EGRP Research Highlights

Epidemiology and Genetics Research Program

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The Epidemiology and Genetics Research Program (EGRP) supports nearly 500 grants and cooperative agreements annually. Investigators from throughout the United States and internationally are funded to conduct population-based research to increase our understanding of cancer etiology and prevention. Some of their recent research findings are highlighted in the following pages. The names of the Principal Investigators of the EGRP-supported grants cited in the published papers appear in boldface print. Also visit EGRP's Web site to view a special section with highlights from any other studies: *epi.grants.cancer.gov*.

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Spring 2005

Genome-Wide Scan Conducted for Prostate Cancer Susceptibility Genes


Jianfing Xu, M.D., Dr.P.H.

In the largest genome-wide scan for prostate cancer susceptibility genes to date, Elizabeth Gillanders, M.D., of the National Human Genome Research Institute, **Jianfing Xu, M.D., Dr.P.H.**, of Wake Forest University (pictured), **Kathleen Cooney, M.D.**, of the University of Michigan, and **William Isaacs, Ph.D.**, of Johns Hopkins University, and colleagues combined four existing hereditary prostate cancer (HPC) study populations and conducted a genome-wide linkage analysis to systematically search for prostate cancer susceptibility genes in 426 HPC families. The power to detect a major prostate cancer gene depends on the number of linked families in the study population; the larger the study population, the more likely it is that a major gene can be detected. The strongest evidence for prostate cancer linkage was found at chromosome region 17q22. Several additional chromosomal regions that are likely to segregate prostate cancer susceptibility genes among specific subsets of HPC families also were identified, including 15q11 among families with late-onset disease and 4q35 among families with four or more affected family members.

Gillanders EM, Xu J, Chang BL, Lange EM, Wiklund F, Bailey-Wilson JE, Baffoe-Bonnie A, Jones M, Gildea D, Riedesel E, Albertus J, Isaacs SD, Wiley KE, Mohai CE, Matikainen MP, Tammela TL, Zheng SL, Brown WM, Rokman A, Carpten JD, Meyers DA, Walsh PC, Schleutker J, Gronberg H, Cooney KA, Isaacs WB, Trent JM. Combined genome-wide scan for prostate cancer susceptibility genes. J Natl Cancer Inst 2004 Aug 18;96(16):1240-7.

Dietary Carotenoids May Protect Against DNA Damage and Bladder Cancer


Xifeng Wu, M.D., Ph.D.

Matthew Schabath, Ph.D., and **Xifeng Wu, M.D., Ph.D.**, of The University of Texas M.D. Anderson Cancer Center, and colleagues evaluated the joint effects of carotenoid intake and genetic instability in risk for bladder cancer. They found that high carotenoid intake was associated with an overall decreased risk for bladder cancer, and that individuals susceptible to DNA damage (as assessed by the comet assay) may be able to reduce their risk through increased dietary intake of carotenoids. There was an inverse association between increasing levels of carotenoid intake and risk for bladder cancer, with the greatest protective effect in the quartile with the highest risk (odds ratio = 0.56). Baseline and mutagen-induced DNA damage were significantly higher in cases than in controls; when analyzed jointly with carotenoid intake, high DNA damage and low carotenoid intake were associated with the highest risk. The study included 423 bladder cancer cases and 467 controls.

Schabath MB, Grossman HB, Delclos GL, Hernandez LM, Day RS, Davis BR, Lerner SP, Spitz MR, Wu X. Dietary carotenoids and genetic instability modify bladder cancer risk. J Nutr 2004 Dec;134(12):3362-9.

Arylamine Exposure Associated With Nonsmoking-Related Bladder Cancer


Mimi Yu, Ph.D.

