EGRP Research Highlights

Epidemiology and Genetics Research Program

Web Site: epi.grants.cancer.gov

Contents

Epidemiology and Genetics Research Program
Division of Cancer Control and Population Sciences
6130 Executive Boulevard, Room 5113, MSC 7395, Bethesda, MD 20892-7395
Telephone: 301-496-9600; Fax: 301-435-6609

National Institutes of Health

U.S. Department of Health and Human Services

September 2004

The Epidemiology and Genetics Research Program (EGRP) supports more than 400 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 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.

Anti-Inflammatory Drugs May Decrease Brain Cancer Risk


Margaret Wrensch, Ph.D.

Use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) has been associated with decreased risk of adult glioblastoma multiforme, which is the most common primary malignant brain tumor, in a study by Niccole Sivak-Sears, Ph.D., of The Ohio State University, and **Margaret Wrensch, Ph.D.**, of the University of California at San Francisco, and colleagues. The population-based study included 236 adults with the cancer and 401 controls. Cases were less likely than controls to report use of at least 600 pills of all types of NSAIDs during the 10 years prior to diagnosis (odds ratio = 0.53). The findings were consistent for aspirin, ibuprofen, and naproxen and/or other NSAIDs. Cases also reported less use of acetaminophen than controls did.

Sivak-Sears NR, Schwartzbaum JA, Miike R, Moghadassi M, Wrensch M. Case-control study of use of nonsteroidal antiinflammatory drugs and glioblastoma multiforme. Am J Epidemiol 2004 Jun 15;159(12):1131-9.

Male Exposure to PAHs Associated With Childhood Brain Cancer


Susan Preston-Martin, Ph.D.

A large international study suggests that a father's exposure to polycyclic aromatic hydrocarbons (PAHs) from tobacco smoke or occupation before conception is associated with an increased risk of childhood brain cancer in offspring. Sylvaine Cordier, Ph.D., of the Institut National de la Sante et de Recherche Medicale in France, and **Susan Preston-Martin, Ph.D.**, of the University of Southern California at Los Angeles, and colleagues analyzed data on 1,218 cases of childhood brain tumors and 2,223 controls from population-based case-control studies in seven countries. Exposure to PAHs in women before conception or during pregnancy was not found to be associated with an excess risk of childhood brain cancer.

Cordier S, Monfort C, Filippini G, Preston-Martin S, Lubin F, Mueller BA, Holly EA, Peris-Bonet R, McCredie M, Choi W, Little J, Arslan A. Parental exposure to polycyclic aromatic hydrocarbons and the risk of childhood brain tumors: The SEARCH International Childhood Brain Tumor Study. Am J Epidemiol 2004 Jun 15;159(12):1109-16.

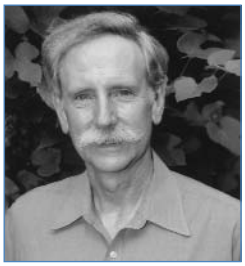
Prophylactic Mastectomy in *BRCA1/2* Mutation Carriers Found Effective Preventive Measure

Timothy Rebbeck, Ph.D.

Bilateral prophylactic mastectomy decreases breast cancer risk in women with *BRCA1/2* gene mutations by about 90 percent, and the risk is reduced by about 95 percent in women who also have bilateral prophylactic oophorectomy, according to a study by **Timothy Rebbeck, Ph.D.**, of the University of Pennsylvania, and colleagues. The findings are consistent with earlier studies, but go further by addressing some of their limitations and providing stronger data on the magnitude of risk reduction. Of 105 mutation carriers with bilateral prophylactic mastectomy in the cohort, two (1.9%) were diagnosed with breast cancer after bilateral prophylactic mastectomy compared with 184 (48.7%) of 378 controls. While the decision to have bilateral prophylactic mastectomy is complex, the scientists conclude, women who have done so have chosen an effective preventive strategy.

Rebbeck TR, Friebel T, Lynch HT, Neuhausen SL, van 't Veer L, Garber JE, Evans GR, Narod SA, Isaacs C, Matloff E, Daly MB, Olopade OI, Weber BL. Bilateral prophylactic mastectomy reduces breast cancer risk in BRCA1 and BRCA2 mutation carriers: The PROSE Study Group. J Clin Oncol 2004 Mar 15;22(6):1055-62.

Smoking Linked to ER-Positive Breast Cancer in Young Women



Walter Willett, M.D., Dr.P.H.

Smoking appears to be a risk factor for estrogen receptor (ER)-positive breast cancer in young adult women, according to a study by Wael Al-Delaimy, M.D., M.P.H., and **Walter Willett, M.D., Dr.P.H.**, of the Harvard School of Public Health, and colleagues. The scientists investigated risk for breast cancer according to hormone receptor status among participants in the Nurses' Health Study (NHS) II, which is a cohort study of 112,844 women who mainly are premenopausal. They found that duration of smoking and smoking at an early age were more likely to increase risk. Women who had smoked for 20 or more years had a 37 percent increased risk of developing ER-positive breast cancer compared to women who never smoked. Women who began smoking before age 15 had a 49 percent increased risk for the cancer. EGRP has funded the NHS II since 1989.

Al-Delaimy WK, Cho E, Chen WY, Colditz G, Willet WC. A prospective study of smoking and risk of breast cancer in young adult women. Cancer Epidemiol Biomarkers Prev 2004 Mar;13(3):398-404.

Statins Not Associated With Increased Risk of Breast Cancer and May Be Protective

Janet Daling, Ph.D.

The cholesterol-lowering drugs called statins do not increase risk of breast cancer among postmenopausal women and may reduce the risk, according to a study by Denise Boudreau, Ph.D., and **Janet Daling, Ph.D.**, of the Fred Hutchinson Cancer Research Center, and colleagues. They found that women who were currently taking statins or who ever used them were not at increased risk of breast cancer. On the other hand, women who regularly took statins for more than 5 years had a slightly decreased risk of the cancer (odds ratio = 0.7). The findings are important because results from previous studies on the carcinogenicity of statins have been inconsistent. They also add to accumulating evidence suggesting that the drugs may have a protective effect. The population-based case-control study included 975 women with breast cancer and 1,007 controls. (Boudreau is now with the Group Health Cooperative, Seattle.)

