$; GG: MST = 65 mos, GA + AA: MST = 137 mos). In the surgery-only patients, an *FZD4* SNP (HR: 0.46, 95% CI: 0.32–0.65; GG: MST = 59 mos, GA + AA: MST = 117 mos) had a significant protective effect after multiple comparisons adjustment. For progression risk, following multiple comparison, an *SP1* SNP (HR: 2.19, 95% CI: 1.45–3.32; GG: MST > 270 mos, GA + AA: MST = 45 mos) and an *MBD1* SNP (HR: 2.41, 95% CI: 1.45–4.0; AA: MST > 270 mos, C + CC: MST = 90 mos) remained significant increased progression risk in the entire and surgery only population respectively. All the associations significant after adjusting for multiple comparisons were validated by Bootstrap resampling method. A strong cumulative effect of these variant genotypes to increase risk and dramatically decrease median event-free time was consistently observed. We also identified potential higher-order gene–gene interactions among these SNPs.

Conclusions: We identified significant association between miRNA-related genetic variants and early stage NSCLC patient clinical outcomes. With validation, our result can be used in the prognosis of clinical outcomes for early stage NSCLC patients.

Published online March 31, 2011.

doi: 10.1158/1055-9965.EPI-11-0095

©2011 American Association for Cancer Research.

The Impact of Detection and Treatment of Carcinoma *In Situ* on Breast Cancer Mortality

Trentham-Dietz A, Sprague BL, Alagoz O, Reaidi P, Rosenberg M, Gangnon RE, Stout NK

Purpose: Ductal carcinoma *in situ* (DCIS), a nonobligate precursor to invasive breast cancer, makes up 20% of new breast cancer diagnoses. DCIS is primarily detected by mammography and has excellent prognosis regardless of therapy choice. We aim to quantify the impact of detection and treatment of DCIS on breast cancer mortality using computer modeling.

Methods: We used a validated microsimulation model to replicate U.S. trends in breast cancer incidence and mortality from 1975 to 2000. All breast cancer tumors began in the *in situ* stage and progressed through more advanced stages with increasing tumor size and lymph node involvement, with a fraction of tumors assumed as nonlethal. Age-adjusted breast cancer mortality was examined under historical U.S. screening and treatment patterns and three alternative scenarios: (1) only women 50 years and older received screening and all breast cancer cases received treatment according to historical patterns, (2) all women

received screening according to historical patterns but DCIS was untreated unless later detected at an invasive stage, and (3) historical screening was used but DCIS was never treated.

Results: The model predicts breast cancer mortality rates declined during the 1990s to a low of 39.9 per 100,000 in 2000, which is consistent with observed mortality based on the SEER program (38.0 per 100,000 in 2000). Delaying mammography until age 50 or postponing treatment until DCIS progressed to invasive cancer increased mortality to 42.4 and 43.2 per 100,000, respectively, by 2000. If DCIS patients did not receive any treatment, mortality remained steady (~51.2 per 100,000) through 2000.

Conclusions: Our model results suggested detection and treatment of DCIS in the U.S. reduced breast cancer deaths in the year 2000 by about 28%. Most of this benefit (92%–94%) could also be achieved if instead mammography began at age 50 or treatment was reserved for invasive breast cancers only.

Published online March 31, 2011.

doi: 10.1158/1055-9965.EPI-11-0096

©2011 American Association for Cancer Research.