Certain arylamine compounds are known human bladder cancer carcinogens. Exposure occurs primarily through cigarette smoking and use of permanent hair dye. Based on recent findings, identifying nonsmoking-related sources of the compounds should be a high priority, say Jinping Gan, Massachusetts Institute of Technology, **Ronald Ross, M.D.**, and **Mimi Yu, Ph.D.**, University of Southern California at Los Angeles, and colleagues. They analyzed data on tobacco smoking and other potential risk factors for bladder cancer and arylamine-hemoglobin adducts in blood samples from patients with the cancer and controls. Elevated


Ronald Ross, M.D.

levels of adducts for three alkylanilines (2,6-DMA, 3,5-DMA, and 3-EA) were independently, statistically significantly associated with bladder cancer risk after adjusting for smoking and other potential risk factors. The increased risk persisted when the analysis was restricted to nonsmokers at time of blood draw. Nonsmokers in the highest quartiles of adduct levels were three to five times more likely to develop bladder cancer than individuals in the lowest quartiles. The study included 298 bladder cancer cases and 308 controls.

Gan J, Skipper PL, Gago-Dominguez M, Arakawa K, Ross RK, Yu MC, Tannenbaum SR. Alkylaniline-hemoglobin adducts and risk of non-smoking-related bladder cancer. J Natl Cancer Inst 2004 Oct 6;96(19):1425-31.

DNA Repair Deficiency Associated With Breast Cancer Risk in Sister Pairs

Rubie Senie, Ph.D.

Deficient DNA repair capacity may influence risk for breast cancer and may be a valuable *in vitro* biomarker to identify high-risk individuals, especially in breast cancer families, according to a study by David Kennedy, Ph.D., and **Rubie Senie, Ph.D.**, of Columbia University, and colleagues. The researchers analyzed DNA repair capacity in lymphoblastoid cells from sister pairs, comparing women diagnosed with breast cancer to their unaffected sisters. The cells were treated with a DNA-damaging carcinogen (benzo[a]pyrene diolepoxide), and those cells of sisters with breast cancer were 8.6 percent less effective than their sisters' cells in responding to the assault. Women who had the lowest levels of DNA repair capability had double the risk for breast cancer compared with women who had the highest capability. The largest differences were found between patients and controls younger than age 40. In addition, the relative risk of breast cancer was nearly 3 times greater between the groups with the most and the least DNA repair capabilities. The study population (158 case patients and 154 controls) was from the EGRP-funded Metropolitan New York Registry of Breast Cancer Families.

Kennedy DO, Agrawal M, Shen J, Terry MB, Zhang FF, Senie RT, Motykiewicz G, Santella RM. DNA repair capacity of lymphoblastoid cell lines from sisters discordant for breast cancer. J Natl Cancer Inst 2005 Jan 19;97(2):127-32.

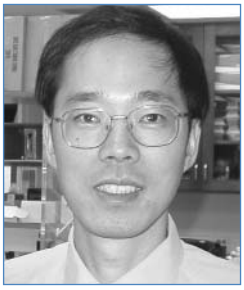
Protective Effect of Breast-Feeding Quantified for *BRCA1* Gene Mutation Carriers

Steven Narod, M.D., Ph.D.

In a large case-control study, researchers examined the relationship between breast-feeding and risk for breast cancer among women with *BRCA1* and *BRCA2* gene mutations. Helena Jernström, Ph.D., Lund University Hospital, Sweden, **Susan Neuhausen, Ph.D.**, University of California at Irvine, and **Steven Narod, M.D., Ph.D.**, University of Toronto (pictured), and colleagues found that women with *BRCA1* gene mutations who breast-fed for longer than 1 year were 45 percent less likely to develop breast cancer than women who had never breast-fed. This protective effect is much greater than has been found in the general population. No association between breast cancer risk and breast-feeding was found for women with *BRCA2* gene mutations, which may reflect underlying differences in the pathogenesis of cancer associated with the two genes, or the smaller number of women with *BRCA2* gene mutations in this study. The study included 965 cases (685 with *BRCA1* and 280 with *BRCA2* gene mutations) and 965 controls who did not have a history of breast or ovarian cancer. The researchers say that the findings provide further evidence of the connection between hormonal changes associated with reproduction and breast-feeding that affect breast cell proliferation and differentiation and breast cancer risk.