Boudreau DM, Gardner JS, Malone KE, Heckbert SR, Blough DK, Dahling JR. The association between 3-hydroxy-3-methylglutaryl conenzyme A inhibitor use and breast carcinoma risk among postmenopausal women. Cancer 2004 Jun 1;100(11):2308-16.

Aspirin May Decrease Risk of Hormone Receptor-Positive Breast Cancer

Alfred Neugut, M.D., Ph.D.

Women who regularly take aspirin seem to be at lower risk of hormone receptor-positive breast cancer than those who do not take aspirin, report Mary Beth Terry, Ph.D., and **Alfred Neugut, M.D., Ph.D.**, of Columbia University, and colleagues. Other studies have suggested that regular aspirin use may protect against breast cancer, but this study is the first to show that aspirin may be more effective at preventing certain types of the cancer.

When the data were analyzed by hormone receptor status, the researchers found that the protective effect for all but estrogen receptor-negative/progesterone receptor-negative cancers. Regular aspirin use was associated with a 20 percent reduction in risk for breast cancer compared with nonuse. An even greater risk reduction (28%) was seen among women who took at least seven aspirin per week. Ibuprofen had a weaker preventive effect than aspirin, and acetaminophen had no protective effect. The study builds on preclinical models showing that drugs such as aspirin inhibit cyclooxygenase (COX), which is a key player in the synthesis of prostaglandins, which in turn stimulate the production of estrogen. The research is from data collected in a major case-control study of the Long Island Breast Cancer Study Project. The analyses were based on data on 1,442 breast cancer patients and 1,420 healthy women.

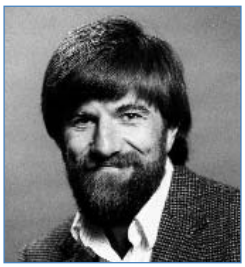
Terry MB, Gammon MD, Zhang FF, Tawfik H, Teitelbaum SL, Britton JA, Subbaramaiah K, Dannenberg AJ, Neugut AI. Association of frequency and duration of aspirin use and hormone receptor status with breast cancer risk. JAMA 2004 May 26;291(20):2433.

Polymorphisms in DNA Repair Genes May Increase Breast Cancer Susceptibility

Susan Hankinson, R.N., Sc.D.

Genetic polymorphisms in double-strand break (DSB) repair genes may affect DNA repair capability and confer susceptibility to breast cancer. **Susan Hankinson, R.N., Sc.D.**, and **David Hunter, Sc.D.**, of Brigham and Women's Hospital and Harvard Medical School, and colleagues prospectively evaluated associations between polymorphisms in three DNA DSB repair genes, *XRCC2, XRCC3,* and *Ligase IV* in a nested case-control study within the Nurses' Health Study (NHS) I. Research suggests that these polymorphisms may be associated with risk of breast cancer.

No overall association was found between the six genotypes examined and risk of breast cancer, but *Ligase IV* T1977C carriers were at increased risk of breast cancer if they had a first-degree family history of the disease (odds ratio = 2.4). An association was not observed for the other genotypes studied (*Ligase IV* C229T (5'-UTR), *XRCC2* G31479A (R188H), *XRCC3* A4541G (5' UTR), A17893G (IVS5-14), and C18067T (T241 M)). The scientists also explored whether genetic variation in the DSB repair pathway might modify the associations of plasma antioxidant status and cigarette smoking with cancer risk. They found a significantly decreased risk of breast cancer for women in the highest quartile of plasma-α-carotene level who did not carry the R188H polymorphism, suggesting that the polymorphism may modify risk of breast cancer. No significant interaction was observed between the genes and smoking behavior. Subtle effects of some of the polymorphisms may be magnified with certain environmental exposures. EGRP has funded the NHS I since 1973.



David Hunter, Sc.D.

Han J, Hankinson SE, Ranu H, De Vivo I, Hunter DJ. Polymorphisms in DNA double-strand break repair genes and breast cancer risk in the Nurses' Health Study. Carcinogenesis 2004 Feb;25(2):189-95.

Growth Factor Gene Variant Not Associated With Postmenopausal Breast Cancer Risk

Brian Henderson, M.D.

Laboratory studies suggest that transforming growth factor-beta (TGF-β) has antiproliferative activity in early breast tumor development and a promoting effect in later stages. A T29C polymorphism in the *TGF-β1* gene has been associated with higher circulating levels of the growth factor and inconsistently with risk of breast cancer in studies. In a large case-control study nested within the Multiethnic Cohort (MEC) Study, the polymorphism was not found to be associated with increased risk of postmenopausal breast cancer. The MEC study, which has been supported by EGRP since 1993, is a prospective study conducted in Hawaii and Los Angeles that includes predominantly postmenopausal Japanese, white, African-American, Latino, and Native-Hawaiian women. The research was conducted by Loïc Le Marchand, M.D., Ph.D., and **Laurence Kolonel, M.D., Ph.D.**, of the University of Hawaii (pictured p. 6), and **Brian Henderson, M.D.**, of the University of Southern California at Los Angeles, and colleagues.

Le Marchand L, Haiman CA, van den Berg D, Wilkens LR, Kolonel LN, Henderson BE. T29C polymorphism in the transforming growth factor β1 gene and postmenopausal breast cancer risk: The Multiethnic Cohort Study. Cancer Epidemiol Biomarkers Prev 2004 Mar;13(3):412-5.

Recent Alcohol Consumption Associated With Increased Breast Cancer Risk


Ronald Ross, M.D.