Prenatal Tobacco Smoke Exposure and Genome-wide Methylation in Adulthood

Flom J, Ferris J, Gonzalez K, Santella R, Terry MB

Genomic DNA demethylation, including demethylation of repetitive elements (which comprise 45% of the human genome), has been linked to increased risk of breast and other cancers. Genomic DNA methylation can be altered prenatally and throughout life and may be a mechanism through which the environment alters disease risk. There is evidence that prenatal tobacco smoke exposure has a persistent impact on genomic DNA methylation; however, no study to date has assessed the association between prenatal smoke exposure and adult repetitive element methylation. We measured repetitive element methylation of Alu, LINE-1, and Sat2 using MethylLight in 92 members of the New York Women's Birth Cohort, a follow-up of former female participants of the New York site of the U.S. National Collaborative Perinatal Project (mean age at blood draw = 43.5, SD = 1.8). Prenatal smoke exposure was reported prospectively. We estimated associations using multivariable linear regression, and used the natural log of Alu, LINE-1, and Sat2 methylation level. Thirty-one (36%) participants were exposed to prenatal smoke. These participants were more likely to smoke at the time of interview ($P < 0.01$). Prenatal smoke exposure was inversely associated with genomic DNA methylation of Sat2 and Alu, adjusted for age, childhood environmental tobacco smoke exposure (ETS) and adult smoking status (exposed vs. unexposed to prenatal smoke: Sat2: $\beta = -0.20$, 95% CI = $-0.39, -0.02$; Alu: $\beta = -0.09$, 95% CI = $-0.26, 0.08$). In

multivariable models, childhood ETS had a positive, borderline significant association with Sat2 methylation ($\beta = 0.17$, 95% CI $-0.02, 0.37$). If replicated in larger studies, these results suggest that prenatal smoke exposure may have a persistent impact on genomic DNA demethylation of Sat2 and Alu in adulthood, and thus may be a pathway through which prenatal smoke exposure impacts adult disease. Results are strengthened by the fact that prenatal smoke exposure data were collected prospectively in the early 1960s, before there was a stigma associated with maternal smoking during pregnancy. These results are consistent with the one study assessing this relation in children. Further studies are needed to confirm this finding and to investigate the underlying biological mechanism.

Published online March 31, 2011.

doi: 10.1158/1055-9965.EPI-11-0097

©2011 American Association for Cancer Research.

Perceived Treatment Assignment and Smoking Cessation in a Clinical Trial of Bupropion

Buchanan TS, Cox LS, Nollen NL, Thomas JL, Berg CJ, Mayo MS, Ahluwalia JS

Research on tobacco cessation pharmacotherapy often relies on double-blind, placebo-controlled randomized trials. These studies are designed to control for the placebo effect (i.e., the influence of participants' expectations on treatment outcome). Psychoactive effects of smoking cessation medications such as bupropion may allow participants to correctly guess their treatment assignment at rates greater than chance. Perceived treatment assignment could potentially impact smoking cessation rates. The aim of this study was to determine the impact of

perceived treatment assignment on end-of-treatment cotinine-verified smoking abstinence among African-American light smokers [≤ 10 cigarettes per day (cpd)] enrolled in a double-blind, placebo-controlled study of bupropion. Participants were randomized to bupropion (150 mg bid) or placebo and received identical written materials and health education counseling. Participants ($n = 390$) included in this study reported their perceived treatment assignment on the end-of-treatment (week 7) survey. They were predominantly female (63.1%), 48.1 years (SD = 11.2), and smoked 8 cpd (SD = 2.5). The majority (81.3%) smoked menthol cigarettes. Participants given bupropion were more likely to correctly guess their treatment assignment (69%; 140/203) than those assigned to placebo (51.3%; 96/187). Quit rates by treatment assignment were 31.5% (bupropion) versus 13.9% (placebo) (OR = 2.78, 95% CI 1.61–5.43, $P < 0.01$). After adjusting for treatment, participants who perceived assignment to bupropion versus placebo were not more likely to be abstinent (OR = 1.37; 95% CI 0.71–2.64, $P = 0.35$). The interaction between treatment and perceived treatment assignment was also nonsignificant. Consistent with two previous studies with bupropion, there was evidence of blinding failure for the treatment group. However, in our study, perceived treatment assignment did not significantly impact cotinine-verified cessation outcome at end-of-treatment (week 7). These findings suggest that the role of perceived treatment assignment on smoking cessation with bupropion may differ for light smokers compared to heavier smokers (>10 cpd) sampled in the two earlier studies. Current findings might indicate that expectations of pharmacotherapy are less salient for light smokers.

Published online March 31, 2011.

doi: 10.1158/1055-9965.EPI-11-0098

©2011 American Association for Cancer Research.