Jernström H, Lubinski J, Lynch HT, Ghadirian P, Neuhausen S, Isaacs C, Weber BL, Horsman D, Rosen B, Foulkes WD, Friedman E, Gershoni-Baruch R, Ainsworth P, Daly M, Garber J, Olsson H, Sun P, Narod SA. Breast-feeding and the risk of breast cancer in *BRCA1* and *BRCA2* mutation carriers. J Natl Cancer Inst 2004 Jul 21;96(14):1094-8.

Synergistic Effects for *STK15* Gene and Estrogen Found in Breast Cancer Risk



Wei Zheng, Ph.D.

The *STK15* gene is a cell-cycle regulator that may interact with estrogen, a cell-proliferation stimulator, in the pathogenesis of breast cancer. Qi Dai, M.D., Ph.D., and **Wei Zheng, Ph.D.**, of Vanderbilt University (pictured), and colleagues found an increased risk for breast cancer associated with a common functional polymorphism in the *STK15* gene 91T → A (Phe → Ile at codon 31), and that the association was modified by indicators of high- or long-term endogenous estrogen exposure, such as high body mass index, long duration of lifetime menstruation, and long duration of menstruation before first live birth. The findings suggest an important role for this polymorphism in breast and other hormone-related cancers. The population-based study included 1,459 breast cancer cases and 1,556 controls among Chinese women in Shanghai.

Dai Q, Cai QY, Shu XO, Ewart-Toland A, Wen WQ, Balmain A, Gao YT, Zheng W. Synergistic effects of STK15 gene polymorphisms and endogenous estrogen exposure in the risk of breast cancer. Cancer Epidemiol Biomarkers Prev 2004 Dec;13(12):2065-70.

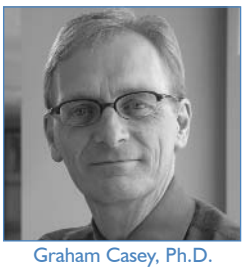
New Estimates Calculated for *BRCA1* Gene Mutation Carriers Among U.S. Non-Hispanic Whites

Alice Whittemore, Ph.D.

Alice Whittemore, Ph.D., of Stanford University (pictured), **Esther John, Ph.D.**, of the Northern California Cancer Center, and **Frederick Li, M.D.**, of Dana-Farber Cancer Institute, and colleagues have developed estimates of *BRCA1* gene mutation carriers among U.S. non-Hispanic whites according to whether they are of Ashkenazi ancestry or not. The estimates were obtained by combining mutation carrier prevalences among two population-based series of breast and ovarian cancer patients with published estimates of cumulative risks for these cancers in mutation carriers and noncarriers. They estimated that 0.24 percent of U.S. non-Hispanic whites without Ashkenazi ancestry have *BRCA1* gene mutations. This is the first precise estimate on the prevalence of *BRCA1* mutations among this population. They also estimated that 1.2 percent of U.S. non-Hispanic whites with Ashkenazi ancestry have *BRCA1* gene mutations, which is in agreement with other studies. The estimates may be useful in guiding resource allocations for counseling, and cancer prevention and detection activities. The breast cancer patients in the study were from the Northern California component of the EGRP-funded Breast Cancer Family Registry.

Whittemore AS, Gong G, John EM, McGuire V, Li FP, Ostrow KL, Dicioccio R, Felberg A, West DW. Prevalence of *BRCA1* mutation carriers among U.S. non-Hispanic whites. Cancer Epidemiol Biomarkers Prev 2004 Dec;13(12):2078-93.

Improved Method Demonstrated To Detect HNPCC Mutations



Graham Casey, Ph.D.

Several genes involved in DNA mismatch repair have been implicated in hereditary nonpolyposis colorectal cancer (HNPCC). Detection of mutations in these genes is crucial for recommending appropriate genetic counseling, screening, and surveillance.