Recent consumption of alcoholic beverages appears to play a larger role in risk of breast cancer than consumption at earlier ages, and the quantity appears to be more important than the frequency, according to research by Pamela Horn-Ross, Ph.D., of the Northern California Cancer Center, and **Ronald Ross, M.D.**, of the University of Southern California at Los Angeles, and colleagues. The analysis from the California Teachers Study indicated that recent drinking of 20 or more grams (0.7 oz.) per day of alcoholic beverages was associated with a 28 percent increased risk of breast cancer compared with no recent drinking. "Recent" was defined as the year before joining the cohort. The greatest risk of breast cancer was found for postmenopausal women. Postmenopausal women who drank 20 or more grams per day of alcoholic beverages and had a history of benign breast disease had a 32 percent increased risk for the cancer compared with nondrinking women without benign breast disease. For postmenopausal women who drank 20 or more grams per day of alcoholic beverages and who took hormone replacement therapy, the risk more than doubled in comparison to nondrinking women who never took hormone replacement therapy.

Horn-Ross PL, Canchola AJ, West DW, Stewart SL, Bernstein L, Deapen D, Pinder R, Ross RK, Anton-Culver H, Peel D, Ziogas A, Reynolds P, Wright W. Patterns of alcohol consumption and breast cancer risk in the California Teachers Study cohort. Cancer Epidemiol Biomarkers Prev 2004 Mar;13(3):405-11.

Alcohol Consumption Associated With Colorectal Cancer in Pooled Analysis

Drinking alcoholic beverages was positively associated with risk of colorectal cancer in an analysis of data from eight cohort studies in North America and Europe. The association was seen consistently in men and women and across studies and was found for cancer of the proximal colon, distal colon, and rectum. There was no clear difference in risk by specific type of beverage. The scientists, who used one measure of alcohol consumption at baseline, concluded that this single determination of alcohol intake correlated with a modest increased risk of colorectal cancer, mainly at the highest levels of intake. The increased risk of colorectal cancer was limited to individuals who drank more than 30

grams (1.1 oz) per day of alcoholic beverages. Individuals who drank between 30 and 45 grams (1.6 oz) per day had a 16 percent increased risk of colorectal cancer compared with nondrinkers. Those who consumed 45 grams per day or more had a 40 percent increased risk. The analysis was based on data on 4,687 colorectal cancer cases who were followed from 6 to 16 years across studies and was conducted by Eunyoung Cho, Sc.D., of the Harvard Medical School, and **Walter Willett, M.D., Dr.P.H.**, of the Harvard School of Public Health (pictured p. 3), and colleagues.

Cho E, Smith-Warner SA, Ritz J, van den Brandt PA, Colditz GA, Folsom AR, Freudenheim JL, Giovannucci E, Goldbohm RA, Graham S, Holmberg L, Kim DH, Malila N, Miller AB, Pietinen P, Rohan TE, Sellers TA, Speizer FE, Willett WC, Wolk A, Hunter DJ. Alcohol intake and colorectal cancer: A pooled analysis of 8 cohort studies. Ann Intern Med 2004 Apr 20;140(8):603-13.

Dietary Changes Associated With Colorectal Cancer in Mexican Americans

Laurence Kolonel, M.D., Ph.D.

Kristine Monroe, Ph.D., of the University of Southern California at Los Angeles, and **Laurence Kolonel, M.D., Ph.D.**, of the University of Hawaii, and colleagues examined changes in dietary practices that might be consistent with the increasing incidence of colorectal cancer in the Mexican-American migrant population of Los Angeles. Some food traditions were retained by Mexican Americans, but the dietary changes resulting from acculturation were significant and support an association between colorectal cancer risk and certain dietary components, especially alcohol as a risk factor and vegetables as protective factors.

The scientists found an 11 percent and 9 percent decrease in calorie-adjusted mean intake of vegetables, excluding legumes, in U.S.-born men and women, respectively, compared with Mexican-born study participants. The decline in mean vegetable intake was lower, 18 percent and 15 percent, respectively, when legumes were included in the vegetable category. There also was a decrease in intake of nonstarch polysaccharides (dietary fiber) from vegetables, 13 percent in men and 10 percent in women. The study is based on data from the EGRP-funded Multiethnic Cohort Study.

Monroe KR, Hankin JH, Pike MC, Henderson BE, Stram DO, Park S, Nomura AM, Wilkens LR, Kolonel LN. Correlation of dietary intake and colorectal cancer incidence among Mexican-American migrants: The Multiethnic Cohort Study. Nutr Cancer 2003;45(2):133-47.

Calcium Associated With Reduced Risk of Colon Cancer in Pooled Analysis

Higher consumption of milk and calcium is associated with reduced risk of colorectal cancer, according to an analysis of data from 10 cohort studies in America and Europe. The inverse associations were consistent across studies and seen for both sexes. For the study, Eunyoung Cho, Sc.D., and **Walter Willett, M.D., Dr.P.H.**, of the Harvard School of Public Health (pictured p. 3), and colleagues analyzed data on 4,992 colorectal cancer cases who were followed from 6 to 16 years. Only milk consumption was statistically significantly associated with lower risk of colorectal cancer, but results for most of the other dairy foods examined were suggestive of an inverse association. Calcium intake was inversely associated with risk of colorectal cancer, with the inverse association being statistically significant only among those in the highest vitamin D intake category. The findings support the idea that moderate milk and calcium intake reduce risk of colorectal cancer.

Cho E, Smith-Warner SA, Spiegelman D, Beeson WL, van den Brandt PA, Colditz GA, Folsom AR, Fraser GE, Freudenheim JL, Giovannucci E, Goldbohm RA, Graham S, Miller AB, Pietinen P, Potter JD, Rohan TE, Terry P, Toniolo P, Virtanen MJ, Willett WC, Wolk A, Wu K, Yaun SS, Zeleniuch-Jacquotte A, Hunter DJ. Dairy foods, calcium, and colorectal cancer: A pooled analysis of 10 cohort studies. J Natl Cancer Inst 2004 Jul 7;96(13):1015-22.

African Americans Have More Aggressive Colon Cancer

Upender Manne, Ph.D.

Upender Manne, Ph.D., of the University of Alabama at Birmingham, and colleagues evaluated differences in survival from colorectal cancer by tumor location and pathologic stage between 199 African-American and 292 non-Hispanic white patients who were treated with surgery alone. African Americans were 50 percent more likely than whites to die within 5 to 10 years, even when they received the same treatment. No significant racial differences in survival were seen in patients with rectal cancer. The scientists suggest that the decreased overall survival observed in African-American patients may not be attributable to tumor stage at diagnosis or treatment for colon cancer, but may be due to differences in other biologic or genetic factors between African-American and white patients. They also found that decreased expression of $p27^{kip-1}$ was an indicator of poor prognosis, irrespective of race, and could aid in identifying patients with aggressive disease.

Alexander D, Chatla C, Funkhouser E, Meleth S, Grizzle WE, Manne U. Postsurgical disparity in survival between African Americans and Caucasians with colonic adenocarcinoma. Cancer 2004 Jul 1;101(1):66-76.

Manne U, Jhala NC, Jones J, Weiss HL, Chatla C, Meleth S, Suarez-Cuervo C, Grizzle WE. Prognostic significance of $p27^{kip-1}$ expression in colorectal adenocarcinomas is associated with tumor stage. Clin Cancer Res 2004 Mar 1;10(5):1743-52.

Founder Mutation in Patients With HNPCC Identified

Albert de la Chapelle, M.D., Ph.D.

Scientists have identified a hereditary genetic mutation that may account for a significant proportion of cases of hereditary nonpolyposis colorectal cancer (HNPCC), also known as Lynch syndrome. HNPCC is the most common form of hereditary colorectal cancer, and mutation carriers are at very high risk of other cancers as well. Henry Lynch, M.D., of Creighton University, and **Albert de la Chapelle, M.D., Ph.D.**, of The Ohio State University, and colleagues studied nine families with a history of HNPCC who were from different U.S. geographic areas. They identified 61 family members from 14 states who had an identical mutation in the mismatch repair gene *MSH2*. This is the first HNPCC founder mutation to be identified in a large distantly related or unrelated population in the United States. The scientists recommend that an assay for the mutation be added to routine *MSH2* testing of individuals at risk for HNPCC in the United States.

Lynch HT, Coronel SM, Okimoto R, Hampel H, Sweet K, Lynch JF, Barrows A, Wijnen J, van der Klift H, Franken P, Wagner A, Fodde R, de la Chapelle A. A founder mutation of the MSH2 gene and hereditary nonpolyposis colorectal cancer in the United States. JAMA 2004 Feb 11;291(6):718-24.

Statins May Reduce Risk of Colorectal Cancer

Stephen Gruber, M.D., Ph.D.

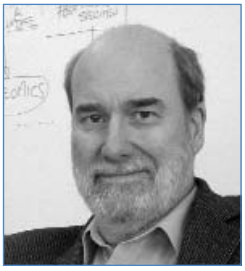
Use of statins for 5 or more years has been found to be associated with a 51 percent reduction in risk of colorectal cancer in a study by **Stephen Gruber, M.D., Ph.D.,** of the University of Michigan Comprehensive Cancer Center, and colleagues. After controlling for potential confounding factors, such as use of aspirin or nonsteroidal anti-inflammatory drugs, the risk associated with use of cholesterol-lowering statins was decreased by 46 percent. The population-based case-control study compared 1,814 colorectal cancer patients and 1,959 controls. The findings were specific to statins and not other types of cholesterol-lowering drugs.

Gruber SB. American Association for Cancer Research annual meeting, June 7, 2004 (oral presentation).

Folate Metabolism Gene Variant May Help Predict Colon Cancer Risk

Martha Slattery, Ph.D.

Folate intake has been associated with reduced risk of colorectal cancer, and 5,10-methylenetetrahydrofolate reductase (MTHFR) is a key enzyme in folate metabolism. Karen Curtin, M.Stat., and **Martha Slattery, Ph.D.**, of the University of Utah, and **John Potter, M.D., Ph.D.**, of the Fred Hutchinson Cancer Research Center, and colleagues investigated the potential for the *MTHFR* polymorphisms *C677T* and *A1298C* to be used to predict increased or decreased risk of colon cancer. When comparing participants with and without colon cancer, they found differences in colon cancer risk among those with specific polymorphisms. Among men, no significant association was found for folate, methionine, or vitamins B_{12}, B_2, or B_6 intake, although a trend toward reduced risk of colorectal cancer was seen among study participants with *MTHFR* wild-type genotypes or a heterozygous/wild-type combination and high folate intake. Men with a variant/wild-type genotype who consumed moderate amounts of alcohol had a decreased risk of the cancer. Among women, lower colon cancer risk was seen with high intake of folate, methionine, or vitamins B_{12}, B_2, or B_6 intake, and the wild-type/variant genotype. Women with the wild-type/variant genotype who consumed moderate amounts of alcohol had a decreased risk of the cancer. For postmenopausal women on hormone replacement therapy, reduced risk was seen only in women with both wild-type genotypes.



John Potter, M.D., Ph.D.

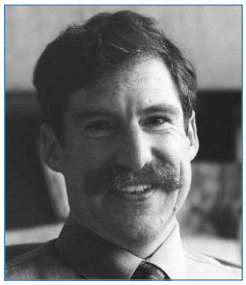
Curtin K, Bigler J, Slattery ML, Caan B, Potter JD, Ulrich CM. MTHFR C677T and A1298C polymorphisms: Diet, estrogen, and risk of colon cancer. Cancer Epidemiol Biomarkers Prev 2004 Feb;13(2):285-92.