Graham Casey, Ph.D., of The Cleveland Clinic, and other **investigators of the Colon Cancer Family Registry (CFR)**, compared the ability of conversion analysis with conventional DNA sequencing to detect heterogeneous germline mutations in mismatch repair genes *MHL1* and *MSH2* in HNPCC patients. Using conventional sequencing, normal copies of genes can sometimes mask mutations in the other allele. Conversion

analysis overcomes this weakness by separating pairs of chromosomes prior to analysis, through generation of human/mouse somatic cell hybrids. Results of this study demonstrated that conversion analysis provided a 33 percent improvement in detection of mismatch repair mutations in 89 colorectal cancer cases and a 56 percent increase in the diagnostic yield of genetic testing, compared with conventional sequencing. The Colon CFR is an EGRP-funded research resource.

Casey G, Lindor NM, Papadopoulos N, Thibodeau SN, Moskow J, Steelman S, Buzin CH, Sommer SS, Collins CE, Butz M, Aronson M, Gallinger S, Barker MA, Young JP, Jass JR, Hopper JL, Diep A, Bapat B, Salem M, Seminara D, Haile R; Colon Cancer Family Registry. Conversion analysis for mutation detection in *MLH1* and *MSH2* in patients with colorectal cancer. JAMA 2005 Feb 16;293(7):799-809.

Insulin-Related Genetic Polymorphisms Associated With Colorectal Cancer Risk

Martha Slattery, Ph.D.

Evidence suggests that insulin-like growth factors (IGF), IGF binding proteins (IGFBP, especially IGFBP-3), and insulin are important in the etiology of colorectal cancer. **Martha Slattery, Ph.D.**, of the University of Utah, and colleagues evaluated associations between polymorphisms in the *IGF1*, *IGFBP3*, *IRS1*, and *IRS2* genes with risk for colorectal cancer, both independently and in combination with each other. They found that both *IRS1* and *IRS2* variants were associated independently with risk for colon cancer. Associations were slightly stronger when polymorphisms were evaluated in combination with one another. The findings suggest that the insulin-related signaling pathway may be important in the etiology of colon cancer but not rectal cancer. Data for this analysis were from a population-based case-control study of 1,346 colon cancer cases and 1,544 controls and 952 rectal cancer cases and 1,205 controls.

Slattery ML, Samowitz W, Curtin K, Ma KN, Hoffman M, Caan B, Neuhausen S. Associations among *IRS1*, *IRS2*, *IGF1*, and *IGFBP3* genetic polymorphisms and colorectal cancer. Cancer Epidemiol Biomarkers Prev 2004 Jul;13(7):1206-14.

Vitamin D Found To Protect Against Colorectal Cancer

Edward Giovannucci, M.D., Sc.D.

Diane Feskanich, Sc.D., and **Edward Giovannucci, M.D., Sc.D.**, of Brigham and Women's Hospital and Harvard University, and colleagues investigated plasma levels of the vitamin D metabolites 25(OH)D and $1,25(OH)_2D$ and risk for colorectal cancer in a nested case-control study within the Nurses' Health Study. The NHS is a large cohort of female nurses funded by EGRP since 1973. The researchers found a statistically significant dose-response relationship between plasma 25(OH)D levels and subsequent risk for the cancer among older women (≥60 years of age at blood draw). The risk was 46 percent lower among women in the highest versus lowest quintile of 25(OH)D. The benefit was seen for cancers at the distal colon and rectum but not at the proximal colon. The study included 193 colon cancer cases and 386 controls. The findings provide additional evidence of the importance of vitamin D for aging adults.

Feskanich D, Ma J, Fuchs CS, Kirkner GJ, Hankinson SE, Hollis BW, Giovannucci EL. Plasma vitamin D metabolites and risk of colorectal cancer in women. Cancer Epidemiol Biomarkers Prev 2004 Sep;13(9):1502-8.

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- Our Division of Cancer Control and Population Sciences (DCCPS) Home page: *cancercontrol.cancer.gov* for grant policy alerts and information on funding opportunities.
- DCCPS Tobacco Control Research Branch: *cancercontrol.cancer.gov/tcrb*
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