Dose, Duration of Aspirin for Colorectal Adenoma Protection Explored

Research has established that regular aspirin use reduces the risk of recurrent colorectal adenoma, but the effective dose and duration of use in an average-risk population is not clear. Andrew Chan, M.D., of Massachusetts General Hospital, and **Graham Colditz, M.D., Dr.P.H.**, and **Walter Willett, M.D., Dr.P.H.**, of the Harvard School of Public Health, and colleagues studied the dose and duration effects of aspirin use on primary prevention of colorectal adenoma among 27,077 women from the Nurses' Health Study I. Within this cohort, there were 1,368 cases of confirmed distal colorectal adenoma. The scientists found that women who regularly used two or more aspirin per week had a 25 percent decreased risk of colorectal adenoma compared with those who did not report regular aspirin use. The greatest protective effect was observed at relatively high aspirin doses for which there was a 50 percent decreased risk of the cancer associated with regular use of more than 14 aspirin per week. Duration of use, when adjusted for the number of tablets taken per week, did not significantly reduce risk. Because use of high doses of aspirin carries its own risks, the scientists stress that more studies are needed before a recommendation can be made about the dosage and duration of aspirin use for the general adult population as a preventative measure against colorectal adenomas. (Drs. Colditz and Willett pictured pp. 10 and 3, respectively.)

Chan AT, Giovannucci EL, Schernhammer ES, Colditz GA, Hunter DJ, Willett WC, Fuchs CS. A prospective study of aspirin use and the risk for colorectal adenoma. Ann Intern Med 2004 Feb 3;140(3):157-66.

Marker for Elevated Insulin Production May Help Predict Colorectal Cancer Risk



Meir Stampfer, M.D., Dr.P.H.

Jing Ma, M.D., Ph.D., and **Meir Stampfer, M.D., Dr.P.H.**, of the Harvard Medical School, and colleagues found that risk of colorectal cancer may be predicted by assessment of insulin production using plasma C-peptide concentrations, independent of known colorectal cancer risk factors and factors related to insulin resistance. They conducted a nested case-control study in the Physicians' Health Study with 176 males who had confirmed diagnoses of colorectal cancer and 294 controls. Blood samples from the cases and controls were assayed for levels of C-peptide, insulin-like growth factor I (IGF-I), and its binding protein 3 (IGFBP-3). The positive association between C-peptide levels and risk of colorectal cancer was found to be independent of IGF-I and IGFBP-3. The study results provide more evidence for the link between elevated long-term insulin production and colorectal cancer risk.

Ma J, Giovannucci E, Pollak M, Leavitt A, Tao Y, Gaziano JM, Stampfer MJ. A prospective study of plasma C-peptide and colorectal cancer risk in men. J Natl Cancer Inst 2004 Apr 7;96(7):546-53.

Colon Cancer Survivors Adopt Healthy Lifestyle Behaviors

Robert Sandler, M.D., M.P.H.

Survivors of colon cancer reported adopting a variety of positive health lifestyle behaviors concerning fruit and vegetable consumption, dietary supplement use, and physical activity following diagnosis of the disease in a study by Jessie Satia Abouta, Ph.D., and **Robert Sandler, M.D., M.P.H.**, of the University of North Carolina at Chapel Hill, and colleagues. The findings suggest that patients have a strong interest in behavior modification following a diagnosis of colon cancer and that health care providers have an opportunity to effectively communicate with their patients about making healthy lifestyle changes. Interestingly, there was little correlation between vegetable intake and any demographic or psychosocial factor, except employment status. The existence of barriers to increasing fruit and vegetable intake was inversely associated with taking a new dietary supplement. The study is from an analysis of data on 278 colon cancer patients and 278 controls in the North Carolina Colon Cancer Study, a population-based cohort of African Americans and whites.

Satia JA, Campbell MK, Galanko JA, James A, Carr C, Sandler RS. Longitudinal changes in lifestyle behaviors and health status in colon cancer survivors. Cancer Epidemiol Biomarkers Prev 2004 Jun;13(6):1022-31.

Carotinoid Intake and Risk of Lung Cancer Examined in Pooled Analysis

Scientists investigated the association between risk of lung cancer and intake of dietary carotenoids using data from seven North American and European cohort studies. They did not find, as some studies have suggested, that dietary sources of β-carotene either were protective or increased risk. However, β-cyptoxanthin, which is found particularly in citrus fruits, was associated with a 24 percent decreased risk of lung cancer when comparing data on individuals with the highest and lowest intakes. The association was present for all histologic types of lung cancer. The other carotenoids studied were not found to be associated with risk of the cancer: α-carotene, lutein/zeaxanthin, and lycopene. These findings were not altered after adjusting for intakes of vitamin C, folate, other carotenoids, and multivitamin use. The study by

Satu Männistö, Ph.D., **Walter Willett, M.D., Dr.P.H.**, and **David Hunter, Sc.D.**, of the Harvard School of Public Health, and colleagues included data on 3,155 lung cancer cases who were followed from 7 to 16 years across studies. (Drs. Willett and Hunter pictured pp. 3 and 4, respectively.)

Männistö S, Smith-Warner SA, Spiegelman D, Albanes D, Anderson K, van den Brandt PA, Cerhan JR, Colditz G, Feskanich D, Freudenheim JL, Giovannucci E, Goldbohm RA, Graham S, Miller AB, Rohan TE, Virtamo J, Willett WC, Hunter DJ. Dietary carotenoids and risk of lung cancer in a pooled analysis of seven cohort studies. Cancer Epidemiol Biomarkers Prev 2004 Jan;13(1):40-8.

Potential Familial Lung Cancer Gene Discovered


Marshall Anderson, Ph.D.

A research team led by **Marshall Anderson, Ph.D.**, of the University of Cincinnati, has discovered a possible susceptibility gene for lung cancer. An interdisciplinary consortium of 12 research institutions and universities, including the National Cancer Institute (NCI) and the National Human Genome Research Institute (NHGRI), identified a major lung cancer susceptibility region on a segment of chromosome 6.

The EGRP-funded Genetic Epidemiology of Lung Cancer Consortium (GELCC) examined 52 families who had at least three first-degree family members affected by lung, throat, or laryngeal cancer. The team found strong evidence that a lung cancer susceptibility gene (or genes) is coinherited with a genetic marker on chromosome 6. Markers on chromosomes 12, 14, and 20 also indicated possible linkage to lung cancer susceptibility, although the results were not as strong.

Another discovery involved the effects of smoking on cancer risk for carriers and noncarriers of the predicted familial lung cancer gene. In noncarriers, the more they smoked, the greater their risk of cancer. In carriers, on the other hand, any amount of smoking increased lung cancer risk. The findings suggest that smoking even a small amount can lead to cancer for individuals with inherited susceptibility.

Bailey-Wilson JE, Amos CI, Pinney SM, Petersen GM, De Andrade M, Wiest JS, Fain P, Schwartz AG, You M, Franklin W, Klein C, Gazdar A, Rothschild H, Mandal D, Coons T, Slusser J, Lee J, Gaba C, Kupert E, Perez A, Zhou X, Zeng D, Liu Q, Zhang Q, Seminara D, Minna J, Anderson MW. A major lung cancer susceptibility locus maps to chromosome 6q23-25. Am J Hum Genet 2004 75:460-74. (Epub ahead of print, Jul 21).

Women and Men Have Similar Risk for Smoking-Related Lung Cancer


Graham Colditz, M.D., Dr.P.H.

Men and women appear to be similarly susceptible to lung cancer, given equal smoking rates, according to a study by Chris Bain, Ph.D., of the University of Queensland, Australia, and **Graham Colditz, M.D., Dr.P.H.,** of Brigham and Women's Hospital and Harvard Medical School, and colleagues. Although lung cancer incidence is higher in men than in women because of differences in patterns of smoking, some case-control studies have suggested that women may be more susceptible to lung cancer than men. To clear up the controversy, the scientists analyzed prospective data on 60,296 women from the Nurses' Health Study I and 25,397 men from the Health Professionals Follow-Up Study, both cohorts funded by EGRP. After controlling for age, number of cigarettes smoked per day, age at smoking initiation, and time since quitting, the scientists found no difference between men and women in overall lung cancer susceptibility. They also reviewed six published prospective cohort studies on the issue. When smoking rates were equal, none of the studies showed that women had a higher risk of lung cancer than men. It is possible, however, that the risk of some subtypes of lung cancer may be higher in women than in men.

Bain C, Feskanich D, Speizer FE, Thun M, Hertzmark E, Rosner BA, Colditz GA. Lung cancer rates in men and women with comparable histories of smoking. J Natl Cancer Inst 2004 Jun 2;96(11):826-34.

The Dietary Folate and Lung Cancer Connection Explored

Qingyi Wei, M.D., Ph.D.

Folate deficiency increasingly is believed to be associated with altered DNA methylation and synthesis and disruption of DNA repair, which might explain reports of a link between folate deficiency and risk of different types of cancer. **Qingyi Wei, M.D., Ph.D.**, and **Margaret Spitz, M.D., M.P.H.**, of The University of Texas M.D. Anderson Cancer Center, and colleagues found low dietary intake of folate to be associated with suboptimal DNA repair capability (as measured by the host cell reactivation assay). Studying a cancer-free population, they found that individuals in the lowest tertile of dietary folate intake had a greater reduction in DNA repair capability than those in the upper tertile of intake. The association also was more pronounced in individuals who did not use folate supplements than in those who did.

In other research, Hongbing Shen, Ph.D., Dr. Spitz, and colleagues found that dietary folate may protect against lung cancer in an analysis of data on 470 lung cancer patients who were former smokers and 472 former smoker controls. Former smokers were studied to avoid confounding bias from smoking. There was an inverse dose-response relationship between increasing intake of dietary folate and decreased risk of lung cancer. The association was especially apparent among those who drank alcoholic beverages, were former heavy smokers, reported having a family history of lung cancer, and those who did not take folate supplements. Dietary folate intake above the control median level was associated with a 40 percent decreased risk of lung cancer. If confirmed by other studies, the findings could have important public health implications for use of folate supplements or diet modification to increase intake of the vitamin in at-risk populations.

Margaret Spitz, M.D., M.P.H.

Wei Q, Shen H, Wang LE, Duphorne CM, Pillow PC, Guo Z, Qiao Y, Spitz MR. Association between low dietary folate intake and suboptimal cellular DNA repair capacity. Cancer Epidemiol Biomarkers Prev 2003 Oct;12(10):963-9.

Shen H, Wei Q, Pillow PC, Amos CI, Hong WK, Spitz MR. Dietary folate intake and lung cancer risk in former smokers: A case-control analysis. Cancer Epidemiol Biomarkers Prev 2003 Oct;12(10):980-6.

A Y Chromosome May Play Role in Risk of Prostate Cancer Among Asians

Silvia Paracchini, Ph.D., of the University of Oxford, **Laurence Kolonel, M.D., Ph.D.**, of the University of Hawaii (pictured p. 6), and **Brian Henderson, M.D.**, of the University of Southern California at Los Angeles (pictured p. 5), and colleagues investigated the role of the Y chromosome in prostate cancer in a case-control study nested within the Multiethnic Cohort Study. The analysis included data on 930 prostate cancer cases and 1,208 controls. The men were African American, white, Latino, and Japanese. Only the Y lineage O3, which was present almost exclusively in the Japanese study participants, was associated with a 63 percent increased risk of prostate cancer. The risk was modified by age and severity of disease. Japanese men under age 65 who had the Y lineage O3 had nearly a fourfold increased risk of developing severe prostate cancer. If studies of other Japanese or Asian populations yield similar findings, the scientists suggest that a systematic evaluation of the genetic changes in this lineage is warranted.

Paracchini S, Pearce CL, Kolonel LN, Altshuler D, Henderson BE, Tyler-Smith C. A Y chromosomal influence on prostate cancer risk: The multi-ethnic cohort study. J Med Genet 2003 Nov;40(11):815-9.

Selenium May Slow Progression of Prostate Cancer

Selenium may help slow progression of prostate cancer, according to a study by Haojie Li, M.D., Ph.D., and **Meir Stampfer, M.D., Dr.P.H.**, of the Harvard Medical School (pictured p. 9), and colleagues. The scientists studied plasma levels of selenium prior to diagnosis of prostate cancer among participants in the Physicians' Health Study. The nested case-control study included 5,896 men who were diagnosed with prostate cancer during 13 years of followup and 577 controls. Levels of selenium prior to diagnosis of cancer were inversely associated with subsequent risk of advanced prostate cancer. The odds ratio was 0.52 for men in the fifth quintile for plasma concentration level compared with those in the first quintile. Also, for men who had above-normal levels of prostate-specific antigen (PSA) at the start of the study, high selenium levels significantly reduced risk of all prostate cancer.

Li H, Stampfer MJ, Giovannucci EL, Morris JS, Willett WC, Gaziano JM, Ma J. A prospective study of plasma selenium levels and prostate cancer risk. J Natl Cancer Inst 2004 May 5;96(9):696-703.

Impaired DNA Repair Capability Associated With Prostate Cancer Susceptibility

John Witte, Ph.D.

Benjamin Rybicki, Ph.D., of the Henry Ford Health System, and **John Witte, Ph.D.**, of the University of California at San Francisco, and colleagues examined the relationship between DNA repair capacity phenotypes and susceptibility to prostate cancer. They studied 506 sibling pairs among whom 637 brothers were diagnosed with prostate cancer and focused on polymorphisms in the *XRCC1* and *XPD* genes. Polymorphisms in these genes have been studied in relation to other cancers, such as lung, breast, and skin cancer, but little has been reported on variants of these genes in relation to prostate cancer. The scientists found a modest (60%) increased risk of prostate cancer in men who had two copies of the *XPD* codon 312 *Ans* allele. The risk was increased threefold when two copies of the *XRCC1* codon 399 *Gln* also were present. The findings suggest that DNA repair genes play a role in development of prostate cancer, particularly if two genes involved in different repair pathways are compromised.

Rybicki BA, Conti DV, Moreira A, Cicek M, Casey G, Witte JS. DNA repair gene XRCC1 and XPD polymorphisms and risk of prostate cancer. Cancer Epidemiol Biomarkers Prev 2004 Jan;13(1):23-9.

Family Cancer History and Risk of Ovarian Cancer Clarified

Marc Goodman, Ph.D.

Ko-Hui Tung, Ph.D., and **Marc Goodman, Ph.D.**, of the University of Hawaii, and colleagues examined the relationship between familial cancer and risk of ovarian cancer. They found that having a family history of breast, ovarian, colorectal, or prostate cancer in first-degree relatives is a risk factor for ovarian cancer. Risk of ovarian cancer was greater for women whose parents, rather than siblings, had a history of breast or prostate cancer, and for women whose parents had been diagnosed with colorectal cancer at an early age. The study provides relevant data on risk of ovarian cancer according to family relationship, age at diagnosis, and histologic subtype of the cancer. Some established reproductive risk factors, including use of oral contraceptives and having had a child, appeared to reduce the risk of familial and sporadic ovarian cancer to a similar extent.

Tung KH, Goodman MT, Wu AH, McDuffie K, Wilkens LR, Nomura AM, Kolonel LN. Aggregation of ovarian cancer with breast, ovarian, colorectal, and prostate cancer in first-degree relatives. Am J Epidemiol 2004 Apr 15;159(8):750-8.

Smoking Associated With Mucinous Epithelial Ovarian Cancer

Lynn Rosenberg, Sc.D.

Confirmation that women who smoke more than one pack of cigarettes per day have about a threefold increased risk of mucinous ovarian cancer compared with women who never smoked is provided in a study by Yuqing Zhang, M.D., and **Lynn Rosenberg, Sc.D.**, of the Boston University School of Medicine, and colleagues. The scientists conducted a case-control study to examine the association between smoking and different types of ovarian cancer. Information on smoking and type of epithelial ovarian cancer was available for 709 women, 74 of whom had the mucinous type. The odds ratios were 1.5 among women who smoked less than one pack of cigarettes per day, 1.4 among women who smoked one pack per day, and 2.9 among women who smoked more than one pack per day compared with never smokers. No association was found between cigarette smoking and epithelial ovarian cancer of cell types other than mucinous.

Zhang Y, Coogan PF, Palmer JR, Strom BL, Rosenberg L. Cigarette smoking and increased risk of mucinous epithelial ovarian cancer. Am J Epidemiol 2004 Jan 15;159(2):133-9.

Aspirin May Decrease Risk of Hodgkin's Lymphoma

Nancy Mueller, Sc.D.

In the first study to examine the association between nonsteroidal anti-inflammatory drugs (NSAIDs) and Hodgkin's lymphoma, scientists found regular aspirin use to be associated with a 40 percent decreased risk of the cancer compared to nonregular aspirin use. The population-based case-control study by Ellen Chang, Sc.D., and **Nancy Mueller, Sc.D.**, of the Harvard School of Public Health, and colleagues compared data on 565 patients with Hodgkin's lymphoma and 679 controls. A reduction in risk was not observed with regular use of other NSAIDs. However, regular acetaminophen use was associated with a 70 percent increased risk of Hodgkin's lymphoma. Regular analgesic use was defined as having taken at least two tablets per week on average over the preceding 5 years. Dose-response relationships also were seen. Aspirin inhibits the transcription factor κB (NF-κB), which is involved in immune and inflammatory responses and which, in laboratory studies, appears to be critical in survival of Hodgkin's lymphoma cells. Perhaps aspirin guards against the cancer in this way.

Chang ET, Zheng T, Weir EG, Borowitz M, Mann RB, Spiegelman D, Mueller NE. Aspirin and the risk of Hodgkin's lymphoma in a population-based case-control study. J Natl Cancer Inst 2004 Feb 18;96(4):305-15.

H. pylori, Gastric Atrophy, and Risk of Cancer Examined

Weimin Ye, M.D., Ph.D., of the Karolinska Institute, and colleagues investigated the relationship among infection with *H. pylori*, gastric atrophy, and three types of cancer—esophageal adenocarcinoma, esophageal squamous-cell carcinoma, and gastric cardia adenocarcinoma. It has been hypothesized that *H. pylori* infection may induce gastric atrophy and thereby reduce acid reflux and help protect against cancer. The scientists found that *H. pylori* infection was associated with a 50 percent to 80 percent reduction in risk of esophageal adenocarcinoma, but gastric atrophy was not associated with risk of the cancer. For squamous-cell carcinoma, *H. pylori* infection was associated with a twofold increased risk, and the risk was higher among those who also had gastric atrophy. This finding suggests that gastric atrophy may be an intermediate step in the pathway from *H. pylori* infection to squamous-cell carcinoma. The population-based study included data on 315 patients with the three cancers and 499 controls. The research was supported by EGRP through a grant to **Hans-Olov Adami, M.D., Ph.D.**, of the Karolinska Institute.

Ye W, Held M, Lagergren J, Engstrand L, Blot WJ, McLaughlin JK, Nyren O. Helicobacter pylori infection and gastric atrophy: Risk of adenocarcinoma and squamous-cell carcinoma of the esophagus and adenocarcinoma of the gastric cardia. J Natl Cancer Inst 2004 Mar 3;96(5):388-96.

Smoking, Diet Associated With *H. pylori*-Related Stomach Lesions

Ikuko Kato, M.D.

Helicobacter pylori (*H. pylori*) infection is known to play a role in the etiology of stomach cancer, yet in countries with a high prevalence of infection, only a small percentage of individuals develop the cancer. This suggests that other factors may modify risk for *H. pylori*-related stomach cancer, and to explore the possibility, **Ikuko Kato, M.D., Ph.D.**, of Wayne State University, and colleagues studied a population in Venezuela with extremely high rates of infection. Duration of refrigerator use was marginally inversely associated with prevalence of premalignant lesions. Cigarette smoking was a significant predictor of intestinal metaplasia and dysplasia. Also, the prevalence of gastric lesions progressively increased with increasing intake of starchy vegetables and with decreasing intake of fresh fruit and fruit juice. No association was observed with alcohol consumption. Smoking cessation and increased fruit consumption may slow progression of stomach cancer.

Kato I, Vivas J, Plummer M, Lopez G, Peraza S, Castro D, Sanchez V, Cano E, Andrade O, Garcia R, Franceschi S, Oliver W, Munoz N. Environmental factors in Helicobacter pylori-related gastric precancerous lesions in Venezuela. Cancer Epidemiol Biomarkers Prev 2004 Mar;13(3):468-76.

Female Kidney Cancer Associated With Being Overweight

Aaron Folsom, M.D., M.P.H.

Being overweight, particularly central adiposity, is an important risk factor for kidney cancer in postmenopausal women, according to research by Kristin Nicodemus, Ph.D., M.P.H., and **Aaron Folsom, M.D., M.P.H.**, of the University of Minnesota, and colleagues. The study extended follow up from earlier analysis of kidney cancer in a cohort of postmenopausal white women who are part of the Iowa Women's Health Study, and examined additional potential risk factors for the disease. Kidney cancer has been increasing among white women in the United States in recent decades, as has the prevalence of obesity. Other potential risk factors for the cancer, which the scientists say merit further study, were higher intake of vitamin C, being nulliparous or having more than two live births, low alcohol intake, and taking copper supplements. The cohort has been funded by EGRP since 1985.

Nicodemus KK, Sweeney C, Folsom AR. Evaluation of dietary, medical and lifestyle risk factors for incident kidney cancer in postmenopausal women. Int J Cancer 2004 Jan 1;108(1):115-21.

Research Methods: Risk Estimates, Cancer Registries

Three papers on research methods may be of interest to epidemiologists:

- University of Southern California at Los Angeles scientists Daniel Stram, Ph.D., and **Brian Henderson, M.D.,** and colleagues outline issues involved in choosing a method of estimating haplotype-specific risk estimates from genotype data for case-control studies of unrelated individuals.
- The EGRP-funded international Breast/Ovarian Cancer Family Registries (CFRs) have published a paper about the infrastructure of the resource and the data and biospecimens available.
- The EGRP-funded Cancer Genetics Network (CGN) has published a paper describing recruitment results and pilot studies from this resource for researchers.

Stram DO, Leigh Pearce C, Bretsky P, Freedman M, Hirschhorn JN, Altshuler D, Kolonel LN, Henderson BE, Thomas DC. Modeling and E-M estimation of haplotype-specific relative risks from genotype data for a case-control study of unrelated individuals. Hum Hered 2003;55(4):179-90.

John EM, Hopper JL, Beck JC, Knight JA, Neuhausen SL, Senie RT, Ziogas A, Andrulis IL, Anton-Culver H, Boyd N, Buys SS, Daly MB, O' Malley FP, Santella RM, Southey MC, Venne VL, Venter DJ, West DW, Whittemore AS, Seminara D; Breast Cancer Family Registry. The Breast Cancer Family Registry: An infrastructure for cooperative multinational, interdisciplinary and translational studies of the genetic epidemiology of breast cancer. Breast Cancer Res 2004;6(4):R375-89.

Anton-Culver H, Ziogas A, Bowen D, Finkelstein D, Griffin C, Hanson J, Isaacs C, Kasten-Sportes C, Mineau G, Nadkarni P, Rimer B, Schildkraut J, Strong L, Weber B, Winn D, Hiatt R, Nayfield S. The Cancer Genetics Network: Recruitment results and pilot studies. Community Genet 2003;6(3):171-7.